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The Role of Oxidative Stress and Systemic Inflammation in Kidney Disease and Its Associated Cardiovascular Risk

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Abstract

Chronic kidney disease (CKD) is a major global health burden, with a prevalence of 10–15% and high mortality rates. In particular, CKD portends a disproportionately high risk of cardiovascular disease beyond the traditional cardiovascular risk factors, with pathophysiological factors such as oxidative stress, inflammation and hyperuricaemia considered to exert an additional role in accelerated atherosclerosis. The presence of heightened oxidative stress and systemic inflammation in CKD is associated with increased mortality. The possible underlying mechanisms include gut dysbiosis, dialysis factors, infections, metabolic acidosis and hyperuricaemia. The state of oxidative stress and systemic inflammation are closely linked and perpetuate each other resulting in progression of CKD and cardiovascular disease. Potential interventions to alleviate the oxidative stress and inflammation in CKD include lifestyle modifications including dietary changes and exercise, optimization of dialysis procedure and pharmacotherapeutic agents including antioxidants. They present a potentially highly effective approach to add to the currently available traditional risk-modification strategies. To date, the majority of the published trials have had a small number of participants with a short duration of follow up. Therefore, no robust evidence has been established. Larger trials with meaningful clinical outcomes and longer follow up are required to evaluate such potential therapies.

Keywords: cardiovascular disease, chronic kidney disease, endotoxin, nitric oxide, oxidative stress, reactive oxygen species, systemic inflammation

1. Introduction

Chronic kidney disease (CKD), defined as an estimated or measured glomerular filtration rate (GFR) <60 mL/min/1.73 m² and/or evidence of kidney damage (usually manifested as proteinuria/albuminuria) for at least 3 months [1], is a major and growing public health burden [2]. It is currently estimated that approximately 10–15% of the world's population suffer from CKD and accounts for 4% of the deaths worldwide [3] and has progressively risen from the 21st to the 17th commonest cause of global years of life lost between 2005 and 2015 [4].

The presence of CKD carries a disproportionately increased risk of cardiovascular disease, which increases with progressive declines in GFR and/or increases in albuminuria/proteinuria [1]. Indeed, CKD is considered the most potent known risk factor for cardiovascular disease [5]. Part of this risk is explained by the frequent clustering of traditional cardiovascular risk factors, such as diabetes mellitus, hypertension, obesity, smoking, dyslipidaemia and depression in patients with CKD. However, traditional cardiovascular risk factors account for less than half of the observed excess cardiovascular risk [6]. Consequently, investigators have evaluated the roles of a range of non-traditional cardiovascular risk factors in patients with CKD, including oxidative stress, inflammation and hyperuricaemia (**Table 1**).

Oxidative stress is a particularly promising avenue of investigation. It is becoming well established that CKD is a state of elevated oxidative stress. This is evidenced by the presence of elevated reactive oxygen and nitrogen species, oxidized end products and reduced levels of antioxidants in patients with CKD [7–10]. Systemic inflammation is also up-regulated in CKD evidenced by higher concentrations of inflammatory markers including C-reactive protein (CRP) and interleukin-6 (IL-6) which have been associated with higher mortality in CKD patients and patients with end stage kidney disease (ESKD) [11, 12]. Oxidative stress and chronically elevated inflammatory state may contribute to accelerated atherosclerosis via direct endothelial injury and alteration in nitrogen handling. Reactive oxygen species (ROS) can also cause direct glomerular and tubulointerstitial injury in the kidneys, resulting in further progression of CKD.

The therapeutic options currently available and shown to be beneficial for CKD are limited to anti-hypertensive agents, particularly renin-angiotensin-aldosterone system (RAAS) blockers. However, these agents are only partially effective, typically lowering the risk of renal and

Traditional risk factors	Non-traditional risk factors
Age	Oxidative stress
Hypertension	Mitochondrial dysfunction
Hyperlipidaemia	Systemic inflammation
Tobacco use	Hyperhomocysteinaemia
Diabetes	Hyperuricaemia
Obesity	Thrombosis
	Adipocyte dysfunction

Table 1. The traditional and non-traditional risk factors for development of cardiovascular disease.

cardiovascular end-points by approximately 20%. There is therefore a pressing need to develop novel, and more effective therapeutic strategies. Therapies targeting oxidative stress and inflammation are promising and may be adjuncts to current therapies targeting traditional risk factors.

This chapter reviews the pathophysiologic mechanisms underlying the heightened oxidative stress and systemic inflammation in CKD, and their association with mortality. Current evidence on various antioxidant and anti-inflammatory therapies are also reviewed.

2. Oxidative stress in patients with CKD

Oxidative stress is a state of excessive pathological pro-oxidant activities relative to antioxidant defense mechanisms. The majority of oxidizing agents are reactive oxygen species (ROS), but others include reactive nitrogen species (RNS), chlorine and carbonyl species.

In CKD, there is accumulating evidence that excess oxidative activity exists with deficient antioxidant protection. Studies in dialysis populations show higher levels of end products of oxidation, such as protein carbonyl, oxidized lipoproteins, F2-isoproteins, advanced oxidation protein products (AOPPs), thiobarbituric acid reactive substances (TBARS), 8-hydroxyl-2'-deoxyguanosine (8OHdG). The free radical superoxide anion production by the pro-oxidant enzyme NADPH oxidase (NOX) is found to be elevated in haemodialysis patients [7]. At the same time, it has been shown that dialysis patients have reduced antioxidant activities of superoxide dismutase (SOD), glutathione, and reduced levels of antioxidants such as vitamin A, C, E, zinc (Zn) and selenium (Se) [7, 8]. In a cross-sectional study of 159 patients (28 to 36 patients in each of the CKD stages 1 to 5) compared with 30 healthy controls, Yilmaz et al. [9] also found that a progressive increase in the levels of oxidative stress marker, malondialdehyde (MDA), while concentrations of antioxidant elements, including SOD, glutathione peroxidase (GSH-Px), Zn, copper (Cu) and Se, fell with increasing levels of kidney dysfunction. The most profound redox imbalances were seen in haemodialysis patients. Therefore, the level of oxidative stress in CKD patients appears to escalate with declining renal function.

These perturbations in oxidant-antioxidant balance begin early in the course of CKD. Fortuño et al. [13] showed increased levels of NADPH-generated ROS in patients with early stage (stages 1 and 2) CKD. Similarly, Yilmaz et al. [9] reported lower levels of activity of the antioxidant enzymes, SOD and GSH-Px, in patients with CKD, including those in stages 1–2.

In kidney transplant recipients, there was an increase in oxidative stress, as evidenced by a rise in MDA immediately after allograft reperfusion [14]. Over the following 2 weeks after transplant, there was a continued rise in MDA, although this was somewhat counterbalanced by a concomitant rise in antioxidant levels, such as GSH-Px. Other oxidative and inflammatory markers, such as IL-6, CRP, tumour necrosis factor- α (TNF- α) and protein carbonyls, significantly declined by 2 months after transplantation [15]. The level of improvement in oxidative stress depended on the level of graft function, such that complete resolution was only possible if renal function returned to normal. At 1 year after transplant, the patients with higher serum creatinine concentrations also displayed higher levels of oxidative stress and

inflammation, such as IL-6, MDA, and transforming growth factor beta (TGF- β), compared to those with normal serum creatinine levels [15].

2.1. Mechanisms of increased oxidative stress

A number of factors have been identified which may contribute to the state of heightened oxidative stress in people with CKD.

