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Review article

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Pathological mechanisms of kidney disease in ageing

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Abstract

The kidney is a metabolically active organ that requires energy to drive processes such as tubular reabsorption and secretion, and shows a decline in function with advancing age. Various molecular mechanisms, including genomic instability, telomere attrition, inflammation, autophagy, mitochondrial function, and changes to the sirtuin and Klotho signalling pathways, are recognized regulators of individual lifespan and pivotal factors that govern kidney ageing. Thus, mechanisms that contribute to ageing not only dictate renal outcomes but also exert a substantial influence over life expectancy. Conversely, kidney dysfunction, in the context of chronic kidney disease (CKD), precipitates an expedited ageing trajectory in individuals, leading to premature ageing and a disconnect between biological and chronological age. As CKD advances, age-related manifestations such as frailty become increasingly conspicuous. Hence, the pursuit of healthy ageing necessitates not only the management of age-related complications but also a comprehensive understanding of the processes and markers that underlie systemic ageing. Here, we examine the hallmarks of ageing, focusing on the mechanisms by which they affect kidney health and contribute to premature organ ageing. We also review diagnostic methodologies and interventions for premature ageing, with special consideration given to the potential of emerging therapeutic avenues to target age-related kidney diseases.

Sections

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Key points

- The kidney is a metabolically active organ that requires energy for processes such as tubular reabsorption and secretion; however, kidney function declines with age.
- Various molecular mechanisms, including cellular senescence, inflammation, mitochondrial function, changes to the sirtuin and Klotho signalling pathways, and the autophagy–lysosome system, are recognized as regulators of individual lifespan and are important factors that govern kidney ageing.
- Chronic kidney disease (CKD) and premature ageing share several common features and pathophysiological mechanisms; CKD is therefore considered a disease associated with accelerated or premature ageing.
- The accelerated ageing phenotype of the kidney in the context of CKD results in a disconnect between the biological age of the kidney and the chronological age of the individual, known as the 'age gap'.
- Emerging technologies and biomarkers hold promise for improving the early detection, diagnosis and management of age-related kidney diseases and premature ageing.
- Targeting the pathways associated with inflammation, mitochondrial function, oxidative stress, senescence and the autophagy–lysosome system holds promise for developing therapeutic interventions to prevent, delay or attenuate age-related kidney diseases and promote healthy ageing.

Introduction

Human life expectancy has increased consistently due to advances in health care. The prevalence of age-related conditions and the average age of patients receiving medical care has risen concurrently — a trend that is particularly conspicuous in nephrology. Multiple studies have shown that the ageing process markedly amplifies the risk of acute kidney injury (AKI) and chronic kidney disease (CKD), thereby imposing substantial burdens on society and the economy[1–3]. This heightened risk is clinically relevant, and implies a predisposition to unfavourable renal outcomes with age; however, the precise mechanisms underlying kidney dysfunction in older individuals remain unknown.

Over a decade ago, researchers described nine hallmarks of ageing, including: genomic instability, telomere attrition, epigenetic modifications, disruption of proteostasis, dysregulated nutrient sensing, cellular senescence, stem cell exhaustion, altered intracellular communication and mitochondrial dysfunction[4]. More recently, the hallmarks of ageing were updated to include disabled macroautophagy (hereafter referred to as autophagy), chronic inflammation and dysbiosis[5]. These hallmarks represent key biological processes that underlie the ageing process and are often implicated in age-related diseases, including CKD. Although not all hallmarks may directly contribute to every aspect of CKD, several connections exist between these hallmarks and the development of kidney disease with age. For example, mitochondrial dysfunction and chronic inflammation are well-recognized hallmarks of kidney ageing. Autophagy, which maintains intracellular homeostasis by degrading cellular components in lysosomes[6], exerts a protective effect against various kidney pathologies[7,8]. Emerging evidence indicates that autophagic activity declines with age and that upregulation of autophagy delays the ageing process[9,10].

Conversely, ageing of the kidney in itself accelerates systemic ageing[11]. New findings have revealed that CKD is an important risk factor for the progressive ageing of other organ systems, such as the brain and heart[12]. These findings highlight the need to separately consider biological and chronological age, and underscore the potential systemic benefits that might be achieved through the use of interventions that target kidney ageing.

These insights highlight the need to comprehensively understand the underlying pathological mechanisms and the intricate interplay between ageing and kidney diseases. In this Review, we describe hallmarks of ageing that are relevant to age-related kidney diseases, and the pathological mechanisms of CKD in the context of premature ageing. Finally, we explore diagnostic approaches and effective interventions for premature ageing, focusing on the potential to target the hallmarks of ageing to promote healthy ageing and prevent age-related kidney diseases.

Pathological drivers of kidney ageing

Kidney ageing is a complex process characterized by structural and functional changes that occur with advancing age[13]. The ageing process is associated with a gradual loss of nephrons, leading to reduced renal mass. A progressive decline in renal blood flow and vascular function is associated with alterations in the structure and function of the renal microvasculature. These alterations are highly age-dependent and affect the development and progression of kidney disease. Consequently, older age is an important risk factor for CKD[1,14,15].

Within the glomerulus, ageing is associated with thickening of the glomerular basement membrane (GBM) and expansion of the mesangial compartment, which leads to glomerular enlargement and hyperfiltration. These changes, coupled with an accumulation of extracellular matrix contribute to progressive glomerulosclerosis[16], which can lead to a subsequent decline in glomerular filtration rate (GFR)[17]. Age-related changes in the glomerular vasculature, particularly in juxtamedullary glomeruli, can result in the formation of an arteriovenous shunt between afferent and efferent arterioles, which may impair osmotic gradient formation and reduce the urine-concentrating ability of the kidney[18].

To compensate for reduced GFR, glomeruli undergo further hypertrophy. However, studies in mice have shown that the number and density of podocytes — which act to maintain and support the GBM — decrease with age[16]. The density of parietal epithelial cells (PECs) also decreases in aged mice; however, the proportion of CD44-positive, activated PECs is increased in aged kidneys. These activated PECs colocalize to phosphorylated ERK and are associated with elevated extracellular matrix proteins, suggesting PEC transformation via epithelial-to-mesenchymal transition. These findings suggest that ageing induces important alterations in PECs, reducing their regenerative capacity and inducing characteristics of pericytes and mesenchymal fibroblasts, which may contribute to glomerulosclerosis[16].

Chronic hypoxia is another important factor that can contribute to kidney injury and influences several pathogenic pathways that can lead to kidney failure[19,20]. The complex microvasculature and high oxygen demands of the kidneys renders them particularly susceptible to hypoxic injury. With ageing, rarefaction of peritubular capillaries, increased oxygen demand by proximal tubule epithelial cells (PTECs) and anaemia can aggravate hypoxia, in turn exacerbating the risk of kidney injury[19,20].

