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Nephron overload as a therapeutic target to maximize kidney lifespan

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Abstract | Kidney lifespan is a patient-oriented outcome that provides much needed context for understanding chronic kidney disease (CKD). Nephron endowment, age-associated decline in nephron number, kidney injury history and the intrinsic capacity of nephrons to adapt to haemodynamic and metabolic overload vary widely within the population. Defining percentiles of kidney function might therefore help to predict individual kidney lifespan and distinguish healthy ageing from progressive forms of CKD. In response to nephron loss, the remaining nephrons undergo functional and structural adaptations to meet the ongoing haemodynamic and metabolic demands of the organism. When these changes are no longer sufficient to maintain kidney cell homeostasis, remnant nephron demise occurs and CKD progression ensues. An individual's trajectory of glomerular filtration rate and albuminuria reflects the extent of nephron loss and adaptation of the remaining nephrons. Nephron overload represents the final common pathway of CKD progression and is largely independent of upstream disease mechanisms. Thus, interventions that efficiently attenuate nephron overload in early disease stages can protect remnant kidney cells and nephrons, and delay CKD progression. This Review provides a conceptual framework for individualized diagnosis, monitoring and treatment of CKD with the goal of maximizing kidney lifespan.

Chronic kidney disease (CKD), as defined by Kidney Disease: Improving Global Outcomes (KDIGO)[1], currently affects ~11–13% of the global population[2–4]. Importantly, CKD is also a major risk factor for cardiovascular disease, irrespective of progression to kidney failure[5]. CKD is therefore a major contributor to the global burden of disease.

Here, we focus on the concept of kidney lifespan — defined as kidney-failure-free lifespan or as time to uraemic death. Prolonging kidney lifespan is an important goal for both patients with CKD and their health-care professionals, and is therefore a crucial patient-oriented outcome. The well-established population-level perspective of CKD is defined by CKD stages but its utility in projecting individual patient outcomes and personalizing risk is limited[1]. Attempts to improve personalized CKD management already include the assessment of individual glomerular filtration rate (GFR) slopes to estimate kidney lifespan. These tools might be enhanced by the use of percentiles of kidney function as a novel approach to discriminate CKD from healthy kidney ageing, both of which are associated with a low GFR, and improve understanding of the pathomechanisms that drive CKD progression. Nephrons challenged by haemodynamic and metabolic overload undergo structural adaptations that promote accelerated loss of kidney epithelia and kidney atrophy, and increase the lifetime risk of kidney failure. By contrast, healthy kidney ageing does not involve nephron overload, nephron adaptation or enhanced risk of kidney failure. Hence, reducing nephron overload is a central therapeutic target to attenuate further decline of kidney function.

In this Review, we provide a unifying concept of CKD progression to help discriminate pathological changes in the kidney from age-associated changes that do not lead to progressive disease. We examine the mechanisms underlying the adaptation of the kidney glomeruli and tubules to increases in haemodynamic and metabolic demands, and argue that nephron overload is a common driver of CKD progression and is therefore a therapeutic target. Finally, we discuss the potential of early intervention in CKD with combination treatments that reduce haemodynamic and metabolic overload in the remaining nephrons as an approach to maximizing kidney lifespan[1–4,6,7], and highlight the economic and sociopolitical barriers to translating these conceptual advances into clinical benefits for patients worldwide.

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Key points

- The current chronic kidney disease (CKD) classification is useful from the perspective of epidemiology, public health care and advocacy. Kidney lifespan is a more individualized, patient-oriented outcome that takes into account linear and non-linear declines in estimated glomerular filtration rate (eGFR) for the prediction of individual prognoses.
- Population percentiles of eGFR acknowledge its age-specific spectrum and, along with individualized eGFR slopes, could help distinguish between healthy kidney ageing and progressive CKD. Percentiles are population-specific and should help identify patients at risk of CKD, as well as improve patient prognosis and management.
- Adaptation to haemodynamic and metabolic overload is observed in the remaining nephrons in CKD but not in physiological kidney ageing. Adaptation is first evidenced by nephron hypertrophy and later by albuminuria.
- Haemodynamic stress promotes podocyte loss directly and metabolic stress is a key driver of loss of tubular epithelial cells. Both types of stress can lead to secondary focal segmental glomerulosclerosis, tubular atrophy and interstitial fibrosis.
- Progressive nephron loss reduces kidney lifespan. Dual blockade of the renin–angiotensin–aldosterone system and of sodium–glucose co-transporter 2 is very potent in both alleviating mechanisms of stress and prolonging kidney lifespan, and hence CKD has become a treatable disease.
- Prolonging kidney lifespan with novel combination therapies is effective in patients with glomerular forms of CKD. Broad implementation of this approach requires effort at all levels, including improving our ability to assess and predict individual kidney lifespan, implementing remnant nephron overload as a pathophysiological concept and a treatment target, and raising awareness that CKD is a treatable disease.

Kidney lifespan and current CKD staging

Current CKD stages are categorical and based on GFR, and/or the presence of proteinuria or albuminuria[1]. GFR is often automatically estimated (eGFR) by laboratories when serum creatinine is tested (creatinine is the second most requested serum test after glucose)[8,9]. Measuring GFR, for example by assessing plasma iohexol clearance, is more precise and more useful than eGFR in certain circumstances, but it is also more time-consuming, costly and not broadly available[10]. By contrast, proteinuria or albuminuria are easy and cheap to measure but are infrequently assessed during routine medical care, resulting in missed opportunities to detect CKD[11]. The current CKD stage categorization was derived from epidemiological studies that investigated the association between GFR thresholds and mortality risk[12]. However, a gap exists between these epidemiological analyses and the interpretation of GFR data in healthy individuals.

GFR decline in healthy ageing. The GFR threshold at which the mortality risk increases is higher in young people and lower in older individuals[13], suggesting that the threshold value for 'abnormal' or 'at-risk' GFR varies with age[14]. This discrepancy complicates the diagnosis of kidney disease based on universal categories that do not take age into account, and becomes problematic if patients without symptoms or increased risk of death are diagnosed with CKD (that is, over-diagnosis)[15]. Many healthy older individuals will have an eGFR of <60 ml/min/1.73 m^2 (CKD definition by KDIGO) without any evidence of underlying kidney disease or of accelerated GFR decline resulting from CKD progression[16]. Of note, the amount of metabolic waste that requires clearance decreases with age and scaling GFR to metabolic rate rather than body surface area attenuates the age-related decline in GFR[17]. Furthermore, an increase in single-nephron GFR (SNGFR; that is, nephron overload) does not occur with healthy ageing despite substantial nephron loss[18]. Broadly, mortality risk does not increase until some process either accelerates nephron loss (for example, kidney disease such as IgA nephropathy, or acute kidney injury (AKI)) or increases metabolic demand (for example, increased requirement for solute handling and excretion of waste products owing to obesity) to an extent that results in overload in the remaining nephrons.

The GFR decline observed with ageing — also termed age-associated loss of renal functional reserve — is associated with an increased risk of AKI and potential harm from nephrotoxic medications, which underlies the need for dose adjustments for medications that are eliminated via the kidney[19]. However, these clinical concerns, although important, do not necessarily reflect the existence of kidney disease and can be addressed without medicalizing the ageing process. Rather, the identification of kidneys that are 'stressed' and in which nephrons undergo adaptation due to pathology beyond the typical age-related loss of nephrons, has the potential to discriminate healthy ageing from progressive pathophysiology.

