

## When kidneys get old: an essay on nephro-geriatrics

Quando os rins envelhecem: um ensaio em nefro-geriatria

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### ABSTRACT

Aging is a nearly universal phenomenon in biology only partially controlled by genetic endowment. Individuals and their organs age at varying rates. The kidneys manifest the aging process by steady loss of nephrons and a corresponding decrease in glomerular filtration rate (GFR) beginning about age 30 years. The mechanisms responsible for this observation are elusive. However, defining chronic kidney disease based on arbitrary, fixed thresholds of GFR in the later phases of life can be problematical as it may over-diagnose CKD in the elderly. A modest, persisting reduction of GFR (around 45-59 ml/min/1.73m<sup>2</sup>) without abnormal proteinuria does not seem to confer much of an adverse effect on mortality and remaining life expectancy in older adults and the development of end-stage renal disease in such subjects is very uncommon. Old kidneys should not be equated with "diseased" kidneys.

**Keywords:** disease; kidney; nephrology.

### RESUMO

O envelhecimento é um fenômeno quase universal na biologia, apenas parcialmente controlado pela dotação genética. Os indivíduos e seus órgãos envelhecem em taxas variáveis. Os rins manifestam o processo de envelhecimento por perda constante de néfrons e uma diminuição correspondente na taxa de filtração glomerular (TFG) a partir dos 30 anos. Os mecanismos responsáveis por essa observação são elusivos. No entanto, a definição de doença renal crônica com base em limiares arbitrários e fixos de TFG nas últimas fases da vida pode ser problemática, pois pode levar a um excessivo diagnóstico de DRC em idosos. Uma modesta e persistente redução da TFG (cerca de 45-59 ml/min/1,73 m<sup>2</sup>) sem proteinúria anormal não parece conferir grande parte do efeito adverso sobre a mortalidade e expectativa de vida remanescente em adultos mais velhos; e o desenvolvimento de doença renal em fase terminal em tais indivíduos é muito incomum. Rins mais velhos não devem ser equiparados a rins "doentes".

**Palavras-chave:** doença; nefrologia; rim.

### WHAT IS "GETTING OLD"?

Getting Old (aging) is a universal biological phenomenon, except perhaps in the genus Hydra, which appears to be immortal.<sup>1</sup> As such, it is difficult to label aging as a disease, at least when a departure from "normality" is a criterion for a disease. The fundamental processes responsible for aging are still incompletely understood, but environment, genes and chance all play important roles.<sup>2-4</sup>

The rate of aging is quite varied, even among identical members of the same species.<sup>5</sup> It has been estimated that genes play a role in about 25% of the

variation in longevity, whilst environment and chance play much larger roles.<sup>6</sup> A progressive defect in the DNA repair mechanisms, accompanied by shortening of the telomeres is a characteristic of normal physiologic aging.<sup>7-9</sup>

Darwinian evolution of the species places a much higher premium on reproductive prowess rather than upon mere longevity. Multiple organs are involved in the aging process, leading to a common phenotype of loss of skin elasticity, slowing of nerve conduction, reduced hair pigmentation, reduced skeletal muscle mass, declining bone density, oogenesis failure (in females),

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stiffening of blood vessels, impaired gastric hydrogen ion secretion, altered taste sensation, slowing of intestinal motility, impaired immunity, reduced lung function from emphysema and, of course, impaired kidney function, among others.

These processes can be accelerated by diseases which tend to aggregate in older persons, such as diabetes, cancer, hypertension and atherosclerosis, largely because the aged have had more time to acquire these degenerative diseases frequently linked to environmental forces (e.g., diet, exercise, infections, toxins).

When one attempts to define these diseases in the older person, it is frequently necessary to adjust criteria for what might be expected from chronological aging per se; for example in the detection of osteoporosis by DEXA scanning<sup>10</sup> or for detection of chronic obstructive pulmonary disease by spirometry.<sup>11</sup>

The disentangling of the intertwined phenomena of age-related disease and physiologic aging can be difficult and challenging. As succinctly captured by Tom Kirkwood in 1999, "grasping the correct distinction between normal aging and disease smacks of a semantic quibble, but words are powerful and the consequences of how we use them can be far-reaching".<sup>12</sup>

### WHAT IS THE AGING KIDNEY?

The kidneys age in a stereotypical fashion, affecting many aspects of their function, such as glomerular filtration rate, large solute permselectivity, water excretion and conservation, sodium chloride homeostasis, acid-base balance, hormonal activity and blood pressure control (Reviewed in 13).<sup>13</sup>

This essay will focus on one of the best studied of these functions; namely glomerular filtration rate (GFR). It is self-evident that the aggregate GFR of both kidneys (wkGFR) is equal to the product of the number of functioning nephrons (NN) and the *average* GFR of single nephrons ( $\text{wkGFR} = \text{NN} \times \text{snGFR}$ ).

