FORUM REVIEW ARTICLE

Inflammation and oxidative stress in CKD and dialysis patients

Running Head: Inflammation and oxidative stress in CKD

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Word count text: 8008
Keywords: Ageing; Allostatic load; Chronic kidney disease; End-stage kidney disease; Inflammation; Oxidative stress, Premature ageing; Senescence; Uremic toxins.

Abstract

Significance: Chronic kidney disease (CKD) can be regarded as a burden of lifestyle disease that shares common underpinning features and risk factors with the ageing process; a complex constituted by several adverse components, including chronic inflammation, oxidative stress, early vascular ageing and cellular senescence.

Recent Advances: A systemic approach to tackle CKD, based on mitigating the associated inflammatory, cell stress and damage processes, has the potential to attenuate the effects of CKD, but also pre-empts the development and progression of associated morbidities. In effect, this will enhance health span and compress the period of morbidity. Pharmacological, nutritional and potentially lifestyle-based interventions are promising therapeutic avenues to achieve such a goal.

Critical Issues: In the present review, currents concepts of inflammation and oxidative damage as key pathomechanisms in CKD are addressed. In particular, potential beneficial but also adverse effects of different systemic interventions in patients with CKD are discussed.

Future Directions: Senotherapeutics, the NRF2–KEAP1 signaling pathway, the endocrine klotho axis, inhibitors of the sodium–glucose cotransporter 2 (SGLT2), and live bio-therapeutics have the potential to reduce the burden of CKD and improve quality of life, as well as morbidity and mortality, in this fragile high-risk patient group.

Significance statement

Patients with chronic kidney disease (CKD) and its associated complications show a dysregulated ageing process, common to the diseaseome of ageing, that includes increased chronic inflammation, oxidative stress, early vascular ageing and cellular senescence. Therefore, systemic approaches to tackle CKD are needed to mitigate the inflammatory, cellular stress and damage processes associated with CKD. Pharmacological, nutritional and potentially lifestyle-based interventions are promising therapeutic avenues to pre-empt the development and progression of CKD-associated comorbidities, thereby enhancing health span and improving quality of life.

1) CKD as a public health priority

Chronic kidney disease (CKD) has been defined as "abnormalities of kidney structure or function, present for >3 months, with implications for health" according to KDIGO guidelines (94). Patients with CKD are classified using different biomarkers of kidney function (e.g. estimated glomerular filtration rate (eGFR) and albuminuria as assessed by albumin-to-creatinine ratio (ACR) (94)), because of their well-established association with CKD progression to end-stage kidney disease (ESKD) and mortality (55, 119). Importantly, mortality is extremely high in ESKD patients requiring renal replacement therapy (RRT) (87, 195). According to a recent ERA-EDTA registry annual report, patients aged 20-44 years on RRT live only one-third of the expected remaining lifetime of the age-matched general population (107). Compared to the general population, patients with CKD have a highly accelerated and premature ageing process, a complex constituted by several adverse components, including vascular disease, chronic inflammation, osteoporosis, periodontal disease, depression, sarcopenia and other maladies (34) (Figure 1). Early vascular ageing (EVA) in particular, resulting in increased arterial stiffness and endothelial dysfunction, is thought to be a crucial patho-mechanism linking CKD with mortality. Thus, several biomarkers of inflammation and endothelial dysfunction are associated with greater arterial stiffness even in apparently healthy adults (221). Furthermore, oxidative stress is also associated with endothelial dysfunction through different mechanisms (150, 244, 249). Collectively, there is a vicious cycle comprising oxidative stress, inflammation, CKD, and premature cardiovascular disease (CVD) (169). As a consequence, therapeutic aims for reducing EVA and CVD mortality in CKD should include control of inflammation, reduction of oxidative stress, and improvement of endothelial dysfunction (31) (Figure 2).

It has also been reported that patients with asymptomatic proteinuria exhibit low-grade inflammation linked to endothelial dysfunction (158). As EVA in CKD can be both a cause and a consequence of the underlying renal disease, factors contributing to this pro-senescence milieu are important potential treatment options in the uremic milieu. In this review, we summarize current concepts of inflammation and oxidative stress in CKD as crucial pathophysiological mechanisms of the uremic phenotype and provide a perspective on possible future treatment options for treating all three components, i.e. CKD, inflammation, and oxidative stress.

2) The many facets of CKD

The main role of the kidney is to maintain the homeostatic balance of a variety of solutes in the blood and to excrete undesirable components. This activity comes at a significant metabolic cost: the kidney and the heart have the highest specific resting metabolic rate of all major organs, roughly twice higher than that of brain or liver (232). In order to carry out their function, the kidneys are highly vascularized and receive roughly a quarter of the cardiac output (139). In addition, the health of the vasculature and the integrity of the endothelium are also crucial for the proper function of the kidney and its ability to filter the blood (245). It is therefore unsurprising that the kidney is an especially vulnerable target for the homeostatic imbalances that accompany CKD: chronic inflammation, oxidative stress, EVA, and accumulation of uremic toxins (31, 33). Oxidative stress stands out as a major contributor to many adverse facets of CKD (Figures 1, 2, and 3) and will be discussed in detail below.

2.1) Chronic inflammation

Inflammation is an essential response mechanism that allows the body to cope with a variety of external (e.g. pathogens) and internal (e.g. damaged or cancerous cells) threats (8). In acute inflammation, a triggering stimulus leads to an inflammatory response involving (i) the release of cytokines and chemokines, most notably interleukins (IL)-1 and IL-6, interferon gamma (IFN-γ), and tumor necrosis factor (TNF) that drive both a localized and a systemic response; (ii) the recruitment and proliferation of immune cells, particularly macrophages and neutrophils; (iii) the eventual clearing of the threat, followed by a return to baseline and tissue repair (8). However, if clearing fails, or the inflammatory

response cannot be switched off, the resulting chronic inflammation leads to tissue dysfunction and damage, including fibrosis, stem cell depletion, and increased cellular senescence (8, 188). Indeed, chronic inflammation is bi-directionally linked to CKD (26). On the one hand, the uremic milieu drives uremic inflammation, which shares common features with the chronic low-grade inflammation associated with ageing, known as "inflammageing"; on the other hand, chronic systemic inflammation leads to dysfunction in the kidneys and can further precipitate fibrosis and the progression of CKD (92, 139, 208). At the same time, uremic inflammation has been mechanistically associated with premature ageing, contributing to processes such as telomere attrition, mitochondrial dysfunction, and dysregulated nutrient sensing (102). In a large proportion of patients with advanced CKD, a systemic inflammatory response is detectable, and the prevalence increases with the progression of CKD stage (26, 102). At the same time, certain components of the immune system, particularly the adaptive immune system, are impaired in a process resembling immunosenescence (42, 127). ESKD patients have lower relative abundance of lymphoid cells, and their T and B cells are more prone to activation-induced apoptosis (127).

