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REVIEW

The conundrums of chronic kidney disease and aging

Richard J. Glassock[1,3] · Aleksandar Denic[2] · Andrew D. Rule[2]

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Abstract Chronic kidney disease (CKD), as presently defined, is a common disorder. Aging is a nearly universal phenomenon that can affect renal anatomy and function, but at variable rates in individuals. Loss of nephrons and a decline in glomerular filtration rate (GFR) is a characteristic of normal aging, called renal senescence. Using fixed and absolute thresholds for defining CKD on the basis of GFR for all ages may lead to diagnostic uncertainty (a conundrum) in both young and older subjects. This brief review will consider the physiological and anatomical changes of the kidney occurring in the process of normal renal senescence focusing on GFR and will examine the relevance of these observation for the diagnosis of CKD using GFR as the distinguishing parameter. Once a better understanding of the pathobiology underlying renal senescence is obtained, specific interventions may become available to slow the process.

Introduction

Chronic kidney disease (CKD), as presently defined, is a common disorder afflicting millions of persons on a worldwide basis, although the incidence rate of CKD appears to be plateauing in many developed countries of the world [1]. Aging is a nearly universal phenomenon (only the genus Hydra is exempted) [2], affecting the function of many organs, including the kidneys [3–5]. In addition, the rate of biological aging varies considerably, even in genetically identical members of the same species. Importantly, many portions of the world are experiencing a substantial higher frequency of elderly in their population, in part, due to a longer human life expectancy [6]. Thus, it is not surprising that the intersection of CKD and aging has created some challenging questions (conundrums) [7]. Among many, these include: (a) what physiological and anatomic processes lead to loss of glomerular filtration rate (GFR) as the aging process proceeds? (b) Should the definitions of CKD be the same in young and old adults? (c) What are the consequences of normal, physiological aging of the kidneys on mortality and morbidity? (d) Can the process of renal aging be altered in a beneficial way? These questions will be addressed in this brief review.

The loss of GFR with aging

A steady decline of GFR (averaging about 0.75–1.0 ml/min/1.73 m^2/year) with aging in otherwise normal adult individuals has been consistently observed in many cross-sectional studies employing estimated (eGFR) as well as measured GFR (mGFR) [8, 9]. Long-term longitudinal studies are far less frequent, for obvious reasons [10]. Taken together, these studies indicate that the trajectory of decline in GFR with aging is quite variable, and often, but not always, independent of blood pressure or cardiac hemodynamics [11, 12], but usually shows a Gaussian distribution, sometimes with a "tail" of accelerated loss of GFR (or creatinine clearance, depending on the study). Some longitudinal studies have claimed stable, or even increasing, levels of GFR for long periods in "healthy" aging, but these have been criticized for including Type 2 diabetics

✉ Richard J. Glassock
glassock@cox.net

[1] Geffen School of Medicine at UCLA, Los Angeles, CA, USA

[2] Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

[3] Present Address: 8 Bethany, Laguna Niguel, CA 92677, USA

and for limitations of calculating a true slope of GFR over time due to a limited number of observations [9]. The predominate view is that in otherwise normal and healthy adults the GFR begins to decline after about age 30 years with some acceleration in the rate after about age 80 years [13–15]. Given this assumption, what accounts for this phenomenon?