Hypoxia triggers adaptive responses in the kidney, including the activation of hypoxia-inducible factors (HIFs), which regulate genes involved in angiogenesis, erythropoiesis, metabolism and cell survival. These adaptive responses might initially be protective, but hypoxia-induced expression of HIF1α in the aged kidney can lead to maladaptive changes and exacerbate CKD progression via the induction of oxidative stress, tubulointerstitial injury and inflammation[20,21]. Conversely, the NAD-dependent histone deacetylase, sirtuin 1 (SIRT1), can mediate a range of cellular responses, some of which are achieved through the deacetylation of lysine residues on HIF1α[21–23]. Decreased expression of SIRT1 in the kidneys of aged mice is associated with a decrease in stress-induced autophagy in response to hypoxia[22,24]. SIRT1 also activates the transcription factor FOXO3a via its deacetylase activity, which induces the transcription of *Bnip3* — a gene involved in mitophagy[25]. In aged mice, decreased SIRT1 mRNA and protein expression in the kidney is associated with an accumulation of abnormal mitochondria[24]. SIRT1 also seems to be important for podocyte morphology and function. Podocyte-specific deletion of *Sirt1* in mice exacerbates age-related glomerulosclerosis and albuminuria, which is accompanied by increased oxidative stress and impaired podocyte maturation[26].

Kidney fibrosis is another important and common manifestation of progressive kidney diseases. Studies from the past few years have identified reductions in basement membrane components, such as laminins, type IV collagen and type XVIII collagen, and increases in interstitial matrix proteins such as collagens I, III, VI and XV, fibrinogens, and nephronectin as a common signature in kidney ageing and disease[27]. Transforming growth factor-β (TGFβ) has an important role in the pathogenesis of fibrosis by upregulating matrix protein synthesis, inhibiting matrix degradation, and altering cell–cell interactions[28], although therapeutic targeting of TGFβ has met with limited success.

Hallmarks of kidney ageing

Growing evidence supports the notion that the above-described pathological drivers of kidney ageing interact bidirectionally with several of the so-called hallmarks of ageing (Fig. 1).

Primary hallmarks and cellular senescence

Genomic instability, telomere attrition and epigenetic alterations. Genomic instability, telomere attrition and epigenetic alterations are categorized as 'primary' hallmarks of ageing, defined as hallmarks that progressively accumulate with time and unambiguously contribute to the ageing process[5]. Genomic instability is associated with an increased risk of DNA damage and mutations over time, resulting in an accumulation of genomic damage with ageing[29]. DNA damage can trigger inflammatory responses and cell death pathways in the kidneys, contributing to CKD progression[30]. In men, age-related mosaic loss of the Y chromosome (mLOY) is associated with various pathologies. Use of single-cell RNA and assay for transposase-accessible chromatin (ATAC) sequencing in human kidneys revealed that mLOY varies by nephron location, with PTECs being most affected[31]. As described above, PTECs are particularly vulnerable to hypoxic injury, which can trigger cell dedifferentiation and may render them particularly susceptible to mLOY[31].

Telomeres are protective caps at the ends of chromosomes that shorten with each cell division. Telomere shortening can trigger cellular senescence. It has been observed in aged kidneys and is associated with various degenerative and age-related diseases, including CKD[32,33]. Notably, telomere shortening is linked to inflammation, low fetuin-A levels and high mortality in patients undergoing prevalent haemodialysis[34]. Dysregulation of epigenetic mechanisms has also been implicated in the development and progression of CKD. For instance, altered DNA methylation patterns have been observed in kidney cells from individuals with CKD, which affect the expression of genes involved in kidney function and fibrosis[35].

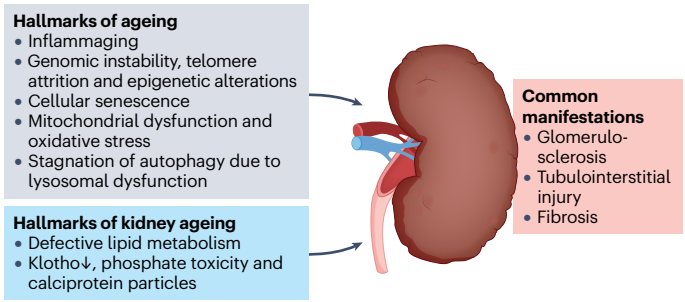

Fig. 1 | The hallmarks of kidney ageing. Several hallmarks of ageing have been linked to pathogenic processes underlying the development of kidney disease. These hallmarks, along with other processes, lead to manifestations that commonly present in patients with chronic kidney disease, including glomerulosclerosis, tubulointerstitial injury and fibrosis, and can therefore be considered hallmarks of kidney ageing.

Cellular senescence. Cellular senescence refers to a state of irreversible cell cycle arrest that can arise in response to various stressors including DNA damage and telomere shortening. It is categorized as an 'antagonistic' hallmark of ageing, which means that it reflects responses to damage and has a more nuanced role in the ageing process. Cellular senescence increases with age[36], and has been implicated in kidney ageing[37–39], in part through the release of pro-inflammatory cytokines and the propagation of inflammation via the manifestation of a senescence-associated secretory phenotype (SASP). Ageing-associated impairment of immune function may allow senescent cells to escape immune clearance. In a model of chronic ischaemia, maladaptive tubular cell senescence, characterized by the upregulation of p16, p19 and p21 expression, was associated with kidney dysfunction and injury[40]. Podocyte senescence also has a central role in kidney ageing. For example, podocyte-specific deletion of CAAT enhancer-binding protein-α (C/EBPα) in aged mice exacerbates podocyte senescence, leading to glomerulosclerosis. Moreover, the ensuing albuminuria induces PTEC senescence[41]. A 2022 study also found that age-related overexpression and hyperactivation of glycogen synthase kinase 3 (GSK3β) drives podocyte senescence by inducing mediators of senescence signalling, such as p16 and p53 (ref. 42). Another study revealed a key role for the immune checkpoint protein, PD1, in podocyte ageing and in SASP induction. Overexpression of PD1 in the podocytes of aged mice correlated with reduced GFR and with increased glomerulosclerosis and in the vascular arterial intima-to-lumen ratio. Blocking of PD1 signalling with a neutralizing anti-PD1 antibody reduced podocyte senescence and inflammatory signalling and was associated with increased podocyte lifespan[43]. These studies highlight the importance of senescent podocytes and PTECs as potential targets in kidney ageing.

The removal of senescent cells through senolysis may ameliorate age-related pathologies[36,39,44]. Indeed, studies in transgenic mouse models show that the removal of senescent cells can prevent or delay tissue dysfunction and extend healthspan[45,46]. Targeted elimination of senescent cells by small-molecule senolytic drugs, by disrupting key senescent events through the administration of

senomorphic agents, or through the inhibition of processes that promote the accumulation of senescent cells, might therefore represent promising therapeutic strategies for preventing or treating age-related diseases[36,47,48]. For example, inhibition of glutaminolysis may represent one approach to target senescent cells. Glutaminase is induced in response to a reduction in the pH of senescent cells following damage to lysosomal membranes. The resulting glutaminolysis induces ammonia production, which neutralizes the pH and aids the survival of senescent cells. By contrast, inhibition of glutaminolysis in aged mice specifically eliminated senescent cells and ameliorated age-related dysfunction and fibrosis of the kidney[49].

