Chronic kidney diseases - a unique clinical model of accelerated vascular ageing can benefit from novel anti-aging therapeutic options

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Abstract

The pathophysiology of vascular disease is linked to accelerated biological ageing and a combination of genetic, lifestyle, biological and environmental risk factors. Within the scenario of an uncontrolled vascular (i.e. arterial) ageing processes, chronic kidney disease stands out as a valid model for detailed functional and molecular studies of this process. The cardiorenal syndrome relates to the detrimental interplay between the kidney and the vascular system. In addition to established risk factors, this group of patients is subjected to 'a plethora of other vascular risk factors, such as inflammation, oxidative stress, mitochondrial dysfunction, vitamin K deficiency, cellular senescence, somatic mutations, epigenetic modifications, and increased apoptosis. A better understanding of the molecular mechanisms through which the uremic milieu triggers and maintains early vascular aging (EVA) processes, has provided important new clues on inflammatory pathways and emerging risk factors alike, and to the altered behavior of cells in the arterial wall. Advances in the understanding of the biology of uremic EVA opens avenues to novel pharmacological and nutritional therapeutic interventions. Such novel strategies hold promises to improve the prevention and treatment of early vascular aging not only in chronic kidney disease but also in the elderly general population in the future.

1. Introduction

Improvement in human life expectancy over the past 100-150 years has not been matched by a similar improvement in health span, due to increased prevalence of 'burden of lifestyle' diseases that form a '*diseasome of ageing*' (i.e., non-communicable chronic diseases, NCCDs). This diseasome includes chronic kidney disease (CKD), recognized as prototype of a NCCD with signs of early vascular ageing (EVA). It has been forecasted that by 2024 CKD will be the 5th leading global cause of years of life lost.[1] In addition to the ageing process *per se*, modern eating habits towards a more carnivorous diet and ultra-processed foods spur on the '*diseasome of ageing*'.[2] It is also conceivable that emerging environmental challenges, such as global warming, microplastics and air pollution further actuate the '*diseasome of ageing*'.[3] Mechanisms that promote cellular longevity tend to decrease in effectiveness with age and therefore it is unsurprising that ageing presents as a major risk factor for NCDD´s, such as cardiovascular disease (CVD), CKD and type-2 diabetes (T2DM). As traditional risk factors only explain about 50% of CV risk, emerging risk factors need to be identified (**Figure 1**). In this context, a silent global epidemic of progressive loss of kidney function, gradually leading to a toxic uremic milieu with vascular damage, may explain a large proportion of EVA.[4] Early diagnosis and early intervention with RAAS inhibitors, SGLT2-inhibitiors, GLP1-RA and mineralcorticoid antagonists may help to reduce the high cardiovascular risk in CKD, especially in combination with T2DM.

In this review we hypothesize that the toxic uremic milieu disrupts normative vascular ageing in cardio-renal diseases. Although it is evident that microvascular dysfunction may also cause kidney disease this important area will not be covered in this review. Detailed mapping of mechanisms that promote early vascular ageing (EVA) in the uremic milieu could be a promising strategy to pre-empt their onset and mitigate their effects also in the non-renal general elderly population. To this end, geroscientists have characterized basic mechanisms of ageing across a range of species to develop candidate anti-ageing therapies, which are currently being tested in trials. Thus, according to the geroscience approach (**Figure 2**), we should target the upstream effects of ageing. This strategy should involve the common drivers of NCCD´s, manifest in nine hallmarks of ageing.[5] So far, methods developed for a single chronic disease have generally failed to mitigate other NCCD´s, and have not translated to the general population, as such approaches have typically been mechanistic and mono disciplined. Clearly, a better understanding of the *intrinsic* mechanisms involved is a bottleneck for improving health span, with the dividend of delaying onset of multiple NCCD´s. Additionally, the effects of the NCCD´s are amplified in the context of *extrinsic* drivers of ageing, such as socioeconomic deprivation, which carries a higher burden of global adversity.[6] Understanding the *extrinsic* factors

underlying these health disparities is critical if we are to develop and apply suitable mitigation strategies to improve global health and wellbeing.

Within the scenario of a rampant ageing processes, reduced kidney function plays a pivotal role. The uremic milieu constitutes a worst case scenario for EVA, due to a combination of allostatic overload from too many stressors, such as inflammation, oxidative stress, increased carbonylation and sympathetic-vagal imbalance, specific pro-ageing factors such as sodium accumulation, hyperphosphatemia and activation of angiotensin II (ANGII) and defective anti-ageing mechanisms such as klotho and testosterone.[7] This results in a mismatch between chronological and biological age, which contributes to a gradual loss in vascular integrity and EVA, [8–10] accompanied by an altered vascular smooth muscle cell (VSMC) phenotype that promotes arteriosclerosis i.e. vascular calcification (VC) and increases cardiovascular risk.[11]

The risk factor profile for EVA has shifted, and while traditional factors, including smoking, hypertension, and LDL-cholesterol levels, have decreased in prevalence,[12] a range of novel risk factors such as inflammation, hyperphosphatemia, gut dysbiosis, Covid-19, clonal haematopoiesis, physical inactivity, senescent cell accumulation, vitamin K deficiency and environmental stressors (global warming and air pollution) may play an increasingly important role. An increased risk for EVA after Covid-19 infection,[13] may turn out to be the leading future global risk factor for CVD.[14] A greater mechanistic and molecular understanding of drivers of uremic EVA is critical for recognition and evaluation of exercise,[15] nutritional,[16] and pharmacological interventions to counteract the high vascular risk in this patient population.[17]

2.1 Pathophysiology of vascular ageing towards CKD

Describing ageing can be achieved both in terms of chronology and in terms of biology. Chronological age is defined as the time elapsed since birth, while biological age is defined as relative physiological capacity or capability at a subsequent point in the life course after birth.[18] As such, it shows substantial inter-individual variation and is often segmental in nature (i.e. organs do not age at the same rate). Additionally, biological age is subject to antagonistic pleiotropy, meaning that both intrinsic and extrinsic factors have differential impact at differing stages of the life course. For example, cellular senescence is vital for normal embryonal development, and can contribute to functional deterioration in aging but it is oncoprotective in early life.[19] As will be discussed in this review, CKD patients present with a range of features consistent with an uncontrolled and segmental ageing process, where increased cellular senescence and vascular calcification (VC) are highly pronounced.[7,20,21] Studies are needed to examine the timeline on how progressive deterioration of renal function promote EVA and increased biological aging.