A plethora of mechanisms are involved in CKD-related immune disruption. Increased blood concentration of several cytokines and inflammatory markers, such as IL-1, IL-6 and C-reactive protein (CRP), mostly released by endothelial cells and circulating monocytes, is associated with CKD (26, 139). This is due both to limited clearance and increased production of these solutes, which can result from factors such as endothelial dysfunction, oxidative stress, increased cellular senescence, greater permeability of the lining of the gastrointestinal tract (periodontitis and gut dysbiosis are co-morbidities in

CKD), calcium (Ca^{++}) phosphate (P_i) overload, sodium accumulation in tissues, and buildup of uremic toxins in the blood (26, 42). The large endothelial surface of the highly vascularised kidneys makes them particularly sensitive to local pro-inflammatory effects (139). Endothelial activation can impair local vasodilatory ability, increase reactive oxygen species (ROS) production, and exacerbate the already physiologically hypoxic state of the renal medulla (139). The nuclear factor-κB (NF-κB) deserves a special mention in the context of inflammation as a key activator of the upregulated uremic inflammatory response and known to be sensitive to activation by increased ROS levels (102) and mitochondrial dysfunction (24). NF-κB is also responsive to inflammatory cytokines, generating a potential positive feedback loop that can sustain inflammation over time (102). The NLRP3 inflammasome also plays an important role as signaling nexus for the activation of NF-κB, responding to such stimuli as increased ROS, release of mitochondrial DNA (mtDNA), extracellular ATP, and more (139). Further direct effects of inflammation on oxidative stress are discussed in the 'Oxidative stress' section below. An increase in advanced glycation end-products (AGEs) can also up-regulate NLRP3 and NF-κB by binding to the AGE receptor (RAGE), thus contributing to CKD progression (243). Interestingly, the central nervous system has recently been shown to play an inhibitory role in the inflammatory response via a reflex mediated by the vagus nerve (10).

It is worth noting that dialysis treatment fails to adequately remove solutes of the size of most cytokines and is therefore unable to fully correct the pro-inflammatory uremic milieu (26). In addition, dialysis itself has a pro-inflammatory effect (123). This is due to a variety of factors: technical, such as vascular access and limited biocompatibility of the membranes and surfaces (44), as well as microbial, such as contamination of dialysis

166 solutions or catheters with either live microorganisms or with microbial components
167 (including the highly pro-inflammatory endotoxins) (102, 123). Better clinical practice and
168 the use of improved materials can, to a degree, reduce this pro-inflammatory effect (42,
169 59). Novel approaches that improve anti-oxidant defenses can also be helpful. For instance,
170 it has been recently shown that vitamin E-loaded membrane dialysers may contribute to
171 reducing the signs of inflammageing associated with dialysis (180).
172
173 2.2) Oxidative stress
174 Oxidative stress is another prominent feature of CKD (Figures 1 and 3); the high
175 metabolic rate of the kidney makes this organ particularly sensitive to oxidative stress and
176 can exacerbate oxidative damage, along with impaired circulation, inflammation, fibrosis
177 and proteinuria (74). In general, an antioxidant defense prevents the accumulation of ROS
178 and reactive nitrogen species (RNS). However, when there is an imbalance between
179 generation of oxidant compounds and antioxidant defense mechanisms, oxidative damage
180 occurs (168). At a systemic level, oxidative stress can contribute to renal dysfunction,
181 vascular diseases, alteration in immune system, metabolic complications, and anemia
182 (Figure 1) (123). Patients on dialysis have a markedly increased oxidative stress compared
183 to CKD patients not on RRT due to increased ROS formation and reduced anti-oxidant
184 defenses (61, 167). As the primary site of redox biochemistry and ROS production,
185 mitochondria are a natural target for ROS damage, with consequences that include mtDNA
186 damage, reduction of mitochondrial mass, disruption of the mitochondrial membrane
187 integrity, leakage of ROS and pro-apoptotic factors, as well as loss of membrane potential,
188 possibly impairing the cell's energetic metabolism or leading to cell death (Figure 3) (187,

210). Dysfunctional mitochondria are major drivers of the intermediate inflammatory phenotype that drives premature ageing in CKD and other burden of lifestyle diseases (196). Thus, Galvan et al. (64) have demonstrated significantly increased mitochondrial ROS in the kidneys of mice with diabetic CKD, compared to glucose tolerant control mice, using an innovative *in vivo* approach. As mitochondria regulate major cellular processes, such as cell proliferation and differentiation, as well as cell death (209), ROS production by damaged mitochondria can induce cell death and inflammation (209). Indeed, mitochondrial dysfunction and reduced levels of PGC-1α, the master regulator of mitochondrial biogenesis, are strongly linked to CKD (19, 54). In addition, a retrograde signaling pathway allows dysfunctional mitochondria to induce specific gene expression changes in the nucleus (131).

Apart from mitochondrial dysfunction, peroxisomes, i.e. intracellular organelles that contribute to redox homeostasis (225), also become dysfunctional in several models of acute kidney injury and CKD (Figure 3) (209, 225); and Vasko et al (225) have recently proposed a dysregulated mitochondria–peroxisome axis as an important mediator of cellular redox homeostasis. Collectively, diminished antioxidant defense capacity (e.g. in peroxisomes) in combination with increased mitochondria ROS lead to a disturbed redox homeostasis in CKD (Figure 3).

In addition, mitochondria are closely connected to the endoplasmic reticulum (ER) (175). As ER stress, as well as mitochondrial dysfunction, are both linked to an increased activation of pro-inflammatory NF-κB signaling (102, 209), the ER-mitochondrial axis (175) might also be involved in an impaired redox homeostasis in CKD (Figure 3).

The cellular metabolic and redox homeostasis crucially depends on the pyridine nucleotides NAD^+/NADH and $NADP^+$/NADPH (Figure 3) (71, 166). Evidence of a defective cellular redox status in CKD has been reported by Canestrari et al. (14) in red blood cells (RBC). In more detail, NADPH in RBC was significantly decreased, whereas RBC oxidized glutathione, i.e. glutathione disulphide, was increased in patients with ESKD compared to controls (14). In contrast, RBC glutathione (GSH) levels were unchanged in patients with CKD and controls (14). Importantly, hemodialysis (HD) further increased RBC oxidized glutathione levels indicating that not only reduced renal function *per se* but also dialysis impairs cellular redox homeostasis in RBC (14). Mechanistically, protein expression and activity of GSH-S-transferase in RBC is increased in ESKD patients compared to control subjects (14, 63), most likely through uremic retention solutes/uremic toxins (63). Translationally, intensified daily vs. conventional HD lowered distinct uremic retention solutes, thereby improving redox status in ESKD (62). It should be noted that most of the studies investigating cellular redox status focus on RBC. However, accumulating evidence indicates that redox homeostasis in CKD is also impaired in other organs/cell types, including muscle (15), endothelial cells, and aortic smooth muscle cells (173).

Besides GSH metabolism, NAD^+ levels are reduced in CKD due to an impaired biosynthesis and augmented consumption (Figure 3) (71, 166). Interestingly, the transcriptional coactivator PGC-1α promotes NAD+ biosynthesis via the *de novo* pathway (Figure 3) (217). Importantly, NAD^+ is also a substrate for the sirtuin family of enzymes that mediate processes including metabolic flux and epigenetic regulation (71). Furthermore, NADPH oxidase (NOX) enzymes are one of the major sources of ROS

besides mitochondria, and their activity in kidney and vascular endothelium can impair blood flow, reduce NO synthesis, and cause hyperhomocysteinemia and kidney damage (109, 229).

Whereas there is convincing evidence that oxidative stress induces inflammation, the evidence of adverse effects of a pro-inflammatory milieu on oxidative stress is less strong. In a uremic environment, peripheral blood mononuclear cells are activated and show a proinflammatory expression signature (251). Infiltrating leukocytes in the kidney can not only release large amounts of proinflammatory cytokines, but also contribute to a respiratory burst by promoting myeloperoxidase-enhanced production of superoxide (74, 168, 178).

