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CKJ Review

CKJ REVIEW

Early aging and premature vascular aging in chronic kidney disease

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ABSTRACT

Aging is the progressive decline of body functions and a number of chronic conditions can lead to premature aging characterized by frailty, a diseased vasculature, osteoporosis, and muscle wasting. One of the major conditions associated with premature and accelerated aging is chronic kidney disease (CKD), which can also result in early vascular aging and the stiffening of the arteries. Premature vascular aging in CKD patients has been considered as a marker of prognosis of mortality and cardiovascular morbidity and therefore requires further attention. Oxidative stress, inflammation, advanced glycation end products, fructose, and an aberrant gut microbiota can contribute to the development of early aging in CKD patients. There are several key molecular pathways and molecules which play a role in aging and vascular aging including nuclear factor erythroid 2-related factor 2 (Nrf-2), AMP-activated protein kinase (AMPK), sirtuin 1 (SIRT1), and klotho. Potential therapeutic strategies can target these pathways. Future studies are needed to better understand the importance of premature aging and early vascular aging and to develop therapeutic alternatives for these conditions.

LAY SUMMARY

CKD is an important cause of premature and accelerated aging. It results in early vascular aging together with arterial stiffness. Several cellular and molecular mechanisms can contribute to the development of early aging in CKD patients. Premature vascular aging in CKD patients has been considered as a prognostic marker of mortality and cardiovascular morbidity. Potential therapeutic strategies can target these pathways.

Keywords: CKD, CKD-MBD, inflammation, vascular calcification

INTRODUCTION

Chronic kidney disease (CKD) is characterized by having structurally and/or functionally abnormal kidneys present for more than >having one or more marker of kidney dysfunction such as albuminuria [1, 2]. It is believed that ~15% of the US general population has been impacted by CKD between 2013 and 2016 [2]. CKD is associated with a number of comorbidities and chronic conditions including premature aging [3, 4].

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The aging process can either be physiological or pathological, which is also termed premature aging. Physiological aging is the result of the functional decline of the body and it is influenced by genetic as well as environmental factors such as socioeconomic status, stress, sedentary lifestyle, diet, smoking, and consumption of alcohol and other drugs [5, 6]. On the other hand, premature aging is characterized by accelerated functional decline that results in aging earlier than expected for chronological age [7]. A number of chronic conditions are associated with premature aging characterized by frailty, a diseased vasculature, the development of osteoporosis, and muscle wasting [3, 8]. CKD, which is one of the major conditions associated with premature and accelerated aging, is also related to early vascular aging and the stiffening of the arteries [3, 9]. The premature stiffening of especially the central arteries in CKD patients has been considered as a marker of prognosis for mortality and cardiovascular morbidity and therefore requires further attention [9–13].

In this review, we first describe the underlying mechanisms of early aging in CKD patients. We then elucidate the characteristics of premature vascular aging in CKD and end-stage renal disease (ESRD) and delineate its clinical implications. We finally explain the key molecular pathways and molecules that are critical for the development of aging and vascular aging while discussing the potential therapeutic strategies that can target these molecular structures.

Early aging in chronic kidney disease

The definition of aging can be broadly described as the progressive loss of the functional ability and the physiological functions of the body together with declining fertility and higher mortality over time [8, 14]. It is influenced by genetic, epigenetic, and environmental factors [15]. Older age is associated with a higher prevalence of chronic diseases and many chronic conditions cause early aging [16–20]. One of the conditions associated with premature and accelerated aging is CKD which is characterized by progressive vascular disease and early vascular aging, muscle wasting, osteoporosis, frailty, and systemic inflammation [9, 21]. Oxidative stress, inflammation, an aberrant gut microbiota, advanced glycation end products, and fructose consumption and are all factors contributing to early aging in kidney disease patients (Fig. 1).

Oxidative stress

Oxidative stress is an important mechanism for accelerated aging and muscle wasting in CKD [22]. Oxidative stress in CKD results from intravenous iron treatment, the activation of the renin-angiotensin system (RAAS), decreased antioxidants, and features related with dialysis such as the incompatibility of membranes or fluids [23, 24]. Mitochondrial dysfunction also contributes to oxidative stress in CKD [25, 26]. Protein bound uremic toxins such as p-cresyl sulfate and indole-3-acetic acid are shown to inhibit mitochondrial oxidative phosphorylation in renal proximal tubule epithelial cells by inhibition of succinate dehydrogenase enzyme [27]. Oxidative stress also causes alterations in the molecular structure of proteins, carbohydrates and lipids with ensuing tissue and organ damage.

Cellular senescence, immunosenescence, and inflammaging

The concept of cellular senescence was discovered in the 1960s by demonstrating the loss of replicative potential in human cells [28]. Senescence is characterized by cell cycle arrest in the G1 or G2 phase, apoptosis resistance, and altered gene expression [29]. Cellular senescence is a physiological process in embryonic development and wound healing but can be pathologic leading to aging and disease states [30]. Senescence has been suggested as a major cause of age-related diseases [31]. Cellular senescence can be induced by various stimuli, such as telomere shortening or dysfunction, mitochondrial dysfunction, epigenetic influences, DNA damage, oncogene activation, and inactivation of tumor suppressor genes [32]. Although senescent cells lose their replicative potential, they remain metabolically active. Senescent cells undergo several proinflammatory and pro-fibrotic changes in gene expression and cellular metabolism. This new phenotype is named senescence-associated secretory phenotype (SASP). SASP is characterized by increased expression and secretion of growth factors, cytokines, proteases, and chemokines [33]. These factors signal nearby cells in a paracrine fashion causing paracrine senescence and altering their surrounding environment [34]. SASP can also modulate the immune system with these factors. It can activate the immune system and increase the elimination of senescent cells or promote the persistence and accumulation of senescent cells [35]. With aging, several cells in the kidney, such as renal tubular epithelial cells, podocytes, mesangial cells, immune cells, and endothelial cells, undergo cellular senescence. However, senescence is most notably seen in renal tubular epithelial cells [36]. Renal tubular cell senescence is associated with the changes seen in aged kidneys, including tubular atrophy, interstitial fibrosis, and glomerulosclerosis. Although SASP might benefit tissue regeneration after an acute kidney injury, prolonged SASP exposure has detrimental effects on tissue function and repair, which eventually cause CKD [37]. Furthermore, SASP causes sterile inflammation and contributes progression of CKD by promoting fibrosis in the kidney [36].