The concept of EVA describes the circumstances where chronological age does not truly reflect actual status of the vascular ageing process. Several biomarkers, assessing preclinical atherosclerotic or arteriosclerotic damage, are under investigation to provide the best definition of vascular age.[22] EVA has been linked to CVD, cognitive impairment, CKD, and pre-eclampsia.[23–25] From a clinical perspective, vascular ageing can be described as a slow process, characterized by age-related changes in functional and structural characteristics of various vasculature components, as well as a decline in endothelium-dependent dilatation that results in increased vascular tone, loss of arterial elasticity, and an increase in arterial stiffness. The key non-modifiable and modifiable factors that influence vascular health and longevity, as well as examples of diseases and conditions featuring early vascular impairment, have recently been summarized.[22] Therefore, CKD serves as a clinical model when biological vascular age differs from chronological age.[26] Features of EVA pertinent to CKD include a) increased arterial stiffness and pulse wave velocity; b) impaired endothelial function and vasodilatation; c) chronic vascular inflammation; d) increased intima media thickness and early atherosclerosis; e) hemorheological disturbances of blood flow; f) capillary rarefaction and dysfunctional regulation; g) shorter telomere length/ lower telomerase activity; h) impaired glucose and lipid metabolism; i) insulin resistance; j) oxidative stress; k) arterial calcification; l) increased deposition of matrix substances; m) small vessel degeneration in brain and kidney; and n) increased left ventricular heart load **(Figure 3).**

When certain risk factors and/or disease states are present, such as hormonal changes, uremic toxin deposition, nutritional qualities and/or obesity, lifestyle factors, smoking, increased LDL-cholesterol, and glucose levels, EVA processes differ between sexes.[27] Additionally, the roles of sex and gender in CKD are emerging.[28] As adverse hypertensive pregnancy outcomes, particularly pre-eclampsia, increases the risk for both CVD and CKD, reproductive health should be appreciated.[29] Although older women are more likely to select conservative therapy and report a higher symptom burden and severity, kidney function tends to decline more quickly in men than in women.[30] Whereas the production of nitric oxide (NO) in the vasculature is better preserved in females, increased activation of ANGII in males favors pro-oxidant, pro-inflammatory, pro-fibrotic and vasoconstrictive processes.[31,32] The distribution of hypertension and obesity also varies between the sexes.[32,33]

2.2 Features of EVA in CKD

The occurrence of abnormal myocardial and blood vessel remodeling in CKD patients may result in cardiovascular complications, such as cardiomyopathy, arteriosclerosis, ischemic heart disease, CHF, cerebrovascular complication and progression to ESKD.[34] The endothelium and medial layer of the vessel wall are affected in part by similar processes resulting in atherosclerosis and arteriosclerosis.[35]

As patients with CKD are at high risk of cardiovascular events, kidney disease *per se* should be regarded as an independent cardiovascular risk factor (**Figure 4**).[17] Functional and structural abnormalities of the vasculature play an important role in the development of CVD and its complications in CKD.[36] Age-related impairments in endothelium-dependent vasorelaxation, increased permeability and vascular inflammation have also been observed.[37] Age-related aortic stiffness occurs at a considerably faster rate in CKD and arterial stiffness is frequently related with VC and reaches the maximum degree observed in humans.[38] This causes increased afterload in the left ventricle, systolic hypertension, left ventricular hypertrophy and delayed diastolic relaxation. When studying EVA, it is crucial to consider the heart as a part of the vascular system and not an independent entity. Include description of macro vs microvascular disease. Age-associated EVA has been regarded as the biggest risk factor for CVD.[39]

Age-related structural changes have two functional effects: the hardening/sclerosis of artery walls (arteriosclerosis) and the loss of distensibility, or increased stiffness.[40] Medial calcification is a disorder distinct from atherosclerosis, associated with increased arterial stiffness,[41,42] diastolic heart failure,[43] and impaired perfusion of a high blood flow organs such as brain, kidney and liver.[44] The structural changes that the arterial wall experiences with vascular ageing will gradually become more pronounced in the presence of comorbidities and/or uremic toxins. Reduced arterial compliance and detrimental pulsatile hemodynamics cause structural alterations, which are principally attributable to loss of wall elasticity with collagen buildup and elastin fragmentation in the media.

Vascular remodeling is triggered by endothelial dysfunction.[45] NO, which dilates blood vessels, is released by endothelial cells in response to flow-mediated shear stress or frictional force of tensile stress, along with other vasoactive substances to maintain vascular homeostasis such as vascular tone, inflammation, coagulation, and smooth muscle cell proliferation.[46] Numerous investigations have revealed that endothelial cells change from a protective to a pro-atherosclerotic phenotype in the presence of factors that raise the CVD risk, with decreased NO availability and increased release of endothelin-1, prostaglandin H2, thromboxane A2 and ROS.[47] Hence, endothelial dysfunction is considered as a primary and dominant driver of EVA.[48]

Arteries gradually lose their "cushioning" role in uremia and become stiff and tortuous because of vascular ageing-induced imbalances between vasoconstrictors and vasodilators. Along with changes in extracellular matrix content, VSMCs switch to a synthetic phenotype that triggers detrimental vascular remodeling process towards elevated stiffness.[49–51] Aortic ageing is associated with high aortic systolic and pulse pressures, early return of wave reflections, lower coronary perfusion pressure, elevated PWV, and aberrant microcirculation.[52] Although muscular arteries are thought to be less impacted by ageing processes,[53] they serve as primary site of VC via VSMC transition to an osteoblast-like cell type in CKD.[54] EVA also associates with senescence-associated endothelial

damage, due to increased apoptosis, decreased endothelial regeneration and a reduction of arteriolar density, which further strengthens the critical role of microcirculation in EVA.[55]

Cerebrovascular insults, cognitive impairment, encephalopathy, and peripheral and autonomic neuropathies are common features in CKD.[56] Proinflammatory factors have been observed to decrease serum NO in the brain vasculature which may contribute to cerebral hypoperfusion.[57] Uremic toxins that affect the nervous system include uric acid, indoxyl sulfate, trimethylamine N-oxide (TMAO) and inflammatory proteins.[58,59] Certain protein-bound toxins and large middle compounds that are poorly removed during dialysis may cause direct neurotoxicity, as well as indirect neurotoxicity, through vascular effects.[60] Studies in murine CKD models have reported blood-brain-barrier (BBB) disruption, oxidative stress, inflammation and mitochondrial dysfunction in the mouse brain, which are fundamental causes of neurochemical and histological abnormalities.[61] The uremic milieu compromises the BBB, as demonstrated by changes in the levels of brain-specific proteins neuron-specific enolase and brain-derived neurotrophic factor in the peripheral circulation.[59] Additionally, TMAO may play a role in the disruption of the gut-blood barrier (GBB) and by extension of the BBB. TMAO is not only a GBB marker and predictor of poor outcome in CKD but may also disrupt BBB maintenance by modulating endothelial tight junction proteins in the microcirculation.[59,62]