2.1.1. Gut dysbiosis

A symbiotic relationship exists between the host and its bacterial flora (also known as microbiota), which are predominantly found in the gastrointestinal tract. In addition to regulating the nutrient absorption and protecting the host from pathological bacteria, the gut microbiota has been increasingly linked to progression of CKD through several mechanisms, including generation of uraemic toxins, enhanced intestinal permeability to endotoxins and alteration of nitrogen handling, all of which contribute to elevated oxidative state.

The breakdown of tyrosine and phenylalanine by the intestinal bacteria produces p-cresyl sulphate (PCS), and the breakdown of tryptophan produces the end product of indoxyl sulphate (IS) in the liver. These two nitrogenous end products have been extensively studied for their role in CKD. They are highly protein-bound in plasma, but as their levels become elevated in patients with CKD, the toxic free fraction level also rises [16]. The serum levels of these toxins have been found to correlate with the extent of damage observed in renal glomerular and tubular cells, tubulointerstitial damage and increased production of reactive oxygen species [16, 17].

Factors influencing the amount of toxins produced include the balance between carbohydrate (in the form of dietary fibre) and amino acids in the large intestine, the intestinal transit time, and the permeability of the gastrointestinal tract. Production of uremic toxins is influenced by substrate availability for fermentation in the colon, notably the balance between carbohydrate (fermentable fibre), and amino acids. A low concentration of fermentable fibre alters the composition of intestinal bacteria to favour more proteolytic bacterial species resulting in the higher production of nitrogenous waste and uraemic toxins. The slower intestinal transit time predisposes to bacteria overgrowth with subsequent production of pro-inflammatory toxins [18].

In addition to the increased production of uraemic toxins in CKD patients, there is evidence that changes in the composition of intestinal bacteria compromise the integrity of intestinal barrier resulting in increased intestinal permeability. This is supported by findings of depletion of the tight junction proteins in the gastrointestinal tract of uraemic patients and drops in transepithelial electrical resistance in colonocytes exposed to the plasma of uraemic patients [19]. Suppression of anti-inflammatory nuclear factor erythroid 2-related factor 2 (NRF2) has also been noted. This may contribute to gut inflammation and reduced expression of epithelial tight junctions, resulting in increased gut permeability [20]. Translocation of bacterial fragments and endotoxins due to increased intestinal permeability may activate the pro-inflammatory pathways in the systemic circulation. For example, increased plasma concentration of lipopolysaccharides due to increased intestinal permeability activates the toll-like receptors (TLR) 2 and TLR4, which in turn activates the nuclear transcription factor kB

(NF-κB). NF-κB is the master initiator of proinflammatory processes and induces the production of cytokines IL-1, IL-6 and TNF-α [21]. The influx of proinflammatory cytokines causes generation of reactive species (**Figure 1**).

2.1.2. Hyperglycaemia

Hyperglycaemia in diabetic kidney disease has direct and indirect roles in increasing oxidative stress. Advanced glycation end products (AGEs) are formed when the carbonyl component is added non-enzymatically to the free amino acid group of proteins or lipids in the presence of chronic hyperglycaemia. The effects of AGEs are executed via various receptors for AGE (RAGE), which in turn activate transcription factors, such as NF-κB, AP1 and SP1, to activate various oxidative pathways. The pathways activated by AGEs cause production of reactive oxygen species with the end results of mesangial expansion, glomerular basement membrane (GBM) thickening and endothelial cell dysfunction. First, AGEs activate the protein kinase C (PKC) pathway in the glomeruli producing ROS and downstream pathologic changes. The second enzymatic pathway is the activation of NOX which directly generates free radicals. In addition to the enzymatic pathways, hyperglycaemia can directly stimulate the formation of TGF-β, again resulting in mesangial expansion, renal hypertrophy and glomerulosclerosis. The presence of increased renin-angiotensin-aldosterone system (RAAS) activity increases the level of angiotensin II which is a potent initiator of inflammatory processes and subsequent oxidative stress [10, 22].

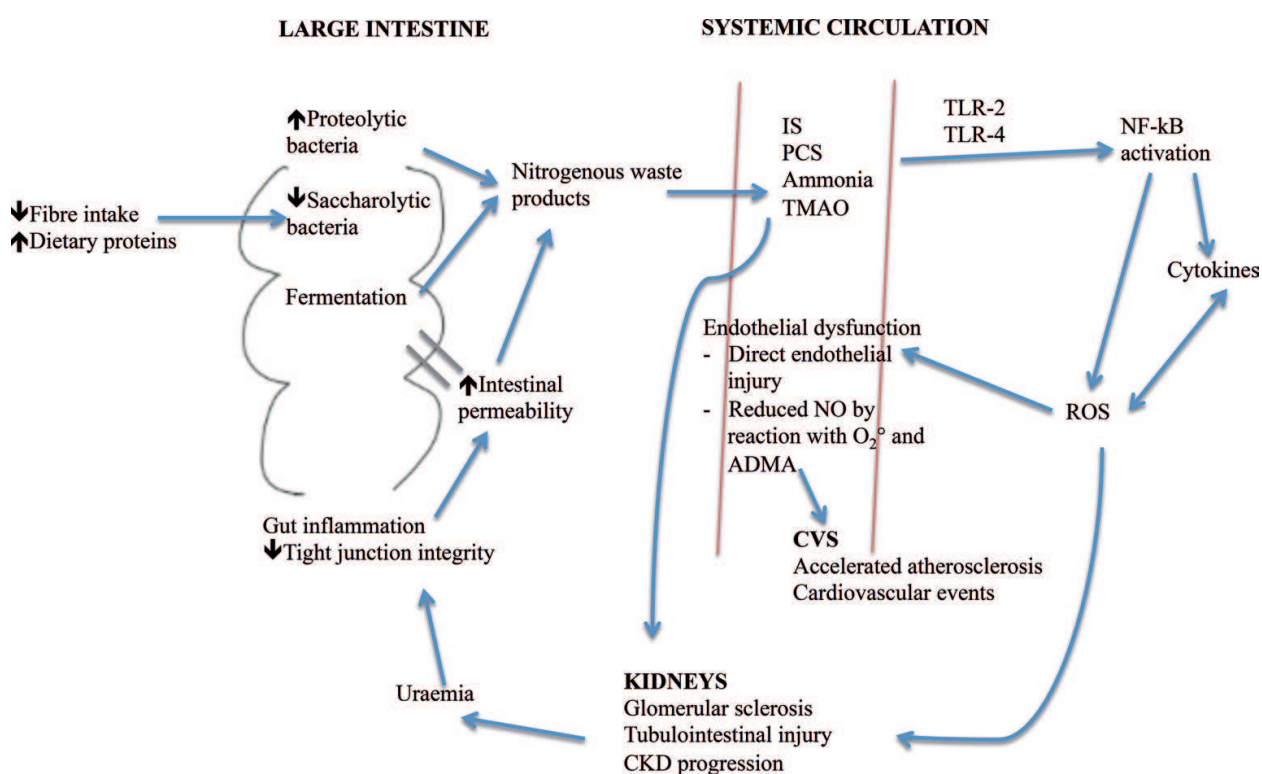


Figure 1. The role of microbiota in the progression of chronic kidney disease and accelerated atherosclerosis. IS, Indoxyl sulphate; PCS, p-cresyl sulphate; TMAO, trimethylamine N-oxide; TLR, toll-like receptor, NF-κB, nuclear factor κB; ROS, reactive oxygen species; NO, nitric oxide; ADMA, asymmetric dimethylarginine; CVS, cardiovascular system.