Senescence can be associated with immune system dysfunction and dysregulation, changes collectively referred to as immunosenescence and inflammaging, respectively [38]. Immunosenescence is considered harmful because it is associated with low-grade sterile inflammation with decreased cellular responses against infections and vaccines [39]. Changes seen with immunosenescene are influenced by several factors such as genetics, nutrition, exercise, exposure to microorganisms, sex, and human cytomegalovirus status [38]. Inflammaging is characterized by high blood levels of proinflammatory cytokines in older individuals [40]. Inflammaging is associated with an increased risk of chronic diseases including cardiovascular diseases, CKD and dementia. Several factors are postulated as risk factors and causes of inflammaging, such as chronic infections, impaired autophagy and cellular degradation, visceral obesity, genetic susceptibility and altered microbiota, and increased gut permeability [41].

Inflammation and metaflammation

Inflammation results from hyperactive innate immunity, which is characterized by activated macrophages and increased proinflammatory cytokines such as interleukin 6, interleukin 1, and tumor necrosis factor [42]. There are also several changes in the adaptive immunity. Decreases in the number and function of naive T cells and increased numbers of memory T cells, especially proinflammatory $CD4^{+}CD28^{-}$ T cells are evidence of immunosenescence in CKD [43]. Visceral obesity, smoking, low-grade infection, and social and psychosocial stresses are associated with increased expression of inflammatory genes [44].

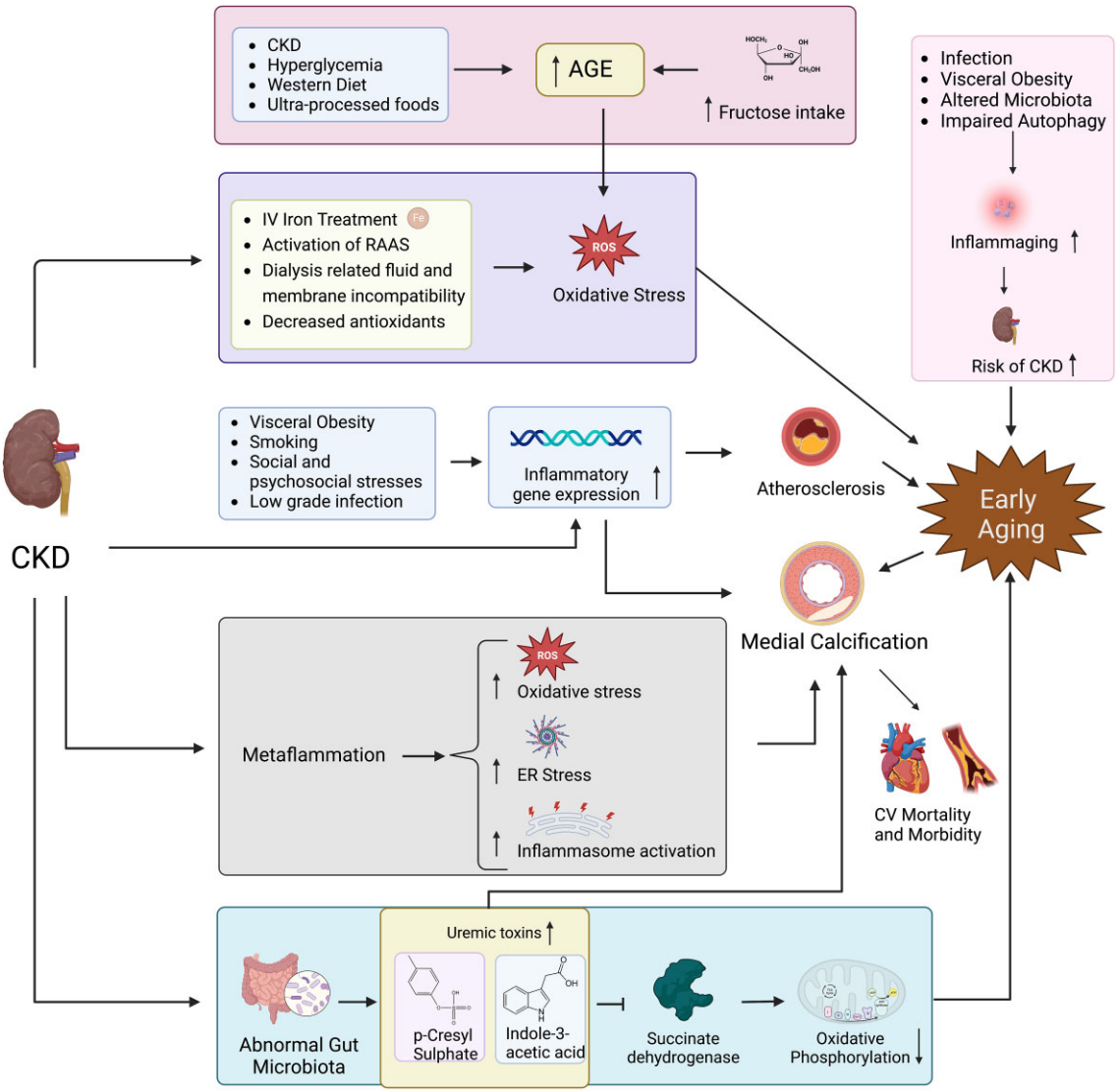

Figure 1: The factors contributing to early aging in CKD. AGE: Advanced glycation end products, CKD: Chronic kidney disease, CV: Cardiovascular, ER: Endoplasmic reticulum, RAAS: Renin-Angiotensin-Aldosterone system, ROS/Oxidative stress.