Factors affecting kidney lifespan. Despite the annual loss of nephrons with age[20], the average biological lifespan of the kidney exceeds average life expectancy. However, kidney lifespan is not the same for all individuals. Mammals are born with a fixed number of nephrons, which typically exceeds that required to meet the metabolic needs of the organism and, therefore, most individuals can tolerate some loss of nephrons over the life course without compromising kidney function[21]. However, nephron development depends on a sequence of signalling events during branching morphogenesis in utero and nephron number varies according to gestational age, birthweight and kidney size[22]. Much of the 13-fold variation in nephron number evident across human populations reflects the multiple factors involved in nephrogenesis in each individual[23]. These factors include maternal age, health and nutrition, race or ethnicity, socioeconomic conditions, environmental exposures

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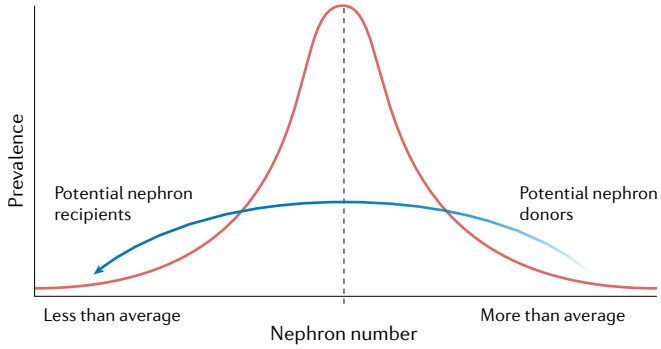
and genetic polymorphisms[23]. Children born small for gestational age, with low weight (birthweight <2.5 kg) or preterm (before 37 weeks of gestation) have fewer nephrons than children born at term with appropriate birthweight[22]. These children are also at higher risk of neonatal AKI, which is more frequent in preterm infants than in those born after 37 weeks of gestation[24]; such kidney insults further compromise nephron number. Population studies have shown that such individuals have an increased risk of developing CKD and kidney failure in later life[25,26] (FIG. 1a). These observations suggest that low nephron endowment at birth reduces the ability of the kidney to compensate for nephron loss and thus shortens kidney lifespan. Moreover, intrauterine stressors not only compromise nephrogenesis but can also induce a developmental programme that increases the risk of hypertension, diabetes and cardiovascular disease (all of which contribute to CKD risk)[27].

The rate of ageing-related annual nephron loss (and GFR decline) can also vary across individuals, which reflects differences in nephron endowment and superimposed stresses that can affect kidney lifespan[28]. For example, progressive forms of kidney disease accelerate the annual loss of GFR beyond the average 0.7–1.0 ml/min/1.73 m^2/year observed in healthy adults and can substantially shorten individual kidney lifespan. In patients with CKD stages G3–G5, complications during pregnancy reduced kidney lifespan by 2.5 years on average[29]. Moreover, episodes of AKI can cause sudden and irreversible loss of large numbers of functional nephrons, shortening kidney lifespan by decades[30,31]. In older individuals, even a mild AKI episode can reduce the remaining kidney lifespan and precipitate the need for kidney replacement therapy later in life[32]. Notably, age distribution is a major determinant of the prevalence of kidney failure in a population[2,33], and the need for kidney replacement therapy continues to increase as populations age. Medical advances continue to increase life expectancy, which might start to exceed the biological lifespan of the kidneys[34,35]. Other risk factors that accelerate loss of kidney function include obesity, diabetes, hypertension and exposure to nephrotoxins, which frequently occur in combination[36,37]. Genetic modifiers, such as the *APOL1* risk variants found in some people of West African ancestry, can also accelerate CKD progression and are thought to exacerbate racial disparities in kidney lifespan, including adverse social determinants in structurally disadvantaged communities[38,39].

Many factors therefore contribute to the variability in nephron number distribution in the population and patients with kidney failure comprise a heterogeneous group of individuals in whom kidney lifespan is shorter than their overall lifespan. Consequently, reducing the number of people with kidney failure in a population requires: measures to improve maternal health before and during pregnancy such that individuals are born with an optimal number of nephrons, as well as minimizing nephron overload in pregnant women[27]; measures to prevent AKI or at least minimize irreversible nephron loss following AKI; measures to minimize nephron loss due to the various forms of CKD through early diagnosis and the use of disease-specific therapies, and/or by targeting the common non-specific mechanisms of CKD progression; and measures to promote healthy lifestyles for optimal kidney ageing. These approaches require awareness of kidney lifespan as a central concept for

a **Nephron endowment**



Renal functional reserve	None or poor	Sufficient	Excellent
Preeclampsia risk	High	Low	Low
Hypertension onset	Early in life	Late in life	None or very late in life
Proteinuria level relative to disease stage	High	Adequate	Low
Trigger for sudden SCr↑ or AKI	Mild injury	Modest injury	Severe injury
CKD progression	Fast	Slow	Minimal
Obesity	High risk of adaptive FSGS	Low risk	No adaptive FSGS
Diabetes	Risk of early nephropathy	Late nephropathy	No nephropathy
Glomerulonephritis	Fast CKD progression	Slow progression	Minimal progression
Post-donation kidney failure risk	High	Low	No risk for donor

b

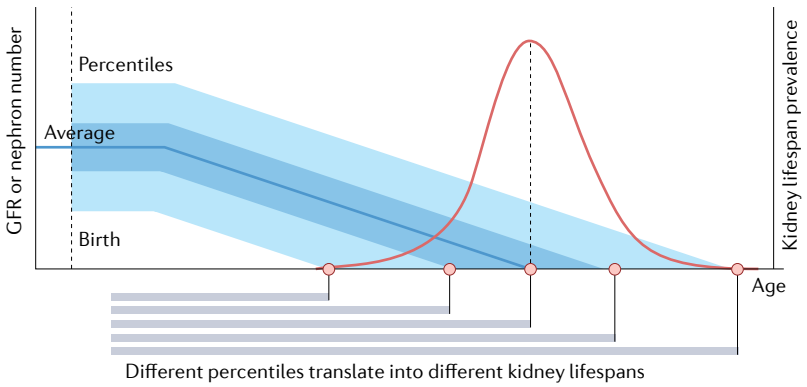


Fig. 1 | **Gaussian distribution of nephron number and GFR percentiles. a** | Nephron endowment is not the same for each individual of a population but follows a Gaussian distribution. Individuals with a low nephron number have a limited capacity to tolerate insults or to compensate for nephron loss and are therefore at risk of developing (progressive) kidney disease. People with higher nephron endowment might be more resistant because they have an abundant nephron reserve; such individuals are well-suited to donate kidneys (that is, 50% of their nephrons). Kidney recipients would mostly include individuals with a low nephron number and a high risk of kidney failure. **b** | From this initial Gaussian distribution, glomerular filtration rate (GFR) percentiles can be derived and calculated over time according the expected age-associated GFR and/or nephron number decline. These percentiles would enable the distinction of ageing-related GFR loss (that is, no change in percentile) from chronic kidney disease (CKD) (that is, a decrease in GFR percentile). Percentiles also illustrate the effect of nephron endowment at birth on baseline nephron number and GFR, and overall kidney lifespan. AKI, acute kidney injury; FSGS, focal segmental glomerulosclerosis; SCr, serum creatinine.

overall health, and as an important patient-oriented outcome beyond the current focus on proteinuria and GFR stages[1]. As life expectancy increases, awareness of kidney lifespan and anticipation of kidney failure later in life can be instrumental in adjusting policies and expectations.

GFR percentiles and nephron number. Throughout the lifespan, accumulation of insults to the kidney will reduce the number of functioning nephrons. The number of remaining nephrons, will either be adequate relative to the metabolic demand to maintain kidney function without the need for adaptation, or it might be insufficient and lead to hyperfiltration (functional overload) in the remaining nephrons with further injury and loss of kidney function over time[40]. This paradigm is well illustrated in transplantation, where after an initial period of compensation, recipients of a kidney that is small relative to their body size have higher risks of proteinuria, hypertension and more rapid loss of allograft function than recipients of a size-matched kidney[41].