Although difficult to study in humans, the investigation of values for the elements of this equation, according to healthy (physiologic) aging, has yielded some interesting findings. Detailed anatomic and physiologic studies of the healthiest of the healthy, normal living donors for kidney transplantation by the Mayo Clinic and Cleveland Clinic have been particularly revealing.<sup>14-19</sup>

We are all born with a complement of nephrons determined in large part by the process of nephrogenesis in utero.<sup>20</sup> This process can be influenced, either negatively or positively by the maternal-fetal nexus. For example, low birth weight (< 2.5 Kg) is associated with a lower complement of nephrons at parturition, and post-natal nephrogenesis is minimal if it occurs at all, except in premature infants.<sup>21-23</sup>

Thus, one can only lose, not gain nephrons as one ages and the NN at any age is determined by NN at birth (nephron endowment) and the rate of post-natal loss of nephrons.

Among 1638 living donors studied by the Mayo and Cleveland Clinic investigators, an average adult 18-29 years old has about 1,008,000 glomeruli per kidney, 991,000 of which are presumably functioning and 17,000 of which have undergone a scarring process known as focal and global glomerulosclerosis (FGGS).<sup>19</sup>

Thus, according to the equation above, if the wkGFR for two kidneys is 110ml/min, the average snGFR of the functioning nephrons in a healthy young adult is about 55 nl/min. By age 70-75 years the average number of glomeruli per kidney has declined to about 660,000, of which 520,400 are presumably functioning and 142,000 have undergone FGGS.<sup>19</sup>

If the normal wkGFR for a healthy 70-75 year old is about 75 ml/min (a loss of 35 ml/min over 5 decades), then the average snGFR is about 57 nl/min, not much different than an adult 50 years younger. Note that the absolute total number of non-sclerotic and sclerotic nephrons decrease by 35% with aging, so some nephrons must have been completely resorbed, as a consequence of atrophy and sclerosis.<sup>24</sup>

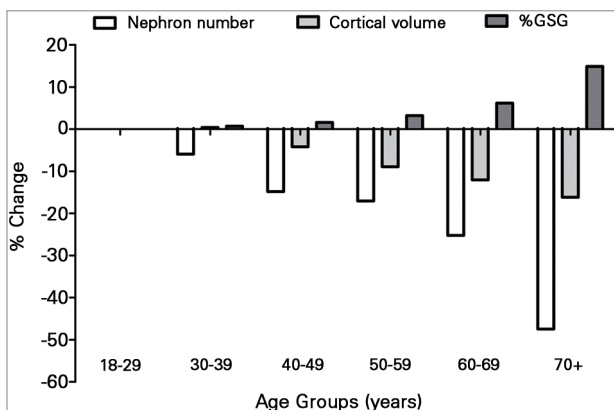
If these derived values represent the true state of renal physiology in the aging kidney, then healthy aging is associated with a substantial decline (35%) in total glomeruli, and an even greater number of functioning (non-sclerotic) glomeruli with aging about 48% (from 991,000 per kidney to 520,400 per kidney) over 50 years.<sup>19</sup>

The mechanisms underlying this loss of nephrons with healthy aging remains uncertain, but unlike nephron loss accompanying surgical reduction of nephron mass or certain disease states associated with loss of function nephron number, the reduction of functioning nephrons in aging is not apparently accompanied by a compensatory increase in snGFR of surviving nephrons, at least not until the extremes of age have been attained.<sup>25</sup>

Also, it is obvious that nephron endowment at birth will have a pronounced impact on the number of surviving functioning nephrons in old age, as the annual loss of nephrons is rather constant, and not greatly influenced by the residual nephron mass.

In addition, it seems that factors in addition to aging per se are responsible for the observed nephron loss other than age per se. The loss of nephrons is accompanied by interstitial fibrosis proportional to the severity of FGS, and by tubular hypertrophy that somewhat attenuate the loss of cortical volume seen in aging kidneys (Figure 1).<sup>19</sup>

**Figure 1.** Percentage change in nephron number, cortical volume, and globally sclerosed glomeruli (GSG) in older age groups relative to 18-29 years old, among 1638 healthy living kidney donors (Figure made from published table).<sup>18</sup> When compared with 18-29 years old as a baseline, 70-75 year olds have 48% fewer nephrons and 15 percentage points higher proportion of globally sclerosed glomeruli, but only 16% smaller cortical volume.