3. Media calcification as a predictor of outcome, and mechanisms behind

As atherosclerosis-related abnormalities are fundamentally different from age-related vascular changes, the addition of a coronary artery calcification (CAC) score to traditional and non-traditional risk factors improves existing models in predicting cardiovascular events in CKD.[63] In a prospective cohort study, we have reported that ~80% of arterial biopsies from middle-aged CKD5 patients have signs of mild to advanced medial calcification, an independent predictor of cardiovascular events.[64] The cause of VC is multifactorial and includes hyperphosphatemia and phenotypic transition of VSMCs into osteoblast-like cells, with accompanying expression of bone-related genes, such as Runt-related transcription factor (RUNX2), Msh Homeobox 2 (Msx2), BMP2 and alkaline phosphatase (ALP) **(Figure 5).**[65] The extracellular matrix becomes mineralized as a result of pro-calcifying stimuli and impairment of inhibitory mechanisms, including those mediated by fetuin A and Vitamin K-dependent proteins like matrix Gla protein (MGP).[66] As renal function declines, the toxic atherogenic milieu builds up uremic toxins, phosphate, IL-6, TNF and disturbs calcium, PTH and FGF-23 homeostasis. Apoptotic bodies due to hypercalcemia trigger the development of hydroxyapatite crystals.[67]

Our knowledge of the pathological events leading to VC has improved dramatically over the past decade. Endothelial cells exposed to uremic toxins and pro-inflammatory cytokines produce vasoconstrictors and enhance production of ECM degradation molecules such as metalloproteinases

(MMP´s) as ROS build-up.[65] Thus, VC is an active process,[68] with similarities to bone mineralization, nucleation, and crystal growth phases. In uremia, the combination of high phosphate and calcium promotes a phenotypic switch in VSMC´s to an osteogenic-chondrogenic phenotype. Biomineralization then commences as a result of matrix vesicles and apoptotic cell bodies presenting nucleation sites for calcium-phosphate crystal formation.[69] This process depends on matrix metalloproteinases (MMPs); in particular MMP-2 activity correlates with the degree of medial calcification and arterial stiffness.[70] FGF-23, vitamin D deficiency and uremic toxins, such as indoxyl sulphate and TMAO, also promote VC (**Figure 5**).[68,71] The pathological process is further compounded by depletion of calcification inhibitors and poor vitamin K status.[10,72] In addition to its established pro-calcifying effects in CKD, phosphate drives a multitude of detrimental outcomes in the vasculature, such as endothelial cell senescence,[88] vasoconstriction and endothelial dysfunction.[73] Furthermore, aged mice on a high phosphate diet demonstrate impaired endothelium-dependent vasorelaxation, which associates with increased expression of inflammatory and fibrotic markers in endothelial and VSMC cells.[74]

The long-term effects of kidney transplantation (Ktx) on VC remain debated. While short-term studies have demonstrated that CAC may be reversed after Ktx, longer-term studies have shown increased CAC post-Ktx, raising the possibility that restoration of renal function may not be enough to reverse VC.[75,76] Unfortunately, current therapies that target intermediate players of bone and mineral metabolism, such as phosphate binders and calcimimetics, fail to arrest or regress VC.[77] A new approach is to target calcium deposits directly (SNF472), a compound that binds to hydroxyapatite growth sites. In a phase 2b trial, SNF472 has been reported to slow progression of CAC and valve calcification in dialysis patients.[78] The existing link between senescence of VSMC´s and the pathophysiology of VC, further strengthen the potential of senolytics.

4. Emerging risk factors for early vascular ageing

During the last 10 years several novel entities that may be significant drivers of EVA in the uremic milieu have been identified. These factors are interrelated, and seems to be a part of intermediate inflammatory phenotype (i.e. inflammageing) that drives premature ageing.

4.1. Inflammation as a driver of vascular aging in CKD

Ageing in humans is associated with chronic low-grade inflammation with increased levels of IL-6 and CRP. Systemic inflammation associate with a higher risk of a NCCD.[79] Multimorbidity, including >three NCCDs and the disease-burden associated with inflammation, increases with age and accelerated vascular ageing processes.[20,80,81] According to the geroscience concept, NCCD´s that accumulate with

age share common underpinning features, including macromolecular damage, increased cellular senescence, diminished Nuclear factor erythroid-2-related factor 2 (Nrf2) activity, proteostasis, mitochondrial dysfunction, persistent low-grade inflammation and stem cell dysfunction. These alterations are accompanied by an age-dependent decline in DNA damage repair mechanisms, which trigger a proinflammatory senescence associated secretory phenotype (SASP) and inflammageing (**Figure 6**).[82,83] These interconnected cellular and metabolic changes do not operate separately, but instead participate in a vicious cycle that drives EVA. Inflammageing is a prominent feature of the uremic phenotype, characterized by elevated levels of inflammatory markers,[84] pro-inflammatory cytokines[85] and repressed expression of Nrf2.[86,87] Biomarkers of inflammation are independent risk predictors of poor cardiovascular outcomes in CKD.[88] The validity of the hypothesis that inflammation is an important driver of ageing processes is widely supported by studies on animal species that exhibit negligible senescence, where chronic sterile age related inflammation is well controlled.[89] During the ageing process, inflammageing is sustained by a variety of endogenous and exogenous stimuli and a chronic stimulation of the innate immune system, leading to immune dysfunction and increased risk of infectious complications.[90] Dysbiosis of the gut microbiota is a prominent feature in NCCD´s that play a central role in inflammageing, as proinflammatory microbial metabolites leaking through the gut contribute to vascular damage.[91] Moreover, the gut microbiota induce inflammageing and disruption of cytokine networks, which promotes a decline in DNA damage repair mechanisms.[92]

The central role of persistent sterile inflammation in the initiation and progression of CKD and EVA, has gained interest in the nephrology community for targeted anti-inflammatory therapies, such as anti-IL-6, anti-IL-1 and Nrf2 agonist treatment.[87,93] A recent review summarized the current understanding of targeting different inflammatory biomarkers. IL-6 was reported to be an independent predictor of outcome in patients starting dialysis >20 years ago,.[94] Subsequently, many studies based on murine data, genetic studies and large epidemiological studies, have reported that IL-6 is a causal and central factor in the atherothrombotic process.[95] The CANTOS trial has shown that canakinumab (monoclonal antibody targeting IL-1β) reduces major adverse cardiovascular event rates in CKD (eGFR <60 ml/min/1.73 m^2).[96] Moreover, in moderate to severe CKD Ziltivekimab reduced expression of biomarkers of inflammation and thrombosis relevant to atherosclerosis in the RESCUE trial.[97] Based on these findings, a cardiovascular outcome trial (ZEUS) using Ziltivekimab, has been initiated in inflamed CKD patients with CVD.