In addition, overhydration is a common complication in CKD, and it can also contribute to systemic inflammation via bacterial or endotoxin translocation due to severe gut edema [45]. Systemic inflammation leads to muscle wasting in CKD [46]. Proinflammatory cytokines produced by senescent cells with the SASP, activates proteolytic mechanisms, and impair muscle regeneration [29]. Inflammation accelerates atherosclerosis and is an independent risk factor for early medial calcification [47]. Accelerated medial calcification is common among patients with uremia and with other chronic inflammatory disorders [48–53]. Metaflammation is described as a long-term low-grade inflammatory state induced by metabolic variations causing increased reactive oxygen species (ROS), inflammasome activation, and endoplasmic reticulum stress, which is important for cell homeostasis and insulin signaling pathways. Therefore, metaflammation can cause cardiovascular morbidities due to induction of endothelial dysfunction and vascular calcifications [54].

Nutrition and digestion: gut microbiota, advanced glycation end products, and fructose consumption

Patients with CKD and ESRD are at risk of having an abnormal intestinal microbiota, characterized by alterations in saccharolytic bacteria to increases in proteolytic bacteria [55–57]. This change in the microbiota results in the production of several uremic toxin precursors in the intestines such as p-cresol and indole, both subsequently metabolized by the colonic mucosa and the liver to indoxyl sulfate and p-cresyl sulfate resulting in a high toxicity specifically targeting the cardiovascular system [55, 57, 58]. The intestines are also known to modulate the immune system both locally and systemically via complex interactions between the gut microbiota and immune system. Short chain fatty acids, which are metabolites produced in the colon by bacterial fermentation, have modulatory functions on the immune system [59, 60]. In addition, with an impaired gut barrier, intestinal bacteria and endotoxins infiltrate the mucosa and translocate

to the blood stream, circulating to different organs and tissues including the kidney contributing to inflammation [61].

Advanced glycation end products (AGEs) are a group of compounds that are formed by the nonenzymatic glycation of lipids, proteins and DNA. AGEs are not only formed during hyperglycemia, but also in states with high oxidative stress such as in CKD [62]. Furthermore, AGEs can be found in ultra-processed foods. The western diet, which is low in fruits and vegetables and high in animal proteins and processed foods, is a risk factor for CKD [63]. During food processing, high temperatures, dehydration, decompression, salt, irradiation, and preservatives significantly alter the lipids, proteins, and carbohydrates and lead to the formation of AGEs within foods [64]. The kidneys are the primary site of AGE excretion and in chronically diseased kidneys the circulating levels of AGEs increase [65]. Excessive AGEs can contribute to the progression of CKD. AGEs and their receptors including advanced glycation end product-specific receptor (RAGE) trigger oxidative stress and inflammation, in turn potentially contributing to aging [66]. Thus, AGEs are related to cardiovascular complications and progression of renal dysfunction as well as early aging in CKD. Excessive intake of fructose is known to be associated with hypertension, diabetes, and metabolic syndrome, which are risk factors for the development of CKD [67, 68]. In animal studies, fructose induces tubular cell proliferation with low-grade tubulointerstitial injury by the induction of chemoattractant proteins such as monocyte chemoattractant protein-1 from tubular cells and intercellular adhesion molecule-1 in renal microvascular endothelial cells [69, 70]. Long-term fructose consumption was shown to increase AGEs and accelerated aging in an animal study [71].

Premature vascular aging in CKD patients

In addition to accelerated aging, CKD and ESRD have been associated with vascular calcification, premature vascular aging and the stiffening of the arteries [9, 72]. Early vascular aging refers to accelerated age-related changes in arterial structure and function [73]. Early vascular aging is characterized by profound medial vascular calcification, which is primarily driven by vascular smooth muscle cells [47]. Early vascular aging is an intermediate cardiovascular endpoint and independent predictor of cardiovascular disease and cardiovascular mortality [74]. Arterial stiffness, which can be measured with carotid-femoral pulse wave velocity, is a hallmark of early vascular aging and pulse wave velocity has been proposed as a marker of early vascular aging [75]. Characteristically, arterial stiffness is much more evident in the aorta as well as the other central arteries compared to those located in the periphery in this patient group [9, 76]. An increased aortic stiffness can be considered to be a contributor to left ventricular hypertrophy and a fall in the perfusion of the coronary arteries as well as a marker of prognosis for mortality and cardiovascular morbidity with the pulse wave velocity of the aorta being an independent predictor for all-cause and cardiovascular mortality [9–12, 77, 78]. Furthermore, small vessel disease in the cerebral structures has also impacted the development of cognitive impairment in CKD patients [79].

The stiffening of the arteries represents the overall aging of the arterial network [9]. Arterial remodeling and enlargement together with a greater arterial stiffness and early vascular aging are seen in the earlier stages of CKD, in line with the fall in renal function [9, 80]. In addition, one study reported that the stiffening of the aorta was independently related to the rate of change of kidney function in individuals with CKD stages 3 and 4 [81]. The independent predictors of ≥25% decrease in kidney function or initiation of renal replacement therapy were the pulse wave velocity of the aorta, systolic blood pressure, and the urine protein-to-creatinine ratio [81].

There is an important relationship in regard to the pulse wave velocity of the aorta and age, in comparison to the general population: A gradual fall in the difference in the mortality rate occurs with increasing age in patients with ESRD [9]. The pulse wave velocity of the aorta has been reported to predict the cardiovascular and all-cause mortality significantly in younger individuals with ESRD [9]. One study reported that a pulse wave velocity >12 m/s was able to present prognostic value in patients with ESRD younger than 60 years of age, however in older individuals this prognostic information was no longer relevant [82]. A 10 to 30 times greater cardiovascular mortality exists in individuals with ESRD in comparison to the general population and among young patients mortality rates are up to 500 times greater [9, 83].