GFR decline with age within a population can be illustrated as percentiles[2] (FIG. 1b). Currently, no method is available to reliably detect nephron number and therefore determining whether the level of kidney function, as determined by eGFR, reflects nephron overload or optimal filtration according to the nephron number remains elusive. In transplantation, for example, post-transplant GFR is often not within the 'normal' range, but whether it is appropriate for a given donor–recipient combination or reflects pathological nephron loss cannot be determined. Formulae combining donor and recipient characteristics (such as age, sex, body weight) and calculated GFRs have been suggested to be able to predict post-transplant GFR but have not yet entered the clinical mainstream[42] because often other superseding factors drive donation, including the availability of a donor. Assessing kidney functional reserve has been proposed as an option to identify patients with subclinical CKD, in whom SNGFR increases as a functional adaptation to nephron loss. Such adaptation might enable these individuals to maintain kidney homeostasis and a normal whole-kidney GFR, but they may have a limited capacity to increase GFR further to compensate for an acute metabolic stressor. For example, an oral protein load in a normal kidney leads to an acute temporary increase in GFR owing to the use of 'reserve' glomerular surface area for augmented filtration (analogous to a kidney 'stress test'). In individuals with subclinical CKD, this renal functional reserve is already being consumed at baseline[21] and further nephron loss would therefore lead to overt, progressive CKD.

Given this understanding of the pathophysiology of progression of kidney disease, and the centrality of nephron number over the life-course as a modulator of the risk of overt CKD, generating percentiles of kidney function based on age-appropriate population distributions (analogous, for example, to blood pressure ranges in children) might facilitate the assessment of kidney function and the risk of kidney disease in an individual. The importance of reliable individualized eGFR determination is well illustrated by the systematic under-diagnosis of CKD among Black individuals owing to the use of race coefficients, which has systematically compounded disadvantage in this population. The converse is probably true for older individuals, in whom CKD is over-diagnosed. The ongoing studies that are investigating the use of race coefficients in eGFR equations[43], new surrogate markers of GFR and new biomarkers to detect nephron overload should increase the data available on GFR distributions at different ages and in diverse populations, which will help determine normal ranges of GFR according to age and devoid of race as a co-determinant[44]. These data could be used to calculate the GFR percentile of an individual and ascertain whether it is within the putative normal GFR for that individual's age. In addition, determination of individualized GFR slope fits from serum creatinine levels obtained across decades might become increasingly feasible in settings of long-term and widespread use of electronic medical records. These data might reveal the relative rate of decline of an individual's kidney lifespan. Such individualized approaches might be superior to cross-sectional GFR determinations because they could account for different starting points for GFR (and nephron number). As GFR decline with age can vary across regions and ethnicities[45], percentiles would need to be based on representative population eGFR data to assure robust predictions. Such a representative percentile matrix might also help to determine the relative risk of CKD progression in individuals with low GFR and proteinuria in comparison with the risk in those without proteinuria, which is an ongoing uncertainty in older patients with reduced GFR.

Identifying individuals in the upper or lower percentiles of expected kidney function for their age might also help to predict the capacity of the kidney to accommodate further nephron loss, for example, following kidney donation. In patients with kidney disease, GFR slopes help discriminate CKD progression from age-related GFR decline[46] but such data can only be gathered over time[47]. Stratification of GFR into population percentiles might also permit more sensitive (that is, earlier) detection of progressive CKD, which would be indicated by a GFR that is within a lower percentile than expected, compared with the current basic CKD stages. The degree of deviation from the expected GFR decline might also predict the risk of developing kidney failure over time[13]. The effectiveness of therapeutic strategies could therefore be evaluated as changes in percentile in addition to the rate of GFR decline, which is already being used. The risk of potential second hits would also be more accurately assessed in the context of kidney lifespan, and this would help guide shared decision-making when discussing, for example, the risk of AKI following certain surgical procedures, the choice of potentially nephrotoxic chemotherapeutic agents, or pregnancy risks in women with pre-existing kidney dysfunction.

Adaptation to remnant nephron overload

Over time, persistent haemodynamic and metabolic stress leads first to loss of kidney cells, and later to loss of functional nephrons. Although kidneys at the higher end of the nephron endowment spectrum might be able to offset this stress over a longer period of time than