4.2. Role of oxidative stress, Nrf2 and sirtuins

In the 1950's, Harman first postulated that free radical overproduction shortens species lifespan.[98] Although it is widely appreciated that ROS mediated damage accumulates with age, ROS and reactive

nitrogen species have important signalling actions under physiological and pathological conditions.[99] Nonetheless, many uremic toxins, including the protein-bound solutes indoxyl sulphate and p-cresyl sulphate, promote oxidative stress in CKD.[100] Increased oxidative stress has also been directly linked with hallmarks of EVA including VC,[101] through the Akt pathway, while a large body of evidence has indicated a direct link with endothelial dysfunction.[102] Depleted antioxidant responses also tip the balance towards oxidative stress, such as failure to switch on antioxidant response element (ARE)-driven gene expression, typical of Nrf2 regulated genes. Nrf2 is repressed by Kelch-like ECH-associated protein 1 (Keap1) under basal conditions, but nuclear translocation is mediated upon exposure to oxidative stress after dissociation from the Keap1-Nrf2 complex, following which it binds to AREs to activate target genes. Consequently, Nrf2 is an important cytoprotectant in response to a range of stresses.[109] As Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription, stimulation of Nrf2 may provide an opportunity to target inflammageing and prevent EVA.[103] Impairment of Nrf2-dependent defence mechanisms is associated with NCCDs.[104] Nrf2 expression decreases with age and silencing of the *Nrf2* gene induces premature senescence.[105,106] As such, the interaction between Nrf2 and p53/p21 may delay cellular senescence and prevent age-related diseases. Thus, functional homeostasis within Nrf2 regulated gene expression networks is crucial for the maintenance of cellular homeostasis.[107] The observation that Nrf2 is suppressed in Hutchinson Gilford progeria syndrome (HGPS), a progeric disease with extreme EVA, provides indications for prevention.[108] Conversely, in long lived species such as naked mole rats, that live up to 10 times longer than similar-sized rodent species, levels of Nrf2 are upregulated.[109] As Nrf2 deficiency/inactivation associates with renal fibrosis, atherosclerosis development[110] and CKD,[111] both synthetic and natural Nrf2 activators are now the subject of clinical trials in CKD patients.

Upregulation of Nrf2 by various Nrf2-agonists, such as heme,[112] antioxidants,[113] metformin,[114] hydrogen sulphide[115] and dimethyl fumarate,[116] have consistently been shown to improve VC in animal models. Hence, targeting inflammageing by upregulation of Nrf2 expression may be an opportunity to arrest EVA. Thus, activation of Nrf2 by nutritional or pharmacological interventions may protect against vascular senescence and EVA.[86] An opportunity to use the concept of 'food as medicine' to target Nrf2 by use of natural bioactive nutrients,[16] such as sulforaphane (a sulphur-containing compound found in cruciferous vegetables) has emerged (**Figure 7**).[117] As a randomized clinical trial showed that treatment with broccoli sprout extract resulted in improved metabolic control in obese T2DM patients the effects of broccoli sprout extracts on vascular function need to be determined. Recent experimental studies have reported that sulforaphane regulates NO synthase activation and NO production in endothelial cells, which protect against ANGII-induced aortic injury.[118] Randomized studies with sulforaphane[119] are thus merited for CKD. Alternatively, inhibitors of the BTB domain and

CNC homolog 1 (Bach1) could also be used to indirectly upregulate Nrf2 and reduce inflammation.[126] One caveat remains here, being that overexpression of Nrf2 has been linked to tumorigenesis and resistance to chemotherapy, a stark reminder that extensive research into timing and context of intervention is required. [120]

Sirtuins (SIRT1-7) are NAD^+-dependent histone deacetylases that regulate biological processes such as cell survival, cellular senescence, DNA repair, proliferation, and apoptosis. As vital nutrient sensors, sirtuins respond to changes in their microenvironment, and form part of the cellular defence mechanism against ROS.[121] While sirtuins respond to ROS by increased expression as a compensatory mechanism, chronic exposure to ROS induces post-translational modifications or affects protein-protein interaction with target proteins, thereby becoming dysfunctional.[122] As with Nrf2, sirtuin expression is generally diminished with ageing.[123] Loss of Sirt1 in VSMCs, for example, causes impaired stress responses and increased senescence.[124]

4.3. Role of vitamin K in the calcification process

Vitamin K is a group name for substances (phylloquinone and menaquinone) that share the ability to serve as cofactors for the microsomal enzyme γ-glutamyl carboxylase. Vitamin K and vitamin K-dependent proteins have been associated with a spectrum of NCCD´s including EVA. The individual vitamin K status is a complex reflection of dietary intake, gut microbiome, medications, and comorbid conditions. Efforts to better understand the links between gut microbiota, vitamin K-producing bacteria, and deficiency of vitamin K in CKD, may lead to personalized nutritional interventions. Vitamin K deficiency is a common feature in CKD.[72] The link between vitamin K and EVA is in part mediated via dp-ucMGP, a potent inhibitor of VC that requires carboxylation by vitamin K to exert calcification inhibition.[125] In addition to its conventional role in blood clotting, vitamin K confers vigorous anti-ferroptotic activity.[126] As ferroptosis contributes to the development of VC, this may be another mechanism by which vitamin K confers vascular protection.[127] Vitamin K1 also dampens vascular inflammation by regulating NF-κB/Nrf2 via activation of Gla proteins. [128] During vitamin K-inhibition, Nrf2 activation ameliorated hemorrhagic transformation in focal cerebral ischemia.[129] A cohort study of almost 500 CKD stage 5 patients has reported that a functional vitamin K deficiency was associated with increased mortality risk independent of VC.[130] As underpowered clinical randomized Vitamin K trials have shown divergent results, fully powered randomized trials should be initiated maybe combining vitamin K2 with a phosphate binder.[131–134]