Although many animal species exhibit similar changes, the most relevant studies are those that have been carried in humans. In this regard, renal transplantation using living donors has provided a unique opportunity to examine this question [16–19]. Precise measurement of GFR (mGFR) can be performed in very healthy (by definition) living donors, along with CT scans and pre-implantation renal biopsies to assess renal macro- and micro-anatomy [20–22]. Since the donors span a wide range of ages, it is possible to probe the relationships between function and anatomy over many decades of aging. These studies have characterized the changes in total kidney, cortical and medullary volumes with health aging, as well as iothalamate clearance as a direct measurement of GFR (Fig. 1) [21, 23]. More relevant to this discussion are the changes in micro-anatomy, specifically glomerular and tubular alterations and glomerular number [20, 23, 24]. The latter can be assessed by counting glomeruli in a renal biopsy specimen, applying Weibel and Gomez stereological models to estimated 3-dimensional glomerular density (number of glomeruli per mm^3), and determining the cortical volume (in mm^3) by three-dimensional reconstruction of CT images [23]. In brief, aging is associated with a rise in the frequency of globally sclerotic glomeruli and a decrease in the total number of non-sclerotic and sclerotic glomeruli, indicating the likelihood that sclerotic glomeruli undergo a process of re-absorption [23]. Thus, at any given point in time (age) the number of functioning (non-sclerotic) glomeruli remaining is a function of the number of nephrons (glomeruli) present at birth (nephron endowment) and the subsequent rate of loss of nephrons with advancing age. The latter appears to decline at a relatively constant rate, with a possible exception of more accelerated decline after the age of 70 years [23]. Glomerular hypertrophy also develops, but this is more conditioned by nephron endowment at birth and certain stressors such as obesity, rather than by loss of glomeruli from the aging process alone. From a functional perspective, whole kidney GFR (wkGFR) declines in parallel with nephron loss, and unlike disease or surgically induced nephron loss, there is little if any "adaptive compensation" of single nephron GFR (snGFR), except perhaps when the nephron loss is severe at the extremes of life. Nephropenia and hypo-filtration in aging are associated with global glomerulosclerosis and stable snGFR [25] while disease-induced and ablation nephropenia and hypofiltration are associated with focal and segmental glomerulosclerosis and an adaptive rise in snGFR in less affected nephrons [26–28]. Interestingly marked albuminuria is not a feature of aging-associated nephrosclerosis [24] whereas it is common in disease-induced and ablation nephropenia [29].

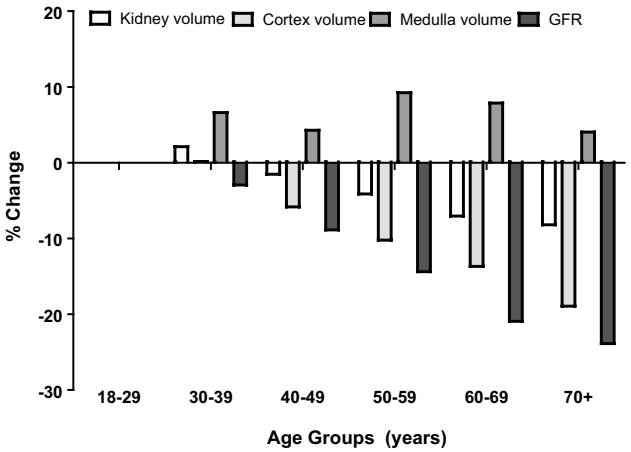

Fig. 1 Percentage change in total kidney, cortical and medullary volumes, and measured GFR among 1638 healthy living kidney donors (Figure made from published data [21]). Overall, when compared to 18–29 year olds, total kidney volume, cortical volume and GFR decline with aging. Until 50 years of age, total kidney volume appears not to decline because of combined effect of cortical volume decline and medullary volume increase. Beyond this point, total kidney volume starts to decline but to a lesser extent than cortical volume, due to relatively stable medullary volume. Interestingly, GFR decline seems to be proportional to the decline in cortical volume

It seems reasonable to assume that the loss of nephrons with aging proceeds as a result of glomerulosclerosis and that the tubulo-interstitial changes observed are secondary to glomerular obsolescence. However, it is acknowledged that the wkGFR decline in disease states shows a good correlation with the degree of chronic tubulo-interstitial fibrosis and tubular atrophy [30], but whether these changes can be inferred to be casually connected to the decline in GFR is uncertain. Studies in aging rats have provided evidence for peritubular capillary rarefaction and renal ischemia, perhaps related to glomerulosclerosis, in the pathogenesis of tubulo-interstitial alterations seen with aging [31].