Overall, early aging of the vasculature and stiffening of the arteries are in close relation to CKD and ESRD. A higher aortic stiffness has been suggested as a prognostic marker and aortic pulse wave velocity has been considered an independent predictor for all-cause and cardiovascular mortality. Given that vascular problems could potentially occur in the initial stages of CKD, clinicians should consider earlier testing of the cardiovascular system in younger or early-stage kidney disease patients to gain information to better understand the prognosis and to direct the treatment strategies of these patients [9]. Furthermore, future large-scale studies are needed to improve our understanding regarding the clinical implications of early aging, premature vascular stiffening and vascular calcification in general in CKD and ESRD patients.

The major molecular pathways associated with aging and vascular aging

Several key molecular pathways and molecules exist that play a role in the development of aging and vascular aging. Potential therapeutic strategies can target these pathways (Fig. 2).

Nuclear factor erythroid 2-related factor 2 (nrf2)

Nuclear factor erythroid 2-related factor 2 (Nrf-2), a basic-leucine-zipper-like transcription factor, is a key regulator of the balance between pro-oxidative or antioxidative defense mechanisms [84]. The major functions of Nrf-2 include the upregulation of the genes encoding for antioxidant or phase II detoxifying enzymes such as NAD(P)H (nicotinamide adenine dinucleotide phosphate) dehydrogenase-1 (NQO1), heme oxygenase-1/2, tryptophan hydroxylase-1 or glutathione-transferase [85]. At basal conditions, the activity of Nrf-2 located at cytosol is suppressed via Kelch-like ECH-associated protein1 (Keap1), which is involved in the ubiquitination and proteasomal degradation of Nrf-2 while oxidative signals result in the nuclear translocation of Nrf-2 [86–88]. Additionally, few Keap-1 independent regulatory mechanisms for Nrf-2 activity have been identified including the activity of glycogen synthase kinase 3β (GSK-3β) and endoplasmic reticulum stress [89, 90]. *In vitro* and *in vivo* studies have demonstrated that over-expression or activation of Nrf-2 result in decline in the expression of proinflammatory cytokines such as the association between over-expression of Nrf-2 at endothelial cells and decreased expression of vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-alpha