2.1.3. Dialysis

The dialysis procedure itself accentuates the heightened state of oxidative stress observed in CKD patients. In haemodialysis patients, the mechanisms of oxidative stress include the use of bioincompatible membranes, contamination of dialysate with bacterial endotoxins, occult infection of clotted vascular access and potential loss of antioxidants during the dialysis procedure. Wu et al. [23] demonstrated that levels of myeloperoxidase (MPO), AOPP and 8-OHdG were significantly higher in patients dialysed with regenerated cellulose membranes compared to those dialysed with synthetic polysulphone membranes. However, even with the use of biocompatible membranes, the haemodialysis procedure can still increase systemic levels of reactive oxygen species by 14-fold during one session [24].

It is known that the endotoxins in the dialysate affect the level of cytokines produced by the peripheral leucocytes. Studies have shown that lower levels of endotoxin contamination correlate with lower levels of inflammatory cytokines and oxidative stress markers. In a meta-analysis of 31 studies involving 1580 dialysis patients, the use of ultrapure dialysate has been found to reduce the oxidative stress markers, pentosidine, MPO and oxidized LDL cholesterol [25].

The loss of antioxidants, especially water-soluble vitamins such as vitamin C, has been demonstrated during the dialysis procedure [24, 26].

2.1.4. Inflammation

CKD has also been noted to be a systemic inflammatory state, which is intertwined with oxidative stress. Inflammatory cells stimulate the release of reactive species at the site of inflammation. Conversely, oxidized end products and ROS stimulate phagocytic cells, such as macrophages and neutrophils, to release inflammatory cytokines as well as more ROS, thereby creating a positive feedback loop of inflammation and oxidative stress state. When the phagocytic cells release ROS, they also induce nearby non-phagocytic cells to release inflammatory cytokines. Studies of oxidative states in people with CKD commonly include the investigation of inflammatory cytokines as the two pathways are intimately inter-related.

Multiple pathways have been identified that highlight the mechanisms of interplay between inflammation and oxidative stress (**Figure 2**). The master regulator of the inflammatory process is NF- κ B transcription factor. Reactive oxygen species, such as H_2O_2 , activate NF- κ B which induces production of an array of inflammatory cytokines as well as activates NOX. These in turn stimulate further release of reactive species. Free radical-induced DNA base modifications can also act via NF- κ B to activate the inflammatory processes.

NOX are responsible for free radical production by cells. They can be activated by inflammatory mediators, such as TGF, angiotensin II and TNF- α via other redox sensitive signal transduction pathways, such as c-Jun N-terminal kinase (JNK).

Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain 3 (NLRP3) is an inflammasome complex involved in the production of cytokines, such as IL-1 β and IL-18. Oxidative stress can activate NLRP3 via oxidized mitochondrial DNA and thioredoxin-interacting proteins. Damaged mitochondria can directly release ROS, which perpetuate oxidative stress and inflammation.

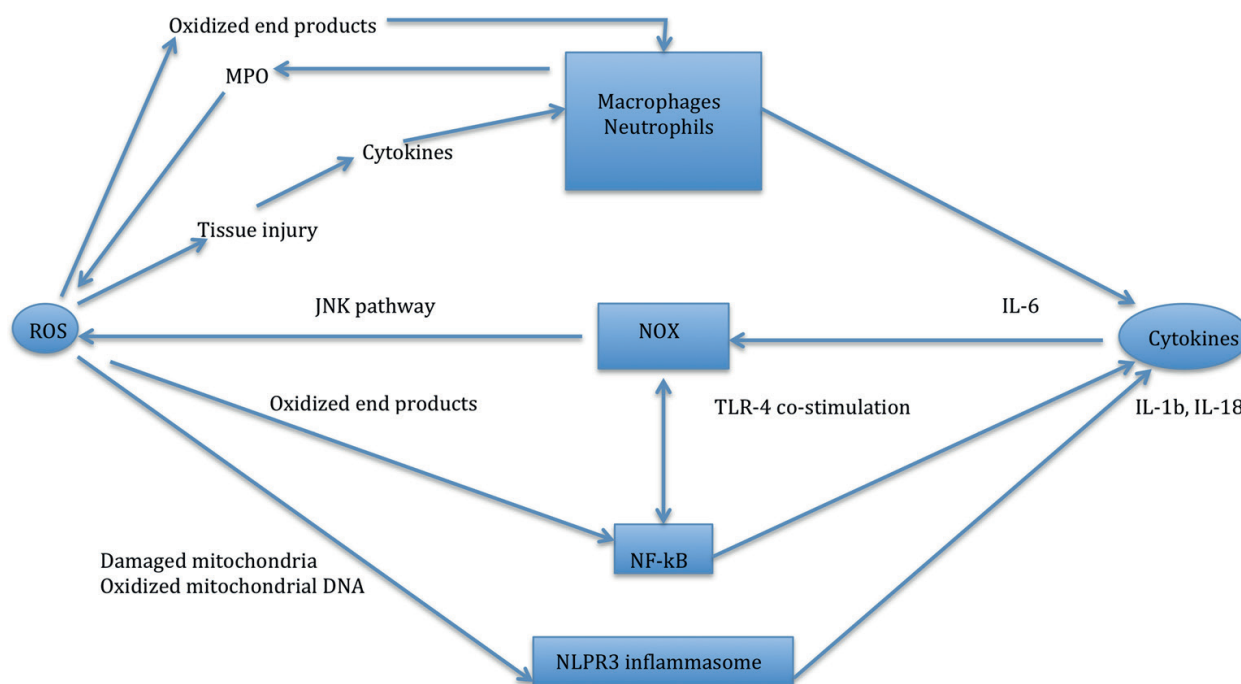


Figure 2. Interrelation between ROS (reactive oxygen species) and oxidized end products signifying the oxidative stress, and cytokines as part of the inflammatory process. ROS, reactive oxygen species; MPO, myeloperoxidase; NOX, NADPH-oxidases; NF-kB, nuclear factor kB; NLRP3, nod-like receptor protein 3; TLR4, toll-like receptor 4; JNK, c-Jun N-terminal; IL, interleukins.

Therefore an event inciting increased oxidative stress can result in an inflammatory response which further propagates the oxidative state, and vice versa.

2.2. Association of oxidative stress with CKD progression and cardiovascular disease (CVD)

A number of mechanisms have been reported to underpin the association between increased oxidative stress and progression of CKD and CVD in patients with CKD.

2.2.1. Oxidative stress markers and vascular disease

Increased oxidized low density lipoprotein (LDL) levels have been recognized as a risk factor for cardiovascular disease in uraemic patients [27, 28]. Oxidized LDLs stimulate the release of inflammatory cytokines from macrophages with subsequent vascular phenotypic changes and platelet aggregation [29], which result in endothelial dysfunction. Oxidized LDL also stimulates further oxidative activity by enhancing the activity of NOX in endothelial cells, juxtaglomerular cells and mesangial cells. Increased levels of ox-LDL in CKD patients correlate positively with carotid atherosclerosis and mortality [30].

Similarly, in patients with CKD, increased carotid intima-media thickness, a marker of atherosclerosis, has been strongly positively correlated with increased levels and activities of NOX, MDA, AOPP, TBARS, 8-OHdG and MPO [24, 31–34] and negatively correlated with SOD and GSH-Px levels [34].

