

# Aging and the Kidneys: Anatomy, Physiology and Consequences for Defining Chronic Kidney Disease

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## Key Words

Aging · Glomerular filtration rate · Chronic renal disease

## Abstract

The varied functions of the kidneys are influenced by the complex process of aging. The glomerular filtration rate (GFR) steadily declines with normal aging, and the progress of this process can be influenced by superimposed diseases. Microscopically, nephron numbers decrease as global glomerulosclerosis becomes more evident. The precise mechanisms underlying nephron loss with aging are not well understood, but derangements in podocyte biology appear to be involved. Classifications of chronic kidney disease (CKD) incorporate GFR values and attendant risk of adverse events. Arbitrary and fixed thresholds of GFR for defining CKD have led to an overdiagnosis of CKD in the elderly. An age-sensitive definition of CKD could offer a solution to this problem and more meaningfully capture the prognostic implications of CKD.

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## Introduction

Aging is a complex and poorly understood process that involves genes, environment and chance [1]. While few patients truly die from ‘old age’ alone, age is a strong independent contributor to mortality. Aging proceeds at variable rates, even among members of the same and identical animal species. Aging is fundamentally due to cellular degeneration (senescence) and faulty repair. It seems to be inevitable in nearly all species, with the possible exception of the genus Hydra [1]. All of the organs and organ systems of humans exhibit the consequences of aging, but this brief review will focus mainly on the kidneys, specifically the glomeruli and their function (glomerular filtration rate; GFR). Several other functions of the kidneys, such as urine concentration and dilution and sodium and potassium homeostasis, can also be influenced by the aging process (see [2] for a review), but will not be discussed here.

## Changes in GFR and Kidney Anatomy with Aging

Both GFR and renal plasma flow (RPF) decline with adult aging, beginning at about age 30 [2, 3]. Around the time one is 80 years old, the RPF declines more rapidly than GFR, leading to a modest increase in filtration fraction. The average yearly decline of GFR between age 30 and 75 in

otherwise healthy individuals is about 0.7–0.9 ml/min [3, 4]. The rate of decline may increase with superimposition of various diseases (e.g. hypertension, diabetes, prostatism) on the aging process per se [4, 5]. Disentangling the effects of aging itself on GFR from that of superimposed diseases can be very challenging. After about age 75 the rate of decline of GFR may accelerate, but still does not progress fast enough to cause kidney failure in the human life span [6].

The normal GFR in a healthy adult male at age 20 is about 100–110 ml/min/1.73 m<sup>2</sup> and can decline to <60 ml/min/1.73 m<sup>2</sup> in a variable fraction (5–25%) of otherwise healthy adults after age 60–65, depending on gender and attained age [3, 7]. The frequency distribution of GFR remains approximately Gaussian at all ages, in otherwise healthy subjects [4, 8]. The decline of GFR with aging is independent of blood pressure in healthy nonhypertensive individuals [5], and occurs even in indigenous populations free of cardiovascular disease [9].

The fundamental origins of the declining GFR with healthy aging are not fully understood. However, studies of healthy living kidney transplant donors (by the Stanford and Mayo Clinic groups) have contributed much to elucidate possible pathways [10–12]. With aging, the kidney cortical volume decreases (in parallel with declining GFR), while the medullary volume increases offsetting to some extent the impact of reduced cortical volume on overall kidney volume [13]. Microscopically, kidney aging is characterized by nephrosclerosis: increasing focal and global (not segmental) glomerulosclerosis (FGGS), interstitial fibrosis/tubule atrophy and arteriosclerosis [14]. The clinical importance of this glomerulosclerosis, in particular, may be different in ‘healthy’ aging compared to disease-induced pathology [15]. In ‘healthy’ aging, the rate of decline of GFR is not correlated with the extent of nephrosclerosis – a decline in GFR of about 0.63 ml/min/1.73 m<sup>2</sup> per year is seen regardless of the sclerosis score on renal biopsy in living donors at any age [16]. The density of nonsclerotic glomeruli decreases by 7% per decade, while the density of FGGS increases by 14% per decade [14]. These microscopic findings suggest that the decline in GFR seen with aging is a phenomenon related to a slowly progressive loss of nephrons from age 30 onward. Compensatory hypertrophy of residual nonsclerotic glomeruli and their attached tubules (nephron hypertrophy) may explain the reduced glomerular density seen in renal biopsies with aging; however, causality should be inferred only from cross-sectional findings with caution. The precise mechanisms responsible for FGGS is also unknown, but animal experimentation and human studies suggest that visceral epithelial cell degeneration (apoptosis and detachment) and