Hypoxia is another factor that is bi-directionally linked to both increased inflammation and oxidative stress in CKD. Thus, hypoxia induces inflammation by several mechanisms but, conversely, inflamed tissue can also become hypoxic (45). Similarly, oxidative stress and hypoxia contribute to each other, most likely through uremic toxins (159) and mitochondrial dysfunction (76). It is interesting to note in this context that sodium–glucose cotransporter 2 (SGLT2) inhibitors (179) and the hypoxia-inducible factor-stabilizing Roxadustat (also known as FG-4592) (122) exert beneficial renal effects at least in part via attenuating renal hypoxia.

While a certain level of ROS and RNS is unavoidable and has a physiological protective role, the elevated production of ROS and RNS, paired with the lower anti-oxidant defense observed in CKD, leads to a redox imbalance and a toxic amount of oxidative stress (33, 36, 74). Due to their high reactivity, ROS can damage a variety of macromolecules, including DNA, proteins and lipids, as well as cell organelles (Figure 3) (109).

DNA damage is of particular concern due to the potential long-term consequences of telomere attrition, DNA mutations, epigenetic dysregulation, and DNA damage signaling (131, 160). Among the four bases found in DNA, guanine (G) is the one most sensitive to oxidation (165); oxidation products of G such as 8-hydroxydeoxyguanosine (8-OH-dG) and 8-oxodeoxyguanosine (8-oxo-dG) are the most common oxidative DNA lesions, as well as established biomarkers of oxidative DNA damage (Figure 3) (123). 8-OH-dG has been associated with mortality in CKD and with carcinogenesis (35, 123), and both 8-OH-dG and 8-oxo-dG are increased in dialysis patients (177, 240). Importantly, 8-oxo-dG pairs preferentially with adenine, rather than cytosine, providing this DNA lesion an additional potential mutagenic mechanism beyond the general DNA damage response (DDR) (177). Interestingly, the stacked G repeats found in telomeric regions are even more sensitive to oxidation and may thus act as a redox-sensitive alarm system through which oxidative stress can cause accelerated telomere attrition and cellular senescence (Figure 3) (131). Given that mitochondria have reduced protection and DNA repair mechanisms compared to the nucleus, mtDNA is particularly exposed to oxidative damage (19, 177). Indeed, 8-oxo-dG lesions have been shown to be twice as numerous in mtDNA compared to nuclear DNA (91). In accordance with these data, Fazzini et al. have recently demonstrated that mtDNA copy number, as a marker of mitochondrial dysfunction and oxidative stress, is an independent predictor for all-cause mortality in 4812 patients from the German Chronic Kidney Disease study (50).

Oxidative stress can damage proteins and lipids through a variety of mechanisms, including ROS, RNS, reactive carbonyl species (RCS), and through the action of reducing sugars, generating a diverse class of compounds that can be categorized as advanced

oxidation protein products (AOPPs), AGEs, and advanced lipoxidation end-products (ALEs) (Figure 3) (59, 226). AGEs in the extracellular matrix (ECM) can impair tissue function, in the case of the vasculature contributing to vascular stiffening and the progression of CVD (102, 218). AGEs can be recognized by the advanced glycation end products receptor 1 (AGER1), RAGE, and soluble RAGE (sRAGE) (201). AGER1 mediates AGE detoxification and exerts an anti-oxidant and anti-inflammatory role, sRAGE acts as a decoy for RAGE, while full-length RAGE activates a number of downstream pro-oxidative and pro-inflammatory effects (201). Diabetes, CKD, and inflammatory diseases have been shown to down-regulate AGER1 and up-regulate RAGE, potentially exacerbating inflammation and oxidative stress (201, 206, 227).

Tyr, Cys and Met residues are particularly prone to oxidation, but other residues such as Lys, Arg, Thr, and His are also susceptible (59, 226). Several oxidation products, including oxidated Tyr and the lipid peroxidation products malondialdehyde (MDA) and F2-isoprostanes, have been found to be increased in the plasma of dialysis patients (33, 59, 123). In more detail, lipid peroxidation contributes to cellular damage and tissue degeneration in CKD. Metabolites, including 4-hydroxy-2-nonenal (HNE), MDA, and F2-isoprostanes, are end-products from the oxidation of unsaturated fatty acids or arachidonic acid and can react with the above-mentioned amino acid residues of proteins, thereby creating ALEs (Figure 3) (53). Several of these lipid peroxidation metabolites have been classified as uremic toxins (38) and show direct adverse effects in CKD. As an example, arachidonic acid-based F2-isoprostane is not only associated with markers of renal function and being increased in HD (67) but also dose-dependently reduces GFR and renal plasma flow in rats (207). Furthermore, F2-isoprostane is associated with markers of inflammation

(67) and directly contributes to an adverse vascular phenotype similar to the clinical challenges observed in patients with CKD. Indeed, this metabolite induces vascular smooth muscle cell (VSMC) vasoconstriction (58), as well as endothelial dysfunction (248) *in vitro*. Importantly, the causal effects of lipid peroxidation radicals on renal function have recently been demonstrated by Kruger et al. (110) who have shown that lipid radicals directly impair podocyte motility and cytoskeletal structure through redox-sensitive RhoA signaling (Figure 3).

As in the case of inflammation, dialysis not only fails to fully correct the oxidative stress associated with CKD, but in fact contributes to it through biocompatibility issues and fluid contamination risk (59). Renal transplantation, on the other hand, appears to correct both the pro-inflammatory and the pro-oxidant status (59, 192). Of particular interest in the context of CKD is albumin, a key plasma protein that is often depleted in the uremic milieu and regarded as a key part of the plasma's anti-oxidant defense, with roles that include plasma thiol and homocysteine (Hcy) homeostasis, Cys and GSH metabolism, and binding of plasma solutes (59, 164). Oxidative damage can modify the Cys-34 residue of albumin and impair the functionality of this protein (164).

The body possesses a range of protective mechanisms that can counteract oxidative stress through enzymatic and nonenzymatic anti-oxidants, but these mechanisms are often impaired in CKD (33). The list of anti-oxidant enzymes includes superoxide dismutase (SOD), catalase, and others regulated by an anti-oxidant response element (ARE) (33). The NRF2-KEAP1 axis is a key player in managing the anti-oxidant response that is down-regulated in CKD (197). In the presence of oxidative stress, the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) is released from kelch like ECH-associated

protein 1 (KEAP1), translocates to the nucleus, and acts as transcription factor regulating the expression of >300 ARE-containing genes involved in cellular stress and damage repair (197, 200). Glyoxalase-1, the main enzyme responsible for detoxification of methylglyoxal and other AGEs, contains an ARE, but the extent to which it may be regulated by NRF2 is still a matter of debate (136, 218). Some important non-enzymatic anti-oxidants include GSH, as well as a range of dietary compounds or elements including vitamin C, E, polyphenols, zinc and selenium (33). Being fat-soluble, vitamin E is particularly important in the prevention of lipid peroxidation, and supplementation has shown positive results in CKD patients (167). A deficiency in dietary anti-oxidants has been reported in CKD patients (33).