Inflammaging

Chronic low-grade inflammation is considered to be an integrative hallmark of ageing, defined as a feature that arises when the accumulated damage inflicted by the primary and antagonistic hallmarks can no longer be compensated for. Ageing affects the composition and function of the immune system, leading to immunosenescence, which is characterized by defective immune responses and increased systemic inflammation (also known as inflammaging)[50]. This maladaptive phenomenon results from various mechanisms, including aberrant inflammasome activation, microbial dysbiosis, the accumulation of senescent cells and primary dysregulation of immune cells[51,52].

Various mediators promote chronic inflammation in CKD, including oxidative stress and the adoption of a pro-inflammatory phenotype by resident kidney cells. The regulation of pro-inflammatory and anti-inflammatory mediators through gene transcription mediated by NF-κB and nuclear factor erythroid 2-like 2 (NRF2), respectively, also has a critical role in the glomerular and tubular cell response to kidney injury[53]. NRF2 protects against AKI and progression to CKD[54,55], and decreased NRF2 expression in aged kidneys may in part underlie the susceptibility of aged kidneys to injury and incomplete recovery after ischaemia–reperfusion injury[56]. Interestingly, one study that integrated GFR-associated loci with transcriptional data developed a molecular map of CKD, which revealed that all pathways aggregated into two main clusters that comprised inflammation-related and metabolism-related pathways, with the NRF2-mediated oxidative stress response pathway serving as a hub between the two clusters[57].

Inflammasome activation is another pivotal mechanism that contributes to inflammaging. Nod-like receptor 3 (NLRP3) can be activated by many danger signals, including reactive oxygen species (ROS), cathepsin released from destabilized lysosomes and aggregated proteins, all of which evoke cellular stress and are involved in the ageing process[58]. Chronic activation of the NLRP3 inflammasome induces the persistent production of pro-inflammatory cytokines such as IL-1β and IL-18, creating a feedback loop of inflammation and tissue damage that accelerates the ageing process[59]. Transcriptomic analyses have revealed that the podocytes of aged mice demonstrate an inflammatory phenotype, characterized by increased levels of the NLRP3 inflammasome, IL-6, TNF and IFNγ. NLRP3 signalling in podocytes is further increased in aged mice following the experimental induction of focal segmental glomerulosclerosis. In human glomeruli, higher expression of NLRP3 is associated with reduced podocyte density, increased glomerular volume and total glomerulosclerosis[60].

Tertiary lymphoid tissues (TLTs) have also received attention for their role in the pathophysiological response to ageing[52]. The formation of TLTs within the kidneys of aged mouse models of AKI prolongs inflammation and impedes repair processes, thereby exacerbating kidney injury[61]. TLTs in non-lymphoid organs act as inflammatory niches to initiate acquired immunity, involving the activation and proliferation of T cells and B cells. Of note, ageing-induced TLTs have been observed in the bladder and liver, as well as in the kidney, suggesting that TLT formation is a systemic effect of ageing[62,63]. In the kidneys, TLTs tend to form beneath the renal capsule, around blood vessels and adjacent to glomeruli[64]. Estimates suggest that they are present in approximately half of kidneys from older people, and that they mature through three stages, with more advanced TLT stages forming in the presence of underlying kidney inflammation or injury[65]. The immunosuppressive drug, dexamethasone, has demonstrated efficacy in preventing and reducing the formation of TLTs in the mouse kidney[61,65], although it is associated with adverse effects and is not specific to TLTs. The expansion of TLTs relies on CD153–CD30 signalling between senescence-associated T cells and age-associated B cells, which emerge with ageing. Blocking this signal suppressed TLT formation and improved kidney function in aged kidney injury models[66]. TLTs have also been linked to pathological conditions independent of ageing. Analyses of protocol kidney biopsy samples after transplantation revealed the presence of TLTs in about 50% of kidneys after 1 month; stage II TLTs (that is, the stage at which follicular dendritic cells develop) were present in approximately 20% of kidneys after 1 year, and their presence correlated with poorer renal outcomes 5 years after transplantation[67]. TLT formation has also been reported in patients with various kidney diseases, including IgA nephropathy and ANCA-associated vasculitis, suggesting potential as a disease-agnostic prognostic indicator and therapeutic target[52]. Further findings indicate that TLTs confer an inflammatory phenotype on PTECs and renal fibroblasts to impair repair capacity; conversely, inflammatory parenchymal cells facilitate leukocyte trafficking and survival and thereby contribute to TLT expansion[68].

Mitochondrial dysfunction and oxidative stress

Mitochondria are the cellular powerhouses that are responsible for producing energy in the form of ATP, which is critical for the reabsorptive capacity of the proximal tubule. The citric acid cycle in the mitochondrial matrix generates ATP by consuming acetyl-CoA and water, reducing NAD^+ to NADH, and releasing carbon dioxide and water. In the aged kidney, low NAD levels and NAD-dependent mitochondrial sirtuin activity are associated with impaired mitochondrial respiration, energy deficiency and ROS accumulation[69]. An NAD^+ precursor, nicotinamide mononucleotide, rescued age-related susceptibility to AKI in a SIRT1-dependent manner in mice[70].

Mitochondrial dysfunction, characterized by impaired oxidative phosphorylation and increased production of ROS, is considered to be an antagonistic hallmark of ageing, and has been observed in aged kidneys and in various kidney diseases[71,72]. Mitochondrial dysfunction can compromise the utilization of cellular oxygen and exacerbate tissue hypoxia in the aged kidney, leading to increased oxidative stress. Increased oxidative stress, characterized by an imbalance between ROS production and antioxidant defence mechanisms, can trigger cell death through apoptosis and ferroptosis. These effects, in turn, induce the release of inflammatory cytokines and contribute to kidney ageing and CKD pathogenesis[69,73,74].

Fibroblast growth factor 21 (FGF21) is a hormone-like member of the FGF family that controls metabolic multiorgan crosstalk by enhancing energy expenditure. It acts as a stress hormone induced by endoplasmic reticulum (ER) stress and mitochondrial dysfunction in several tissues[75]. Studies from the past decade have revealed that FGF21 counteracts kidney disease progression during ageing and obesity by maintaining mitochondrial homeostasis and decreasing oxidative damage in mice[71,76].