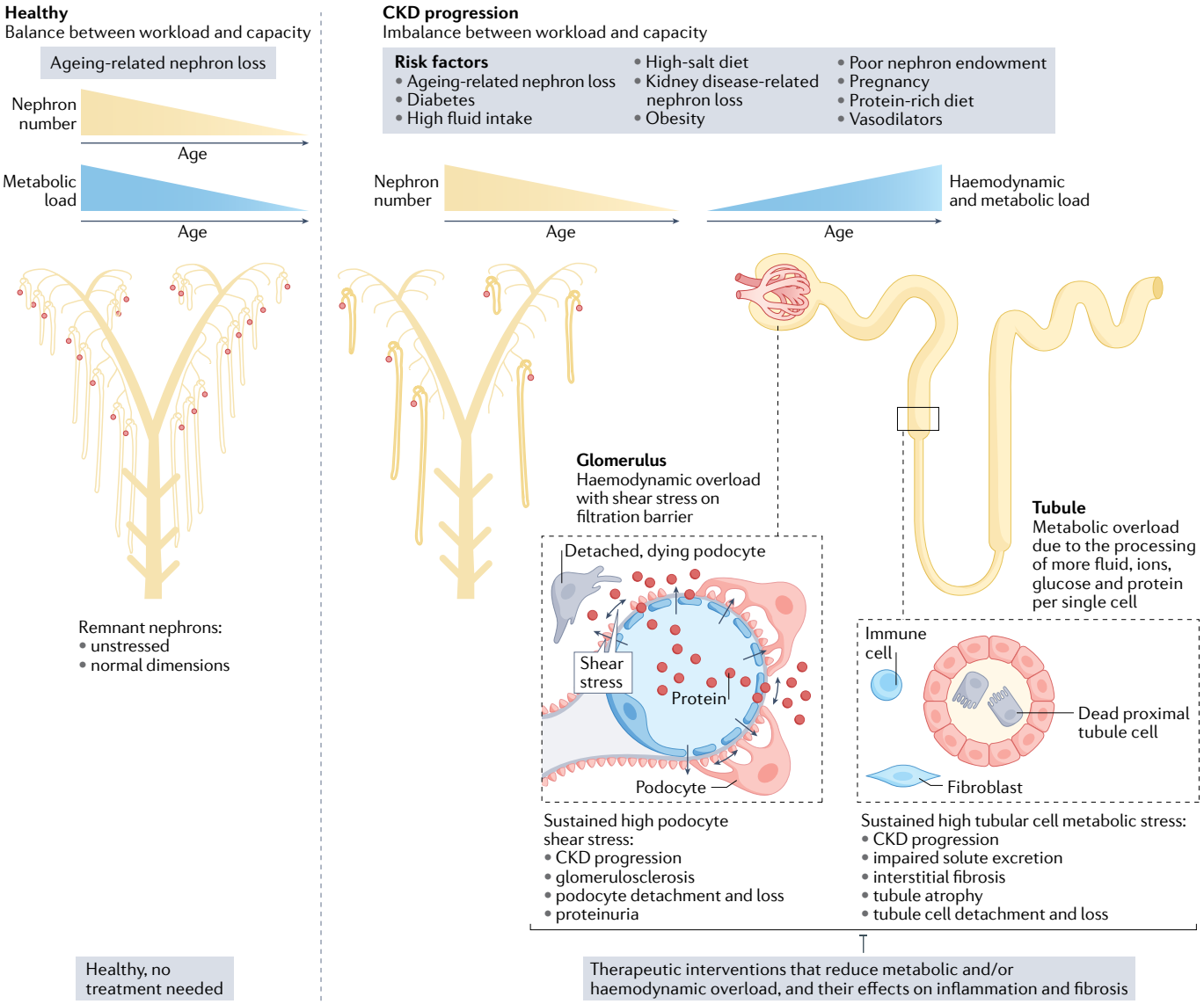


Fig. 2 | **Adaptations to nephron overload and CKD progression.** Healthy kidney ageing involves loss of kidney function capacity that is in balance with the metabolic needs of the body, hence nephron dimensions, which are indicative of nephron load, remain normal. By contrast, chronic kidney disease (CKD) progression reflects an imbalance between kidney function capacity and the metabolic demands of the body. Many factors contribute to this imbalance (for example, a decline in the number of nephrons (or kidney cells) or an increase in metabolic demand); a combination of various risk factors is frequent. Nephron hyperfiltration increases the single-nephron glomerular filtration rate (GFR), which increases the shear stress on the filtration barrier and the metabolic stress of single tubule epithelial cells. Beyond a certain threshold, these conditions of stress result in detachment and loss of epithelial cells, which further increases the stress on the remaining cells, and leads to a vicious cycle of kidney cell loss and CKD progression. Proteinuria, GFR loss, metabolic acidosis, bone disease and cardiovascular complications are clinical signs of the declining capacity of the kidneys to cope with the constant demands for fluid filtration and metabolite clearance. Reducing haemodynamic and metabolic overload by controlling the initial risk factors or using a combination of renin–angiotensin–aldosterone system inhibitors and sodium–glucose co-transporter 2 inhibitors can reduce the imbalance between demand and capacity in the remaining nephrons.

those with a low nephron number, beyond a certain threshold, the remnant nephrons can no longer compensate for nephron loss. Beyond this tipping point, CKD progresses independently of the original trigger of kidney injury and overload-related pathomechanisms add on to those of ongoing genetic, immunological, metabolic or toxic kidney disease[48–50] (FIG. 2).

Physiological nephron adaptation. In healthy individuals, kidney perfusion, glomerular filtration and tubular reabsorption oscillate in circadian rhythms that are associated with patterns of fluid and food intake (for example, lack of intake during sleep)[51]. Processing of large amounts of food and beverages engages otherwise underutilized superficial nephrons (that is, the kidney functional reserve)[52]. Transient or persistent weight gain also probably demands additional kidney activity as any increase in body weight increases the amount of fluid and metabolic waste that needs to be processed[21]. Of note, increasing fluid load at a given filtration surface area increases intraglomerular pressure and podocyte shear stress[53], whereas the proximal tubule has to recover

higher amounts of metabolites from the filtrate[54] (FIG. 2). In most individuals, the kidneys have sufficient functional reserve to handle the physiological oscillations of fluid and metabolites associated with circadian or seasonal rhythms[21]. Moreover, many people with healthy kidneys and a normal nephron number can withstand large increases in metabolic demand, such as those imposed by pregnancy, obesity or excess protein intake, without developing kidney disease. Notably, the loss of nephrons due to age-related nephrosclerosis observed in otherwise healthy individuals[55], is associated with physiological GFR decline but is not accompanied by albuminuria or proteinuria, and does not seem to reflect an underlying pathology in most individuals given that the metabolic demand also declines with age[13,56].

Similarly, uninephrectomy-related hyperfiltration and increased tubular reabsorption in the nephrons of the remaining kidney (for example, in kidney living donors) does not lead to progressive CKD in the absence of additional risk factors, such as obesity[57]. Of note, single-kidney GFR only increases ~30% after kidney donation, although it can rise further in response to additional metabolic demand[6,40,58] (FIGS 1a,2). Therefore, the compensatory increase in SNGFR following kidney donation does not seem to be maladaptive[59]. Similarly, temporary high glomerular perfusion (for example, in healthy pregnancy) does not lead to podocyte injury in otherwise healthy kidneys[60]. Glomerular capillary pressure is kept constant across a broad range of perfusion pressures via autoregulation of pre-glomerular and post-glomerular arteriolar resistance, which prevents glomerular hypertension.

Structural adaptations to nephron overload. Sustained single-nephron hyperfiltration, resulting either from nephron loss or glomerular hyperperfusion, can induce intraglomerular hypertension that injures endothelial cells and mesangial cells, and imposes pathological vertical shear stress on podocytes[53]. Intraglomerular hypertension also triggers expansion of the glomerular tuft (that is, glomerulomegaly) to increase the filtration surface; glomerulomegaly is a morphological marker of haemodynamic nephron overload[61] (FIGS 2,3a). This process involves endothelial and mesangial cell expansion but terminally differentiated podocytes have a more limited capacity for structural adaptation and hypertrophy. When mature podocytes re-enter the cell cycle to enable cell division, they lose their actin cytoskeleton-dependent structural stability, which can cause mitotic catastrophe, detachment from the glomerular basement membrane and cell loss[62,63] (FIG. 3b,c). Consequently, as glomerular size increases, podocyte density declines and horizontal shear stress on podocytes rises[53,64,65]. Compensatory increases in filtration surface might remain stable following uninephrectomy but stressors that increase the filtration load (for example, weight gain, pregnancy or diabetes) or further nephron loss (for example, AKI or persistent kidney injury) potentially elevate podocyte shear stress in the remaining nephrons. This increase can lead to disruption of the podocyte layer, podocyte detachment and loss, and can initiate glomerulosclerosis[29,53,63,66] (FIG. 2).

In the proximal tubule, the higher amount of filtrate demands an increase in reabsorption capacity, which is achieved through the upregulation of transporters, and by increasing tubule diameter and length[54]. Whether the epithelial cells of the proximal tubule increase in number, size or ploidy has not been fully elucidated and might differ after uninephrectomy in patients with obesity or diabetes, or after injury-related nephron loss[67] (FIG. 2). Greater filtrate loads also lead to an increase in the diameter of distal tubules and collecting ducts but the underlying mechanisms are unclear[68]. In advanced CKD, the remaining nephrons are few and large (FIGS 3d,e). Injury-related nephron losses are associated with substantial interstitial fibrosis, which stabilizes enlarged remnant nephrons[69]. However, interstitial fibrosis increases the distance between peritubular vessels and the tubular lumen (FIG. 3f), which compromises the diffusion of metabolites between the tubules and the vasculature, and might therefore further impair the function of the remnant nephrons (FIG. 2). Of note, little evidence supports the concept that the fibrotic interstitial matrix per se induces nephron loss[70].

Nephron overload and irreversible cell loss. Physiological loss of podocytes and shedding in normal urine is well documented and probably contributes to the development of glomerulosclerosis during healthy kidney ageing[71]. The capacity of kidney epithelial cells to withstand haemodynamic and metabolic stress is limited, and hence chronic persistent nephron overload leads to epithelial cell loss by detachment[63] (FIG. 3c). This effect has been well described for podocytes in states of persistent glomerular hyperfiltration using electron microscopy[53,72], immunostaining or lineage tracing of podocytes within cellular casts inside tubules[73] or urine[74], or by measuring 'podocyturia', which is a quantitative biomarker of CKD progression[75].

Similar stress-related cell loss occurs in tubule epithelial cells, especially in proteinuric glomerular diseases because the metabolic activity of proximal tubule cells greatly increases to enable the enhanced uptake, breakdown and processing of the filtered proteins[76]. This metabolic stress triggers not only tubulointerstitial inflammation but also the detachment and irreversible loss of proximal tubule cells[76]. Although patients with chronic nephropathies do not typically present with urine containing a 'muddy brown sediment' with abundant granular casts, which is observed in patients with acute tubular necrosis, their urinary sediment often contains detached tubule cells[71] (FIG. 3d). Indeed, single-cell RNA sequencing has revealed the presence of a vast diversity of tubule epithelial cells in the urine of patients with diabetic kidney disease[71].