It is also worth emphasizing that in states of hypo-filtration, nephron endowment at birth is an important modifying factor [32, 33]. Nephron endowment at birth is highly variable and influenced by multiple factors, including maternal malnutrition, utero-placental insufficiency, and exposure to nephrotoxic agents. Low birth weight and possibly short adult stature are surrogates for low nephron endowment. Starting life's journey with a deficit in nephrons is very likely to have an effect on the aging kidney, that is characterized by progressive nephron loss. Adaptive changes in snGFR shortly after birth may restore whole kidney

GFR to "normal" as the expense of hyperfiltration in the remaining nephrons. With aging and further nephron loss there may be little further adaptation of snGFR so the number of nephrons remaining parallels the decline in whole kidney GFR (except possibly at the extremes of old age). The main point is that if one begins life with a deficit in nephrons, future physiological renal senescence tip an individual patient under the threshold of GFR used to define CKD. Thus, it can be postulated that some cases of "CKD" in older adults is primarily the consequence of the "bad luck" if being born with too few nephrons. If this postulate is true it opens an avenue of a primary preventative strategy focused on improving in-utero nephrogenesis and minimizing damage to an already reduced nephron mass in early infancy. It is not possible to predict the degree of nephrosclerosis in renal biopsies by examining wkGFR alone at any age in healthy normal subjects [24]. While the anatomic and functional changes associated with healthy aging have been well described in animals and man, progress in unravelling the molecular and cellular pathways responsible for these changes have been tantalizingly slow, and we still have much to learn.

Age and the definition of CKD

Ever since "generic" CKD was first defined in 2002 [34], controversy has arisen over whether the same GFR criteria can be applied equally across the age spectrum, and no consensus has yet appeared to resolve the differences of opinion [35–38]. The connotations of this debate are far-reaching as an aging society will generate many new cases of CKD from an age-insensitive definition of CKD based on fixed and immutable thresholds of GFR. The original decision to select a threshold of <60 ml/min/1.73 m^2 regardless of the presence or absence of features of "kidney damage" (e.g. abnormal albuminuria, urinalysis, imaging, or biopsy) was in a real sense arbitrary, as the evidence pertaining to the prognostic effects of a reduced GFR had not yet been analyzed extensively. In retrospect it was a reasonable decision as the value was about 50% of the mGFR of a healthy 20 year old adult (standardized to 1.73 m^2 BSA). Subsequent extensive epidemiological studies involving millions of subjects corroborated the notion that a decline in GFR below this threshold was associated with an increased risk of adverse events [mortality, ESRD, Acute Kidney Injury (AKI)] and this risk was aggravated by the concomitant presence of abnormal albuminuria (in a graded, non-threshold manner) [39–43]. In a seminal study, Hallan et al. showed that the risk of adverse events from a reduced GFR was blunted by age, but increased in an absolute and relative manner in all ages when GFR fell below 60 ml/min/1.73 m^2 [44]. In a re-analysis of the same data we suggested that all-cause mortality was lowest at values of GFR >75 ml/min/1.73 m^2 in young adults and lowest at values of GFR down to 45 ml/min/1.73 m^2 in older adults [19]. Other epidemiological studies have shown no excess mortality or curtailment of remaining life-expectancy in elderly adults with GFR in the range of 45–59 ml/min/1.73 m^2 *in the absence of albuminuria* [45, 46]. There is broad agreement that any increase in albumin excretion rate above average normal values is associated with an increase in risk of adverse events, including mortality, ESRD and AKI. This has led to calls for adjusting the definition of CKD (Stage G3A/A1 according to KDIGO) to make it more "age-sensitive" and to avoid over-diagnosis of CKD in the rapidly blooming elderly population [34, 47]. One could also argue for an upward adjustment of the GFR threshold to about 75 ml/min/1.73 m^2 in young persons, so as to avoid under-diagnosis of CKD in this portion of the population. Supporting this notion, re-analysis of Hallan et al. data shows that for ages 18–54 years, the adjusted hazard ratios for those with GFR of 60–74 ml/min/1.73 m^2 versus those with GFR >105 ml/min/1.73 m^2 is 1.54 (when albumin to creatinine ratio is <10) [19]. In addition, a literature review of the normal GFR range in children, adolescents and young adults, supports raising the threshold of CKD for younger patients to 75 mL/min/1.73 m^2 [48].