Reactive oxygen species may also promote direct injury of vascular endothelial cells by inducing significant increases in nucleic acid damage in CKD patients [35].

2.2.2. Direct toxicity of oxidized end products

Oxidative stress (induced by H_2O_2) in experimental models of human proximal tubular epithelial cells is demonstrated to cause apoptosis and reduce mitosis of the renal cells. The results are highest when combined with induction of cell senescence, which itself can be induced by oxidative stress [36].

Gut-derived uraemic toxins, in addition to promoting oxidative stress, may exert direct toxicity to renal and cardiovascular tissues. In animal models, IS is implicated in the causation of vascular smooth muscle proliferation, aortic calcification, and vascular wall thickening thereby contributing to increased cardiovascular risk [16]. At the same time, it is also associated with reduced renal function, increased glomerular hypertrophy and glomerular sclerosis, signifying nephrotoxicity [16]. Similar findings were noted in human observational studies, where strong associations were observed between IS, free IS, PCS with cardiovascular disease [16, 37]. In a cross-sectional study involving 149 patients with CKD stages 3 and 4, Rossi et al. [38] investigated the potential mechanisms of toxicity of these uraemic toxins. It was found that the free forms of IS and PCS correlated positively with the level of inflammatory markers (IFN- γ , IL-6 and TNF- α) and negatively with the antioxidant GSH-Px. The total PCS concentration correlated positively with carotid-femoral pulse wave velocity as a measure of arterial stiffness. These findings suggest roles for elevated inflammatory and oxidative stress states as the causes of vascular and renal dysfunction.

Trimethylamine-N-oxide (TMAO), a metabolic end product of choline that is metabolized by the gut microbiota, has also been found to be correlated with an increased risk of cardiovascular disease [39].

2.2.3. Alterations in nitrogen handling

Nitric oxide is a free radical that plays an important role in regulation of endothelial function and regional blood flow by acting as a smooth muscle relaxant. The major pathway for nitric oxide production is by conversion of L-arginine by endothelial nitric oxide synthase (NOS) enzyme. Asymmetric dimethyl arginine (ADMA) is an inhibitor of NOS by competing with L-arginine and therefore reducing the availability of nitric oxide. It plays a significant contributory role in the development of endothelial dysfunction, and also correlates with proteinuria and progression of renal disease [40].

Yilmaz et al. [9] studied 159 patients with CKD stages 1–5 compared to 30 healthy controls. In addition to findings of reduced antioxidant activity and increased oxidative end products, it was also found that the levels of ADMA were higher in CKD patients compared to controls and were negatively correlated with renal function. The levels of oxidized LDL and ADMA were also found to be inversely related to brachial artery endothelium vasodilation. These findings raise the possibility that the elevated oxidative stress present in patients with CKD results from impaired endothelial function due to the inhibition of NOS by ADMA.

Additionally, reactive oxygen species degrade the critical co-factor of NOS causing functional impairment. Super-oxide anion also reacts with nitric oxide forming peroxynitrite thereby

reducing availability of nitric oxide to the vascular smooth muscle. Peroxynitrite, due to its oxidative and nitrosative properties, perpetuates the vascular injury [40].

3. Systemic inflammation in patients with CKD

Systemic inflammation, most commonly evidenced by an elevation of CRP, is frequently observed in people with CKD, even early stage disease. In CKD, this systemic inflammation has been ascribed to a complex biological reaction in response to exposure to inciting exogenous stimuli such as bacterial pathogens or endogenous stimuli such as injured cells. It is mainly characterized by involvement of the cells of innate immune system and release of acute phase proteins and cytokines.

The most studied inflammatory marker in CKD patients is CRP. Elevated levels of CRP and the presence of a chronic inflammatory process in haemodialysis patients was first observed in 1980s with evidence accumulating over time of the heightened inflammatory state in CKD. CRP is produced by the liver as part of anti-inflammatory response and the rate of metabolism is nearly constant. Earlier studies involved mainly in haemodialysis patients where the elevation was noted consistently. The interest then expanded to non-dialysis ESKD patients and peritoneal dialysis (PD) patients. It is found that CRP is elevated even in ESRD patients receiving conservative care and also in PD patients [41]. This inflammatory state has in turn been linked with progression of CKD and CVD.

More recently, other biomarkers of inflammation have been studied. In the large Chronic Renal Insufficiency Cohort (CRIC) study [42], inflammatory markers (IL-1 β , IL-1receptor antagonist, TNF- α , and fibrinogen and in addition to CRP) were found to be negatively correlated with kidney function and positively correlated with albuminuria (a marker of kidney damage). Another study showed an inverse correlation between IL-6 and kidney function [12]. The pattern of elevated pro-inflammatory cytokines (IL-1, IL-6, TNF- α) with low anti-inflammatory cytokines (IL2, IL4, IL5, IL12, CH50 and T cell number) has also been described in haemodialysis patients [43]. CRP, IL-6 and IL-10 levels are significantly higher in ESKD patients compared to controls and the levels did not change significantly after initiation of maintenance haemodialysis [44]. In another study, it was noted that CRP levels actually increased after initiation of haemodialysis [41].

Other markers of inflammatory status involve adipokines. There are proinflammatory adipokines and anti-inflammatory adipokines secreted by adipose tissue. Finally, the National Health and Nutrition Examination Survey (NHANES) demonstrated that levels of pro-inflammatory adipokines were higher in CKD patients than in the general population and that and the ratio of pro- to anti- inflammatory adipokines predicted mortality in PD patients [45].

3.1. Mechanisms of increased systemic inflammation

3.1.1. Gut dysbiosis

In addition to promoting oxidative stress, gut dysbiosis may also promote systemic inflammation in patients with CKD. Endotoxemia activates TLR4 on endothelial cells and macrophages

thereby leading to activation of NF- κ B pathway and ultimately resulting in the production of inflammatory cytokines, chemokines, adhesion molecules, reactive oxygen species and systemic inflammation [39]. Gut-derived uraemic toxins, IS and PCS, are also associated with elevated levels of inflammatory markers such as IL-6, TNF- α , and interferon- γ (IFN- γ) [38]. Higher levels of IS and PCS have been documented in patients with CKD compared to the healthy population [46] and positively correlated with endothelial dysfunction [37].

3.1.2. Infection

Localized or systemic infections are more common in patients with CKD and in turn activate inflammatory and oxidative stress pathways. Dialysis patients are also at higher risk of infections due to presence of foreign bodies such as venous catheters, PD catheters or arteriovenous grafts, predisposing to blood stream infections. Periodontitis is also much more common in patients with CKD compared to normal population and has been linked with heightened cardiovascular risk. In an analysis of 861 CKD patients from NHANES data with a median follow up of 14.3 years, periodontitis was found to be associated with higher mortality. The presence of periodontitis increased the 10-year all-cause mortality from 32% (95% CI 29–35%) to 41% (36–47%), comparable to addition of diabetes to CKD at 43% (95% CI 38–49%) [47].

3.1.3. Dialysis

CKD patients display increased levels of inflammatory markers even prior to initiation of dialysis. Following commencement of dialysis, studies have variably shown either no change or a worsening of inflammatory and oxidative state [41, 44]. In haemodialysis patients, traces of lipopolysaccharides from dialysate contamination may stimulate the inflammatory process, which may be ameliorated by the use of ultrapure dialysate [48]. The presence of a foreign body, such as an arteriovenous graft, has also been shown to be associated with higher CRP levels and lower albumin levels, indicating a chronic inflammatory process [49]. Dialysis membranes may also have an impact, with cuprophane membranes eliciting higher levels of inflammatory biomarkers than other biocompatible membranes (polyamide or polycarbonate) [50]. Similarly, in PD patients, inflammation may be triggered by PD catheters and dialysis fluids [51].