Glomerular volume does not increase with aging, but shows an inverse relationship to functioning nephron mass, likely as an expression of varying nephron endowment at birth.<sup>19</sup> In autopsy series and in living patients (donors) of varying age (infants and adults) without any known kidney disease the mean total NN varied between 606,000 to 1,430,000 per kidney.<sup>19,23,26-30</sup>

In addition to healthy aging and lower wkGFR, the clinical characteristics that independently associate with lower functioning nephrons (non-sclerotic glomerular number) in healthy live donors are shorter height, family history of ESRD, and higher serum uric acid, but not obesity, hypertension (mild), albuminuria or gender.<sup>19</sup>

The causal nature of these associations is unknown. It has been reported that the birth weight was predictive of adult height,<sup>31</sup> which is consistent with the findings that lower birth weight associates

with fewer nephrons. Furthermore, the association of lower nephron number and history of ESRD may be explained by genetic/familial factors which cause low nephron number and increase ESRD risk.

Thus, the characteristics of nephron anatomy and function in aging are now fairly well known even though the mechanisms for these temporal patterns of biology remain uncertain. Potential mechanisms include molecular pathways involving mTOR signaling, sirtuins, Klotho, energy utilization, DNA damage and repair, cellular signaling, cell cycle aberrations and podocyte apoptosis and replenishment.<sup>32-39</sup>

In this context, the changes in glomerular permselectivity with aging are of particular interest. On average albumin excretion rates increased modestly in healthy aging, but this does not correlate with functioning nephron number.<sup>19</sup> However, albuminuria does highly correlate with glomerular enlargement, the latter of which may be a manifestation of nephron endowment rather than nephron loss with aging.<sup>14</sup> Disentangling the different effects of low nephron endowment and the physiologic loss of nephrons with aging will require additional study.

### WHAT ARE THE CONSEQUENCES OF NORMAL KIDNEY AGING ON THE DIAGNOSIS OF CHRONIC KIDNEY DISEASE (CKD)?

At present any adult subject of any age over 20 years can be *diagnosed* as having CKD (Stages 3, 4 or 5), if the wkGFR (measured or estimated) falls below 60ml/min/1.73m<sup>2</sup> even in the absence of any signs of "kidney damage", the latter most commonly identified by abnormally elevated urinary albumin excretion (urine albumin to creatinine ratio [uACR] in a random "spot" urine of > 30 mg/gm [3 mg/mmol]).<sup>40,41</sup>

Moreover, the value of GFR must be sustained at or below this threshold for at least 3 months.<sup>40</sup> Failure to adhere to the temporal requirement for diagnosis of CKD will lead to a "false positive" rate of diagnosis of CKD of at least 30-35%.<sup>42,43</sup> It is well known that a substantial fraction (15-30%) of otherwise "healthy" adults (non-diabetic, no known kidney disease) attain a GFR of 45-59 ml/min/1.73m<sup>2</sup> by age 65-70 years of age, females more commonly than males.<sup>44</sup>

In most cases (70-80%) this reduced wkGFR is not accompanied by abnormal albuminuria so subjects are assigned to a G3A/A1 category of CKD (according to KDIGO, 2012).<sup>41</sup> Considering that this

reduction in wkGFR falls within ranges identified as part and parcel of "healthy" kidney aging and physiologic decline in NN, as discussed above, it seems logical to consider that an absolute, non-age sensitive definition of CKD, based on GFR alone leads to a "medicalization" of normality and to "over-diagnosis" of CKD in a significant number of elderly subjects.<sup>43,44</sup>

This would be more likely to occur in individuals of low-birth weight. It has been suggested that a diagnosis of CKD in such patients aids in prediction of future adverse events, such as death, end-stage renal disease cardiovascular events, acute kidney injury or toxicity for water-soluble drugs.<sup>40</sup>

While this may be true for a younger population, in the elderly CKD Category G3A/A1 is not associated with any significant reduction in remaining life expectancy nor does it consistently and reliably predict an excess of mortality or ESRD.<sup>40</sup> A substantial number of the elderly with a diagnosis of Category 3 CKD remain stable or undergo "spontaneous" remission and the risk of dying is much higher than developing and requiring treatment for ESRD.<sup>39</sup>

Whether knowledge of CKD G3A/A1 in the elderly prevents toxic adverse drug reactions is more of a hypothesis than a demonstrated reality.<sup>45</sup> Adding a diagnosis of CKD Category G3A/A1 adds little to "scoring" of CVD Risk by any of many conventionally used scoring systems (such as the Framingham Risk Score or the AHA/ACC ASCVD Risk Estimator).<sup>46</sup> In this regard, the presence of abnormal albuminuria, not a requirement for diagnosis of CKD G3A/A1, is much more important as a risk predictor in the elderly and in the young.

Taken together, these considerations have led to calls for modifying the GFR-based diagnosis of CKD, to make it more age-sensitive means of GFR, so as to avoid over-diagnosis in the elderly and under-diagnosis in the young.<sup>43</sup> However, Hallan, *et al* and the CKD Prognosis Consortium<sup>40</sup> conducted an extensive meta-analysis of numerous data-bases derived from diverse epidemiological studies (n = 2,051,044).