The widespread use of estimating formulas for GFR (eGFR) adds another layer of complexity to the issue of defining CKD, both in young and elder subjects. Obviously, such eGFR determinations are necessary in large epidemiological studies (N > 10,000) as urinary clearance or plasma disappearance methods for assessing GFR are too costly, cumbersome or difficult to perform on such a large scale [1]. However, they are practical and very informative in smaller (N = 200–2000) cohort studies or clinical trials.

The caveats for use of eGFR in diagnosis CKD are numerous [49–52]. The values are not very precise or accurate, different formulas give different results for diagnosis (especially in aging persons), non-GFR determinants can bias results (sarcopenia for creatinine-based formulas and inflammation, obesity, diabetes and thyroid disease for cystatin C based formulas). Also age itself is a variable in the estimating formulas, and the age coefficient in the formula was optimized for prediction of mGFR not outcomes [1, 50]. These non-GFR determinants can give rise to substantial differences among individual eGFR formulas for estimating risk adverse events [51, 52]. Unique eGFR formulas have been designed and validated for use in the elderly [53]. In addition, progress is being made on devising and testing of new formulas for estimating renal function that can be used in a broad array of ages (The Full Age Spectrum or FAS equation) [54]. However, it is important to understand that a more accurate formula for estimating GFR will itself do nothing to address the problems created

by an age-insensitive single GFR threshold for defining CKD.

An issue of over-riding importance in defining CKD generally is the duration content incorporated into current clinical practice guidelines (e.g. KDIGO). Legitimate CKD can only be recognized if the abnormalities persist for 3 months or longer. The seminal work of Gharbi et al. [55] has highlighted this issue by showing that "one-off" epidemiological studies employing only a single determination of eGFR or albuminuria lead to a significant over-diagnosis of CKD (30% or more) in older adults and under-diagnosis of CKD in more youthful subjects, with over-diagnosis having a quantitative sly greater impact on overall presence of CKD than under-diagnosis. The point is that a single determination of an eGFR less than 60 ml/min/1.73 m^2 can lead to a "false" diagnosis of CKD in many older subjects and therefore the epidemiological estimates of the prevalence of CKD using one-off testing strategies contains significant errors.

The consequences of healthy aging of the kidneys

It is acknowledged that aging exposes individual to diseases that result from the accumulation of tissue injury or genetic mutations in the presence of faulty or decaying systems of repair [3]. Thus, the normal decline of renal function with aging is often entangled with diseases that cluster in the aged, such as diabetes, atherosclerosis, auto-immunity and cancer, any one of which might have a deleterious effect on the kidney. Then too, evidence has gradually assembled indicating that subtle degrees of renal function decline can incite pathophysiological changes that can be directly injurious to non-renal organs or organ systems (e.g. heart, vasculature, endocrine) [39, 45, 56–58]. Disentangling the effects of a physiological aging-related decline in GFR (renal senescence) from "disease" can be very challenging.

Nevertheless, data from analysis of older age populations with GFR values in the range of 45–59 ml/min/1.73 m^2 in the absence of abnormal albuminuria (compatible with a diagnosis of CKD Stage C3A/A1 and also within the 95% confidence limits of a normal GFR for age) have not *consistently* shown any increase in all-cause mortality compared to similarly aged subjects with GFR values >60 ml/min/1.73 m^2 [see 57, 58] also in the absence of abnormal albuminuria and remaining life expectancy is not altered [19, 45]. Of course, the absolute risk of all-cause mortality is increased with aging and some studies have shown that this absolute age-associated risk is enhanced by low GFR [44]. Also, the risk for developing and receiving treatment for ESRD is quite low in such subjects and their risk of dying (usually of cardiovascular disease) is much higher than the risk of reaching treatment for ESRD [46, 59, 60]. Healthy Subjects (living donors) with GFRs in the range of 45–59 ml/min/1.73 m^2 may have some degree of "nephrosclerosis" on renal biopsy, have fewer nephrons when they were age 20 years [24], and may have subtle biochemical alterations, like slightly elevated intact parathyroid hormone (iPTH) levels [61], but can this be called a "disease"? This is a semantic issue that revolves around what is health and what is "disease". If one adopts the stance that a "disease" must have some identifiable morbidity for the sufferer, then an isolated GFR of 45–59 ml/min/1.73 m^2 in an elderly man or woman may not rise to equate with CKD. Also, whether eGFR formulas are suitable in the elderly for avoiding adverse events from a renally toxic agent or a water soluble potentially harmful medication remain uncertain [62, 63]. Unfortunately, we only have observational and not randomized controlled data to examine this issue in a critical fashion.

