Chronic kidney disease (CKD) is a major public health problem worldwide with continuously growing epidemic characteristics and heavy cardiovascular (CV) comorbidity. CKD and CV risk have a parallel course, and CV disease is the leading cause of death in end-stage kidney disease (ESKD) patients, accounting for about 50% of mortality [1].

During the past decades, atherosclerosis and CV disease have been associated, at least partially, with excessive overproduction of reactive oxygen species (ROS) and oxidative stress (OS) has emerged as a novel risk factor for CV mortality in CKD and ESKD patients [2]. OS occurs when the formation of ROS exceeds the buffering ability of the naturally occurring endogenous antioxidant defense mechanisms, thus resulting in injury and oxidation of cells and tissues and ultimately leading to CV disease. Overproduction and accumulation of ROS is present even at early CKD stages, progresses along with eGFR decline to ESKD, and is significantly reversed after kidney transplantation. Due to their high reactivity and ephemeral nature, direct and accurate measurement of ROS is very difficult. An alternative approach for assessing the redox status in CKD and ESKD is to measure the products resulting from protein, lipid, DNA, or carbohydrate damage caused by free radicals. Plasma protein carbonyls (PCO) might serve as reliable biomarkers of OS in CKD; since they are chemically stable with long half-life, their sampling is relatively easy, and there are several validated accurate detection methods; and moreover, PCO reflects accurately the state and degree of OS [3]. The oxidation of biomolecules by ROS starts very early in CKD, progresses in parallel with deterioration of kidney function, and is further exacerbated in ESKD. Circulating PCO levels are higher in patients with early CKD compared to healthy individuals and are gradually increased with reduction of estimated glomerular filtration rate (eGFR) [3]. Compared to predialysis CKD stage 4, ESKD patients undergoing dialysis present significantly increased OS. This is attributed to various factors. Typically, in this stage, physicians give strict dietary restrictions to dialysis patients to avoid consumption of fruits and vegetables that are rich in potassium to prevent hyperkalemia, thus resulting in a reduced intake of dietary antioxidants, vitamins, and flavonoids. Moreover, a certain amount of antioxidants (such as vitamin C and trace elements) is lost during every hemodialysis (HD) session. However, the main trigger for OS in HD is the contact of patients’ blood with the bioincompatible, artificial dialysate, and membrane, resulting in activation of white blood cells and overproduction of ROS, after 10 minutes of every HD session [4]. Other HD-related factors causing overproduction of free radicals include the infusion of iron, anemia and inflammation, malfunctioning fistulae, the use of central venous catheters, and the use of heparin and erythropoietin agents [4]. In PD, where nearly all the above factors are absent, one might expect that the OS should be minimal. This is not the case at all; PD patients...
experience increased OS compared to predialysis CKD patients, but much less than HD patients. In PD, the main culprit for OS is the bioincompatible dialysate, which progressively damages the peritoneal membrane. Among proteins that are subjected to oxidative modification of their structure and function in dialysis patients, albumin is a well-established marker of nutritional and inflammation status and an independent predictor of all-cause mortality. Although PD patients present lower PCO levels and oxidized albumin levels than HD, it should be noted that a certain amount of serum albumin is also lost during PD procedure [3].

The clinical implications of OS in CKD are serious and cover a vast area of adverse events, including inflammation, atherosclerosis, CV disease, progression of CKD to ESKD, and death from any cause. Among these, the association of OS with inflammation and atherosclerosis is undisputed. Endothelial dysfunction (ED), the hallmark of atherosclerosis presents early in CKD, is triggered by OS and inflammation and is associated with CV mortality [5]. Since the first stage of ED is the oxidation of lipids and the formation of foam cells, it is crucial to investigate the pathophysiological mechanisms underlying this process.

Proprotein convertase subtilisin/kexin type 9 (PCSK9), by regulating the expression of low-density lipoprotein (LDL) cholesterol receptor, is implicated in inflammation and ED of CKD patients. Doumousi et al. [6] performed a cross-sectional study enrolling 92 predialysis CKD patients (stages II–IV) and found that, although not correlated with eGFR, proteinuria, OS, and inflammation, plasma PCSK9 levels were associated with lipid parameters and ED, assessed by soluble intercellular adhesion molecule-1 levels. Moreover, treatment with statins increases circulating levels were associated with lipid parameters and ED, and covers a vast area of adverse events, including inflammation, atherosclerosis, CV disease, progression of CKD to ESKD, and death from any cause. Among these, the association of OS with inflammation and atherosclerosis is undisputed. Endothelial dysfunction (ED), the hallmark of atherosclerosis presents early in CKD, is triggered by OS and inflammation and is associated with CV mortality [5]. Since the first stage of ED is the oxidation of lipids and the formation of foam cells, it is crucial to investigate the pathophysiological mechanisms underlying this process.

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the possible beneficial effect of short fatty acid supplementation (acetate, propionate, and butyrate) in streptozotocin-induced type 2 diabetes/high-fat diet and DKD mice and in glomerular mesangial cells from high glucose-induced mouse models [17]. Administration of fatty acids, especially butyrate, decreased insulin resistance, prevented proteinuria development and eGFR decline in animals, and suppressed the hyperglycemia-derived OS in mouse glomerular cells, thus suggesting a potential renoprotective effect of short fatty acids, through improvement of OS.

Antioxidant agents may also have a role in the prevention of acute kidney injury (AKI) that may result from nephrototoxic agents or treatments, because the main pathophysiologic pathway in these cases is formation of ROS [18]. NAC has been widely used to prevent contrast-induced nephropathy, a common complication following the exposure to imaging iodinated contrast media [19]. To protect tumor patients treated with cisplatin from AKI, amifostine is usually prescribed as an add-on chemoprotective drug; however, this drug has several side effects. An experimental antioxidant agent (XH-003) has been shown to exert chemoprotective properties similar to that of amifostine, but without causing the adverse side effects of the drug. In the experimental study by Liu et al., HX-003 was shown to decrease the cisplatin-derived AKI through reduction of free radicals and upregulation of the activity of the antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase [20].

This special issue is compatible and consistent with our attempt to elucidate the pathophysiologic mechanisms through which OS affects cells, tissues, organs, and biomolecules and its impact on health outcomes in CKD and ESKD. The increasing knowledge of the pathophysiology might provide further insights in the management of OS and in the evaluation of novel, therapeutic, antioxidant treatments that might benefit CKD and ESKD patients at the clinical level. This is an ongoing process, and we still need more evidence and data.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