2.3) Early vascular ageing

Early vascular ageing is a prominent feature of CKD that is associated with increased cardiovascular risk (199). Its causes have not been fully elucidated, but the existing evidence points to a key role for calcification driven by Ca^{++} and P_i homeostasis in the blood, as well as inflammation and allostatic load (186). Physiological levels or Ca^{++} and P_i are sufficiently high to induce spontaneous precipitation of calcium phosphate; however, this process is normally prevented by plasma proteins, primarily fetuin A, that bind crystallization nuclei into calciprotein particles (CPP) and prevent their growth (112). In CKD, however, the plasma concentration of P_i is increased due to dysregulation of the klotho-fibroblast growth factor 23 pathway that is responsible for P_i excretion and homeostasis (113). At the same time, fetuin A levels drops due to persistent inflammation, leading to a loss of the major protective mechanism (12, 102, 142). As a result, CPP´s

accumulate and are taken up by VSMC causing stress, cellular senescence, and a shift towards an osteogenic phenotype. This, in turn, leads to increased deposition of crystals in the extracellular matrix and eventually media calcification and vascular stiffness (102, 230). Vascular endothelial cells also play a role in EVA. It has been shown that uremic serum induces ER stress and up-regulation of the pro-inflammatory NF-κB signaling in endothelial cells (102).

2.4) Cellular senescence

One major contributing factor to the accumulation of damage within the vascular system is cellular senescence, a state of permanent growth arrest of the cell that can be caused by a number of triggers, including oxidative stress, telomere erosion, persistent DNA damage signaling and oncogene activation (22). The transition into a senescent state is mediated by the p53/p21 and/or the p16/pRb pathways (22). Senescent cells are metabolically active, but physiologically non-contributory (193). They contain damage foci and are essentially pre-cancerous; however, they are resistant to apoptosis and survive by up-regulating a number of senescent cell anti-apoptotic pathways (SCAPs) (193). This feature enables senescent cells to survive some insults that would normally kill "healthy" cells (97). At the same time, this creates a "vulnerability" that allows specific killing of senescent cells through the use of senolytic compounds, as discussed below (193). Senescent cells exhibit a senescence-associated secretory phenotype (SASP) and release a range of factors, including pro-inflammatory cytokines and matrix metalloproteinases that increase inflammation, damage the ECM and induce senescence in other cells, either through the NF-κB pathway or via a paracrine mechanism (172, 193) that generates a non-cell-

372 autonomous pro-senescence effect. Senescent cells are normally cleared by the immune
373 system, but this process is not perfect and, as organisms age, they tend to accumulate in
374 the body, though they remain a minority of the cells even at a very old age (9). However,
375 due to the SASP, senescent cells play an important role in tissue dysfunction and
376 accelerated ageing associated with CKD (34). In patients with advanced CKD, immune-
377 senescence markers are increased and a low relative telomere length is associated with
378 mortality (27), especially in dialysis patients (16, 27). Indeed, a number of experiments in
379 which senescent cells were cleared, or added in animal models, points to a causal link
380 between cellular senescence and a number of features of ageing (6, 7, 97). Recent
381 preliminary evidence suggests that senescent cell clearance may also be beneficial in
382 humans (73).
383
384 2.5) Uremic toxins and their effects on the kidneys and vascular function
385 In advanced CKD, several organic compounds that accumulate in the body (219) produce
386 an adverse response to the biological system (222). In recent years, a large number of such
387 compounds, i.e. uremic toxins, has been identified and subsequently categorized into small
388 water-soluble molecules, protein-bound molecules and middle molecules (38, 138, 223).
389 For a variety of these uremic toxins, adverse cardiometabolic associations have been
390 described with the most convincing clinical implications for the protein-bound uremic
391 toxins indoxyl sulfate (IS) and p-cresyl sulfate (PCS). Both these toxins increase CpG
392 hypermethylation and decrease mRNA and protein expression of the ageing-associated
393 klotho gene in proximal tubule epithelial cells (204). Furthermore, they induce oxidative
394 stress by a variety of mechanisms, including increased NADPH oxidase activity and ROS

production (234), but also a reduced anti-oxidative activity, i.e. reduced superoxide scavenging activity in the kidneys (157) or levels of anti-oxidants (43). Moreover, although IS and PCS have been shown to reduce mitochondrial mass by mitophagy (205), it should be noted that several other uremic toxins also attenuate mitochondrial function in human conditionally immortalized renal proximal tubule epithelial cells *in vitro* (143). In keeping with such a postulate, i.e. IS mediates pro-senescent effects through the induction of ROS (190), the anti-oxidant N-acetylcysteine inhibits IS-induced activation of p53 *in vitro* (190).

Besides these progeric effects on the kidney, uremic toxins also affect vascular function in CKD (154). Furthermore, IS induces protein expression of p53, p21, and senescence-associated β-galactosidase (SA-β-gal) also in human aortic VSMC *in vitro* and N-acetylcysteine suppresses IS-induced effects (141). Furthermore, AST-120, which adsorbs uremic toxins and their precursors within the gastrointestinal tract (4), reduces the expression of these senescence and oxidative stress markers in the area of aortic calcification in uremic rats (141). Uremic toxins further impair vascular function through endothelium-dependent effects (153). Thus, IS significantly increases ROS production in human umbilical vein endothelial cells (HUVEC) *in vitro* (85, 161) were it enhances IL-1β-induced oxidative stress. Both N-acetylcysteine and apocynin pretreatment inhibit the additive adverse effects of IS and IL-1β (183). Furthermore, oxidative stress and uremic toxins up-regulate microRNA-92a in endothelial cells resulting in endothelial dysfunction and atherosclerosis (182). These data are further supported by a translational study using AST-120 in CKD patients, which demonstrated improved endothelial function as assessed by flow-mediated endothelium-dependent vasodilatation (247).

Besides these studies, predominantly investigating protein-bound molecules, larger middle molecules, as well as small water-soluble compounds, could also significantly contribute to the development of CKD complications by mediating a pro-inflammatory and oxidative stress phenotype. Using an innovative scoring system, middle molecules and small water-soluble compounds scored lower for their toxicity and overall experimental and clinical evidence compared to protein-bound molecules (224). Among the most relevant members of both groups were asymmetric dimethylarginine (ADMA), trimethylamine (TMA)-N-oxide (TMAO), uric acid, as well as β2-microglobulin, ghrelin, and parathyroid hormone (224). As an example, ADMA is related to an inflammatory (228) and oxidative stress (236) phenotype and associates with an adverse outcome in patients with CKD (128). Middle molecules, such as pro-inflammatory cytokines, adipokines, and other hormones (224), also contribute to increased inflammation and oxidative stress, as well as other cardiometabolic risk factors (39). Whereas small water-soluble compounds can be removed by dialysis (224), dialytic removal of middle molecules is more difficult in conventional hemodialysis (164). Importantly, different dialysis strategies, for instance using protein-leaking dialyzers removing also larger middle molecules, can decrease markers of inflammation and oxidative stress compared to standard dialyzers (60), supporting the hypothesis that the full spectrum of uremic toxins can contribute to oxidative stress and pro-senescent phenotype in both kidneys and the vascular system with most pronounced effects for protein-bound toxins. Thus, inhibition of uremic toxins is a potential treatment option in CKD potentially attenuating cardiovascular morbidity and mortality.