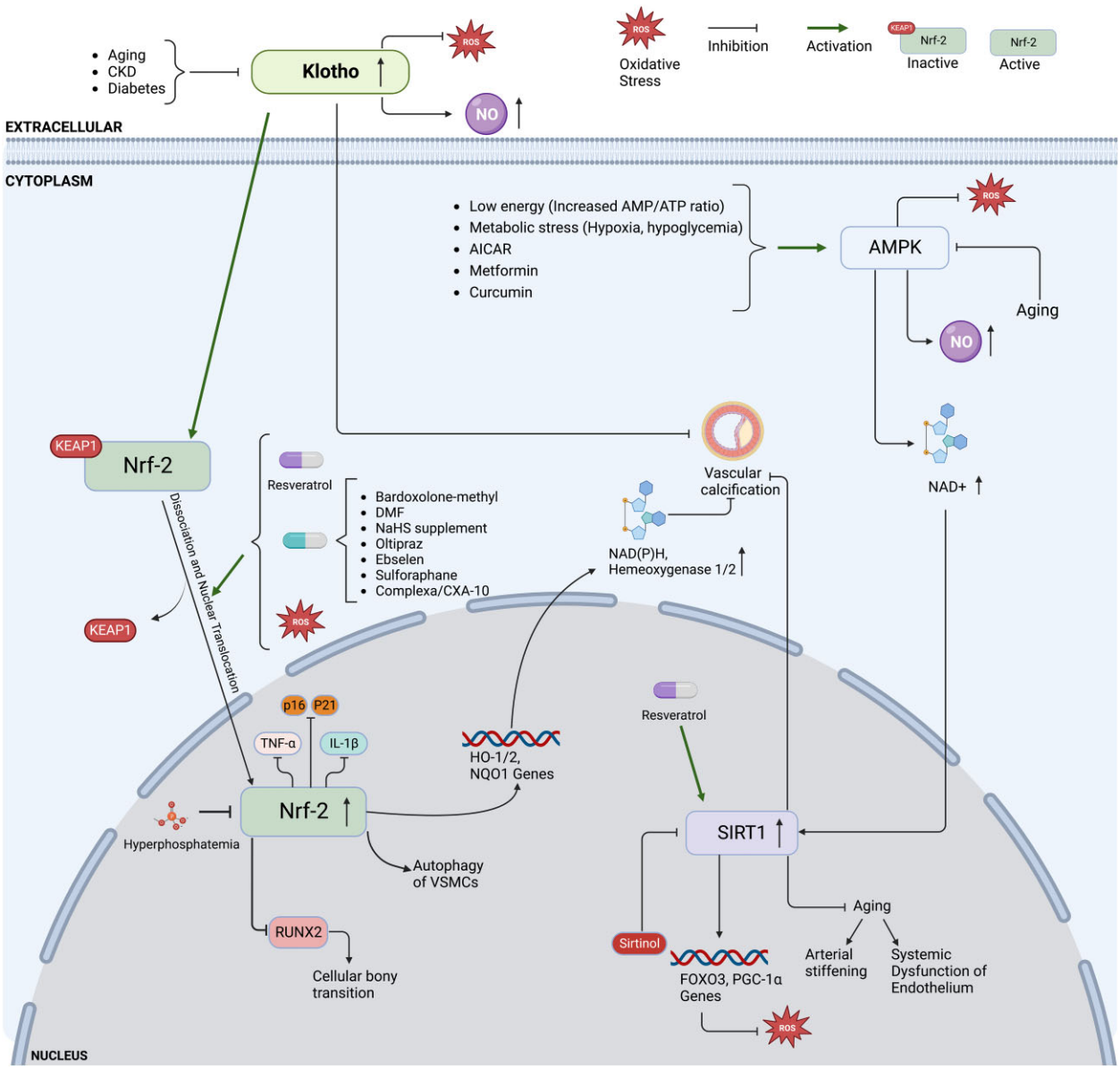

Figure 2: The major molecular pathways associated with aging and vascular aging. KEAP1 maintains Nrf-2 in the inactivated state. Oxidative stress and several medications such as resveratrol activate and translocate Nrf-2 via the dissociation of KEAP1. Activated Nrf-2 upregulates the genes encoding antioxidants such as NQO1 and HO-1/2 that, in turn, inhibit vascular calcification. Hyperphosphatemia suppresses the activity of Nrf-2. Klotho activates Nrf-2 while also increasing NO, decreasing oxidative stress and potentially improving vascular dysfunction. AMPK can be activated via metabolic stress, low energy states, AICAR, metformin, and curcumin. The activity of AMPK decreases in aging resulting in arterial stiffening and endothelial dysfunction. Activated AMPK decreases oxidative stress and elevates NO. AMPK also increases, via NAD^+, SIRT1 activity that plays a role in inhibiting aging and vascular calcification. SIRT1 also has an antioxidant function through the transcription of FOXO3 and PGC-1α. Furthermore, SIRT1 inhibits arterial stiffening and endothelial dysfunction that result from aging. SIRT1 can be activated by resveratrol. AICAR: Aminoimidazole carboxamide ribonucleotide, AMP: Adenosine monophosphate, AMPK: AMP-activated protein kinase, ATP: Adenosine triphosphate, CKD: Chronic Kidney Disease, DMF: Dimethyl fumarate, FOXO3: Forkhead Box O3, HO-1/2: heme oxygenase-1/2, IL-1: Interleukin 1, KEAP1: Kelch-like ECH-associated protein 1, NAD+: Nicotinamide adenine dinucleotide, NaHS: Sodium hydrosulfide, NO: Nitric oxide, NQO1: NAD phosphate) dehydrogenase-1, Nrf-2: Nuclear factor erythroid 2-related factor 2, PGC-1α: Peroxisome proliferator-activated receptor-gamma coactivator-1- alpha, p16(CDKN2A): Cyclin-dependent kinase inhibitor 2A, p21 (CDKN1A): Cyclin-dependent kinase inhibitor 1, ROS/Oxidative stress, RUNX2: Runt-related transcription factor 2, SIRT1: Sirtuin 1, TNF-α: Tumor necrosis factor-α, VSMC: Vascular smooth muscle cell.

(TNF-α) [91–93]. A study in which the effects of T-cell specific augmentation of Nrf-2 on mice are being reviewed has demonstrated that upregulation of Nrf-2 is associated with higher levels of CD25(+) and FOXP3(+) regulatory T cells and lower levels of proinflammatory cytokines such as TNF-α, interferon-gamma (IFN-γ), and interleukin-17, thus, leading to protection from ischemia-reperfusion injury-induced acute kidney injury (AKI) [94]. A study conducted on 2155 patients with stage 1–5 CKD has identified five metabolites for which serum levels are highly linked to the markers of kidney injury. Among those five metabolites, supplementation of cultured human kidney cells with 5-methoxytryptophan (5-MTP) results

in the inhibition of NF-κB signaling and amelioration of renal interstitial fibrosis in response to ischemia-reperfusion injury that is mediated via the upregulation of Nrf-2 signaling pathway [95]. Moreover, studies conducted on rats have illustrated that supplementation with sulforaphane, a Nrf-2 agonist, leads to decline in arsenic-induced nephrotoxicity mediated via decline in the formation of renal ROS and lipid peroxidation products, DNA damage, and increased formation of phase II antioxidant enzymes [96].

Early vascular aging has been linked to vascular stiffening, higher risk for cardiovascular diseases, and cardiovascular mortality while the exact underlying pathophysiological mechanisms are unclear [97]. Along with chronic low-grade inflammation, increased oxidative stress and formation of ROS result in endothelial dysfunction that has been associated with vascular calcification and cellular senescence [98]. *In vitro* and animal studies have shown that supplementation with sodium hydrosulfide, an activator of Nrf-2/Keap-1 signaling system, results in the upregulation of HO-1/2 and NQO1, both of which are antioxidant enzymes, causing the amelioration of vascular calcification [99, 100]. Moreover, Nrf-2 activation leads to the suppression of cellular bony transition mediated via runt-related transcription factor 2 (Runx2) [101]. Hyperphosphatemia among CKD patients have shown to suppress Nrf-2 activity both at transcriptional, translational and post-translational levels while administration of resveratrol, an agonist for Nrf-2, has been linked to decline in the deposition of mineralized matrix at vasculature, decline in mitochondrial damage, and intracellular calcium deposition, therefore reversing the hyperphosphatemia-related vascular alterations [102, 103]. Furthermore, treatment of mice or rat subjects with dimethyl fumarate (DMF), another activator of Nrf-2, has led to significant decline in vascular calcification at aorta and carotid artery even under hypercalcemic and hyperphosphatemic environments [104, 105]. Interestingly, activation of Nrf-2 results in the autophagy of vascular smooth muscle cells to ameliorate vascular calcification through undiscovered pathophysiological mechanisms [106].

The role of Nrf-2 signaling in cellular senescence, a state characterized by cellular growth arrest without losing metabolic activity, has been investigating various cell types including cardiac muscle cells, vascular endothelial cells, and epithelial tissues [107–109]. Studies conducted on Nrf-2 knockout mice have illustrated that Nrf-2 depletion results in the upregulation of cellular senescence markers such as cyclin-dependent kinase inhibitor 2A (p16INK4a, CDKN2A) and cyclin-dependent kinase inhibitor 1 (p21, CDKN1A), increased production of proinflammatory cytokines involved in the process such as interleukin-1beta (IL-1β) and TNF [110]. The underlying mechanism is not clear, nevertheless, one hypothesis includes the downregulation of Nrf-2 via miRNAs derived from senescent cells such as miR-126, miR-21, and miR-100 [111]. Moreover, a study conducted by Stenvinkel *et al.* on patients with living donor kidney transplantation showed that expression of cyclin-dependent kinase inhibitor 2A (p16INK4a, CDKN2A) is also related to the severity of vascular calcification in ESRD [112].