In addition to environmental stress, genetic polymorphisms can increase susceptibility to cell loss. Important examples include the *APOL1* risk alleles, variants of podocyte genes involved in the maintenance of the slit diaphragm or the podocyte cytoskeleton (for example, mutations in *NPHS1* or *NPHS2*, which are associated with focal segmental glomerulosclerosis lesions), and mutations in collagen type IV genes that compromise the

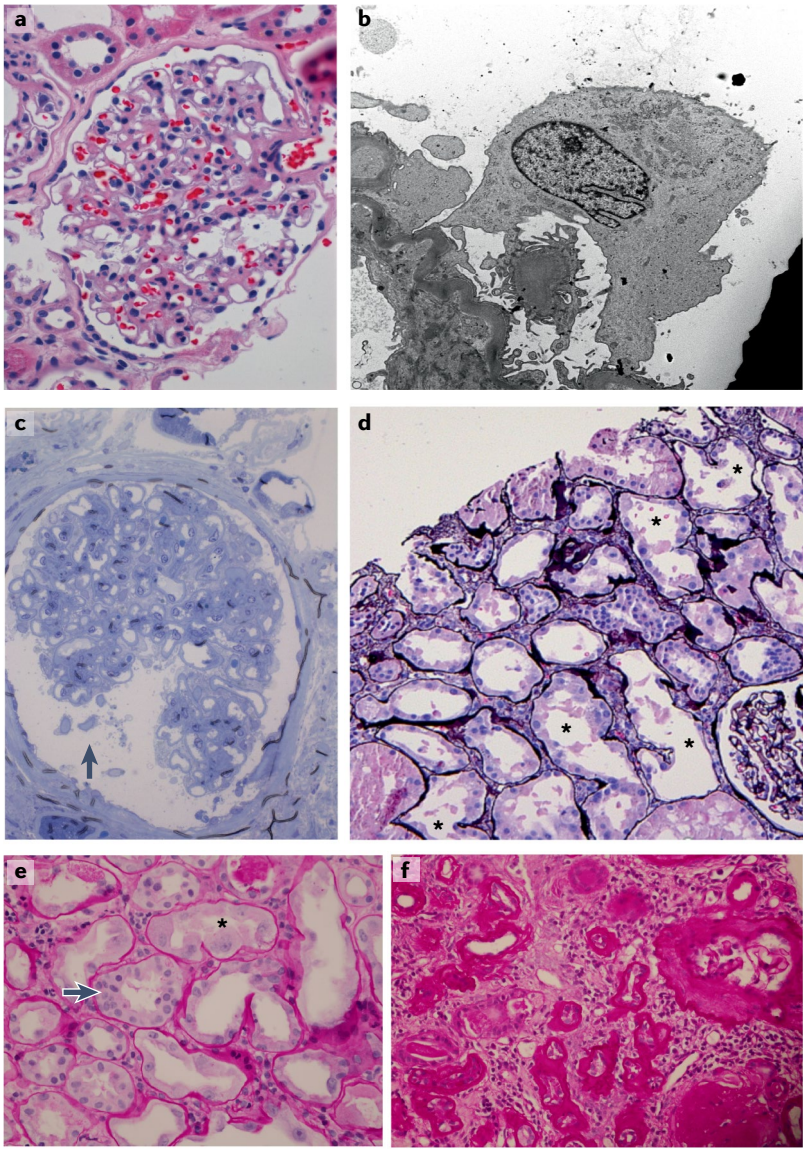


Fig. 3 | **Structural adaptations of nephrons.** Glomerular hypertrophy (also termed glomerulomegaly) is a structural hallmark of adaptation to haemodynamic overload that occurs in diabetes or when the number of nephrons is inadequate for the organism's body mass (panel **a**, kidney biopsy sample from a 32-year old man with advanced sickle cell nephropathy showing hypertrophic remnant glomeruli; glomerular cross section diameter >180–200 μm; periodic acid–Schiff (PAS) stain; ×200). As the filtration surface increases, podocytes stretch to maintain coverage of the expanding surface area. Five stages of glomerular change in response to glomerular enlargement have been described in experimental animals: stage 1, normal resting podocytes; stage 2, non-stressed podocyte hypertrophy; stage 3, adaptive podocyte hypertrophy with structural podocyte component synthesis (panel **b**, kidney biopsy sample from of a 52-year-old man with chronic kidney disease (CKD) showing increased podocyte cytoplasmic volume; transmission electron microscopy; ×4,000); stage 4, decompensated podocyte hypertrophy manifested by loss of key proteins (for example, Wilms tumour protein, podocalyxin and nephrin); stage 5, podocyte detachment (panel **c**, kidney biopsy sample from a patient with advanced diabetic kidney disease; the arrow indicates loss of podocytes in the urinary space; toluidine blue stain; ×100). Podocyte loss into the urine is the dominant consequence of segmental or global glomerulosclerosis following podocyte detachment. Primary tubulointerstitial diseases lead to tubule epithelial cell injury and loss in the urine (panel **d**, kidney biopsy sample from a 48-year-old individual with focal segmental glomerulosclerosis and heavy proteinuria; asterisks show tubule epithelial cell loss; silver stain; ×100). In CKD, some tubules undergo adaptive hypertrophy leading to enlarged tubule epithelial cells (panel **e**, kidney biopsy sample from a patient with CKD; the asterisk marks enlarged tubular epithelial cells and the arrow shows focal hyperplasia; PAS stain; ×100). Severe loss of epithelial cells results in tubular atrophy and the presence of remnant atubular glomeruli that do not contribute to kidney function; atrophy can be associated with diffuse interstitial fibrosis (panel **f**, kidney biopsy sample from a patient with CKD; PAS stain; ×200), although fibrosis rarely precedes tubular injury and atrophy, suggesting that it is a consequence rather than a cause of nephron loss.

integrity of the glomerular basement membrane and the filtration barrier[64].

The primary mechanisms that drive progressive CKD from primary tubulointerstitial diseases differ from those underlying the progression of primary glomerular diseases because, in tubulointerstitial diseases, haemodynamic overload only occurs at advanced disease stages[77]. Specifically, the primary pathology leads to tubular epithelial cell injury and loss accompanied by interstitial inflammation and fibrosis[77]. The remaining epithelial cells must then compensate to meet the metabolic demand, which requires cellular adaptations that trigger further interstitial inflammation and fibrosis, leading to CKD progression and tubular atrophy[78].

Risk factors for nephron overload-induced CKD. The ability to compensate for nephron loss without compromising kidney homeostasis depends not only on nephron number but also on the haemodynamic and metabolic overload of the kidney (BOX 1). For example, in hyperglycaemic states, increased sodium and glucose reabsorption in the proximal tubule disrupts vascular autoregulation and single-nephron hyperfiltration ensues[49,50]. Obesity and/or a salt-rich diet also increase haemodynamic and/or metabolic kidney overload[79]. Importantly, the reduced ability to enhance nephron function in response to additional demand, and persistent single-nephron hyperfiltration and hyper-reabsorption are central pathogenic mechanisms in CKD progression[80,81]. A hyperfiltering kidney is therefore more vulnerable to additional metabolic demands or increased filtration pressures[60]. For example, the risk of CKD after kidney donation increases with donor BMI, which suggests that the threshold at which single-nephron hyperfiltration can no longer be maintained without tipping the balance towards proteinuria, podocyte loss and progressive glomerulosclerosis is reached earlier in individuals with increased metabolic demand owing to body weight[57]. Similarly, individuals with reduced kidney functional reserve, for example, due to low nephron endowment and/or obesity, have a higher risk of progressing to mesangial expansion with diffuse and nodular glomerulosclerosis in the setting of

hyperglycaemia than those with preserved kidney functional reserve[80,82]. By contrast, in lean individuals and/or those with high nephron endowment, diabetic kidney disease is less likely to develop, or to develop only after decades of poor control of hyperglycaemia or in the presence of other risk factors[82].