Altering the phenomenon of renal aging

Like the general problem of life extension by specific interventions, alteration of the rate of renal aging by some "elixir of youth" is more imagination than reality. Anti-aging strategies are under intense investigation [64–66]. Inhibitors of mTOR, calorie restriction, altering sirtuin metabolism are a few of the prominent areas of research. Little progress in expected in altering renal senescence until we more fully understand its patho-biological origins. Since nephron endowment at birth is such an important factor in the determination of the state of GFR in later life, efforts to improve maternal and fetal nutrition and avoiding fetal dysmaturity and prematurity will likely have beneficial effects in the longer term [33, 67, 68]. Therapeutic agents or diets that increase GFR in the short term may have longer term deleterious effects by inducing "hyper-filtration" injury in residual nephrons that have already expended most of their adaptive capacity [69–72]. Certainly, avoidance of nephrotoxic drugs and environmental agents (like smoking and pesticides) are valuable steps, but their overall impact is uncertain. Control of the rise in systolic blood pressure that commonly accompanies aging in non-diabetic subjects, largely due to reduced compliance of large vessels is not likely to be helpful and may be harmful. There is no obvious association between the observed modest elevation of blood pressure and GFR decline in Caucasian, non-diabetic, middle-aged and older adults in the general populations [73]. The situation in African–Americans may be quite different, in part due to the presence of high-risk APOL1 alleles that seem to promote glomerulosclerosis and a decline in GFR [74–76]. It seems likely that post-natal interventions to slow renal senescence in

a clinically meaningful way will need to be introduced early in life (possibly before puberty) and would appropriately be focused on those subjects with a low nephron endowment at birth [77, 78].

Summary and perspectives

The kidneys undergo a systematic decline in nephron mass with aging, largely due to progressive glomerular obsolescence. This seems to be a programmed event whose renal consequences are modified by nephron endowment at birth. Unlike disease-induced or surgical ablation of nephrons, aging glomeruli undergo global glomerulosclerosis and show few signs of adaptive hyperfiltration in residual less-affected nephrons. Correspondingly, whole kidney GFR declines in parallel with the reduction in nephron mass.

When the GFR reaches values of 45–59 ml/min/1.73 m^2, even in the absence of abnormal albuminuria, elderly subjects can be diagnosed as having CKD, even though this may be merely a manifestation of physiological renal senescence, not disease. Errors in defining CKD can be introduced by "one-off" testing of eGFR or albuminuria. Disentangling the effects of co-morbidity and renal senescence can be challenging in individual subjects, but concomitant and persisting abnormal albuminuria/proteinuria is most often a sign of disease. For many subjects without co-existing comorbidity or abnormal albuminuria such a level of GFR may not confer any greatly enhanced risk for shortening of life expectancy or other adverse events. Unfortunately, at present there is little from the interventional perspective that can (or should) be done to modify the loss of GFR with aging, but once a better understanding of the fundamental pathobiology is obtained, specific interventions may be possible. Prevention of the consequences of nephron loss from aging by promoting a more normal nephron endowment at birth (e.g. avoiding premature births or altering fetal dysmaturity) seems feasible.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committees and with the 1994 Helsinki declarations and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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