Defective lipid metabolism

Although the kidney comprises only 0.5% of the total body weight, it uses approximately 10% of the oxygen consumed by the body. Mitochondrial β-oxidation of non-esterified free fatty acids represents a major source of renal ATP, particularly in PTECs, which have a particularly high energy demand and relatively little glycolytic capacity[77–82]. Although not strictly considered a hallmark of ageing, emerging evidence suggests that lipids have crucial roles in regulating ageing and longevity, and that lipid metabolic enzymes undergo substantial changes during ageing[83]. Omics studies have identified alterations in lipid metabolism, including defective fatty acid oxidation (FAO) by PTECs, in aged mouse kidneys[84]. Importantly, defective FAO and the intracellular deposition of lipids in PTECs has been linked to the development of fibrosis in mouse and human kidneys[85]. Multiple studies have now highlighted the contributory role of defective lipid metabolism, particularly dysregulated fatty acid metabolism, in CKD progression[69,82].

Several transcription factors, including ESRRα[86] and PPARα[87], as well as the transcriptional coactivator PGC1α[88], regulate FAO in PTECs. Reduced expression of ESRRα, PPARα and PGC1α has been observed in both AKI and CKD in mouse and human kidneys, associated with impaired FAO, reduced ATP levels, an accumulation of lipids and loss of PTEC integrity[25,69].

Klotho, phosphate toxicity and calciprotein particles

Klotho is expressed in the kidney, especially in the distal tubule, and functions as the coreceptor for FGF23, a bone-derived hormone that induces phosphate excretion into urine. *Klotho* deficiency leads to premature ageing and shortened life expectancy in mice; mice lacking Klotho also develop complications similar to those in patients with kidney failure, including atherosclerosis, ectopic calcification, osteoporosis, skin atrophy and gonadal dysfunction. These effects are mitigated by a low phosphate diet, indicating that they are caused by phosphate overload. Furthermore, expression of the gene that encodes Klotho decreases with CKD progression[89,90]. In addition, Klotho mitigates the progression of AKI to CKD in mice through the activation of autophagy[91], and dysregulation of lipid homeostasis induced by *Klotho* deficiency promotes AKI to CKD transition[92]. Therefore, a decline in systemic and renal Klotho levels may be considered a novel hallmark of kidney ageing, although it should be noted that Klotho was not associated with clinical outcomes in a large, diverse, well-characterized cohort of patients with CKD. Moreover, Klotho deficiency did not confound the association of FGF23 with mortality or heart failure hospitalization in that study[93].

Hyperphosphataemia contributes to the pathophysiology of CKD; it is also independently implicated in cardiovascular and all-cause mortality in patients with CKD, attributed to endothelial dysfunction and vascular calcification[11,94,95]. Inorganic phosphate activates the AKT–mTOR pathway and shortens the lifespan of *Klotho*-deficient mice[96]. Phosphate may also accelerate kidney ageing in humans[97]. Although the adverse effects of phosphate over-consumption are largely overlooked, contemporary dietary habits often involve the consumption of phosphate-rich foods such as red meat and dairy products, along with the widespread use of phosphate-containing food additives in processed foods[98–100].

Mechanistically, dietary phosphate induces an increase in circulating FGF23, which acts on the Klotho receptor in kidney tubules to inhibit phosphate reabsorption and thereby increase urinary phosphate excretion[98]. If the concentration of phosphate in the tubule fluid surpasses its solubility threshold, it forms calcium phosphate precipitates, ultimately forming colloidal particles known as calciprotein particles (CPPs). These CPPs can cause direct injury to PTECs and induce inflammation through the binding and activation of Toll-like receptors[98]. The decline in nephron numbers with age or injury places a greater phosphate burden on each remaining nephron, leading to further elevations in FGF23 levels and thereby perpetuating a vicious cycle[98]. We have shown that autophagy in PTECs acts as a mechanism to protect the kidney from phosphate overload-induced injury in mice[94].

Magnesium is an essential ion that regulates numerous physiological and pathological processes. Magnesium deficiency is very common in old age[101], and hypomagnesaemia predicts mortality and CKD progression in individuals with diabetic kidney disease (DKD)[102]. In a cross-sectional study that compared the prevalence of electrolyte abnormalities in 5,126 patients with CKD who were not on dialysis, hypomagnesaemia was the most common electrolyte abnormality (14.7%) with similar prevalence across stages of CKD. Proteinuria was a risk factor for hypomagnesaemia — an effect that may be mediated by renal magnesium wasting[103].

Emerging data also support an association between the consumption of ultra-processed food and the risk of incident CKD[104,105]. One potential mechanism for this association may be the toxicity of inorganic phosphate in food additives. Alternatively, the association may be driven by a lower intake of magnesium. Indeed, a population-based cohort study found an association between lower dietary intake of magnesium and decline in kidney function[106]. The importance of dietary magnesium is recognized particularly in the context of phosphate toxicity. In hemi-nephrectomized mice, a low-magnesium diet exacerbated kidney injury induced by a high-phosphate diet, associated with a marked downregulation of Klotho expression in the kidney[107]. Dietary magnesium may also inhibit intestinal phosphate absorption[108]. Moreover, magnesium might prevent phosphate-induced mitochondrial dysfunction by attenuating phosphate-induced mitochondrial permeability transition, cell death and PTEC inflammation[109]. Additionally, findings in dolphins suggest that CPP-induced kidney injury is attenuated by magnesium[110]. In a cohort study in patients with CKD, higher serum phosphate levels were associated with an increased risk of kidney failure only when serum magnesium levels were low[109]. These findings suggest that the hazardous nature of ultra-processed food attributable to phosphate may be amplified by magnesium deficiency.

The consumption of ultra-processed food by patients with CKD may also predispose individuals to, and/or exacerbate, uraemic metabolic derangements, such as insulin resistance, metabolic acidosis, hypertension and gut dysbiosis[100]. Trimethylamine *N*-oxide (TMAO) is a gut microbiota-derived metabolite of dietary phosphatidylcholine and carnitine and betaine, which are commonly found in red meat, eggs and certain fish; in experimental models, TMAO caused kidney injury and tubulointerstitial fibrosis[111]. In a 2024 study of community-based adults in the USA, higher plasma TMAO levels were associated with a higher risk of incident CKD and a greater rate of kidney function decline[112]. Thus, the role of high phosphate and TMAO in red meat and food additives in processed food may be an underestimated contributor to the kidney ageing process and should be considered in the context of therapeutic interventions.