4.4. Role of mitochondrial dysfunction

Given the importance of intact mitochondrial function in regulating fundamental cellular processes, such as redox homeostasis, apoptosis and calcium homeostasis, it is unsurprising that mitochondrial

dysfunction has been postulated as a hallmark of ageing (**Figure 6**).[5,135] Mitochondrial dysfunction, with accumulated mitochondrial ROS production, contributes to the functional decline of organ systems associated with ageing, resulting in a wide range of age-related disorders, including cancer.[136] Conversely, overexpression of antioxidant proteins, such as catalase, targeted to the mitochondria, reduces H_2O_2 production, improves age-related physiology and extends life span.[137] Mutations in mitochondrial DNA correlate with both longevity and CKD progression,[138,139] calcific valve disease,[140] atherosclerosis,[141] T2DM,[142] and HGPS[143] all of which are characterized by mitochondrial dysfunction. Features commonly reported in CKD include changes in mitochondrial morphology, remodelling, increased ROS production and both decreased biogenesis and ATP production,[138] which correlate with the severity of disease.[139] Correspondingly, mitochondria from the skeletal muscle of CKD5 patients show distinct ultrastructural abnormalities, along with decreased mitochondrial volume, density, and DNA copy number. Conversely, BNIP3, a marker of mitophagy, is increased.[139,144]

Although mitochondrial function in the vascular tissue has not been characterized, *in vivo* observations suggest that mitochondrially derived ROS contributes to vascular dysfunction in CKD. Studies on rat models of CKD have reported that ROS induces VC and osteoblastic transition of VSMCs.[145,146] The relationship between mitochondrial dysfunction and VC in CKD has been suggested to be time-dependent, with mitochondrial hyperfunction occurring at an early stage of hyperphosphatemia, causing overproduction of ROS, leading to altered vascular function.[147] As VC drives mitochondrial dysfunction, the mechanistic link appears bi-directional (**Figure 3**).[148] Nevertheless, targeting mitochondrial dysfunction, particularly through inhibition of ROS, offers novel therapeutic opportunities for uremic EVA. Increased mitochondrial fission exacerbates oxidative stress and inhibiting this process could potentially improve EVA.[148] Irisin, known to alleviate oxidative stress and apoptosis in kidney cells,[149] reduce excessive mitochondrial fission, VSMC osteoblastic transformation and calcium deposition in CKD-associated VC.[150]

The proposed link between mitochondrial dysfunction and gut microbial dysbiosis opens a route for dietary strategies and/or use of probiotics, prebiotics, or symbiotics to achieve a more salutogenic gut microbiota and thus improved mitochondrial and vascular function.[151,152] The relatively recent introduction of SGLT2 inhibitors in the treatment of CKD has generated new insight in mitochondrial function. SGLT2 inhibitors induce a distinctive salutogenic metabolic pattern within the evolution and progression of cardiorenal disease, which mimics physiological changes evolved during evolution in aestivating animals.[153] The metabolic changes observed after treatment with SGLT2 inhibitors are characterized by organ protection due restoration of mitochondrial biogenesis, a reduction in oxidative and endoplasmic reticular stress and a decrease in activity of profibrotic and proinflammatory metabolic pathways that preserve cellular integrity and viability.[154]

4.5. Senescent cells – an emerging target for treatment of EVA

Cellular senescence (CS) is defined as a state of irreversible cellular growth arrest, accompanied by a proinflammatory phenotype.[5] CS is a central hallmark of ageing, which can be induced by several primary drivers of ageing, such as mitochondrial dysfunction, telomere erosion and DNA damage. Recent experimental studies have shown that an increase in lifespan and health span can be achieved by targeting CS.[155] Mechanistically, pathways leading to the state of senescence are complex, and can involve the p53/p21WAF1/CIP1 and the $p16^{INK4A}$ tumour suppressor pathways to enable growth arrest. An important aspect of CS is the SASP, which promotes disease and the spread of senescence to adjacent healthy cells. Senescent cells are resistant to apoptosis through expression of senescence associated anti-apoptotic pathways (SCAPs); consequently, CS linger in tissues and promote dysfunction and disease.[69] Both $p16^{INK4A}$ and $p21^{WAF1/CIP1}$ are markers of CS, but no universal marker of senescence has yet been identified. Markers reflecting different aspects of the senescence phenotype must be used in composite to achieve identification of CS.[156] Although one study examining SASP mediators has found different stimuli and cells excrete distinct secretory phenotypes, certain SASP mediators are conserved components of the proinflammatory phenotype.[157,158]

Senotherapies can be categorised into distinct strategies: *prevention*; *senolytics*, compounds that target SCAPs; or *SASP modification*, otherwise known as senostatics or senomorphics. At present, senotherapies have not been investigated in the setting of CVD in CKD. However pre-clinical and clinical studies looking at the direct impact of senotherapies in CVD have indicated how this drug class can be integrated in the background of uremia (**Figure 7**). Preventative strategies that target pathways leading to the accumulation of senescent cells include caloric restriction, physical exercise, phosphate control, and the modulation of gut microbiota, as well as sirtuin/Nrf2/Klotho agonists.[159] This strategy may appear intuitive, however considering CS contributes to ageing subject to antagonistic pleiotropy, complete CS ablation may be detrimental to wound healing and development.[160,161] However, caloric restriction, which delays CS and slows progression of VC and ageing, extends the lifespan in mice, rats and primates.[109] In fact, in response to caloric restriction in rats, expression of $p16^{INK4a}$ has been reported as attenuated in the kidney and heart.[162]

Another approach to diminish the detrimental effects of CS has been to target an adverse secretome by senostatic therapy. SASP modulation has gained attention in recent years, but researchers must still review serious potential side effects considering SASPs' role in wound healing.[163] Several compounds have shown promise in clinical applications and rapamycin,[164] JAK/STAT inhibitors,[165] and metformin inhibit the proinflammatory SASP response.[166] Long-term administration of Dasatinib and Quercetin (D+Q), to specifically remove CS, increases lifespan and improves health

span in normatively aged mice[167] and alleviated vasomotor dysfunction in aged in mice with established atherosclerosis.[188] These promising pre-clinical findings have led to the use of D+Q in clinical trials for diabetic CKD, where SC burden was reduced in adipose tissue.[168] Fisetin, another senolytic, is currently being investigated in clinical trials after exciting pre-clinical data. This naturally occurring flavanoid promoted apoptosis in senescent HUVECs,[169] and increased lifespan in wild-type mice.[170] Lastly, Navitoclax, has been reported to rejuvenate aged hematopoietic stem cells in mice,[171] and to improve survival in aged-mice following acute myocardial infarction.[172] However, Navitoclax has not progressed to the clinic due to concerns over effects on non-SC, further emphasising safety and efficacy issues.[173] As senescent cell's Sirt1-associated bystander effects are driven by the SASP and production of extracellular vesicles, agonists such as resveratrol may be a another promising therapeutic intervention for EVA.[69] It should also be noted that there are limited data on adverse events from human clinical trials. As such, caution on the use of senotherapies, particularly in the context of multi-morbidity, needs to be maintained.[174] The complexity surrounding senescence and tumour therapy has been described as a "double-edged sword", since senotherapy inhibits tumour growth, but also primes tissue for future relapse.[175]