3.1.4. Metabolic acidosis

Metabolic acidosis is increasingly more common with more advanced stages of CKD due to impaired renal excretion of acid generated by the body's metabolic processes. In patients with stage 2–4 CKD in the CRIC study, each mmol/L reduction in plasma bicarbonate concentration was associated with a 3% increased risk of progression to ESKD, although there was no association with mortality [52]. In haemodialysis patients, metabolic acidosis has been associated with increased circulating levels of the pro-inflammatory cytokine, IL-6, which was counterbalanced to some extent by increased levels of the anti-inflammatory cytokine, IL-10, and likely reflected a counter-regulatory mechanism [53]. On the other hand, another study by Ori [54] reported increased levels of IL-6 and reduced levels of IL10 indicating greatly augmented inflammatory status.

3.1.5. Vitamin D deficiency

In CKD, vitamin D levels are invariably reduced to various extents. In addition to its role in bone mineral metabolism, vitamin D has been associated with immunologic regulatory and antioxidant functions. For example, vitamin D has been found to potentiate the antioxidant effect of alpha-Klotho protein by increasing its gene expression [55]. Consequently, vitamin D receptor knockout mice have been reported to have augmented DNA damage and increased production of NADPH-dependent superoxide anion production [55]. In mouse models of HIV nephropathy, the downregulation of vitamin D receptor expression was observed together with increased reactive oxygen species generation and DNA damage, which was improved by vitamin D agonist supplementation [55].

3.1.6. Oxidative stress

A pathologic condition that increases oxidative stress, e.g. ischemia reperfusion injury, simultaneously and subsequently activates inflammatory pathways resulting in a state of both elevated inflammation and oxidative stress. The prominent feature is the two way cross-talk between NOX, NF- κ B, inflammasomes and phagocytic cells such as macrophages, resulting in production of both ROS and inflammatory cytokines. The knowledge of underlying pathways and mechanisms are evolving due to ongoing research in this area.

3.2. Association of inflammation with CKD progression and CVD

In parallel with oxidative stress markers, increases in inflammatory markers have been associated with adverse cardiovascular and mortality outcomes. For example, plasma IL-6 levels have been recognized as an independent predictor of cardiovascular events, atherosclerosis progression and all-cause mortality [44]. Similarly, higher CRP levels correlate with increased carotid artery intima-media thickness in predialysis patients [56] and with increased mortality in both haemodialysis patients [57] and peritoneal patients [58]. Furthermore, Wanner et al. [11] found that a single CRP measurement can predict overall and cardiovascular mortality in the following 4 years. Haemodialysis patients with CRP levels in the highest quartile were associated with a 2.4- to 4.6-fold higher risk of all-cause mortality and a 1.7- to 5.5-fold higher cardiovascular mortality compared to those with CRP levels in the lowest quartile [11, 59]. Similarly, in a prospective observational study involving 62 haemodialysis patients, total mortality was 37.1% and cardiovascular mortality 16.1% at the 2 year follow up. All-cause and cardiovascular mortality were significantly increased at CRP levels above 5 mg/L [60].

4. Potential therapeutic strategies targeting oxidative stress and inflammation

With the increasing understanding of the mechanisms underpinning oxidative stress and systemic inflammation in CKD, various interventions have been explored to address these issues (Table 2). The challenging aspect of this complex pathological state is that inflammation and

oxidative stress are two very intertwined processes. A primary disorder with elevated oxidative stress would inevitably end up with increased inflammatory state and vice versa. Since multiple cellular components, pathways and end products are involved in the pathogenesis and perpetuation of oxidative stress and inflammation, it has been difficult to attain a clinically meaningful impact by therapy targeted at just one aspect. With the exception of RAAS inhibition that has been well established to improve renal and cardiovascular outcomes in patients with CKD, the evidence for the majority of other interventions has been limited by small studies with short follow up duration, high degrees of heterogeneity and limited data available on patient-level outcomes.

4.1. Lifestyle modifications

4.1.1. Dietary interventions

Dietary management is an integral part of the treatment of CKD, especially in its advanced stages. The current scope of dietary modification includes fluid restriction, sodium, potassium and phosphate restriction, and achievement and maintenance of a healthy body weight.

It has been shown that the uraemic toxins, IS and PCS, are produced by the breakdown of nitrogenous waste products by gut bacteria and are associated with negative renal and cardiovascular outcomes due to systemic inflammation and oxidative stress. Dietary modifications have been explored in order to reduce the production of uraemic toxins by the gut bacteria. It is found that the balance between protein and dietary fibre intake appears to have a more significant impact on the production of uraemic toxins than the absolute intake of either protein or fibre alone. Rossi et al. [61] performed a cross-sectional study of 40 CKD stage 4 and non-dialysis CKD 5 patients and correlated the protein-fibre index with serum IS and PCS levels. It was found that the ratio of the protein to fibre intake had significant associations with the serum IS and PCS levels. The total dietary fibre intake had significant associations with PCS but not with IS and the total protein intake had no association with either toxin.

The benefit of dietary fibre supplementation has also been explored in order to increase the carbohydrate content in the colon and to reduce protein fermentation. In a randomized controlled study involving 56 haemodialysis patients, fibre supplementation was found to significantly reduce the level of IS, and to a lesser extent the level of PCS at 6-week follow up [62]. In another non-randomized prospective study, significant reductions in PCS but not IS were found in haemodialysis patients when given dietary fibre supplements [63]. In a large population based cohort study involving 1110 community-dwelling elderly men (around 45% of participants with $GFR < 60 \text{ ml/min/1.73 m}^2$), dietary fibre intake was found to be associated with higher GFR, lower CRP and lower mortality at 10 year follow-up [64]. In a meta-analysis of 14 studies on dietary fibre supplementation in CKD patients, reduction in serum creatinine and urea was noted [65]. However, the trials are very small ($n = 3\text{--}22$) and the dose of fibre supplementation was also highly variable. While the available data suggest dietary fibre supplementation may slow the progression of CKD, robust studies with meaningful clinical end points are lacking.

Nitrogenous waste products can be reduced by dietary protein restriction, which in turn would favour the growth of saccharolytic bacteria over proteolytic bacteria in the colon.

Lifestyle modifications

1. Dietary interventions

- Increased dietary fibre intake
- Protein restriction
- Increased fibre-to-protein ratio
- Sodium restriction
- Fluid restriction
- Pomegranates
- Soy milk

2. Prebiotics and probiotics

3. Exercise

Optimization of dialysis procedure

1. Use of ultrapure dialysate

2. Modification of dialysis membranes

- Biocompatible membranes
- High-flux membranes
- Vitamin E-coated membranes

3. Modification in dialysis technique and frequency

- Online haemodiafiltration
- Short daily, extended, frequent dialysis sessions

Pharmacologic therapies

1. Oral absorbents

2. Allopurinol

3. N-acetyl cysteine

4. Omega-3-polyunsaturated fatty acids

5. Bardoxolone

6. Statins

7. Cytokine therapies

Antioxidants

1. Vitamin E

2. Vitamin C

3. L-carnitine

4. Coenzyme Q-10

5. Miscellaneous antioxidants

- Vitamin A, selenium, zinc, methionine, alpha-lipoic acid, curcumin
-

Table 2. Interventions in studies to improve oxidative stress and systemic inflammation in chronic kidney disease.