Nephron overload as a CKD therapeutic target

Diabetes, obesity, pregnancy, systemic hypertension and high dietary protein intake increase GFR and promote haemodynamic nephron overload[81,83]. Similarly, dilation of the glomerular afferent arteriole probably underlies the increase in proteinuria caused by medications that increase GFR, such as the antihypertensive dihydropyridine calcium channel blockers[84,85]. Indeed, dihydropyridine calcium channel blockers might not attenuate CKD progression unless systolic blood pressure is controlled such that intraglomerular pressure does not increase[86]. The anti-inflammatory drug bardoxolone can also immediately increase GFR and proteinuria[87], which has raised concerns that it might not only lack renoprotective effects but might accelerate glomerular injury and annual GFR loss by exacerbating hyperfiltration[88,89] (FIG. 4a). However, bardoxolone can also enhance the expression of antioxidative genes[90], which might reduce metabolic stress and/or endothelial dysfunction, and could outweigh its potential contribution to nephron overload. The overall effect of this drug on GFR decline remains under investigation. Interventions that might increase nephron overload must therefore be used with caution, especially in individuals with additional risk factors for CKD progression, such as diabetes and hypertension[88,89]. By contrast, drugs that reduce the haemodynamic and metabolic workload of nephrons (for example, inhibitors of the renin–angiotensin–aldosterone system (RAAS) and sodium–glucose co-transporter 2 (SGLT2) inhibitors[91–93]), prolong kidney lifespan (FIG. 4b). This effect would be similar to that of β-blockers, which increase heart lifespan in patients with cardiac failure by reducing cardiac workload. In view of the pathophysiology of the structural and metabolic adaptation to nephron overload, such interventions should be initiated early to attenuate the irreversible kidney damage caused by maladaptive responses[94].

Treatment of CKD has two interconnected goals — reducing cardiovascular events and mortality, and slowing CKD progression[36]. Adequate management of anaemia and blood pressure, glycaemic control (in patients with diabetes), use of lipid-lowering and antiplatelet agents, a healthy diet and physical activity contribute to both goals[1,95–98]. Among these factors, treating hyperglycaemia and hypertension, weight loss, reduction of animal protein and salt intake, and RAAS inhibition have thus far been the main approaches to mechanistically reduce proteinuria and CKD progression by attenuating haemodynamic and metabolic nephron overload[1,83] (FIG. 5a).

Currently, the most effective strategy to reduce nephron overload in CKD involves the combination of RAAS and SGLT2 inhibitors (FIG. 5b). The relative risk reductions in clinical trials of SGLT2 inhibitors have been impressively large such that the risks of substantial eGFR decline (>40% or >50%), kidney failure and death due to kidney or cardiovascular disease are reduced by ~40% compared with the standard-of-care (that is, RAAS inhibition with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker)[91–93,99–101]. Importantly, the renoprotective effect of SGLT2 inhibitors is observed in patients with CKD, with or without diabetes[102]. Clinical trials investigating SGLT2 inhibitors were the first in the field of nephrology to be stopped early for overwhelming efficacy and dapagliflozin is the first therapeutic for kidney disease to demonstrate a reduction in all-cause mortality[91,92,103], which offers hope to all patients with (proteinuric) CKD. Whether dual RAAS–SGLT2 inhibition can have similar renoprotective effects in patients with tubulointerstitial forms of CKD, including polycystic kidney disease or non-albuminuric forms of CKD or in kidney allograft recipients remains unclear.

In patients with CKD and diabetes, alternative treatment options continue to emerge. Several glucagon-like peptide 1 (GLP1) receptor agonists, which are glucose-lowering agents, have protective effects on the kidneys and heart in patients with type 2 diabetes, from early to advanced stages of CKD. GLP-1 receptor agonists are thought to primarily reduce kidney injury by antioxidant and antifibrotic actions rather than effects on glomerular haemodynamics and metabolic workload of the tubules[104]. In addition, the mineralocorticoid receptor antagonist finerenone has been shown to reduce the risk of major kidney disease end points (40% eGFR decline, kidney failure or death due to kidney disease) in patients with type 2 diabetes and CKD[105]. This agent has less prominent glomerular haemodynamic actions than SGLT2 inhibitors and might exert its protective effect through attenuation of inflammation and fibrosis[106]. The SONAR trial[107] also showed a potential

Box 1 | **Nephron overload and the risk of CKD progression — an example**

An 80-year-old individual with no previous kidney disease has 50% of nephrons left owing to physiological ageing and a total glomerular filtration rate (GFR) of 50 ml/min/1.73 m^2:

- Scenario A: In the absence of obesity, diabetes, proteinuria, or other risk factors or injury, the remaining number of nephrons is sufficient for the needs of an 80-year-old body. Filtration pressure and single-nephron GFR will be normal and hence nephron dimensions (that is, glomerular size) will also be normal. Annual GFR decline will be <1 ml/min/1.73 m^2/year and will remain in the same percentile. Glomerulosclerosis and interstitial fibrosis seen in such kidneys would reflect normal ageing and renin–angiotensin–aldosterone (RAAS) or sodium–glucose cotransporter 2 (SGLT2) inhibition would be unlikely to alter the risk of CKD progression.
- Scenario B: In the presence of obesity, diabetes or proteinuria (or a combination of these risk factors), glomerular hyperfiltration (that is, an increase in single-nephron GFR) and tubular hyper-reabsorption (leading to oxidative stress) might induce structural adaptations on the remaining nephrons (namely, glomerulomegaly and tubulomegaly). These alterations accelerate the loss of podocytes and tubule cells, leading to kidney atrophy. Annual GFR loss will be >1 ml/min/1.73 m^2/year and therefore result in a decrease in GFR percentile. In addition to optimizing body weight, glycaemic control and salt intake, such an individual would probably benefit from a reduction in the haemodynamic and metabolic overload of the remaining nephrons with dual RAAS–SGLT2 inhibition. This benefit is probably independent of the cause underlying the initial nephron loss (for example, diabetic kidney disease or IgA nephropathy)[91].