3) CKD and allostatic load

Individual trajectories of age-related health and disease progression are affected by inter-individual differences in exposomes (i.e. physical and social environment, psychological, lifestyle and nutritional risk factors acting independently, cumulatively, or synergistically with an individual's genome and epigenome over their life course). The 'burden of wear and tear' is manifest as both physiological and molecular allostatic (over)load (Figure 4). Maintenance of physiological homeostasis in the face of allostasis, thus becomes increasingly difficult as uremic toxins accumulate in the course of CKD (186). Consequently, CKD can be viewed as a burden of lifestyle disease that is part of a "diseasome of ageing" (156) that shares common underpinning features and risk factors with the ageing process. In addition to chronic inflammation, oxidative stress and EVA, both the ageing process and CKD are also associated with sarcopenia, frailty, cognitive dysfunction, diminished NRF2 expression and an altered gut microbiome (103, 186, 189, 197). The interplay between the exposome and the genome is thus mediated via the epigenetic landscape of ageing and reflected in changes in gene expression (186). In particular, changes in the methylome (i.e. DNA methylation) are of particular interest, as they provide a direct mechanistic link between the foodome (i.e. individual diet, its composition and the chemical structure of the ingredients), the gut microbiome, and the epigenome (130, 186).

3.1) The role of the gut microbiome

Maintenance of the methylome depends on a limited natural synthetic capacity for generating methyl donor metabolites, supplemented by the acquisition of methyl donor

metabolites and cofactors of the one-carbon metabolic pathway, such as choline and betaine, through diet and the microbial metabolic activity in the gut (132). The gut microbiota has gained significant attention in recent years and is increasingly seen as a "supplementary organ" with complex interactions with the rest of the body, relevant for health and disease (139). A range of gut microbes can metabolize compounds to (i) betaine that feeds into methyl donor group production and (ii) to generate TMA, which in turn gets oxidized by the liver into TMAO (186). TMAO has been shown to have pro-atherogenic and pro-inflammatory properties and may play a central role in inflammageing, age-related epigenetic changes, as well as CKD and CVD (41, 100, 140). Another microbial gut metabolite of note is butyrate, which has been shown to inhibit histone deacetylases involved in the regulation of chromatin (51). Epigenetic dysregulation is also a hallmark of ageing and CKD (188).

A relatively novel finding is the association of CKD with intestinal dysbiosis and increased gut permeability, which can increase the leakage of bacterial DNA, endotoxins, and potentially whole microorganisms into the bloodstream (102, 137, 184). The gut microbiome has been shown to play an important role also in directly interacting with the immune system (118). In particular, loss of anti-inflammatory taxa may contribute to the increase in inflammation associated with CKD (25). Alkyl catechols, produced by certain bacteria from plant phenolic compounds, can up-regulate NRF2 and thus may also play a role in improving anti-oxidant defenses and provide increased resilience in CKD patients (197).

4) Novel treatment approaches

As the landscape for potential therapies directed against the aforementioned mechanisms is broad, we have selected five groups of therapies for discussing potential treatment options (Figure 5). Thus, senotherapeutics are discussed as senescence is closely related to oxidative stress and inflammation (22). NRF2 is an attractive treatment target controlling oxidative stress and inflammation in many burden of lifestyle diseases, including CKD (28). We further present kidney-secreted klotho as a potential renal target for the treatment of inflammation (124, 252), oxidative stress (96), and premature ageing (115) in CKD. Moreover, we describe SGLT2 inhibitors as one of the most interesting and already approved pharmaceutical compounds for CKD and associated complications. Finally, live biotherapeutics are discussed with special emphasis on the foodome and gut microbiome (130).

4.1) Senotherapeutics

The prominent involvement of cellular senescence in CKD suggests that drugs that can target senescent cells, termed senotherapeutics, can be a novel treatment avenue for CKD. It is worth noting here that the body can tolerate a certain amount of senescent cells without apparent harm (73, 211). It is only above a certain threshold that cellular senescence becomes a problem (73). Therefore, even if senotherapies do not get rid of all senescent cells, as long as they can provide sufficient clearance to bring the senescent load below the critical threshold, they have a chance of providing a meaningful benefit (73). Indeed, several studies have shown benefits of senotherapy after a clearance of approximately 30% of the senescent cell population (73).

Recent times has seen the development of the field of Geroscience, which champions the translational aspects of research on ageing. The development of senotherapies falls under its aegis. This includes development of (i) senolytics - compounds that selectively kill senescent cells. Examples include repositioned drugs such as Dasatinib, typically used in combination with alkyl-catechols such as Quercitin, which remove the apoptotic block in senescent cells; and (ii) senostatics or senomorphics, that suppress the SASP without killing the senescent cells themselves (57, 73, 171).

The development of serotherapeutics, and in particular senolytics, is exciting. They have clearly demonstrated significant health benefits in pre-clinical – and, recently, possibly clinical – models (6, 7, 73, 90, 97). Due to the immaturity of the field, however, several caveats need noting, though it must be stressed that these do not preclude translational use of senotherapeutic agents, which would appear churlish based on pre-clinical data. Firstly, when and where to use these agents in the life course. Antagonistic pleiotropy (237) is a concept that is pertinent in this respect, as it stipulates that what is good for you in old age is not necessarily good for you at a younger age and vice versa. Cellular senescence firmly falls under its umbrella, being onco-protective in old age, but undesirable when young as it reduces physical capability (186). The long-term effects of senotherapeutics applied under normative conditions for ageing and in disease thus need to be established. Secondly, another concern is that their use may in the longer-term lead to depletion of the body's regenerative capacity and or contribute to adverse changes in the epigenetic landscape, both of which are hallmarks of ageing. Thirdly, different senotherapeutic agents have different levels of efficacy in different cell types, making it unclear which treatment – or combination of treatments – would be best suited as a therapy

in the context of age-related multi-morbidity, or to treat dysfunction in a multi-cell type organ such as the kidney.

4.2) NRF2

The NRF2 system may provide a targeted node for intervention that is common to the range of morbidities manifesting within the diseasome of ageing (197). More specifically, NRF2 expression is low in several burden of lifestyle diseases, including autoimmune (e.g. multiple sclerosis), respiratory (e.g. smoking-related lung emphysema), gastrointestinal (e.g. primary biliary cholangitis), metabolic (e.g. insulin resistance and non-alcoholic steatohepatitis), and neurodegenerative (e.g. Huntington disease) (29, 197). NRF2 and its repressor KEAP1 are key regulators of cellular stress and damage defenses and therefore represent potential treatment options for a wide range of disease states. In CKD, single nucleotide polymorphism studies of the NRF2-coding *NFE2L2* gene have revealed a link with outcome (191). Furthermore, in addition to its beneficial effects on components of metabolic syndrome (241), NRF2 is also associated with attenuated risk for progression of diabetic kidney disease (DKD) (89) and to be in the center of inflammation- and metabolism-related pathways for CKD (134).