These were not an unselect general population based studies and selection bias is a concern. These investigators found that the fully adjusted hazard ratio (HR) for all-cause mortality rose significantly above that of the comparison group (eGFR of 85 ml/min/1.73m<sup>2</sup>) in all ages 18 and above when the eGFR fell below 60 ml/min/1.73m<sup>2</sup>, suggesting that

an age-calibration of eGFR threshold is not needed to determine a risk-based categorization of CKD.<sup>39</sup>

Similar findings were shown for the risks of treated ESRD. However, for adjusted all-cause mortality the HR values associated with any given eGFR < 60 ml/min/1.73m<sup>2</sup> were greatly attenuated by advancing age. No such attenuation of fully adjusted HR for treated ESRD by advancing age was observed, but the absolute rate of ESRD (per 1000 subjects) was extremely low (< 1%) for subjects over 75 years of age until the eGFR fell substantially below 45 ml/min/1.73m<sup>2</sup>.

In a re-analysis of the Hallan *et al.*<sup>40</sup> data, we<sup>47</sup> calculated adjusted hazard ratios for all-cause mortality using a reference value of eGFR that varies by age, and found that the lowest HR risk for fully adjusted all-cause mortality was lowest in subjects ages 18-54 at an eGFR of 75 ml/min/1.73m<sup>2</sup> or greater, and was lowest for subjects age 65 years and old over 75 years of age at an eGFR of 45-104 ml/min/1.73m<sup>2</sup> (Figure 2).

**Figure 2.** A proposed modification of CKD classification based on adjusted hazard ratios for all-cause mortality by categories of estimated glomerular filtration rate (eGFR) and age groups in patients with albumin/creatinine ratio less than 30 mg/g (calculated from published table);<sup>40</sup> Color schemes: grey: reference group; white: HR ≤ 1.30; yellow: HR 1.31-2.00; orange: HR 2.01-4.00 and red: HR > 4). eGFR shown in mL/min/1.73 m<sup>2</sup>; Albumin to creatinine ratio shown in mg/g.

eGFR	Albumin-Creatinine ratio	Age groups			
		18-54	55-64	65-74	>75
>105	<10	Ref	1.39	1.61	1.57
	10-29		1.53	1.65	0.51
90-104	<10	1.17	Ref	1.01	0.93
	10-29	1.30		1.17	1.27
75-89	<10	1.12	0.88	Ref	0.96
	10-29	1.30	1.04		1.01
60-74	<10	1.54	0.95	1.04	Ref
	10-29	1.64	1.09	1.09	
45-59	<10	3.14	1.39	1.19	1.15
	10-29	3.16	1.80	1.35	1.18
30-44	<10	9.20	2.97	2.00	1.64
	10-29	9.19	2.84	2.30	1.63
15-29	<10	13.46	6.15	3.86	2.79
	10-29	11.77	4.77	3.22	2.49

The values for HR in those ages 55-64 were intermediate between the young and the old. In a recent French, "Three-City" prospective cohort study, among community-dwelling individuals older



than 65 years, the authors found the increased risk of mortality in both sexes if eGFR was less than 45 mL/min/1.73m<sup>2</sup>.<sup>48</sup> Two more recent studies among elderly individuals, one from Italy and the other from Sweden, independently demonstrated association of higher mortality with CKD category 3B but not 3A.<sup>49,50</sup>

Taken together, we strongly believe that this analysis provides a powerful argument in favor of the need for an age-sensitive approach to diagnosing CKD based on GFR alone, perhaps using a threshold of < 45 ml/min/1.73m<sup>2</sup> rather than < 60 ml/min/1.73m<sup>2</sup> in those over 65 years of age.

These caveats do not apply to subjects with overt albuminuria or with other features suggesting a chronic disease (such as metabolic acidosis, normocytic normochromic anemia, elevated parathyroid hormone or hyperphosphatemia), but these abnormalities are distinctly very uncommon the elderly with an isolated eGFR of 45-59ml/min/1.73m<sup>2</sup>.<sup>51</sup>

## SUMMARY AND PERSPECTIVES

Aging is a universal phenomenon (or nearly so). All organs and systems of humans are involved in this process, including the kidneys, even though the mechanistic details for the aging of the soma are still being unraveled.

A decline in GFR is a part of the process of kidney aging, largely due to the progressive loss of nephrons. This phenomenon has implications for the diagnosis and classification of CKD, using conventional GFR-based criteria.

The modest reduction of GFR seen in the elderly (eGFR = 45-59ml/min/1.73m<sup>2</sup>) does not seem to have much effect on risk for shortened life expectancy or other adverse events so long as it is not accompanied by overt proteinuria. Old kidneys should not be equated with "diseased" kidneys.

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