Dysregulation of autophagy

Defective autophagy has a crucial role in the pathogenesis of age-related diseases by exacerbating tissue damage and impairing the regenerative capacity of organs. Emerging evidence suggests that

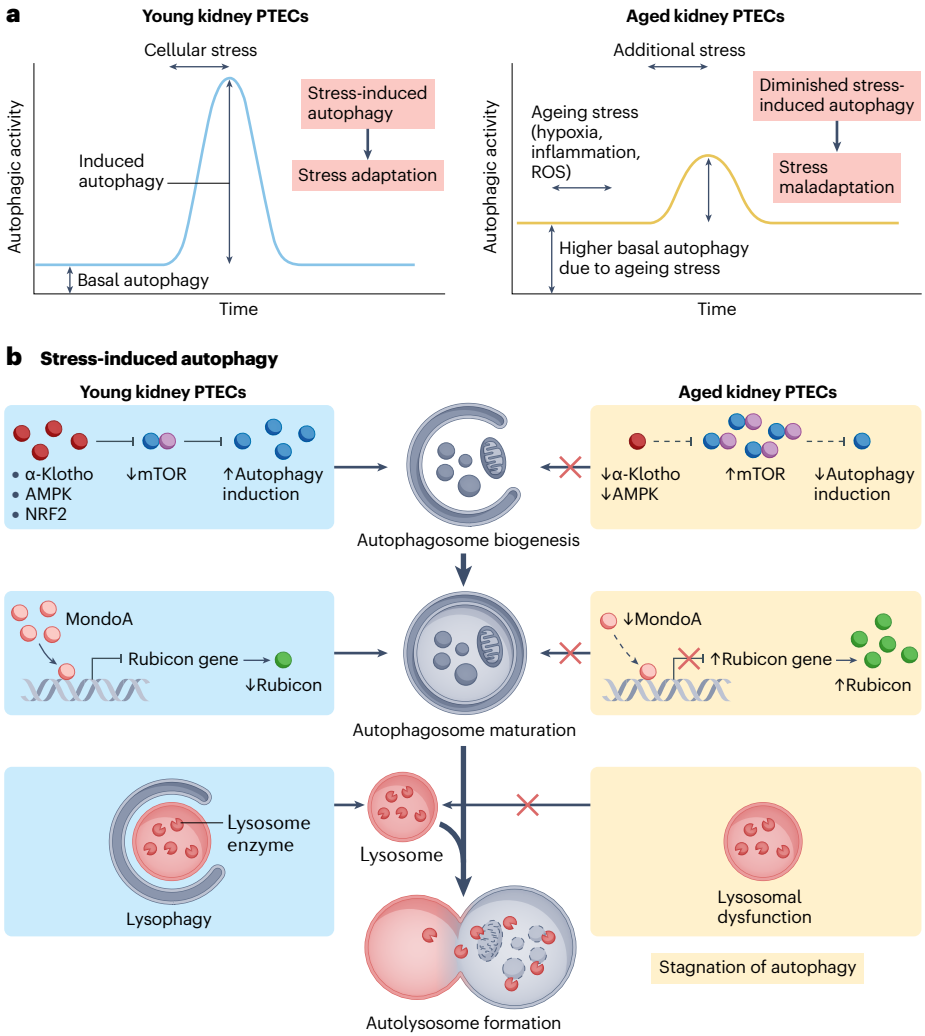

Fig. 2 | Molecular mechanisms of autophagy dysregulation in ageing. a, In proximal tubular epithelial cells (PTECs) from young mice, autophagy increases in response to cellular stress as an adaptive mechanism. By contrast, PTECs from aged mice demonstrate higher basal autophagy due to persistent ageing stress. However, the ability of aged cells to increase autophagic activity in response to additional stressors is impeded. The *x*-axis represents time (hours to days), and the *y*-axis represents autophagic activity. **b**, Age-dependent dysregulation of autophagy is induced by lysosomal dysfunction and/or abnormal autophagosome maturation rather than decreased autophagosome biogenesis during kidney ageing. Specifically, increased levels of mTOR in aged kidneys in response to decreases in α-Klotho and AMPK inhibits the induction of autophagy. Downregulation of the glucose-responsive transcription factor, MondoA, with age, leads to increased expression of Rubicon — a negative regulator of autophagosome maturation. Moreover, lysosomal dysfunction in PTECs may also contribute to the age-dependent dysregulation of autophagy. ROS, reactive oxygen species. Adapted with permission from ref. 117, Elsevier.

although basal autophagic activity increases with ageing due to the increased presence of pathological ageing stressors, the capacity of autophagy to upregulate further in response to additional stressors accelerates kidney ageing and may be associated with age-related kidney diseases[71] (Fig. 2a).

In the aged kidney, the cumulative effect of autophagy impairment is thought to accelerate the decline in kidney function. This hypothesis is supported by the finding that aged (24-month-old) mice with deficiency of autophagy specifically in PTECs exhibit a significant deterioration in kidney function and fibrosis, concomitant with mitochondrial dysfunction, mitochondrial DNA abnormalities and nuclear DNA damage[71]. Obese mice fed a high-fat diet (HFD) exhibit similar hallmark features of kidney ageing at 12 months of age, along with evidence of dysfunctional autophagy, supporting the notion that dysregulation of autophagy can accelerate kidney ageing[77].

Interestingly, the mitigation of disease progression by Klotho may be partly mediated through the induction of autophagy[91]. This hypothesis is supported by the finding that dysregulation of autophagy not only promotes CKD but also increases AKI vulnerability[71,77,113,114], probably by reducing the ability of kidneys to respond to stressors.

Lysosomal dysfunction. Lysosomes are catabolic organelles that degrade intracellular constituents through autophagy and extracellular components through endocytosis, phagocytosis and macropinocytosis[115]. Lysosomal functions are tightly regulated by the transcription factors TFEB and TFE3 (ref. 115). The high endocytic activity of the kidney places a high burden on PTEC lysosomes[116,117], highlighting their role as central organelles in PTEC homeostasis, in metabolic regulation and in the response to environmental changes, including nutrient stressors, ER stress and defects in proteostasis[115]. Indeed, lysosomal dysfunction is a common feature of senescent cells[49], and giant autolysosomes containing undigested material have been observed in atrophic PTECs[76], suggesting that lysosomal dysfunction in PTECs is — at least in part — responsible for the age-dependent dysregulation of autophagy. Moreover, a 2024 study showed that HKDC1, a target of TFEB, prevents cellular senescence by maintaining both mitochondrial and lysosomal homeostasis[118].

Lysosomal dysfunction has been linked to a variety of diseases, including autoimmune, metabolic and kidney diseases[119]. HFD-induced obesity in mice triggers lysosomal dysfunction and defective autophagy, which exacerbates renal lipotoxicity[77]. Although lipid

overload induces autophagy to repair organelle membranes and maintain PTEC integrity, overloading of lysosomes leads to the stagnation of autophagy, which in the context of lipotoxicity manifests as an accumulation of phospholipids in lysosomes[120]. Interestingly, an accumulation of phospholipids was observed in tubular lysosomes in renal biopsy samples from older patients with CKD and from patients with obesity and CKD[77,116,121]. The induction of TFEB-mediated lysosomal exocytosis has therefore emerged as a potential approach to alleviate lipotoxicity by expelling accumulated phospholipids[121].