4.6 Role of genomic instability and CHIP in EVA

DNA damage affects most, if not all, aspects of the ageing phenotype, making it a potentially unifying cause of ageing. Genomic instability and DNA changes, inclusive of chromosomal translocations, changes in ploidy, DNA insertions and deletions of <1Kb and point mutations, accumulate during organismal ageing, because of both spontaneous (intrinsic) or damage-induced (extrinsic) events.[5,176] Consequently, excessive DNA damage, or insufficient DNA repair, drives genomic instability. This enables pathogenic processes, as CS, inflammation and apoptosis, that can affect both the macro- and microvasculature (**Figure 6**).[177,178] Indeed, DNA damage has been linked to both CKD and the development of EVA.[178,179] Elevated DNA damage and genomic instability have already observed in mild CKD,[201] and both worsen with declining kidney function and predict poor prognosis.[180–182] Results from studies exposing lymphocytes to UV-light or irradiation have suggested that CKD patients suffer from DNA repair impairment as well as increased radiosensitivity,[183–185] both of which associate with disease severity.[186] However, it is unknown if the uremic DNA damage is solely due to a genetic predisposition to inadequately repair DNA lesions, or solely, or in part, attributable to the toxic milieu with high levels of ROS that negatively impact DNA repair and induce DNA damage. Genetic variants are likely to play a role, as DNA polymorphisms in DNA repair pathways and antioxidant genes associate with measures of genomic damage, instability, and oxidative damage in CKD.[187] The impact of ROS on genomic instability can also be gauged by the associated degree of telomere shortening,[188]

in patients starting kidney replacement therapy.[189] In CKD, shorter telomeres associate with inflammation, mortality, and CVD.[190,191]

The accumulation of genomic alterations over the human life course also involves a range of other DNA mediated events, such as somatic and non-somatic mutations, resulting in tissues that are mosaics of clones originating from single stem cells.[192] In blood, age-associated low-frequency mutations can lead to clonal expansion of a (genetically) distinct subpopulation of hematopoietic stem cells, termed clonal hematopoiesis of indeterminate potential (CHIP).[193] CHIP is defined by the presence of a putative oncogenic clonal mutation in a minimum of 4% of nucleated blood cells without overt detection of neoplasia.[194] Such blood cell clones arise through the mutation providing a selective growth advantage. More than 50% of these mutations are found in genes involved in the regulation of the epigenetic landscape of ageing, including DNA methyltransferases *DNMT3A* and *TET2*, as well as the chromatin regulator *ASXL1*. However, it remains undetermined why mutations in these genes leads to selective growth advantage.

Inherited (germline) genetic variations influence the acquisition of CHIP and the somatic mutation rate per year varies greatly across mammalian species, displaying a strong inverse correlation with lifespan.[195,196] In humans, CHIP is rare in those aged <40 years, but can be found at >10% levels in those aged ≥70 years. Although CHIP is a common age-related phenomenon, it is not clear if it is an inevitable consequence of the normal ageing process. Unsurprisingly, recent studies have reported that CHIP is associated with NCCDs, along with a higher risk of stroke,[197] gout,[198] CHF,[199] and poor kidney function.[200] Longitudinal studies on DNA methylation have shown that CHIP associates with epigenetic age acceleration, where *TET2* mutation-carriers had about a 6-year increase in age acceleration and those with DNMT3A mutations had 3–4-year increase, respectively,[201] suggesting that CHIP is related to biological age. It remains to be proven if changes in DNA methylation clocks are reflective of causal changes in the epigenetic landscape of ageing, or simply reflective of somatic mutation burden within a given species and or epigenetic drift.

CHIP appears to be associated with a substantially elevated risk for all-cause mortality and an increased risk of CVD.[202] Importantly, CHIP may even be a more important cardiovascular risk factor than traditional Framingham risk factors, such as smoking and hypertension.[203] Although the CHIP-CVD link has not been well-studied in CKD, a recent study from UK Biobank has reported an association between myeloid CHIP and increased risk of adverse outcomes, as defined by a composite endpoint of either death, myocardial infarction or stroke.[204] Results reported so far have suggested that the increased cardiovascular risk might be due to increased inflammation in innate immune cells carrying these mutations.[205] A large proportion of the CHIP-associated mutations are located in genes involved in epigenetic regulation of inflammation, including *DNMT3A, TET2* and *ASXL1*, as well as the *JAK2* gene

encoding type II cytokine receptor family member.[206,207] Indeed, preclinical murine models carrying common CHIP mutations present with atherosclerosis, indicating the fundamental nature of their relationship with CVD and cardiovascular mortality, possibly mediated by an increased inflammatory burden.[208,209] This relationship is multidimensional, as an elevated inflammatory status is associated with CHIP and increasing evidence suggest inflammation drives clonal expansion of mutated hematopoietic stem cells, creating a viscous cycle.[210,211] Correspondingly, CVD *per se* has been proposed as being both a cause and consequence of CHIP, as it increases hematopoietic stem cell division, which results in accelerated clonal expansion and production of inflammatory leukocytes.[212] Additionally, inflammation-promoting lifestyle factors, such as chemotoxic exposure, smoking and diet, all seem to affect steady state hematopoiesis.[211] Notably, in the context of ageing and age-related disease, it has been reported that Nrf2 regulates haematopoietic stem cell function via mediation of redox balance in the stem cell niche.[19] It seems intuitive that this would have a direct bearing on CHIP, as Nrf2 is a key regulator of cytoprotective defenses.