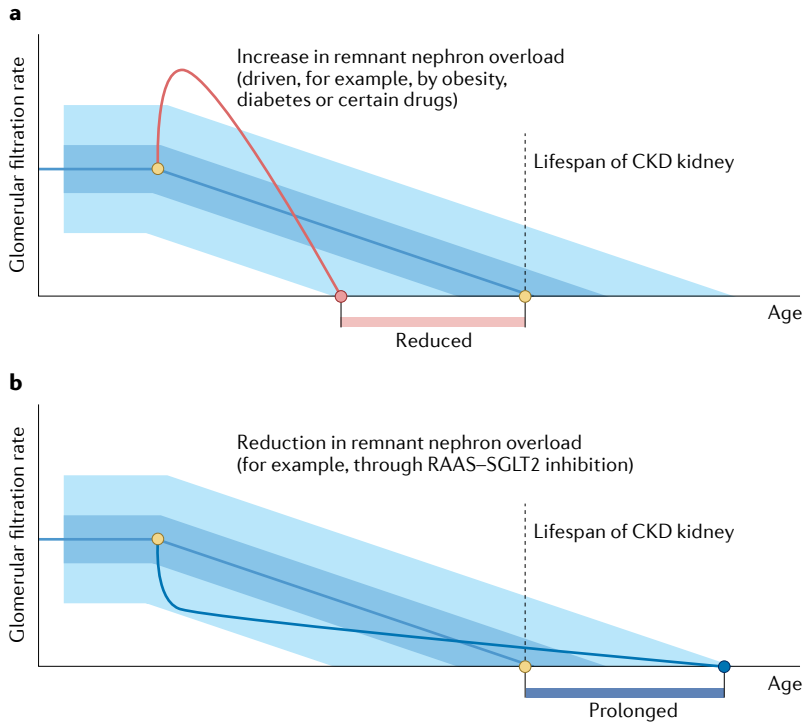


Fig. 4 | **Modulation of haemodynamic and metabolic overload, and its effect on kidney lifespan. a** | In patients with chronic kidney disease (CKD), conditions that increase glomerular filtration rate (GFR) and therefore haemodynamic overload, such as diabetes or obesity, are well known risk factors for increased proteinuria and accelerated disease progression. The initial increase in single-nephron GFR (red line) becomes maladaptive over time and leads to further nephron loss, resulting in a shortened kidney lifespan. **b** | Kidneys in which remnant nephrons are overloaded should benefit from a reduction in haemodynamic and metabolic load to increase kidney lifespan. Inhibitors of the renin–angiotensin–aldosterone system (RAAS) and of sodium–glucose cotransporter 2 (SGLT2) initially reduce GFR (blue line) and are associated with renoprotective effects that are likely to extend kidney lifespan.

role for endothelin A receptor blockade, as atrasentan reduced the risk of the composite kidney end point of doubling of serum creatinine, kidney failure or kidney disease death in patients with CKD and diabetes by 35%. Endothelin A blockade interferes with multiple mechanisms of CKD progression as it promotes a reduction in glomerular haemodynamic pressure, in injury of endothelial cells and podocytes, and in inflammation in the tubulointerstitium and glomerulus[108]. Moreover, a post hoc analysis of the SONAR trial revealed that patients who concurrently received SGLT2 inhibitors during the atrasentan enrichment phase had an additional reduction in albuminuria of nearly 30% and fluid retention was mitigated by a mean of 1.2 kg, which suggests that this drug combination might have synergistic efficacy and safety benefits[109].

These clinical trials now define CKD as a treatable entity and offer a growing selection of therapeutic agents for patients with and without the CKD-accelerating risk of diabetes. Although disease-specific treatments remain the mainstay of CKD treatment, particularly during the early stages of the disease, before the reduction in nephron number and consequent nephron overload, the ability to attenuate nephron overload as a pathway towards kidney dysfunction shared by a variety of kidney diseases with different aetiologies, is poised to provide renoprotection and reduce CKD-associated cardiovascular risks. This broad potential is especially important because the cause of CKD is frequently unknown, or specific therapies that target the causal mechanism are not available. In addition, multifactorial CKD is highly prevalent and CKD is often diagnosed only after substantial kidney damage has already occurred (that is, when the kidney can no longer compensate for nephron overload)[36,82]. Importantly, CKD due to tubulointerstitial disorders, where mechanisms of tubular injury and interstitial fibrosis prevail, might especially benefit from therapies that target inflammation, fibrosis and epithelial stability (FIG. 5c). However, once nephron loss has introduced glomerular hyperfiltration and excessive tubular reabsorption in the remnant nephrons, RAAS–SGLT2 inhibition might attenuate further CKD progression (FIG. 5b).

Given that CKD and its major risk factors are extremely common, collaboration between nephrologists and primary care clinicians, diabetologists and cardiologists is essential for early detection and intervention at a time point when treatments are likely to have the greatest chance of success. Better definition of CKD and development of interdisciplinary teams that advocate for the care of patients with CKD will help to address this challenge[110].

Economic and sociopolitical barriers. The emerging toolbox of drugs available to address nephron overload to attenuate CKD progression are highly promising, but they will mainly benefit patients in high-income countries where kidney care is covered by medical insurance or universal health coverage. In the low-resource settings of the Majority World, where the need for intervention might be greatest, these new agents are unlikely to be available at affordable prices and at scale. Inequities in access to care for kidney failure arise from the high costs of medications, dialysis and transplantation[111]. In high-income countries, individual health-care costs (related and unrelated to CKD) increase exponentially as disease advances — from 1.1–1.7-fold higher health-care costs than in the general population in the early stages of CKD, to 1.3–4.2-fold higher in the late stages of the disease[112]. Among patients with advanced disease, most of the health-care spending originates from the high-level care needs of a small number of patients[113]. Compared with the general population, costs for haemodialysis, peritoneal dialysis and transplantation are 45-fold, 29-fold and 11-fold higher, respectively[112,114]. In low-income settings, the costs of dialysis for an individual might reach >100-fold the average health expenditure per person[115]. Moreover, patients with kidney disease frequently have comorbidities that increase in severity as CKD progresses and the need for additional health care for these comorbidities further increases the associated costs[116].

The risk of kidney disease is strongly associated with social and structural factors hence, addressing the Sustainable Development Goals might reduce the global burden of kidney disease by improving prevention[39]. Several population-level prevention measures would not only improve overall health but might also reduce the burden of kidney disease indirectly — for example, by reducing the prevalence of obesity, limiting environmental