Abnormal maturation or biogenesis of the autophagosome. Available evidence suggests that age-dependent dysregulation of autophagy is induced by lysosomal dysfunction and/or abnormal autophagosome maturation rather than decreased autophagosome biogenesis (Fig. 2b). Rubicon is a negative regulator of autophagosome maturation[122]. Levels of Rubicon increase in the kidney of aged mice; and knockout of *Rubicon* in aged mice is associated with improved autophagosome maturation and decreased kidney fibrosis[123]. The glucose-responsive transcription factor, MondoA, directly suppresses *Rubicon* expression and inhibits cellular senescence, in part by activating autophagy[124]. Notably, MONDOA expression is downregulated in renal biopsy samples from older individuals and patients with CKD[124,125].

Nutrient sensing pathways, such as the AMPK and mTOR pathways, are positive and negative regulators of autophagosome biogenesis, respectively[126], and have been implicated in the pathogenesis of CKD[127]. Levels of AMPK and mTOR are decreased and increased, respectively, in aged kidneys, whereas drug-induced AMPK activation and mTOR inhibition suppress CKD progression in mice[117]. The oxidative stress response factor, NRF2, also interacts bidirectionally with autophagy processes. Specifically, NRF2 activation enhances autophagy to mitigate oxidative stress and cellular damage, and conversely, the induction of autophagy can promote NRF2 activation[128]. Dysregulation of NRF2 or autophagy — which commonly occurs in aged kidneys — may disrupt this crosstalk and accelerate kidney ageing[71].

CKD and premature ageing

A growing body of literature demonstrates that CKD is an important risk factor for the ageing of other organ systems in humans[12,129,130]. This link may underlie the association between CKD and frailty in older individuals.

Biological versus chronological age

Chronological age alone does not fully capture the complexity of the ageing process in relation to organ function, which is also influenced by a multitude of genetic and environmental factors. Biological age, which reflects the physiological state of an individual, can be accelerated by various lifestyle choices and environmental exposures. These influences can lead to a disconnect between chronological and biological age, known as the 'age gap', which serves as a valuable complementary measure in assessments of organ ageing[131] (Fig. 3). Consequently, efforts to promote healthy ageing necessitate a deeper understanding of biological age and the molecular mechanisms that influence biological age.

The exposome refers to the cumulative impact of environmental exposures throughout an individual's lifetime, and includes lifestyle factors, diet, pollutants and stressors. These exposures interact with, and modify various physiological processes, affecting various aspects that are relevant to the health of the individual and contributing to the ageing process[132]. For example, numerous stressors can activate inflammatory responses, disrupt the microbiota balance, induce oxidative stress and impair mitochondrial function, thereby increasing the risk of lifestyle-related diseases that accumulate with age[133]. Emerging environmental factors such as global warming, deforestation and pollution may exacerbate these effects[133].

The role of CKD in the ageing process

CKD is associated with accelerated or premature ageing to the extent that the biological age of patients with CKD is approximately 5 years older than their chronological age. Moreover, and as mentioned previously, CKD is an important risk factor for the progressive ageing of other organ systems such as the brain and heart[12] (Fig. 4).

The higher biological age of the kidney in patients with CKD relative to chronological age may be mediated by pathophysiological mechanisms that are common to both ageing pathways and CKD[11,134]. For example, hormonal imbalances, glycative stress and nitrogenous metabolites, as well as the above-described hallmarks of ageing, that contribute to CKD progression, such as inflammation and oxidative stress, contribute to premature ageing in the kidney, but also contribute to the ageing of other systems, particularly the vessels and muscles. This accelerated ageing phenotype manifests as an increased burden of age-related conditions and comorbidities, such as cardiovascular disease, cognitive impairment, sarcopenia and frailty[11,134,135]. These effects culminate in a high risk of cardiovascular events and sarcopenia, contributing to impaired health status, reduced quality of life and premature mortality in individuals with CKD[134,136].

Frailty in patients with CKD

Frailty is a multidimensional concept that encompasses various aspects of health, independence and quality of life, typically in older patients[137]. It refers to a systemic state of increased vulnerability to stressors due to age-related declines in physiological reserves and functional capacity. Frailty is characterized by diminished strength, endurance, balance and cognitive function, as well as increased susceptibility to adverse health outcomes such as disability, falls, hospitalization and mortality[137].

In older patients with CKD, frailty is particularly relevant due to the overlapping risk factors and pathophysiological mechanisms shared between frailty and CKD (Fig. 4). These include chronic inflammation,

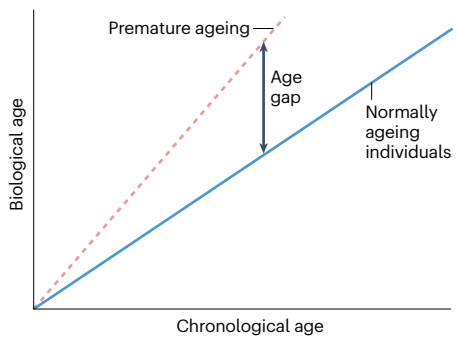

Fig. 3 | The concept of biological age versus chronological age. Biological ageing refers to the decline in tissue or organismal function, whereas chronological ageing simply indicates the time passed since birth. In individuals who age 'normally', chronological age equates to biological age. The difference between biological age and chronological age is denoted as the 'age gap' and serves as a complementary indicator of ageing. Chronic kidney disease accelerates the biological ageing of the kidney and promotes premature ageing via a multiorgan disease network.

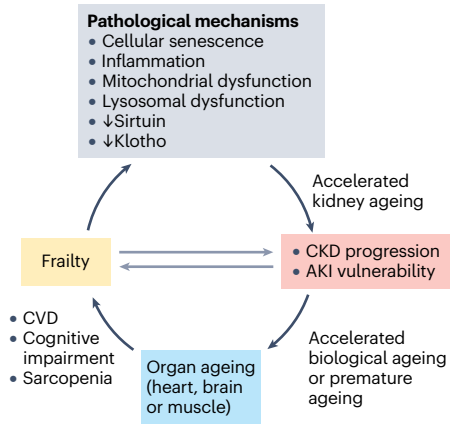

Fig. 4 | Interactions between premature ageing, frailty and CKD. Susceptibility to chronic kidney disease (CKD), acute kidney disease (AKI) and CKD progression is influenced by a variety of pathological mechanisms that overlap with the classic hallmarks of ageing. CKD is associated with a higher biological age — indicative of accelerated or premature ageing — and is a risk factor for the ageing of other organ systems in humans via a multiorgan disease network. This accelerated ageing phenotype manifests as an increased burden of age-related conditions and comorbidities, such as cardiovascular disease (CVD), cognitive impairment and sarcopenia, and is associated with an increased risk of frailty. Frailty and premature ageing in turn may exaggerate the pathologies of kidney ageing and disease. The exposome, defined as the cumulative impact of environmental exposures throughout an individual's lifetime, may exacerbate this cycle, leading to further deterioration of kidney health and contributing to the overall ageing processes.

sarcopenia, protein energy wasting, comorbidities and polypharmacy. Moreover, frailty may exacerbate CKD progression and increase the risk of adverse events[138]. Collectively, these findings underscore the systemic benefits that can be achieved through interventions targeting kidney ageing and disease.