Mechanistically, NRF2 can induce the generation of NADPH and the expression of anti-oxidant enzymes through the ARE in the promoter regions of target genes (29). Thus, an NRF2-mediated anti-oxidant response is activated in human CKD glomeruli that are under increased oxidative stress (89). Interestingly, higher levels of oxidative stress and damage, as assessed by 8-oxo-dG staining, were evident in glomeruli of NRF2-deficient mice compared to wild-type controls (89). Besides its anti-oxidative response, NRF2 exerts

direct and indirect anti-inflammatory effects through the inhibition of NF-κB signaling (214) and pro-inflammatory cytokines, e.g. IL-1b and IL-6 (99). Moreover, ER stress, which can activate a maladaptive unfolded protein response (UPR) potentially affecting different renal pathologies (84), is directly linked to NRF2. Thus, ER stress induces nuclear translocation and DNA-binding activity of NRF2, as well as NRF2-dependent gene expression in 3T3-L1 adipocytes in a protein kinase RNA-like ER kinase (PERK)-dependent fashion (30), i.e. one of the major adaptive UPR pathways (83). Importantly, these findings were also validated in human kidney 2 (HK-2) tubular epithelial cells (20). NRF2 nuclear translocation is further mediated by ER-produced H_2O_2 during ER oxidative protein folding, which in turn is related to intracellular Ca^{++} homeostasis (66). As ER stress also directly causes premature senescence (125, 126), NRF2 hypothetically can link tissue dysfunction and premature aging in CKD, not only through anti-oxidative effects, but also by affecting cell organelle stress/crosstalk. In addition, autophagy as one of the key mechanisms for clearance of mis-folded proteins (32), is also bi-directionally linked to NRF2 through the adaptor protein p62 (88). Thus, the NRF2 inducer sulforaphane exerts beneficial renal effects in a model of obesity-related glomerulopathy with higher potency compared to the conventional anti-oxidant N-acetylcysteine (129). Lu et al. (129) have demonstrated that on top of the well-established anti-oxidative effects, NRF2 enhances markers of autophagy in podocytes (129), a finding similar to data obtained in pancreatic islets (121) and cardiomyocytes (231). By way of contrast, when autophagy is diminished in adipocytes, the adaptor protein p62 accumulates and acts as an endogenous inducer of NRF2 (13) by competing for NRF2 binding to KEAP1 (101). It needs to be pointed out that chronic activation of autophagy can also have deleterious effects. Thus, induction of

p62 expression and subsequent NRF2 might stimulate tumor growth (82, 235). Indeed, NRF2 is related to cancer progression, metastasis, as well as resistance to chemo- and radiotherapy (174).

Keeping the aforementioned issues in mind, NRF2-based treatment could be one option to reduce the chronic burden of lifestyle diseases and particular CKD by attenuating persistent inflammation, oxidative stress, as well as ER stress and autophagy. Several targets for NRF2 activation have recently been summarized including both pharmacologic and nutriceutical compounds (29). Bardoxolone is one of the most promising pharmacological candidates with positive renal outcome data in a phase 2 trial in patients with DKD (162). Using a closely related bardoxolone analog in rodents, NRF2 treatment has been shown to improve redox balance, mitochondrial function, and to suppress inflammation (144). However, previous treatment approaches for patients with DKD using bardoxolone have been terminated (250) due to an excess of heart failure hospitalizations in the bardoxolone group. Interestingly, *post-hoc* analyses have recently demonstrated that bardoxolone users were significantly less likely to develop a composite renal endpoint (23). Thus, the question remains whether bardoxolone exerts positive effects on renal function in carefully selected patients without signs of heart failure, which is presently being investigated in randomized controlled trials (21). Besides pharmacological compounds (29), nutritional NRF2 modulators have been described (197), and distinct nutritional components can modulate NRF2 especially in CKD (46). Among others, the alkyl-catechols sulforaphane (inter alia derived from broccoli) and curcumin (inter alia derived from turmeric plant) appear to be the most attractive candidates (46, 197). Few studies have investigated the effects of nutritional NRF2 modulators in human burden of lifestyle

diseases (111), such as CKD (17, 18). Importantly, curcumin's effects to decrease renal fibrosis, inflammation, and oxidative stress (2, 3) have been already validated in several small randomized controlled trials in CKD (2) and HD (3) patients. Taken together, NRF2 is a promising candidate for the treatment of inflammation, oxidative stress, and related disturbances, including ER stress and autophagy, in numerous chronic burden of lifestyle diseases, including CKD, and several pharmacological and non-pharmacological treatment options are already available.

4.3) Klotho

Klotho is a single-pass transmembrane protein predominantly expressed in the kidneys that regulates ageing and morbidity (114). Klotho-deficient mice display increased renal inflammation (124, 252), oxidative stress (96), a senescent phenotype (124), decreased autophagy (185), as well as a premature ageing (115) – a condition resembling the deleterious features of CKD. As patients and animals with CKD have decreased protein levels of klotho in the plasma, urine, and the kidneys (79), targeting klotho is a promising approach for the prevention of progression, complications, and the premature ageing processes in renal dysfunction (78).

Like NRF2, klotho expression in CKD can be targeted by different approaches, either by increasing endogenous klotho expression or direct administration of exogenous klotho (253). From a practical perspective, this might be achieved from an epigenetic approach via demethylation of the klotho promoter and/or associated histone deacetylation to loosen the local chromatin configuration (149, 253). In this context, it is notable that IS and PCS directly induce hypermethylation of the Klotho gene (149, 204). Furthermore,

several drugs, already approved for the treatment of other diseases frequently observed in CKD, up-regulate klotho expression (253). However, and in contrast to extensive studies in rodents, human data for klotho-based treatment approaches are lacking. While no human study to date has investigated distinct klotho therapies, including administration of exogenous klotho on CKD (254), several clinical trials on endogenous klotho inducers have been published. The peroxisome proliferator-activated receptor γ agonist pioglitazone, for example, increases renal klotho expression and reduces oxidative stress (242). Thus, thiazolidinedione treatment, i.e. pioglitazone, in patients with CKD reduces markers of renal dysfunction possibly by affecting oxidative stress, inflammation, and other CKD-associated maladies (reviewed in (176)). Furthermore, several vitamin D analogs induce the expression of klotho in distinct tissues, as well as increase urinary and serum klotho levels (117, 170). Conversely, vitamin D deficiency is associated with increased oxidative stress, inflammation, and cellular senescence (i.e. “inflammageing” (56)) (52) and vitamin D supplementation improves markers of oxidative stress according to a recent systematic review and meta-analysis (181). However, data from studies in patients with CKD show conflicting results of vitamin D receptor activators and their effects on markers of oxidative stress (86, 213, 216). Moreover, statins have been observed to increase *klotho* mRNA expression (146) and further data suggest that statins (246) reduce oxidative stress in experimental cyclosporine nephropathy via modulation of klotho. However, in patients with CKD statin treatment, as part of an anti-oxidative therapy, does not induce circulating klotho compared to placebo (1) and atorvastatin treatment does not reduce oxidative stress (49). Randomized controlled trials indicate that the effects of statins on mortality in CKD are also independent of inflammation (108, 202), suggesting that the beneficial *renal*

effects of statins on klotho observed in rodents do not translate in increased *systemic* klotho and oxidative stress in humans. In addition, activation of the nuclear androgen receptor (e.g. by testosterone) increases renal klotho gene expression (77). Direct administration of exogenous soluble klotho is another option to increase circulating klotho levels, which has been reported to exert renoprotective effects in rats with AKI (80) and mice progressing from AKI to CKD (185). In conclusion, animal and human data on endogenous klotho inducers show contradicting results for *renal* compared to *systemic* oxidative stress and inflammation in CKD.