faulty replacement from parietal epithelial cells progenitors may be operating [17–19]. The resultant ‘podocytopenia’ can also influence single nephron filtration rate (SNGFR), by altering hydraulic permeability or the surface area available for filtration [20]. The changes in SNGFR among nonsclerotic glomeruli in human aging remain uncertain due to methodological issues, but if single nephron hyper-filtration occurs in residual nephron secondary to nephron loss, then hemodynamic stress on podocytes could contribute to their degeneration. So far, increased (or decreased) SNGFR has not been observed consistently in aging human kidneys until very advanced ages [21]. Thus, the major changes in whole kidney GFR with aging can be attributed primarily to nephron loss. Since podocytes are nonreplicative, terminally differentiated cells it is unlikely that post-mitotic (Hayflick type) senescence is involved; however, recent studies have shown an increase in podocyte numbers in glomeruli of adults compared to children, so new podocytes might be generated with aging, at least in early years [22]. A major unanswered question is how does nephron endowment at birth affect the physiologic process of loss of GFR with aging. Specifically, would a low nephron endowment at birth (due to fetal undernourishment) result in an acceleration of glomerular aging and an earlier or more prominent decline in GFR with aging?

### **The Relevance of Aging-Associated Changes in GFR for Diagnosis of CKD and Assessment of Risk of Adverse Events**

According to contemporary schema for classification of chronic kidney disease (CKD; KDIGO, 2012), any subject, regardless of age, with a GFR (measured or estimated) of <60 ml/min/1.73 m<sup>2</sup> sustained for at least 3 months has CKD (Stage 3–5, depending on the magnitude of the decline in GFR <60 ml/min/1.73 m<sup>2</sup>) irrespective of the presence or absence of other signs of kidney injury (e.g. albuminuria) [23]. As a result, half of adults over age 70 can be ‘diagnosed’ as having CKD [24, 25]. This conclusion conflates a reduced GFR with a ‘disease,’ and presumes that all sustained decreases in GFR <60 ml/min/1.73 m<sup>2</sup> are a manifestation of a disease of the kidneys, even though (as discussed above) this can and does occur in healthy aging. Clearly some elderly adults with reduced GFR do have a kidney disease – one that will more often than not be accompanied by abnormal albumin excretion or an abnormal urinary sediment. A great majority of individuals receiving the ‘label’ of CKD over age 65–70 years are identified by an ‘isolated’ decline of eGFR between values of 45

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥90	Green	Yellow	Orange
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59	>65 years Yellow	Orange	Red
			≤65 years Green			
	G3b	Moderately to severely decreased	30–44	Orange	Red	Red
	G4	Severely decreased	15–29	Red		
G5	Kidney failure	<15	Red	Red	Red	

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

**Fig. 1.** A proposed age-calibrated classification of CKD based on eGFR, albuminuria and risk of adverse events (adapted from reference [23] – from Glasscock R et al. [unpublished]; color schemes: green = no CKD or very low risk; yellow = CKD and low risk; orange = CKD and moderate risk; red = CKD and high risk).