Diagnostic implications

Current diagnostic methods for kidney diseases involve a combination of clinical evaluation, blood and urine tests, imaging studies, and in some cases, kidney biopsy. A number of emerging technologies and biomarkers hold promise for improving the early detection, diagnosis and management of age-related diseases, including kidney disease[131,139–142].

Emerging technologies and biomarkers

Advances in single-cell transcriptomics have markedly enhanced our understanding of cellular heterogeneity and the molecular processes underlying kidney injury and ageing[131,139,141,142]. For instance, use of single-cell RNA sequencing (scRNA-seq) facilitated the characterization of a dedifferentiated VCAM1$^+$ population of PTECs and revealed its broad relevance in kidney injury and fibrosis[141,143]. In addition, scRNA-seq of freshly dissociated cells from healthy and stenotic mouse kidneys enabled the identification of stenotic kidney epithelial cells undergoing both mesenchymal transition and senescence[40]. Single-nucleus RNA sequencing on aged mouse kidneys with TLTs identified pro-inflammatory and profibrotic VCAM1$^+$ injured PTECs with activation of NF-κB and IFN-inducible transcription factors[68]. Profiling studies have also led to the identification of biomarkers of ageing, which have the potential to aid the identification of individuals who may be frail and/or at risk of multimorbidity, or to define the most suitable therapeutic targets in a given patient or disease setting. Of note, longitudinal and deep multiomics profiling of 106 healthy individuals aged between 29 and 75 years of age revealed correlations between 'omics' measurements, including transcripts, proteins, metabolites, cytokines, microorganisms and clinical laboratory values, and age[144]. For example, components related to acute-phase response signalling, inflammation such as HMGB1 and Toll-like receptor signalling pathways and the coagulation pathway increased with age. Moreover, the study confirmed the positive association between age and HbA1c level and between age and apolipoprotein A-IV protein (ApoA4) level.

As described above, senescence is considered to be an important cellular mechanism that underlies kidney ageing and susceptibility to injury[36]. SA-β-Gal, p21 and p16, pro-inflammatory cytokines, and markers of oxidative stress, including malondialdehyde and 8-OHdG, are indicative of cellular senescence[74].

Lipidomics technologies have also provided insights into the pathophysiological changes that underlie kidney disease and ageing at the cellular and molecular levels[145]. For instance, urinary levels of various phospholipids (such as bis(monoacylglycerol)phosphate (BMP) — a lysosomal phospholipid the tissue levels of which are increased in patients with phospholipidosis) are increased in obese mice[121]. A 2024 study in which untargeted lipidomics was performed on samples from mice of different ages identified a number of molecules from different lipid classes that exhibited common and tissue-specific changes[146]. For example, levels of BMP containing polyunsaturated fatty acids were increased in the kidney in aged mice[146].

A growing body of evidence suggests that mitochondria may represent a promising diagnostic and therapeutic target for age-related kidney diseases. Mitokines are signalling molecules that enable communication of local mitochondrial stress to other mitochondria in distant cells and tissues. Among these molecules are FGF21 and growth differentiation factor 15 (GDF15)[147]. Interestingly, deficiency of autophagy specifically in the skeletal muscle of mice induced the secretion of FGF21 from skeletal muscle, which protected against diet-induced obesity and insulin resistance[148]. FGF21 is also robustly induced by disturbances in autophagy in PTECs and protects against CKD progression in mice[76]. These data imply that FGF21 could act as a compensation mechanism for autophagy stagnation and mitochondrial dysfunction during kidney ageing[147].

As described above, CPPs can cause direct injury to PTECs and induce inflammation. We have shown that serum levels of a fetuin-A mineral complex, composed of fetuin-A, fibrinogen, fibronectin 1 and calcium, are correlated with extraosseous calcification stress in patients on haemodialysis[149]. These findings are supported by those of a more recent study, which showed that circulating levels of CPPs are correlated with inflammation and vascular calcification or stiffness in patients with CKD[150]. In that study, circulating CPP levels were quantified using a fluorescent probe that bound to calcium phosphate crystals, which may also prove useful for the evaluation of cardiovascular risk in patients with CKD. Another potential tool for the evaluation of cardiovascular risk is skin autofluorescence — a measure of advanced glycation end-products (AGEs) in skin collagen. AGEs can be obtained through dietary sources or produced endogenously, and are associated with oxidative stress and inflammation. Skin autofluorescence could therefore be considered a potential surrogate marker of ageing[151,152].

Assessment of premature ageing in older patients with CKD

The susceptibility of the kidney to premature ageing and the association between CKD and age highlights the potential utility of an objective

measure of biological (as opposed to chronological) age. An epigenetic ageing clock, based on epigenetic marks at specific genomic loci, may represent one approach to estimate biological age. Interestingly, a 2024 study that estimated biological age based on blood biomarkers, skin autofluorescence and three separate DNA methylation-based epigenetic clocks revealed that kidney transplantation, but not dialysis, partially reduces the acceleration of biological age in patients with advanced CKD[153].

Therapeutic implications

Improved understanding of the molecular mechanisms underlying age-related kidney diseases and premature ageing has led to the discovery of novel molecular targets that may decelerate the ageing process and/or protect the kidney from ageing-associated factors[154,155]. Of note, although anti-ageing drugs hold great potential, their current status is one of promise rather than proven efficacy and safety in the context of human ageing. As research in this field progresses, a strategic, evidence-based approach to their use will be essential. This approach should prioritize high-risk individuals initially, incorporate principles of personalized medicine based on biomarker and genomic insights, and integrate comprehensive and appropriately supported modifications to lifestyle. It will also be important to address ethical, social and public health implications that may arise from the development of anti-ageing drugs to ensure that such therapeutic advances benefit society as a whole.

The long-term safety of anti-ageing drugs is a critical concern. Continuous monitoring of patients will be essential, with regular assessment of biomarkers and health outcomes to adapt treatment plans and ensure ongoing effectiveness and safety.

Approaches to target pathological mechanisms of kidney ageing

A variety of strategies have been investigated to target the pathological mechanisms of ageing, including those that target cellular senescence, inflammatory pathways, mitochondrial dysfunction and the Klotho–phosphate–FGF23 axis[134]. As described above, targeted elimination of senescent cells through the use of senolytic drugs has been proposed as a therapeutic strategy for preventing or treating age-related diseases. In one study, intermittent oral administration of senolytics to naturally aged mice or to mice transplanted with senescent cells alleviated physical dysfunction and increased survival[156]. Some senolytic agents, notably dasatinib and quercetin (D + Q) and fisetin, have progressed to clinical testing for use in conditions including DKD[157–161]. Findings from an open label, phase I trial in patients with DKD demonstrated that a 3-day oral course of D + Q reduces the proportion of senescent cells in adipose and skin biopsy samples as well as circulating SASP factors in blood samples, suggesting that senolytics can reduce senescent cell burden and alleviate symptoms associated with age-related diseases[158]. Moreover, a 2024 study revealed that SGLT2 inhibitors exert an indirect senolytic effect in mice by increasing immune surveillance of senescent cells through downregulation of PDL1 expression[162].