4.4) SGLT2 inhibitors / Other approaches

SGLT2 inhibitors were introduced as a new class of glucose-lowering medication, and the first members received their EMA- and/or FDA-approval in 2012/2013. SGLT2 inhibitors induce glucosuria by different mechanisms, but particularly through reduced tubular reabsorption of glucose (37). With respect to effects in CKD, data from randomized controlled CVD outcome trials have shown beneficial renal effects for empagliflozin (233), dapagliflozin (239) and canagliflozin (147). Since a recent renal outcome trial with a pre-specified primary renal endpoint has confirmed these findings (163), SGLT2 inhibitors are considered as a novel therapy for CKD due to type 2 diabetes reducing the risk of dialysis, transplantation or death and protecting against AKI (148). Potential mechanisms through which SGLT2 inhibitors improve renal function include beneficial hemodynamic, vascular, metabolic, anti-oxidative, inflammatory, hypoxic and diuretic effects (69). Although hemodynamic changes due to altered tubulo-glomerular feedback (95) are often believed to be a key mechanism of SGLT2 inhibitors, inflammation and oxidative stress,

667 as well as renal hypoxia, could also play major roles. Indeed, recent data suggests that
668 SGLT2 inhibitors protect kidney function through improvement of renal hypoxia (72, 179).
669 As hyperglycemia causes tubular senescence via a SGLT2- and p21-dependent pathway in
670 the type 1 diabetic kidney (98), the effects of SGLT2 inhibitors on kidney senescence,
671 SASP and NRF2 expression need to be tested. Human studies suggest that SGLT2
672 inhibitors reduce circulating markers of inflammation and improve the adipocytokine
673 profile (11). As several adipose tissue-secreted cytokines are associated with inflammatory
674 markers in CKD (40, 75, 104, 105, 151), Bonnet and Scheen (11) have suggested that
675 SGLT2 inhibitors act on adipose tissue, as well as on distinct other organs, to reduce
676 *systemic* inflammation. Regarding *renal* inflammation, data are limited to rodent studies
677 (11, 93), where the SGLT2 inhibitor empagliflozin reduced renal inflammation in mouse
678 models of DKD (65, 152, 220). SGLT2 inhibitors have also improved *renal* oxidative stress
679 in several rodent models of DKD. In more detail, different SGLT2 inhibitors reduced
680 oxidative stress in diabetic rats (152, 155) or mice (68, 212) by improved anti-oxidant
681 enzyme activities (155), suppression of the AGE/RAGE-axis (152), as well as decreased
682 production of ROS and *Nox4* expression (68, 212). It should be noted however, that these
683 effects of SGLT2 inhibitors on rodent DKD cannot specifically determine the cause of
684 reduced inflammation/oxidative stress. Thus, a direct effect could still be possible. In
685 contrast, they might also be the result of secondary improvements due to lower body
686 weight, improved hyperglycemia, and other effects. It also has to be pointed out that there
687 is a lack of rodent models of DKD replicating the main features of human DKD (5) and
688 there is a huge difference in the renal phenotype, e.g. on albuminuria, between standard
689 diabetic mouse models compared to accelerated models (106, 215). This is congruent with

690 a general feature of laboratory studies, where the rodents employed are metabolically
691 morbid and lacking appropriate features of either human pathogenesis or normative ageing
692 (120, 133, 156). A biomimetic approach identifying wild animals that during evolution in
693 extreme environments have developed mechanisms that protect them against ageing, CKD
694 and metabolic dysfunctions may yield important additive clues (135, 198). Therefore,
695 carefully matched animal experiments are needed to verify the results excluding secondary
696 effects. If such pleiotropic effects, i.e. independent of metabolic and hemodynamic
697 changes, can be confirmed, SGLT2 inhibitors can be a treatment target for other CKD
698 causes than just DKD – a concept being currently investigated for example in the EMPA-
699 KIDNEY study (70).
700
701 4.5) Live biotherapeutics
702 Multiple studies have linked gut dysbiosis and CKD (102, 194). CKD patients often display
703 reduced microbial diversity, though this finding is not always consistent between studies,
704 accompanied by a decrease in bacteria producing short-chain fatty acids (SCFA) from fiber
705 and an increase in bacteria that produce uremic toxins such as TMAO, IS, and PCS (139,
706 194). Possible biotherapeutic treatment strategies for CKD include dietary therapy,
707 prebiotics (ingredients that stimulate the growth of a desired microorganisms), probiotics
708 (live microorganisms), synbiotics (combining both prebiotics and probiotics), as well as
709 host and bacterial enzyme inhibition (48). However, given the dietary restrictions,
710 therapies, and frequent comorbidities found in CKD patients, further studies may be
711 warranted to identify specific causal links and therapeutic options (116, 194). For instance,
712 potassium and phosphorus intake are restricted in CKD patients due to the increased risk

713 of adverse outcomes, but these restrictions also limit fruit and vegetable intake and affect
714 the gut microbiome (116). Nevertheless, a number of studies have found beneficial effects
715 in CKD patients for a range of diets, most notably a Mediterranean or a vegetarian diet
716 (139).

717 Perhaps in part due to the limits of current knowledge, studies with probiotics and
718 prebiotics have produced inconsistent results (194). Increasing microbial SCFA production
719 has been proposed as a possible therapeutic intervention (81). SCFA regulate immunity,
720 blood pressure and glucose metabolism; to be involved in the health of colonic epithelial
721 cells, signal transduction, epigenetic maintenance and autophagy; and to ameliorate kidney
722 dysfunction (81, 116, 238). Alternatively, decreasing the intestinal production of uremic
723 toxins can also be a valid approach (194), and studies have shown some efficacy using
724 synbiotics or prebiotics (139, 238).

725 One enzymatic approach has focused on acarbose, an inhibitor of α-glucosidase
726 that limits the hydrolysis of polysaccharides and oligosaccharides in the intestine,
727 stimulating the growth of saccharolytic bacteria, reducing the production of p-cresol (145).
728 Indeed, studies in healthy volunteers indicate that acarbose may shift gut microbial
729 metabolism away from proteolytic fermentation and towards saccharolytic fermentation
730 (47). Importantly, acarbose therapy is also associated with experimental longevity (203).
731 Another strategy under investigation is the use of 3, 3-dimethyl-1-butanol (DMB), an
732 inhibitor of microbial TMA production, that has led to decreased levels of TMAO in the
733 blood and reduced atherosclerotic lesion development (145).
734

5) Conclusions

Increasing healthcare costs in patients with CKD, overall detrimental outcomes, and deficiency of optimal treatments, including organ donation, place a tremendous pressure on healthcare providers, scientists, and patients and their families *per se*. Innovative therapeutics based on the identification of selective injury targets might serve to develop precision medicine to optimize healthcare costs, disease monitoring, targeted interventions, as well as outcomes, including patients' quality of life. In this review, we view CKD as a burden of lifestyle disease, underpinned by a dysregulated ageing process common to the "diseaseome of ageing". A systemic approach to tackle CKD, based on attenuating the associated inflammatory, cell stress, mitochondrial dysfunction and damage processes, has the potential to mitigate the effects of CKD, but also pre-empt the development and progression of associated morbidities. In effect, this will enhance health span and compress the period of morbidity. Pharmacological, as well as nutritional and potentially lifestyle-based, interventions are promising therapeutic avenues to achieve such a goal.

Figure legends

Figure 1. M

The main effects of oxidative stress on the damage of different organs and functions in chronic kidney disease (CKD). CKD and its complex comorbidities are crucially connected through oxidative stress. Thus, increased renal oxidative stress contributes by several mechanisms to CKD progression, thereby causing end-stage kidney disease (ESKD) and associated complications. Oxidative stress further induces early vascular ageing (EVA) and its major components, i.e. increased arterial stiffness and endothelial dysfunction, linking EVA with cardiovascular (CV) morbidity and mortality. Oxidative stress also gives rise to a pro-inflammatory milieu and its associated complications. In addition, oxidative stress is associated with metabolic disturbances contributing to cardiometabolic and CV complications. Oxidative stress further contributes to anemia and its sequelae. EPO, Erythropoietin; NLRP3, NLR family pyrin domain containing 3; NRF2, Nuclear factor erythroid 2-related factor 2.