However, the benefit of protein restriction per se in CKD patients is overshadowed by the risk of malnutrition and its complications.

Dietary sodium restriction has been explored as a potential strategy for reducing systemic inflammation either directly or indirectly via reducing fluid overload and extracellular volume expansion [66–68]. In a randomized controlled study involving 53 haemodialysis patients, significant reductions in CRP, IL-6 and TNF- α were found in the sodium-restricted group at 8 weeks, which persisted at 16 weeks [69]. However, in a randomized trial by Campbell et al. [70] in patients with stage 3 or 4 CKD, no differences in inflammatory markers were observed after 2 weeks. The apparent disparity in the results of these two studies may be explained by the different stages of renal failure and the duration of intervention.

Pomegranates contain polyphenols, which are known to have antioxidant and anti-inflammatory properties. The number of trials studying on the effect of pomegranate extract or juice on inflammatory markers has been increasing over the last 15 years [71]. There have been a few human trials with varying durations of follow up between 1 day and 12 months. Observed changes in inflammatory markers were variable but the randomized controlled study with longest duration of follow-up of 12 months demonstrated reductions in all inflammatory markers in haemodialysis patients [72].

Soy milk contains isoflavones that are a subgroup of polyphenols with antioxidant properties. Although there have only been small studies with short follow up durations, soy milk has been reported to reduce inflammatory markers and improve renal function deterioration, proteinuria and lipid profile [73].

4.1.2. Prebiotics and probiotics

A number of studies have been conducted to explore the effect of supplementation of synbiotics (a combination of prebiotics and probiotics) on clinical outcomes in both dialysis and non-dialysis CKD patients. These studies have generally noted reductions in uraemic toxins (dimethylamine, nitrosodimethylamine, blood urea nitrogen, plasma p-cresol) and improvement in gastrointestinal scores and quality of life, although reductions in uric acid and alterations in microbiota have not been consistently identified [16, 39]. In a recent randomized, placebo-controlled cross over trial (SYNERGY) [74], 37 patients with stage 4 or 5 CKD (non-dialysis) received synbiotic treatment or placebo for 6 weeks, followed by a wash-out period of 4 weeks and a cross over to the alternative treatment arm for a further 6 weeks. The prebiotic component consisted of high-molecular weight inulin, fructo-oligosaccharides and galacto-oligosaccharides. The probiotic component consisted of nine different bacterial strains including *lactobacillus*, *bifidobacteria* and *streptococcus* genera. The administration of synbiotics significantly reduced serum PCS levels and favourably modified the gut bacteria. In a pre-specified analysis in which patients who received antibiotics during the study were excluded, serum IS levels were also significantly reduced by the symbiotic intervention. No significant changes in anti-inflammatory markers were noted. Thus, the study provided proof of concept that synbiotics can modify the gut microbiota and serum uraemic toxin levels in people with CKD. A larger randomized, placebo-controlled trial with 12-month follow up is currently underway which may yield more definite answers regarding the clinical utility of the synbiotic therapy.

4.1.3. Exercise

Physical exercise has been reported to improve proteinuria and progression of renal function in non-dialysis CKD patients [75] and improve cardiac function and other cardiovascular risk factors in haemodialysis patients. Although multiple pathways can be involved, reduction in the systemic inflammatory state and modulation of immune function may be a major contributing factor for these benefits.

An improvement in inflammatory markers has been noted after bouts of acute exercise or regular long-term exercise with both resistance training or aerobic exercise programs. Viana et al. [76] studied 15 predialysis CKD patients and found that 30 min of walking promoted an anti-inflammatory milieu by increasing the anti-inflammatory cytokine IL-10. An increase in serum IL-6 concentration was also noted, although the authors concluded that the muscle-derived IL-6 in the study exerted anti-inflammatory effects rather than the pro-inflammatory IL-6 β . The group also followed up the patients after 6 months of a regular walking exercise program (30 min per day for 5 days a week) and found that the increased IL-10 levels were sustained with a reduction in the ratio of IL-6 to IL-10. T cell and monocyte activation were down-regulated without an effect on the numbers likely representing the modulation of a chronically elevated inflammatory state. In a randomized controlled trial involving 26 non-dialysis CKD patients, resistance exercises for 45 min 3 times a week were also found to reduce CRP and IL-6 after 12 weeks, together with improvements in muscle mass and endurance [77].

4.2. Optimization of dialysis

Given the significantly elevated oxidative stress and systemic inflammatory levels observed in dialysis patients, different modifications to conventional dialytic therapy have been investigated. These interventions include the use of ultrapure dialysate to reduce endotoxin load, changes in membrane types (such as biocompatible membranes, high-flux membranes, and vitamin E coated membranes), modifications in the dialytic techniques (such as on-line haemodiafiltration) and alteration of dialysis frequency (such as short daily dialysis or nocturnal dialysis).

To reduce the inflammation induced by bacterial endotoxins in the dialysate, the use of ultrapure dialysate was investigated. In the meta-analysis by Susantitaphong et al. [25], 31 studies were analysed which included 16 single-arm studies, 5 non-randomized studies and 10 randomized controlled trials. It was found that the use of ultrapure dialysate compared to conventional dialysate significantly reduced CRP and IL-6 levels in all studies. Single arm studies showed a decrease in TNF- α and IL-1 although the controlled trials failed to show a significant decrease in these markers. In terms of oxidative stress state, all studies showed significant decreases in pentosidine, MPO and ox-LDL levels. These findings support the use of ultrapure dialysate as a standard of care in dialysis therapy.

Sequelae of bioincompatible membranes in activation of complement and inflammatory pathways have been long recognized [78]. The historic use of bio-incompatible cellulose-based membranes has now been replaced by use of biocompatible synthetic membranes such as polysulphone and polypropylene.

Due to its antioxidant properties, vitamin E has been used as a membrane surface modifier to improve biocompatibility and confer additional benefit with respect to oxidative stress.

A recent meta-analysis conducted by D'Arrigo et al. [79] included 60 studies, 23 of which were randomized controlled studies and 37 were non-randomized studies. Improvement in oxidative stress was evidenced by a decrease in MDA and TBARS, without any change in other parameters, such as SOD or NOX. Reduction in ox-LDL levels became significant after improving heterogeneity by excluding three parallel studies. The use of vitamin E-coated membranes reduced the IL-6 levels without any change in CRP.

The clearance of pro-oxidant middle molecules, such as uraemic toxins, in haemodialysis may be enhanced by online haemodiafiltration. Using data from a large randomized controlled trial CONvective TRANsport Study (CONTRAST) investigating the mortality and cardiovascular outcomes of online haemodiafiltration versus conventional low flux haemodialysis, Den Hoedt et al. [80] analysed a sub-group of 405 patients for changes in inflammatory markers after 3 years. Significant differences in the CRP and IL-6 levels became apparent after 6 months of the study. However, mortality and cardiovascular benefits were not noted in the main study.

Increasing dialysate flow rate, utilizing super-flux membranes or adding a sorbent to dialysate could also potentially improve the clearance of gut-derived, protein-bound uraemic toxins. A small study found that increasing the dialyzer mass transfer area coefficient by using two dialyzers in series improved the clearance of protein-bound molecules compared to the conventional use of a single dialyzer. Another small study also showed that by increasing the dialyzer size and dialysate flow in nocturnal haemodialysis patients, the clearance of IS and PCS were enhanced [16].