Despite its central role in the physiology of cellular senescence, vascular calcification, and vascular aging, the efficiency of treatment strategies targeting Nrf-2 is not well established. A phase I human clinical trial investigating the role of once daily administration of bardoxolone-methyl, a Nrf-2 agonist, on 47 patients with advanced stage solid organ tumors or lymphoma demonstrated potential beneficial effects with few dose-limiting adverse effects, mainly being hepatotoxicity, while upregulation of Nrf-2 is mediated via upregulation of NQO1 mRNA levels [113]. Moreover, another Nrf-2 agonist referred as DMF is currently at phase III for the treatment of multiple sclerosis [114]. Furthermore, there are multiple ongoing clinical trials investigating the clinical utility of various Nrf-2 activators such as DMF (NCT02784834, NCT02546440, NCT00810836), bardoxolone-methyl (NCT00550849, NCT00811889, NCT01351675), oltipraz (NCT00006457, NCT02068339), sulforaphane (NCT01008826, NCT02880462, NCT02801448, NCT03220542), sulforadex (NCT01228084), ebselen (NCT03013400), and complexa/CXA-10 (NCT02248051, NCT03449524, NCT03422510). Despite promising initial results from early phase clinical trials, there is clear need for future studies investigating the effects of Nrf-2 agonists on vascular calcification, malignancies, and vascular aging.

AMP-activated protein kinase (AMPK)-sirtuin 1 (SIRT1)

AMP-activated protein kinase (AMPK) and Sirtuin 1 (SIRT1) are both associated with vascular aging and age-related kidney damage [115–118]. AMPK and SIRT1 are closely linked, characterized by AMPK-deficient states causing an improper activation of SIRT1 and its downstream pathways in reduced energy states [116–118]. AMPK elevates SIRT1 activity by rising NAD^+ levels in the cell and therefore regulates the downstream SIRT1 signaling molecules such as forkhead box O3 (FOXO3) and peroxisome proliferator-activated receptor-γ coactivator 1 (PGC1 or PPARGC1A), which also act as potential substrates for AMPK [119–122].

AMPK is a serine-threonine kinase that, through the serine-threonine liver kinase B1 (LKB1)-AMPK pathway, is activated via metabolic stresses that block ATP generation such as hypoxia and hypoglycemia or increase ATP use such as the contraction of muscles [123]. AMPK can also be activated by metformin and aminoimidazole carboxamide ribonucleotide (AICAR) [118, 124]. AMPK, which is crucial in energy-sensing, also plays an important role in energy balance, stress resistance, and metabolism [118, 123].

Lesniewski *et al.* showed that exercise decreased oxidative stress and elevated nitric oxide bioavailability leading to the restoration of endothelium-dependent dilation (EDD) in old mice and that AMPK once active showed similar effects to exercise [125]. In comparison to younger controls of 3–6 months of age, older mice (28–30 months) had decreased arterial AMPK levels and suppression of EDD by superoxides [125]. AMPK activated by AICAR resulted in an elevation of arterial AMPK and reversal of the impaired EDD [125]. Similarly, one study showed that AMPK activity was reported to be decreased in the cerebral arteries of aged rodents and the administration of curcumin ameliorated aging associated cerebrovascular dysfunction through the AMPK/uncoupling protein 2 (UCP2) pathway [126]. Furthermore, activating AMPK by using metformin has been suggested to increase endothelial function in rodents with type 1 and 2 diabetes [118, 127, 128]. In addition, one clinical study reported that short-term metformin use ameliorated arterial stiffness and endothelial function in young women with PCOS, suggesting the activation of AMPK via metformin a key underlying mechanism explaining these results [129]. Several trials (NCT03309007, NCT01765946) have investigated the effect of metformin on anti-aging through AMPK signaling. Kreutzenberg *et al.* (NCT01765946) have reported that prediabetic individuals had improved effector pathways known regulate longevity in animal models following metformin therapy [130].

These findings suggest that AMPK signaling is a crucial pathway related to aging and vascular aging. Future preclinical and large-scale clinical studies are needed to better understand the

role of AMPK and to guide therapeutic strategies through this pathway.

SIRT1 plays an important role in longevity and is responsible for the deacetylation of histone and non-histone proteins for the modification of transcription factors, coregulators, and proteins to adjust gene expression in accordance with the current energy state of the cell and to resist stress by tempering proinflammatory and oxidative stress pathways [118, 131–134]. SIRT1 activity has been shown to decrease oxidative stress, proapoptotic pathways, and inflammation, and improve telomere stabilization, DNA repair pathways, and insulin sensitivity [118, 135]. SIRT1 is known to inhibit renal inflammation, fibrosis, and renal cell apoptosis [136]. Decreased levels of SIRT1 aggregate renal fibrosis, a characteristic feature in CKD [137]. Several animal studies investigated mechanisms of SIRT1-related renal fibrosis, including decreased matrix metalloproteinase 14 expression and disinhibition of profibrotic TGF-β1 [138, 139]. The role of SIRTs in the pathogenesis of kidney diseases is nicely summarized previously in a comprehensive review [140].

Studies have postulated that decreased SIRT1 may be critical in the development of a dysfunctional vascular endothelium associated with aging [141–144]. An increased production of SIRT1 in endothelial cells contribute to the prevention of systemic dysfunction of the endothelium and a heightened stiffening of large arteries, both changes related to aging [145–147]. Furthermore, a study with endothelial SIRT1-deleted mouse found that SIRT1 deletion is associated with accelerated senescence of endothelial cells with impaired endothelial dependent vasodilation [148]. Endothelial senescence can explain endothelial dysfunction. Although endothelial senescence shows similar features to other types of senescence, it also shows some unique features [149]. A unique feature of endothelial SASP is its role in arterial dysfunction, including increased levels of ROS and reduced nitric oxide levels [116]. In one study, Donato *et al.* showed that in older (30 months) mice aortic protein expression of SIRT1 was significantly decreased compared to younger mice (5–7 months) and acetylcholine induced peak EDD was significantly inferior in isolated femoral arteries with aging [141]. The application of SIRT1 inhibitor sirtinol led to a decreased EDD in both young and old mice [141]. Furthermore, SIRT1 is shown to be a potential inhibitor of vascular calcification with reduced SIRT1 being associated with vascular calcification development and activated SIRT1 resulting in decreased vascular calcification [136, 150–153]. These studies suggest that SIRT1 is an important molecule in vascular dysfunction and aging and could potentially give rise to therapeutic strategies to combat this condition.