Of note, continuous or acute elimination of senescent vascular endothelial cells, particularly in liver sinusoids, disrupts blood–tissue barriers and leads to fibrosis, as these cells are not replaced after removal and have important structural and functional roles[163]. Other concerns include a potential increased risk of thrombocytopenia and neutropenia[47]. On the other hand, the induction of senolysis through inhibition of glutaminolysis[49] may more specifically eliminate senescent PTECs where glutaminolysis is active[164], highlighting the importance of a strategic approach in the development of senolytic therapies.

Targeting of mitochondrial function is another potential approach to ameliorate age-related diseases. Mitochonic acid 5 (MA-5) is a mitochondrial-targeted drug that has shown potential in preclinical models of kidney disease[154]. Mechanistically, MA-5 seems to attenuate oxidative stress-induced expression of the cytokine, GDF15, facilitate mitochondrial ATP production and reduce levels of ROS, suggesting that MA-5 may have potential as a drug for the treatment of several mitochondrial diseases[155].

Therapeutic interventions that target autophagy pathways, such as mTOR inhibitors and autophagy enhancers, are also under investigation as potential strategies to promote kidney health[117]. Of note, the activation of autophagy may place strain on the lysosomal system, highlighting the need to also maintain lysosomal homeostasis. We have shown that supplementation with the polyunsaturated fatty acid, eicosapentaenoic acid — which attenuates the palmitic acid-induced redistribution of phospholipids from cellular membranes into lysosomes — reduces several hallmarks of kidney ageing in HFD-fed obese mice, including dysfunctional autophagy, lysosomal and mitochondrial dysfunction, inflammation and fibrosis[78].

Mounting evidence also suggests that FGF21 can alleviate age-related metabolic disorders, such as atherosclerosis, obesity, diabetes and some cardiovascular diseases, by maintaining mitochondrial homeostasis and preventing stagnation of autophagy[76]. These findings are supported by the observation that transgenic mice that overexpress *Fgf21* have an extended lifespan[75,165]. Notably, randomized controlled trials have demonstrated positive outcomes of FGF21 analogues in patients with severe hypertriglyceridaemia and non-alcoholic steatohepatitis[166,167], suggesting that these agents may also demonstrate benefits in patients with CKD.

Approaches to target the gut–kidney axis

Gut dysbiosis, defined as an imbalance in the microbial composition of the gut, can lead to a loss of beneficial bacteria, the overgrowth of pathogenic bacteria and reduced microbial diversity[168,169]. Gut dysbiosis can be influenced by various factors including diet, use of antibiotics, infections and chronic diseases, and has been linked to numerous health conditions, including kidney disease[99]. The gut–kidney axis refers to multidirectional interactions between gut microbiota, gut microbiota-derived metabolites such as TMAO and the kidney that can contribute to progression of CKD[168]. As described above, TMAO has been associated with inflammation, oxidative stress and vascular dysfunction, with elevated levels associated with increased cardiovascular risk and kidney impairment[51,170]. Importantly, gut dysbiosis can increase the abundance of bacteria that convert dietary nutrients into trimethylamine (TMA), which is subsequently oxidized to TMAO[169].

In patients with CKD, the reduced ability to excrete TMAO contributes to higher circulating levels, which exacerbates kidney damage. Dysbiosis-related inflammation can also affect kidney function through the release of inflammatory cytokines and endotoxins[168,171]. Interventions to manage TMAO and dysbiosis include reduced intake of red meat and choline-rich foods, increased fibre intake, and use of probiotics and prebiotics to support a healthy gut microbiota, although the evidence supporting the efficacy of these interventions is weak. Interestingly, in a 2022 study, high levels of 3-carboxy-4-methyl-5-propyl-2-furanpropionate, a biomarker of fish intake, were found to confer health benefits independently of TMAO and other clinically relevant confounders, prompting the researchers to suggest that fish intake might counteract the unfavourable actions of TMAO[172].

Pharmacological approaches to target TMAO, such as inhibitors of TMA formation and TMAO scavengers, are also being explored[111].

Dietary interventions in patients with CKD

In the absence of pharmacological therapies, behavioural approaches, such as calorie restriction, regular exercise and certain anti-inflammatory medications, are currently the most promising strategies to promote healthy ageing[173]. Protein restriction may reduce the risk of CKD progression, but might increase the risk of sarcopenia. A 2024 study suggested that a low-protein diet that is prescribed and monitored is safe in older adults with CKD approaching kidney failure[174].

Current evidence suggests that adopting plant-based diets has few risks but potential benefits for preventing and delaying the progression of CKD[175,176]. The potential mechanisms underlying these benefits are manifold. Plant phosphorus has a lower bioavailability than animal phosphorus and might therefore enable better control of hyperphosphataemia. The consumption of plant foods might increase levels of micronutrients such as magnesium, which may lower the cardiovascular risk associated with hyperphosphataemia[177]. Furthermore, plant-based diets might also help to manage and prevent some of the symptoms and metabolic complications of CKD[175,176]. Of interest, sulforaphane – a natural compound derived from broccoli and broccoli sprouts – not only ameliorates obesity-related kidney disease by enhancing autophagy, but also ameliorates age-related mitochondrial dysfunction and renal impairment via activation of NRF2 (refs. 178,179). Dietary bioactive compounds, such as phenolics, flavonoids and carotenoids are non-nutrient natural compounds found in various fruits, vegetables and other plant-based foods that may help to maintain cellular homeostasis and promote health through the regulation of autophagy and epigenetic marks, and the reduction of senescence and oxidative stress[180].

Conclusions and future perspectives

CKD is associated with accelerated biological ageing, as evidenced by cellular senescence, inflammation, mitochondrial dysfunction, oxidative stress and defective autophagy. Improved understanding of the pathological mechanisms underlying this premature ageing phenotype in CKD could unveil novel therapeutic avenues for preventing age-related complications and improving outcomes in affected patients. Kidney ageing is not solely determined by genetic factors but can also be influenced by lifestyle, environment and concurrent illnesses. Therefore, assessments of CKD risk for early preventive measures should focus on biological age rather than chronological age. Despite the existence of numerous markers of biological age, their correlations with each other are often lower than anticipated[131,181], indicating that various markers may capture distinct facets of the ageing process. Further research is therefore needed to validate and refine existing ageing biomarkers while also identifying more accurate and robust indicators of kidney ageing. By pinpointing factors and diseases that affect the pace of kidney ageing, several anti-ageing strategies have been proposed to promote healthy kidney ageing and delay the development of age-related kidney diseases. Improved understanding of the intricate interplay between the hallmarks of kidney ageing and susceptibility to age-related pathologies holds promise for the development of clinical interventions aimed at fostering long-term kidney health and improving overall health outcomes.

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