In terms of dialysis duration and frequency, short daily dialysis (3 h sessions for 6 days a week) was associated with significantly reduced levels of CRP compared with conventional dialysis (4 h sessions for 3 days a week) with corresponding improvement in erythropoietin stimulating agent sensitivity [81]. In a meta-analysis by Susantitaphong [82], there was improvement in cardiac parameters, such as left ventricular mass index (LVMI), left ventricular ejection fraction (LVEF) and blood pressure, in patients using frequent (2–8 h, > thrice weekly) or extended (>4 h, thrice weekly) haemodialysis, compared to a conventional (≤ 4 h, thrice weekly) haemodialysis schedule. Beyond utilization of ultrapure dialysate and high-flux online haemodiafiltration, the addition of further convective permeability by utilizing hyper high flux membranes did not confer any extra benefits in oxidative stress markers [83].

4.3. Pharmacologic therapies

4.3.1. Oral absorbents

AST-120 is the only oral charcoal absorbent available to reduce the absorption of indole in the gastrointestinal tract, thereby reducing the systemic concentrations of IS. It is possible that other uraemic toxins are also absorbed. It is widely used in CKD patients in a number of Asian countries to prolong the time to initiation of dialysis. Initial retrospective and prospective studies showed an enhanced clearance of the toxins as well as improved clinical outcomes with AST-120 [16]. However, in two randomized controlled trials (EPPIC-1 and EPPIC-2) [84] involving 2035 patients with moderate to severe CKD (sCr 2–5 mg/dL for men and 1.5–5 mg/dL for women at screening) in 13 countries, AST-120 did not significantly alter the primary composite end point of dialysis initiation, transplantation or doubling of serum creatinine compared

with placebo (HR 1.03, 95% CI 0.84–1.27, $p = 0.78$ in EPPIC-1 and HR-0.91, 95% CI 0.74–1.12, $p = 0.37$). Notwithstanding their apparent lack of efficacy in these large trials, the main limitations of orally administered absorbents is poor compliance due to pill burden with the need to take 30 pills a day, and gastrointestinal side effects, such as constipation, diarrhoea, nausea, abdominal distension and flatulence.

4.3.2. Allopurinol

Uric acid is the final product of purine metabolism. Production of uric acid is catalysed by the enzyme xanthine oxidase, which also generates reactive oxygen species in the process. Hyperuricaemia has been found to be associated with increased RAAS activity [85], hypertension [86], endothelial dysfunction [87] and cardiovascular disease [88]. It is also associated with higher mortality in patients with non-dialysis CKD patients [89] as well as haemodialysis patients [90]. A number of single centre studies have shown that inhibition of xanthine oxidase by allopurinol or febuxostat may slow the progression of renal disease and improve cardiovascular outcomes [91, 92]. In the meta-analysis by Bose et al. [93] involving eight randomized controlled studies of allopurinol treatment found that no significant changes in glomerular filtration rate (GFR) in five studies, but improvement in serum creatinine concentrations in three studies. There was appreciable heterogeneity in the studies in terms of baseline GFR (three studies with baseline GFR > 67 mL/min/1.73 m²), follow up duration (4–24 months) and etiology of CKD. They were all single centre studies with small sample sizes ($n = 36$ –113). Since the publication of the meta-analysis, a long-term follow up outcome of a previous trial by Goicoechea et al. [94], and four additional randomized trials have been published. Goicoechea et al. [94] found that there was reduction in the number of renal and cardiovascular events in the allopurinol arm compared to the control group (HR 0.32 and HR 0.43 respectively) at 5 years of follow up. However, definitive conclusions regarding the safety and efficacy of urate lowering therapies in CKD cannot be drawn at this stage.

Currently there are three multi-centre, randomized, double-blinded prospective trials being conducted. The first trial, *the CKD-FIX Trial: Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase*, will involve 620 patients with CKD stage 3 or 4 and albuminuria and decline in GFR of at least 3 mL/min/1.73 m² in the preceding 12 months. Hyperuricaemia is not mandatory for inclusion. The intervention will be allopurinol dose escalated from 100 mg daily to 300 mg daily in a stepwise manner according to patient tolerance. The follow up period will be 104 weeks and the primary outcome measure of changes in GFR will be assessed. The second trial, *FEATHER Trial: FEbuxostat versus placebo rAndomized controlled Trial regarding reduced renal function in patients with Hyperuricemia complicated by chRonic kidney disease stage 3*, will titrate febuxostat dose from 10 to 40 mg in the first 9 weeks in 400 participants with CKD stage 3. Hyperuricaemia with serum uric acid 7.1–10 mg/dL is required for inclusion in the study. The primary outcome measure of GFR slope will be assessed. The third trial, *The Preventing Early Renal Function Loss (PERL) Allopurinol Study*, will include subjects with type1 diabetes with albuminuria, GFR 45–100 mL/min/1.73 m² and serum uric acid ≥ 4.5 mg/dL. The primary outcome measure of GFR will be measured at the end of the three-year study period. At the conclusion of the current trials, it is hoped that more robust evidence will be obtained regarding the effect of uric acid lowering therapy on progression of renal disease in patients with pre-existing CKD.

4.3.3. *N-acetyl cysteine*

N-acetyl cysteine provides L-cysteine, which is the rate-limiting precursor to glutathione synthesis, thereby enhancing antioxidant defenses. It also acts as a scavenger of free radicals. Even though there is evidence of reduction in oxidative activity in animal models and dialysis patients [95–97], a small randomized controlled trial in patients with proteinuria and early CKD showed no difference in proteinuria between patients treated with N-acetyl cysteine and placebo [98].

4.3.4. *Omega-3-polyunsaturated fatty acids*

Eicosapentaenoic and docosahexaenoic acids are the two major bioactive omega-3 fatty acids mainly derived from dietary sources. In animal models, they have been shown to improve the anti-oxidant systems and reduce inflammation and tubulointerstitial fibrosis [99]. Numerous studies have been conducted in dialysis patients investigating their effects on inflammatory markers, nutritional status and lipid profile. In haemodialysis patients, there is evidence of inhibition of up-regulation of endothelial chemokines [100] and reduction of all-cause mortality [101]. However, a study conducted in continuous ambulatory peritoneal dialysis (CAPD) patients did not show any significant changes in SOD and reduced glutathione (GH) levels [102]. In non-dialysis CKD patients, IL-1 β and TBARS were reduced and SOD and GH levels were improved, but no effect on IL-6 and TNF- α was noted [103, 104].