Several compounds have been investigated to evaluate the effect of SIRT1 activation on vascular dysfunction, and among these the best studied molecule is resveratrol. This molecule acts as an activator of SIRT1 as well as functions through $\leq$15 other pathways including as an agonist of Nrf-2 together with antioxidant and phytoestrogen effects [102, 118, 154–157]. One study has shown that resveratrol administered to older aged mice had a significant decrease in markers of aging such as lower albuminuria, inflammation, apoptosis in the endothelium of vessels and an elevated elasticity in the aorta, improved motor coordination, decreased cataracts, and a preservation of bone density [158]. However, this study could not detect a prolonged lifespan in mice treated with resveratrol [158].

As of January 2022, there were a total of 194 listed trials on resveratrol on https://clinicaltrials.gov. Among these, 18 studies have investigated the effects of resveratrol on vascular conditions (NCT01842399, NCT01668836, NCT03597568, NCT01564381, NCT02246660, NCT02690064, NCT03436992, NCT04633551, NCT03743636, NCT04449198, NCT01881347, NCT03762096, NCT02998918, NCT01185067, NCT02137421, NCT03253913, NCT05093244, NCT04117022). One study assessed the role of caloric restriction and resveratrol on the sirtuin system in women and men between 55 and 65 years of age (NCT01668836) [159]. This study was conducted on 48 healthy subjects randomized to 30 days of resveratrol (500 mg/day) or caloric restriction (1000 cal/day) [159]. Both resveratrol and caloric restriction led to an elevated plasma levels of SIRT with no difference between the two groups, however, plasma levels for an endogenous secretory receptor for an advanced glycation end product (esRAGE) were not changed and was similar for both groups [159]. SIRT1 and esRAGE are associated with the protection of the vasculature [159]. These results indicate that an increase in both molecules occur following resveratrol administration, which can potentially have a protective effect on vascular dysfunction; future studies are needed to investigate this condition.

Overall SIRT1 is a crucial molecule in the prevention of vascular dysfunction that can be targeted as a therapeutic strategy and resveratrol is a promising agent which functions by acting on SIRT1. Future large-scale clinical studies with long follow-up times as well as preclinical studies to understand the pathophysiologic mechanisms underlying this molecule are needed.

Phosphate and klotho

Hyperphosphatemia has a crucial role in early aging in patients with CKD. As clearance decreases in CKD, increased levels of inorganic phosphate can cause vascular aging and inflammation [160]. In addition, hyperphosphatemia could precipitate oxidative stress [161]. The activation of osteogenic genes, the production of hydroxyapatite, and vascular calcifications have all been linked to high phosphate levels. Owing to their sensitivity to inorganic phosphate concentrations, vascular smooth muscle cells can alter and adjust some of their functions. These modifications in response to changes in inorganic phosphate trigger calcification-promoting processes [162].

Klotho exists as a membrane-bound and soluble form. The soluble form can act as a hormone and regulate glycosidase and transporter actions whereas the membrane-bound klotho plays a role in FGFR signaling [163]. Low klotho levels are correlated with kidney dysfunction, increased risk of atherosclerosis, and accelerated aging [164]. Klotho deficiency is one of the markers of early aging and an important contributor of vascular calcification leading to the hyperplasia of the intimal layer, calcification of the media, endothelial dysfunction, an increased stiffness within the arteries, hypertension, and impairments in vasculogenesis [165–168].

In one of the earliest studies investigating the role of klotho in the aging process, Kuro-o *et al.* showed that a defective expression of the klotho gene led to a phenotype similar to human aging in mice, which consisted of a decreased lifespan, arteriosclerosis, osteoporosis, infertility, emphysema, and atrophied skin [169]. Later studies reported that the over-expression of klotho led to a prolonged life span, provided protective cardiac effects, and decreased oxidative stress in mice [118, 170–172]. Futhermore, klotho concentrations are reported to fall with increasing age in humans with a decrease in klotho levels by 2-fold from 40 to 70 years of age [173, 174]. Klotho levels are also known to decline in several frequently seen diseases such as CKD, diabetes, and neurodegenerative conditions [175].

Table 1: The: current knowns and unknowns surrounding early aging and premature vascular aging.

Knowns	
Oxidative stress due to uremic toxins, activated RAAS, and decreased antioxidants cause muscle wasting and early aging.	Cellular senescence, immunosenescence, and inflammaging cause sterile inflammation, aggravating kidney damage.
Visceral obesity, smoking, low-grade infection, and social and psychosocial stresses are associated with increased expression of inflammatory genes.	Metainflammation contributes to cardiovascular morbidities through endothelial dysfunction and vascular calcifications.
Altered gut microbiota and impaired gut barrier contribute to systemic inflammation.	AGEs and high fructose diet are both risk factors and drivers of the progression of CKD and early aging.
Early vascular aging in CKD causes arterial remodeling, increased arterial stiffness, cardiovascular morbidity, and mortality.	Aortic stiffness is suggested as a prognostic marker, and aortic pulse wave velocity has been considered an independent predictor for all-cause and cardiovascular mortality.
Nrf-2 reduces oxidative stress, renal interstitial fibrosis, and vascular calcification in CKD through several mechanisms.	AMPK and SIRT1 are closely linked signaling proteins protective against vascular calcification and are related to longevity.
Klotho is a signaling protein with two forms: the free form in the cytosol and the membrane-bound form. Klotho levels correlate with kidney function, and its deficiency significantly contributes to vascular calcification in CKD.	
Unknowns	
Nrf-2 depletion results in the upregulation of cellular senescence markers such as p16INK4a (CDKN2A) and p21 (CDKN1A). However, the underlying mechanisms are not clear.	Nrf-2 stimulates the autophagy of vascular smooth muscle cells to ameliorate vascular calcification through undiscovered pathophysiological mechanisms.
Future preclinical and large-scale clinical studies are needed to understand the role of AMPK to better guide therapeutic strategies through this pathway.	Resveratrol is a promising agent acting on SIRT1, Nrf-2 as well as several other pathways. Future large-scale clinical studies with long follow-up times and preclinical studies are needed to understand the pathophysiologic mechanisms underlying this molecule.
Recombinant klotho and gene therapy strategies are promising approaches. However, further studies are required to evaluate these therapeutic mechanisms better and transition their use toward the clinics.	