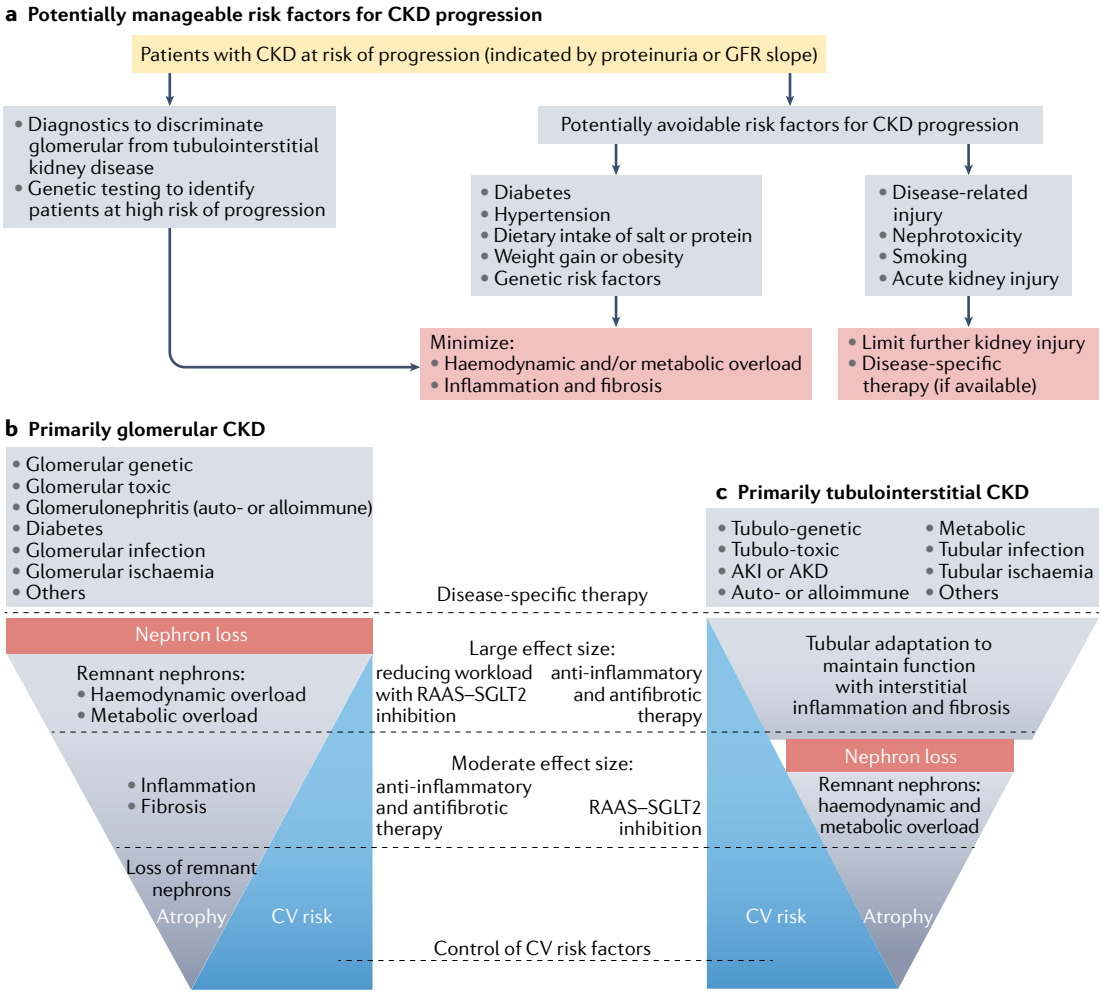


Fig. 5 | **Pathophysiological mechanisms and treatment targets in glomerular versus tubular forms of CKD.** **a** | Many risk factors for chronic kidney disease (CKD) progression can be managed to reduce risk. Injury-related risk factors include specific kidney diseases, for which there might be disease-specific therapies (for example, myeloma, infection or autoimmunity). However, the central element of CKD treatment is primary prevention of further injury as well as primary prevention or treatment of haemodynamic and metabolic overload in the remnant nephrons. This approach includes optimization of body weight, glucose and blood pressure, and dietary measures. Dual inhibition of the renin–angiotensin–aldosterone system (RAAS) and sodium–glucose cotransporter 2 (SGLT2) also decreases nephron overload. Targeting tissue inflammation and fibrosis might have additional benefits, especially in patients with primary tubulointerstitial disease. Genetic testing for *APOL1* and other gene variants that compromise kidney cells and structures can help identify patients at risk of accelerated CKD progression in all forms of kidney disease who might benefit the most from these therapeutic interventions. **b** | For decades, two competing concepts have tried to explain CKD: the Brenner theory of glomerular hyperfiltration and the central role of interstitial fibrosis. Current clinical trial data from dual RAAS–SGLT2 inhibition provide strong support for the former hypothesis of haemodynamic and metabolic overload as the central upstream driver of CKD progression when the underlying kidney disease is a primary glomerular disorder. Part **b** adapted with permission from REF.[129], Oxford Academic. **c** | However, patients with primary tubulointerstitial disorders such as polycystic kidney disease, acute kidney injury (AKI)-induced CKD, interstitial nephritis, nephrocalcinosis and genetic tubulopathies were excluded from these trials. Dual RAAS–SGLT2 inhibition might not benefit these patients as much as those with glomerular disease because nephron loss and adaptive hyperfiltration occur downstream of tubular injury; however, the metabolic benefits might be important. For patients with tubulointerstitial diseases, promoting anti-inflammatory, cytoprotective and antifibrotic pathways might be an effective first-line treatment. AKD, acute kidney disease; CV, cardiovascular; GFR, glomerular filtration rate.

pollution, or improving access to safe water and hygiene. Of note, the cost-effectiveness of such measures is not easy to determine as it might not be possible to estimate how many CKD cases would be prevented.

Screening for CKD would permit early diagnosis and early initiation of affordable medication to prevent CKD progression effectively. However, screening measures in the general population have thus far not been found to be cost-effective[117,118]. Importantly, these studies all predate the availability of SGLT2 inhibitors, which might substantially alter such calculations as indicated by a cost-effectiveness analysis based on the characteristics of the patients in the CREDENCE study cohort modelled for the UK National Health Service in England[119].

A screening strategy does appear to be cost-effective when targeted to individuals with known risk factors for CKD such as hypertension or diabetes[118]. Screening of individuals with additional risk factors such as low birthweight or preterm birth might also be cost-effective. Of note, screening data have been derived from high-income settings; whether screening is a cost-effective approach in low-income settings remains unknown and should be a research priority[117]. Given the high costs of dialysis and transplantation, kidney failure means almost certain death in many low-income settings[120]. Thus, the 'value' of screening and the imperative to diagnose and treat early might be considerably different in the Majority World compared with high-income settings. Additionally, low-income regions often lack high-quality primary health care, and issues related to the appropriateness of prescriptions, as well as the availability and affordability of medications are common — improved diagnosis alone is therefore not enough to improve patient outcomes[120,121]. Whether raising expectations with screening that cannot be met by health-care systems in low-resource settings will cause unanticipated harms remains to be investigated and should fuel calls to improve the quality and capacity of primary care globally[117].

Conclusions

Haemodynamic and metabolic overload of remnant nephrons is a central pathogenic mechanism in CKD progression but remains difficult to detect early in clinical practice. A marker of nephron number that could be implemented in the clinic would be ideal as it would permit the calculation of SNGFR as the total GFR divided by nephron number, and therefore enable the detection of hyperfiltration even when total GFR is normal or slightly reduced[122–126]. Such a marker is not yet available. Given the natural age-associated decline in GFR, historical longitudinal data from health records can be used to calculate individual eGFR slopes to identify individuals with a rate of GFR decline that exceeds that expected to be induced by ageing alone. Such individualized historical eGFR trends would be more accurate than single time-point eGFR comparisons with population-level distributions. However, currently no consensus exists on how age should be used as a criterion in CKD diagnosis, possibly because classing the kidneys of older individuals with histological glomerulosclerosis, and/or modest scattered interstitial fibrosis and tubular atrophy as 'healthy' is considered problematic.

The stratification of individuals according to age-specific GFR percentiles would clarify whether GFR loss is pathological or an expected consequence of aging, and would improve the prediction of an individual's risk of CKD progression beyond the current matrix of total eGFR and albuminuria, which overestimates disease risk in people with healthy kidney ageing and might lead to unnecessary treatment, and might also underestimate the risk in younger people and lead to lost opportunities for intervention.

The molecular mechanisms underlying the adaptive responses of the kidney tubules to metabolic overload and kidney stress are less well understood than those of the glomeruli. Specifically, the (patho)physiology of tubule cell stress, cell loss, compensatory hypertrophy of remnant differentiated tubule epithelial cells and the capacity of progenitor cells to regenerate lost tubule cells remains poorly described. In addition, the pathophysiology of the few enlarged nephrons that sustain residual kidney function in advanced CKD warrants investigation.

The concept of kidney lifespan inspires the ambition to target and maximize kidney failure-free lifetime in patients with CKD far beyond current treatment goals. Patients with indicators of kidney overload such as an annual GFR decline beyond that due to healthy ageing, albuminuria and/or obesity, as well as patients with diets rich in salt and animal protein, might benefit from RAAS–SGLT2 inhibition to reduce nephron overload and prolong their kidney lifespan. Adding other drugs to this combination might further expand kidney lifespan and potential new candidate drugs continue to emerge[127,128].

However, equitable access to these novel treatments remains a challenge. Most patients with CKD do not receive nephrology care and primary care physicians might lack adequate training to be able to identify individuals at risk of CKD progression who might benefit from such treatments. Solving this logistical problem is important. More cost-effectiveness data are required in the era of SGLT2 inhibition, including from diverse health systems to identify which populations should be targeted for screening and early intervention. Advocacy is needed at all levels to alert decision makers and the public to the potential benefits of early interventions, especially in countries with limited access to kidney replacement therapies.

These are exciting times for health-care professionals and for those living with kidney diseases. The framework presented here might help to better conceptualize CKD not only by integrating new information into existing knowledge but also by distilling decades of debates about CKD pathophysiology and care. This unified concept of CKD progression, and the centrality of pathogenic mechanisms in glomerular and tubulointerstitial forms of CKD might help advance the way we approach kidney disease to maximize kidney lifespan along with longevity.

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