Although the current understanding of CHIP and EVA in CKD remains in its infancy, the mechanistic links observed between increased cardiovascular risk and increased inflammatory burden, especially in relation to innate immune cells carrying these mutations, offer scope for new, targeted, treatment strategies. *TET2*-mutation-driven CHIP with myeloid *TET2* deficiency and increased expression of the IL-1b/NLRP3 inflammasome could be a key target, as it leads to worsened cardiac function in CHF. Notably, increased IL-1b/NLRP3 inflammasome expression is a prominent feature of CKD.[213] Indeed, IL-1b inhibition with canakinumab reduces major adverse cardiovascular event rates in CKD, particularly among those with a robust anti-inflammatory response to initial treatment.[96] The impact of *TET2* mutation in context of IL-1b inhibition in CKD remains unknown, but in a post-hoc analysis of the CANTOS trial, in which treatment groups were stratified according to *TET2* gene variants, the reduction in major adverse cardiovascular events increased from 15 to 64%.[214] The common gain-of-function mutation in *JAK2* is another potentially important target. Pre-clinical models have successfully explored blockage of JAK2 with Ruxolitinib in atherothrombosis and showed that Ruxolitinib downregulates proinflammatory cytokines and NLRP3 inflammasome expression in ischemic stroke injury.[215] Thus, genetic testing may allow selection of patients with CKD that would benefit most from targeted inhibition of IL-1b and NLRP3. Management of CHIP might therefore involve precision medicine with an individualized plan based on somatic genotype, comorbidities, life expectancy, and traditional cardiovascular risk factors.

4.7. Role of epigenetic alterations

Dysregulation of the epigenetic landscape is another hallmark of ageing that accompanies genomic instability. The epigenetic landscape comprises both canonical and non-canonical sets of features. Canonically, these comprise genomic DNA methylation and post-translational modification of chromatin. Non-canonically, the epigenetic landscape comprises non-coding RNAs that reciprocally regulate gene expression networks in response to environmental perturbation.[216] In mammals, increasing age also sees widespread genomic hypomethylation. By way of contrast, CKD and CVD show specific features of hypermethylation, which may reflect a superimposition of patho-mechanistic features on a background of locus specific hypermethylation.[217] In keeping with this postulate, the de-repression of long interspersed nuclear elements (LINEs) with activation via demethylation, drives interferon production in SC and promotes age-associated inflammation. [218,219] Histone post-translational modifications have also been reported in CVD,[220] and mirror changes observed with physiological senescence,[221] at or near LINE element arrays.

4.8. Role of increased apoptosis and necroptosis in EVA

Routine cell turnover and tissue homeostasis depend on controlled apoptosis and necroptosis. Dysregulation of apoptosis and necrosis is a feature of ageing and ageing-associated diseases. The molecular mechanisms underpinning apoptosis are strongly regulated involve the serial activation of cysteine proteases termed as caspases.[222] Cellular stresses, such as DNA damage, activated oncogenes, hypoxia, oxidative stress, and radiation can stimulate the intrinsic apoptosis pathway. In contrast, the extrinsic pathway for apoptosis activation involves signaling through the TNF-receptor family. Age-related imbalances in pro- and anti-apoptotic gene expression lead to an increase in apoptosis.[223] Even without disease-associated pro-apoptotic factors, ageing alone may promote apoptosis in a variety of tissues, including arteries.[224] A pro-inflammatory vascular phenotype promotes endothelial apoptosis. This has been attributed to decreased bioavailability of NO or upregulation of oxidative stress; both common features of CKD.[225] As increased endothelial cell apoptosis correlates with upregulation of TNF, an inflamed vascular wall promotes EVA and vascular dysfunction.[223] VSMC apoptosis mediated by endoplasmic reticular stress is a key aetiological component of CKD that promote EVA.[226] Increased apoptotic cell death plays a role in the development of atherosclerosis, and the microvascular rarefaction associated with ageing.[227]

Extensive research has investigated how necroptosis affects inflammation and how it relates to various age-related disorders. The necrosome, an amyloid-like structure, is the central component of the necroptosis signaling pathway. This is dependent on receptor-interacting serine-threonine kinase 3 and mixed lineage kinase domain-like proteins. A significant cause of inflammation and a possible driver of inflammageing is necroptosis-associated buildup of damage-associated molecular patterns,[228]an activator of NLRP3 inflammasome.[229] In mouse models, up-regulation of necroptosis

pathways promote aorta aneurysm progression.[230] An increase in autophagy is an aspect of anti-aging therapies that is also frequently observed. Collectively, mechanisms involved in programmed apoptosis or necroptosis are intriguing targets for treatments of EVA in CKD.

5. The exposome of EVA

Strategies designed to mitigate the effects of the '*diseasome of ageing'* and EVA need not solely be clinical in nature. Holistic approaches to health, including One Health, and Planetary Health have been proposed to address global health issues, from food safety to zoonotic diseases, not specifically the NCCDs (**Figure 7**).[231] Social and geo-physical environments can be both salutogenic and pathogenic. Psychological stress imposed by a threatening social and geo-physical environment accelerates ageing processes and sequelae of poor health.[232] By 2050, two thirds of the world's population is expected to be urban, which is likely to exacerbate NCCDs and promote EVA. Both diminished urban biodiversity and air pollution may exacerbate microbial dysbiosis and reduce Nrf2 expression.[233,234] Consequently, air pollution has been associated with an increase in prevalence of not only CKD, but also respiratory disease, CVD, T2DM and obesity.[19,235] Design of more salutogenic or biophilic environments and a biomimetic research approach could help address this increased risk.[236] Perhaps of more immediate benefit, is that such an approach is compatible with a strategy to enhance the function of Nrf2 and to maintain a normative microbiome in the current industrialised period of the Anthropence.[2] Incorporation of a forest canopy into the building design for example, has proven salutogenic effects on cardio-renal diseases in an urban setting.[237]

Non-prescribed medical interventions to enhance health and to promote well-being are enjoying a resurgence, as modern science provides a solid underpinning evidence base for how these might be effective.[238] Their widespread adoption, however, remains to be accomplished. While mindfulness and cognitive-behavioural therapy has proven effective at reducing stress, anxiety and depression, other strategies remain to be proven. Patients with CKD are at high risk of stress and depressive disorders especially when inflamed.[239] As a positive correlation between green space living and a decrease in blood pressure has been reported, the impact of green space living on EVA requires further studies.[240]

6. Conclusions

This review provides up-dated high-level summary of the current knowledge and the current research front of EVA in CKD. The pathogenic mechanisms underlying EVA and development of VC in the uremic milieu include traditional risk factors in combination with emerging risk factors, such as sterile inflammation, oxidative stress, vitamin K deficiency, mitochondrial dysfunction, senescent signals,

mutations, epigenetic alterations, and increased apoptosis. The excedingly high risk for EVA allows detailed physiological and molecular studies of EVA in a prevalent progeric group, that can be used as a 'magnifying glass' to study otherwise slow vascular ageing processes. Although a multitude of key discoveries on EVA have recently been made, much remains to be discovered, especially the elucidation of how the toxic uremic milieu affects somatic mutations and DNA damage repair in EVA.