AGE: Advanced glycation end products, AMPK: AMP-activated protein kinase
CKD: Chronic kidney disease, Nrf-2: Nuclear factor erythroid 2-related factor 2, p16INK4a (CDKN2A): Cyclin-dependent kinase inhibitor 2A, p21 (CDKN1A): Cyclin-dependent kinase inhibitor 1, RAAS: Renin-Angiotensin-Aldosterone system, SIRT1: Sirtuin 1

Klotho has also been shown to play a role in vascular changes. One study reported that serum klotho concentrations were lowered by ∼45% in individuals with arterial stiffness and hypertension [176]. Furthermore, klotho-haplodeficient (Klotho+/−) mice demonstrated significant elevations in in pulse wave velocity and blood pressure suggesting worsening arterial stiffness and hypertension [176]. Klotho-haplodeficiency (Klotho+/−) was also shown to decrease endothelial nitric oxide synthase (eNOS) expression in the aorta as well as lead to impairments in the endothelial functions in the resistance arteries and the aorta in mice [118, 176, 177]. Increasing klotho has been associated with improving the antioxidant protective defensive mechanisms in rats and mice, thus potentially contributing to the ameliorations in endothelial function [118, 178]. In addition, in Otsuka Long–Evans Tokshuma fatty rats that embark important risk factors associated with atherosclerosis such as obesity, hyperglycemia, hypertriglyceridemia, and hypertension, adenovirus-mediated klotho gene delivery was reported to improve the dysfunction of the vascular endothelium, elevate the production of nitric oxide, decrease heightened blood pressures, and contribute to the prevention of medial hypertrophy and perivascular fibrosis [179]. Of note, the blood pressure effects of klotho gene delivery have not been reliable and consistent throughout the literature [118, 178].

A few reviews have also emphasized the interactions and the interdependency between klotho and the mTOR, AMPK, and SIRT1 pathways as they all play a part in vascular aging [116, 118]. Furthermore, Klotho was reported to be an activator of Nrf2 in several preclinical studies [175, 180–183]. This activation potentially contributes to the prevention of kidney and vascular diseases [175].

Given the potential detrimental effects associated with low klotho, an important therapeutic goal would be to reverse this situation and increase its levels. Several studies have shown that a safe target would be to revert klotho back within or near normal values instead of increasing its levels more than the normal range [175]. It is also worth mentioning that the majority of information regarding the therapies surrounding klotho were derived from rodent-based studies [175].

In a recent review, Prud'homme *et al.* summarized the current clinical drugs and those under development as well as the supplements and several other therapeutic mechanisms that increase klotho levels [175]. Among the currently available medications, RAAS inhibitors (losartan, valsartan), statins (atorvastatin, pitavastatin, simvastatin fluvastatin), peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists (rosiglitazone, ciglitazone, pioglitazone), mechanistic target of rapamycin (mTOR) inhibitors (rapamycin, everolimus), vitamin D, glucagon-like peptide-1 (GLP-1) receptor agonist

(exendin-4) and dipeptidyl peptidase-4 (DPP-4) inhibitors (linagliptin, sitagliptin, vildagliptin), metformin, pentoxifylline, antiplasmodial (dihydroartemisinin), and endothelin-1 receptor antagonist (Atrasentan) have all been shown to elevate klotho in a variety of conditions in different studies [175]. Moreover, a recent study investigated the cardiorenal protective role of sodium glucose co-transporter-2 inhibitors (SGLT2i) in patients with diabetic kidney disease. The group receiving SGLT2i had statistically increased serum klotho levels. The same study also found that SGLT2i prevented klotho decrease due to high glucose concentrations in cultured proximal tubular cells [184].

Future large-scale studies are needed to better understand the role of these drugs on klotho and how the potential increase of this molecule contributes to the clinical effects of these drugs. Among the available experimental therapies, recombinant klotho and gene therapy strategies are promising approaches [175]. However further studies are required to better evaluate these therapeutic mechanisms and transition their use toward the clinics.

CONCLUSION

CKD is an important cause of premature, accelerated aging and can result in early vascular aging together with the stiffening of the arteries. The current knowns and unknowns surrounding early aging and premature vascular aging are summarized in Table 1.

Several underlying mechanisms such as oxidative stress, inflammation, advanced glycation end products, fructose, and an aberrant gut microbiota can contribute to the development of early aging in CKD patients. Premature vascular aging in CKD patients has been considered as a prognostic marker of mortality and cardiovascular morbidity. There are several key molecular pathways and molecules that play a role aging and vascular aging. Potential therapeutic strategies can target these pathways. Future studies are needed to better understand the importance of premature aging and early vascular aging to develop therapeutic alternatives for these conditions.

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This article does not contain any studies with human participants or animals performed by any of the authors.

AUTHORS' CONTRIBUTIONS

- Contributed substantially to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: Cem Tanriover, Sidar Copur, Mehmet Kanbay, Ali Mutlu, Ibrahim Batuhan Peltek.
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