4.3.5. *Bardoxolone*

Nuclear factor erythroid 2-related factor (Nrf-2) is a nuclear transcription factor which generates the production of antioxidant enzymes via induction of antioxidant response element (ARE) genes. It is activated by increased oxidative stress, such as reactive oxygen and nitrogen species, and induces the ARE gene. This in turn results in production of reducing factors such as NADPH and the elimination of reactive oxygen species by antioxidant enzymes such as SOD and GSH-Px [105]. In animal models, reduced activity of Nrf-2 produced tubular injury and progressive fibrosis which can be ameliorated by administration of Nrf-2 activators [106]. In a randomized controlled trial involving 227 diabetic CKD patients, improvement in the renal function was noted at 24 weeks which persisted at 52 weeks in the intervention group with Nrf-2 activator, bardoxolone methyl [107]. Based on these initial findings, a prospective, randomized controlled trial was conducted in 2185 patients with type 2 diabetes mellitus and stage 4 CKD with the intervention of bardoxolone methyl (20 mg daily per os) versus placebo [108]. At 9 months, the patients receiving bardoxolone methyl experienced a significantly higher rate of heart failure-related hospitalizations or deaths (hazard ratio 1.83, 95% CI 1.32–2.55, $p < 0.001$) prompting premature termination of the trial. Bardoxolone methyl did not reduce the risk of the primary composite end-point of ESKD or death from cardiovascular causes (HR 0.98, 95% CI 0.70–1.37, $p = 0.92$). Although further trials are underway addressing this aspect, the potential therapeutic role of bardoxolone methyl in patients with CKD appears limited.

4.3.6. *Statins*

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are well-established treatment for hypercholesterolemia. New evidence has recently emerged that statins may have

an additional role in improving systemic inflammation. In a meta-analysis by Deng et al. [109], nine randomized controlled trials involving 3098 dialysis patients were analysed. Three studies assessed CRP and six studies utilized hs-CRP. One study also included IL-6 and TNF- α in the assessment. All the studies found significant reductions in CRP and hsCRP in the patients treated with statins, while the control group experienced an increase or no change in inflammatory markers. IL-6 levels did not change but there was a significant decrease in TNF- α in one study. Overall, there is evidence that improvement in systematic inflammatory status achieved by statins may play a contributory role in primary and secondary prevention of atherosclerosis.

4.3.7. Cytokine therapies

Attempts have been made to directly target pro-inflammatory cytokines by investigating the role of anti-IL-1, anti-IL-6 and TNF- α . In a small, randomized controlled trial with 22 haemodialysis patients, administration of an IL-1 β antagonist improved the levels of hs-CRP and IL-6 and anti-inflammatory adiponectin after 4 weeks [110]. Currently, the available evidence of the direct anticytokine therapy is limited.

4.4. Antioxidants

A number of small trials have been conducted using antioxidants of various types, such as vitamins, naturally occurring dietary extracts, and trace elements. Of the current available information, the Cochrane systematic review in 2012, prior to the BEACON study, concluded that antioxidants confer a significant reduction in serum creatinine, changes in GFR and risk of ESKD but no difference in cardiovascular outcomes [111]. However, there was a high degree of heterogeneity in the meta-analysis. In another meta-analysis on diabetic kidney disease, it was found that there was a significant reduction in albuminuria, but no evidence in other renal outcomes [112].

4.4.1. Vitamin E

The vitamin E family consists of tocopherols in saturated form, and tocotrienols in unsaturated form with a side chain of an isoprenoid. They both play a role in reducing oxidative stress by scavenging free radicals, inhibiting pro-inflammatory pathways and increasing levels of other antioxidants. Meta-analyses of studies in haemodialysis patients using vitamin-E coated dialysis membranes, and oral supplements in CKD patients failed to improve any clinical outcomes although some studies did show improvements in oxidative markers [79, 112, 113]. In a randomized controlled study, *Secondary prevention with antioxidants of cardiovascular disease in end stage renal disease* [114], 196 haemodialysis patients were randomized to vitamin E group receiving 800 IU/day or placebo and followed up for 519 days. At the end of the study period, there was a 40% reduction in cardiovascular end points in the group receiving vitamin E, mainly driven by a reduction in the incidence of myocardial infarction. In contrast, a post-hoc analysis of another randomized controlled study, *Heart Outcomes Prevention Evaluation* [115], involving 993 patients with mild to moderate renal insufficiency, found no benefit from administration of vitamin E 400 IU/day (RR 1.03, CI 0.79–1.34, $p = 0.82$). The apparent disparity in findings between the two studies may be due to the differences in the degree of renal impairment and dose of vitamin E. Nevertheless, the role of vitamin E in mitigating cardiovascular risk in CKD patients remains uncertain at this point in time.

4.4.2. Vitamin C

Vitamin C exerts its antioxidant properties by acting as an electron donor to free radicals. A number of small studies have found improvements in inflammatory markers such as CRP [116], hsCRP [117], and 8-OHdG [118] in haemodialysis patients. In a meta-analysis of randomized controlled trials examining use of antioxidants in diabetic kidney disease, vitamin C reduced albuminuria in some studies but had no effect on GFR [111]. All the studies were small ($n = 14\text{--}29$) with short durations of follow up (4 weeks to 12 months) and generally were of suboptimal methodologic quality. Consequently, no conclusions can currently be drawn regarding the safety and efficacy of vitamin C therapy in patients with CKD.

4.4.3. L-carnitine

Carnitine is an endogenous product of amino acid metabolism produced in the liver. It acts as a transporter of long chain fatty acids across the mitochondrial membrane by reversibly substituting the acyl group of Coenzyme A, forming acyl-carnitine. Once the fatty acids have been transported into the mitochondrial matrix, acyl-carnitine dissociates to form L-carnitine again and coenzyme A is regenerated. L-carnitine has been noted to reduce the oxidative stress through increased glutathione levels, increased GSH-Px activity, and a decreased MDA levels. In a meta-analysis by Chen et al. [119] of 49 RCTs involving 1734 haemodialysis patients, L-carnitine was found to improve CRP and LDL levels. However, in another meta-analysis by Yang et al. [120] involving 25 RCTs, contradictory evidence was found in that L-carnitine did not appreciably alter inflammation, oxidative stress, hyperlipidaemia or quality of life. Currently, there is insufficient evidence to support L-carnitine administration to CKD patients.

4.4.4. Coenzyme Q10

Coenzyme Q10 is a ubiquinone which contains one quinone group and 10 isoprenyl units. It acts as an enzyme co-factor in inner mitochondrial cell membranes protecting against damage from free radicals produced by oxidative phosphorylation. It also stabilizes the cell membranes as an electron and proton carrier and restores vitamin E in its antioxidant form. Early studies in rat models of diabetic nephropathy showed reduced mesangial expansion and tubulointerstitial fibrosis after administration of mitochondrial-targeted coenzyme Q10 [121]. Two recent studies in dialysis patients showed significant reductions in F2-isoprostanes and isofurans at high doses of 1200 g and 1800 g respectively [122, 123]. Further studies exploring the effects of Coenzyme Q10 on disease progression in CKD patients and cardiovascular complications in dialysis patients will be valuable.

4.4.5. Miscellaneous antioxidants

Studies have been conducted to explore the role of other antioxidants, such as vitamin A, selenium, zinc, methionine, alpha-lipoic acid, and curcumin. However, thus far, there is no strong evidence to support their routine use in clinical practice.

5. Future directions

CKD constitutes a state of increased oxidative stress and systemic inflammation. These processes are pathogenetically interrelated and there is increasing evidence that they may contribute to CKD progression and a disproportionately increased cardiovascular risk through the promotion of endothelial dysfunction, atherosclerosis and vascular calcification. The various mechanisms of action of this increased oxidative stress are increasingly being elucidated. Interventions to reduce oxidative stress and inflammation in these patients present novel, and potentially effective approaches to add to the currently available traditional risk-modification strategies. Due to the complex interrelation between reactive oxygen species and inflammatory markers, it is possible that simultaneous, multiple targeted approaches may be required to effectively address the pathological changes in CKD and its associated cardiovascular risk. Larger trials with meaningful clinical outcomes and longer follow up are required to further evaluate such potential therapies.

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