Disclosures

PS reports serving in advisory or leadership roles for Astellas, AstraZeneca, Baxter, Fresenius Medical Care (FMC), GlaxoSmithKline, Reata, and Vifor; receiving honoraria from Astellas, AstraZeneca, Baxter, FMC, Novo Nordisk, Boerhinger Ingelheim and Pfizer/Bristol Square Myers (BSM); receiving research funding from AstraZeneca and Bayer; serving on advisory boards for AstraZeneca, Baxter, FMC, GlaxoSmithKline, Reata, and Vifor. PSh is a Scientific reviewer for Mars UK Ltd and funded by an IPP award between Constant Pharma and UoG. All other authors declare no competing interests.

Funding

The work was supported by the Hjärt lungfonden (PS), CIMED (PS, AW), Swedish Research Council (Vetenskapsrådet 2018-00932 GOING-FWD) (KK), Stiftelsen Stig och Gunborg Westman (AW, PS), Njurfonden (PS, KK, SA) and EU Innovative Training Network "CaReSyAn" (H2020-MSCA-ITN-764474) (PS, SH).

Abbreviations:
ALP - Alkaline phosphatase
AKT - Acute kidney disease
ANGII - Angiotensin II
BBB - Blood-brain-barrier
BMP2 - Bone morphogenetic protein 2
Cbfa1 - Core-binding factor subunit alpha-1
CKD - Chronic kidney disease
CVD - Cardiovascular disease
CHIP - Clonal hematopoiesis of indeterminate potential
CAC - Coronary artery calcification
CS - Cellular senescence
DAMPs - Damage-associated molecular patterns
EVA - Early vascular ageing
ESKD- End stage kidney disease
ECM - Extracellular matrix
GBB - Gut-blood barrier
eGFR- Estimated glomerular filtration rate
HGPS - Hutchinson Gilford progeria syndrome
Keap1 - Kelch-like ECH-associated protein 1
Ktx - Kidney transplantation
LINEs - Long interspersed nuclear elements
MMPs - Matrix metalloproteinases
MRA - Mineralcorticoid antagonists
dp-ucMGP - Matrix Gla protein
Msx2 - Msh Homeobox 2
Nrf2 – Nuclear factor-erythroid-2- related factor 2
NO - Nitric oxide
NCCD's- Non-communicable chronic diseases
eNOS – Nitric oxide synthase
PWV- Pulse wave velocity
RAAS - Renin-angiotensin-aldosterone system
ROS- Reactive oxygen species
RUNX2 - Runt-related transcription factor
SIRT – Sirtuins
SASP - Senescence associated inflammatory cytokine secretion
SCAPs - Senescence associated anti-apoptotic pathways
T2DM - Type-2 diabetes
TMAO – Trimethylamine N-oxide
TNF - Tumor necrosis factor
VSMC - Vascular smooth muscle cells
VC - Vascular calcification

Figure Legends:

Figure 1: Emerging cardiovascular risk factors. Red jigsaw pieces e.g. hypertension, sex, diabetes etc. are established risk factors for cardiovascular disease. White jigsaw pieces, including but not limited to senescent cell accumulation, sleep disorder and gut dysbiosis, are emerging risk factors for cardiovascular disease. Piecing together established and emerging risk factors is paramount to understand their interplay, and how we can therapeutically target common pathways to treat multiple diseases that cluster with age simultaneously.

Figure 2. Schematic illustrations depicting approaches to study the interrelation of ageing, burden of lifestyle diseases and death.

Figure 3. Proposed underlying mechanisms that drive early vascular ageing in the uremic milieu. Among others, vascular calcification, a hallmark of early vascular ageing in CKD, could be a cause or an effect.

Figure 4. Schematic representation of the underlying relationship between cardiovascular disease and chronic kidney disease. The broken arrows indicate pathways by which CVD can trigger CKD; orange solid lines indicate how CKD can induce CVD. Traditional and non-traditional risk factors associated with cardiorenal syndrome are also shown. **Abbreviations:** CKD: chronic kidney disease, CVD: cardiovascular disease.

Figure 5: Mechanisms promoting of vascular calcification in the context of CKD. The imbalance between calcification inhibitors and inducers are considered a key driver of vascular calcification in CKD, a hallmark of early vascular ageing. Circulating and local triggers promote transdifferentiation of VSMCs from a contractile to synthetic, osteoblast-like phenotype. Key mechanisms associated with vascular calcification such as uremic toxins retention and dysregulation of the FGF23-Klotho axis, as well as established markers of ectopic vascular calcification, are also depicted. **Abbreviations:** VSMCs: vascular smooth muscle cells, CKD: chronic kidney disease, ALP: Alkaline Phosphatase, BMP2: Bone morphogenetic protein 2, RUNX2: Runt-related transcription factor 2, MSX2: Msh homeobox 2, CBFA1: core-binding factor α-1, MMPs: matrix metalloproteinases. IS: indoxyl sulphate, PAG: Phenylacetylglutamine, TMAO: Trimethylamine N-oxide.

Figure 6. Schematic illustration of cell-autonomous and non-cell-autonomous mechanisms in CKD-related vascular ageing. The model shows that traditional and non-traditional risk factors orchestrate ageing processes simultaneously endothelial and smooth muscle cells within large vessels and microcirculation through four broad mechanisms (i.e., inflammation, oxidative stress, mitochondrial dysfunction, and senescence). Other factors, i.e., environmental factors, gut dysbiosis, dietary factors and Nrf2 dysregulation, are also involved in this complex mechanism. The resulting functional dysregulation of vascular cells promotes the development of a wide range of age-related vascular pathologies. **Abbreviations:** Nrf2: Nuclear factor erythroid 2–related factor 2, TMAO: Trimethylamine N-oxide, PAG: Phenylacetylglutamine.

Figure 7: Emerging therapies for cardiovascular disease in CKD. Schematic representation of three novel approaches to target treatment of cardiovascular disease in CKD: senotherapies, agents that target cellular senescence; biomimetics, applying elements of alternative model organisms to treat human disease, and exposome, defined as the sum of all environmental exposures across the life course. **Abbreviations:** CKD: chronic kidney disease IL: Interleukins, Nrf2: Nuclear factor erythroid 2-related factor 2.

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