and 59 ml/min/1.73 m<sup>2</sup> (CKD Stage 3A/A1 by KDIGO criteria), whereas younger subjects usually receive a diagnosis of CKD because of a finding of abnormal proteinuria, rather than reduced eGFR [26]. In the elderly, this has been suggested to be an example of ‘overdiagnosis’ of CKD due to the inappropriate use of a single, arbitrary and absolute threshold for defining CKD based on measured GFR or eGFR [27, 28]. It is debatable whether such values of measured GFR or eGFR in older subjects contribute very much to the determination of risks of adverse cardiovascular (CV) events or mortality [29]. Adding GFR-based CKD Stage to standard risk prediction (e.g. Framingham Risk Scores) for CV events does not meaningfully improve classification of risk, and eGFR has not been incorporated into most such scoring systems used widely in clinical practice [29]. Recently, Malmgren et al. [30] have shown in elderly Swedish women that relative mortality risk (fully adjusted for comorbidity) is not associated with

CKD Stage 3A (compared to non-CKD), regardless of the method used to determine eGFR by serum creatinine-based equations. In the same study, CKD Stage 3B was strongly associated with enhanced mortality risk (hazard ratio of 2.2–3.5), depending on the eGFR-creatinine formula used. In an exhaustive meta-regression analysis involving the CKD Prognosis Consortium, Hallan et al. [31] showed that the relative risk for all-cause mortality associated with a decline in eGFR (adjusted for albuminuria and comorbidity) is attenuated by age, but that using a common reference point of an eGFR of 80 ml/min/1.73 m<sup>2</sup> that mortality risk was increased at all ages when eGFR fell below 60 ml/min/1.73 m<sup>2</sup>. They also showed that such mortality is increased in younger subjects (age 18–54) even when the eGFR is <75 ml/min/1.73 m<sup>2</sup>. In a reanalysis of the Hallan et al. [31] data, Denic et al. [8] have shown that the lowest risk range for eGFR decreases from >75 ml/min/1.73 m<sup>2</sup> in younger adults to a range of 45–104 ml/

min/1.73 m<sup>2</sup> in the subjects over 75 years of age. It has been argued that a 20% higher relative risk of mortality with CKD Stage 3A in the elderly is important because it translates into a high absolute risk of mortality [31]. This occurs because of the underlying high mortality rate in the elderly. A CKD classification system justified on how well it detects absolute mortality risk still needs to account for the limited human life expectancy. It also remains debatable as to whether there really is even an increased risk of mortality in all age groups for CKD Stage 3A. Another study found that the remaining life expectancy of subjects over age 30 with CKD Stage 3A is not any different than those without CKD [32]. The development of treated end-stage renal disease (ESRD) is relatively uncommon in older subjects with CKD Stage 3A/A1, and is at least in part attributed to death before reaching ESRD [33]. Evidence that these older subjects die from their CKD rather than with their CKD is lacking.

Based on these considerations, a proposal has been advanced to modify the risk stratification (also called a ‘heat map’) for individuals above and below the age of 65 [23] (fig. 1). If this proposal were adopted, the prevalence of prognosis (risk)-stratified CKD in general adult populations might decline from about 11–13 to 5% or less, and referrals for evaluation of ‘supposed’ CKD in the elderly could be reduced by 70% or even more. ‘Overdiagnosis’ of CKD in the elderly is largely avoidable if assessment of risk-based criteria for diagnosis is calibrated in an age-

sensitive manner. Such a suggestion does not deny the theoretical value of determining eGFR or mGFR to avoid overdosing water-soluble drugs excreted mainly by GFR, though this should be proven by prospective controlled trials rather than simply assumed.

## Conclusions

Aging of an organism proceeds at variable rates, as influenced by genes, environment and chance. The kidneys participate in this physiologic process, and one manifestation is a decline in GFR, usually beginning after age 30. This process appears to be due to a steady loss of nephrons from global glomerulosclerosis perhaps as a result of visceral glomerular podocyte degeneration and inadequate repair. Such a physiological decline in GFR with aging has important ramifications for diagnosis of CKD and in the estimation of risks for adverse events, including mortality. We contend that the current schema for classification of CKD based on GFR should be redesigned to be age-calibrated. This would better reflect both the underlying biology of the aging kidney and the risks of mortality and ESRD.

## Disclosure Statement

The authors have no conflicts of interest to declare.

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