Figure 2. CKD and its pathophysiological consequences. Patients with CKD experience complications through different key patho-mechanisms including oxidative stress, uremic toxins and inflammation, that are interrelated. These pivotal features of impaired renal function contribute to an adverse phenotype of patients with CKD, which in turn correspond to CKD progression, as well as increased morality. Renal replacement therapy, e.g. dialysis treatment, can influence both the key patho-mechanisms and the deleterious CKD phenotype in a beneficial (i.e. inhibitory [green]) or adverse (i.e. stimulating [red]) fashion. CV, Cardiovascular.

Figure 3. Processes of protein, lipid, DNA, and cell organelle damage, as well as impaired cellular redox in CKD. The redox imbalance in CKD due to increased oxidative stress and decreased anti-oxidant defenses leads to protein,

lipid, DNA, as well as cell organelle damage. Protein damage, either by advanced oxidation protein products (AOPPs), advanced glycation end-products (AGEs) or advanced lipoxidation end-products (ALE's), contributes to structural renal defects, as well as pro-inflammatory and pro-oxidative effects both in the kidneys and systemically. Lipid damage as a consequence of increased concentrations of metabolites from the oxidation of unsaturated fatty acids, e.g. 4-hydroxy-2-nonenal (HNE), malondialdehyde (MDA); or arachidonic acid (F2-isoPs [F2-isoprostanes]), directly induces adverse changes in renal hemodynamics but can also react with the amino acid residues of proteins, thereby creating ALE's that can signal through redox-sensitive RhoA. DNA damage in the nucleus and in mitochondria (mtDNA) occurs through oxidation of guanine (G) with oxidation products of G such as 8-hydroxydeoxyguanosine (8-OH-dG) and 8-oxodeoxyguanosine (8-oxo-dG). DNA damage is further associated with cellular senescence. Several cell organelles are damaged in CKD and uremic environment. Thus, the endoplasmatic reticulum (ER) in CKD is dysfunctional. Furthermore, peroxisomes, cellular organelles with redox function, are also dysfunctional in CKD. Moreover, mitochondria in patients with CKD show reduced mass, integrity, and function. Nicotinamide adenine dinucleotide (NAD+) can attenuate protein, DNA, and organelle damage but is depleted in CKD due to impaired biosynthesis and augmented consumption. The PPARγ co-activator 1α (PGC-1α) improves mitochondrial biogenesis, as well as increases NAD biosynthesis through the *de novo* pathway. By phosphorylation, NAD+ further contributes to the cellular redox state through NADP+ and its conversion to NADPH in the pentose phosphate pathway. NADPH is then further linked to glutathione (GSH)/glutathione disulfide (GSSG) metabolism, crucially contributing to the anti-oxidant defense. Beneficial (green) or adverse (red) effects are depicted by arrows.

Figure 4. Allostatic load in health and disease. The presence of stress generated by the external environment and the internal milieu causes allostasis. The associated

accrual of ‘wear and tear’ results in an allostatic load. The body adjusts its physiology to compensate for this in order to maintain physiological homeostasis. However, over time the allostatic load will accrue to a point of allostatic overload when physiological homeostasis becomes dysregulated and pathology can arise, unless a therapeutic intervention reestablishes homeostasis.

Figure 5. Novel treatment concepts for inflammation and oxidative stress for the reduction of CKD complications. A) Senotherapeutics act by clearing or mitigating the effects of senescent cells and suppressing the SASP, thus counteracting ageing and reducing inflammation. **B)** Activation of the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) in CKD reduces renal inflammation and oxidative stress and improves the pro-senescent milieu in CKD. By these renal, as well as similar systemic, effects NRF2 can potentially reduce CKD progression and complications. **C)** Endogenous or exogenous activation of klotho improves renal inflammation and oxidative stress. Klotho further improves the vascular phenotype, i.e. calcification and renal ageing. **D)** Inhibitors of the sodium–glucose cotransporter 2 (SGLT2) increase glucosuria and improve metabolic function, e.g. reducing body weight, blood glucose, blood pressure. Besides these glucosuria-related effects, SGLT2 inhibition reduces renal inflammation, hypoxia, and oxidative stress. Furthermore, SGLT2 inhibitors directly induce beneficial hemodynamic changes through tubuloglomerular feedback and improve renal vascular function. **E)** Live biotherapeutics can reduce inflammation caused by gut dysbiosis and reinstate a healthier metabolism in the gut, reducing the production of uremic toxins and increasing the production of health-promoting metabolites.

Declaration of interest

Peter Stenvinkel serves on scientific advisory boards of Baxter, Reata, and Astra Zeneca. Ognian Neytchev is funded by a research award to Paul Shiels from Constant Pharma (Mass. USA). Thomas Ebert has served as a consultant for Sanofi-Aventis, as well as on a scientific advisory board of Boehringer Ingelheim Pharma. The other authors of this manuscript have nothing to declare.

Funding

TE was supported by a Novo Nordisk postdoctoral fellowship run in partnership with Karolinska Institutet, Stockholm, Sweden, a Karolinska Institutet Research Foundation grant, as well as by the EFSD Mentorship Programme supported by AstraZeneca. AW, KK, PS, and TE were further supported by Njurfonden (Swedish Kidney Foundation). PS was supported by the Swedish Heart and Lung Foundation (No 20160384), as well as the Strategic Research Programme in Diabetes at Karolinska Institutet (Swedish Research Council grant No 2009-1068). KK received other grants from the Swedish Research Council (No 2018–00932). PGS is supported by awards from 4D Pharma and Constant Pharma.

Author contributions

T.E., O.N., P.S., and P.G.S. wrote the manuscript and researched literature. A.W. and K.K. contributed to the discussion and reviewed/edited the manuscript.

List of abbreviations

8-OH-dG	8-hydroxydeoxyguanosine
8-oxo-dG	8-oxodeoxyguanosine
ACR	Albumin-to-creatinine ratio
ADMA	Asymmetric dimethylarginine
AGE	Advanced glycation end-products
ALE	Advanced lipoxidation end-products
AOPP	Advanced oxidation protein products
ARE	Anti-oxidant response element
CKD	Chronic kidney disease
CPP	Calciprotein particles
CRP	C-reactive protein
CVD	Cardiovascular disease
DDR	DNA damage response
DKD	Diabetic kidney disease
DMB	3, 3-dimethyl-1-butanol
ECM	Extracellular matrix
eGFR	estimated glomerular filtration rate
ER	Endoplasmic reticulum
ESKD	End-stage kidney disease
EVA	Early vascular ageing
HDL	High-density lipoprotein
IFN-γ	Interferon gamma

IL	Interleukin
IS	Indoxyl sulfate
KEAP1	Kelch like ECH-associated protein 1
MDA	Malondialdehyde
mtDNA	Mitochondrial DNA
NF-κB	Nuclear factor-κB
NRF2	Nuclear factor erythroid 2-related factor 2
PCS	p-cresyl sulfate
RAGE	AGE receptor
RBC	Red blood cells
RCS	Reactive carbonyl species
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RRT	Renal replacement therapy
SASP	Senescence-associated secretory phenotype
SCAP	Senescent cell anti-apoptotic pathway
SCFA	Short-chain fatty acids
SGLT2	Sodium–glucose cotransporter 2
TMAO	Trimethylamine (TMA)-N-oxide
TNF	Tumor necrosis factor
VSMC	Vascular smooth muscle cells

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