NEWS & VIEWS

Nephron loss in the ageing kidney — it's more than you think

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Nephron number varies widely in healthy adults. The extent to which this variation is due to differences in nephron endowment at birth and/or nephron loss with ageing is unclear. A recent study used a novel approach to identify a previously unappreciated high loss of nephrons with ageing in healthy kidneys.

Total nephron number in healthy human kidneys varies widely, and low nephron number is associated with an increased risk of adult hypertension and chronic kidney disease (CKD)[1]. Small autopsy studies (of 20–50 individuals) reported a 2–4-fold variation in nephron number in healthy kidneys[2]. In larger autopsy studies, nephron number varied 7.3-fold in white Americans ($n = 135$) and 12.8-fold in African Americans ($n = 159$)[2,3]. How much of this variability in nephron number is due to variation in nephron endowment at birth, and how much is due to loss of nephrons with ageing is difficult to assess, although a 4.5-fold variation in nephron number was reported in 15 children aged <3 years[4]. In their recent study on nephron number and ageing, Denic *et al.* reported the surprising finding that the number of non-sclerotic functional glomeruli (NSG) decreased by almost 50% from young adulthood (18–29 years) to old age (70–75 years)[5]. The progressive decline in the number of NSG was approximately proportional to the age-related decline in glomerular filtration rate.

Denic *et al.*[5] estimated the numbers of NSG and globally sclerotic glomeruli (GSG) in 1,638 living kidney donors who underwent a predonation CT scan (to measure renal cortical volume) and a protocol core-needle biopsy at the time of donation (to estimate glomerular density using the Weibel and Gomez

method[6]) (FIG. 1). Multiplication of the cortical volume by the estimated glomerular density provided estimates of the total numbers of NSG and GSG in the kidneys. Acceptable criteria for donation varied between the three clinics that participated in the study, but generally included a 24 h urine albumin level <30 mg and a normal-for-age glomerular filtration rate. Mild hypertension in older donors and moderate obesity (<35 kg/m²) were not exclusion criteria.

> ❝ nephron loss induced by overt kidney disease should be distinguished from that related to ageing ❞

Denic and colleagues hypothesized that the decline in nephron number with ageing would be proportional to the decline in cortical volume seen on CT scans and to the increase in glomerulosclerosis seen in biopsy samples. Surprisingly, however, they found that nephron loss with ageing was far greater than expected based on these changes. Their data suggests that nephron number decreases progressively with healthy ageing. In the youngest age group (18–29 years; $n = 246$), total nephron number was 1,007,275, comprising

990,661 NSG and 16,614 GSG, whereas in the oldest age group (70–75 years; $n = 11$), total nephron number was 662,124, comprising 520,410 NSG and 141,714 GSG[5]. These values demonstrate several important findings. Firstly, the number of functional NSG was nearly 50% lower (difference of 440,000 NSG) in the oldest group than in the youngest group; secondly, the number of GSG was 8.5-fold higher in the oldest group than in the youngest group; and thirdly, compared with the number of glomeruli in the youngest group, almost 350,000 glomeruli had disappeared without a trace in the oldest group.

Surprisingly, cortical volume was only 16% lower in the oldest group than in the youngest group (far less than the between-group difference in mean total nephron number ~34%), suggesting that tubular hypertrophy compensates in large part for nephron loss. Similarly, the degree of glomerulosclerosis in biopsy samples did not account for the extent of nephron loss. These findings contrast with those of Keller *et al.*, who found only a small proportion of obsolescent glomeruli in 20 individuals aged between 35 and 59 years (10 healthy individuals and 10 with hypertension)[7]. In that study, hypertensive individuals had lower nephron numbers than healthy age-matched individuals, which the researchers attributed to lower nephron endowment because little glomerulosclerosis or scarring, which indicates substantial postnatal nephron loss, was found. According to Denic *et al.*, evidence of nephron loss is usually lacking, which is compatible with the observation that considerable nephron loss occurs with age[5], with a parallel increase in the prevalence of hypertension, and that those nephrons usually disappear "without leaving recognizable traces" (REF. 8).

Perhaps the major limitation of the new study is the method used to estimate the number of NSG and GSG. The gold-standard technique for estimating the total number of glomeruli (and thereby nephrons) in a kidney is the disector/fractionator method[9]. Denic and colleagues' study would have been strengthened if estimates obtained using their approach based on cortical volume and glomerular density[5] had been validated against disector/fractionator estimates using either human autopsy specimens or perhaps kidneys from large experimental animals.
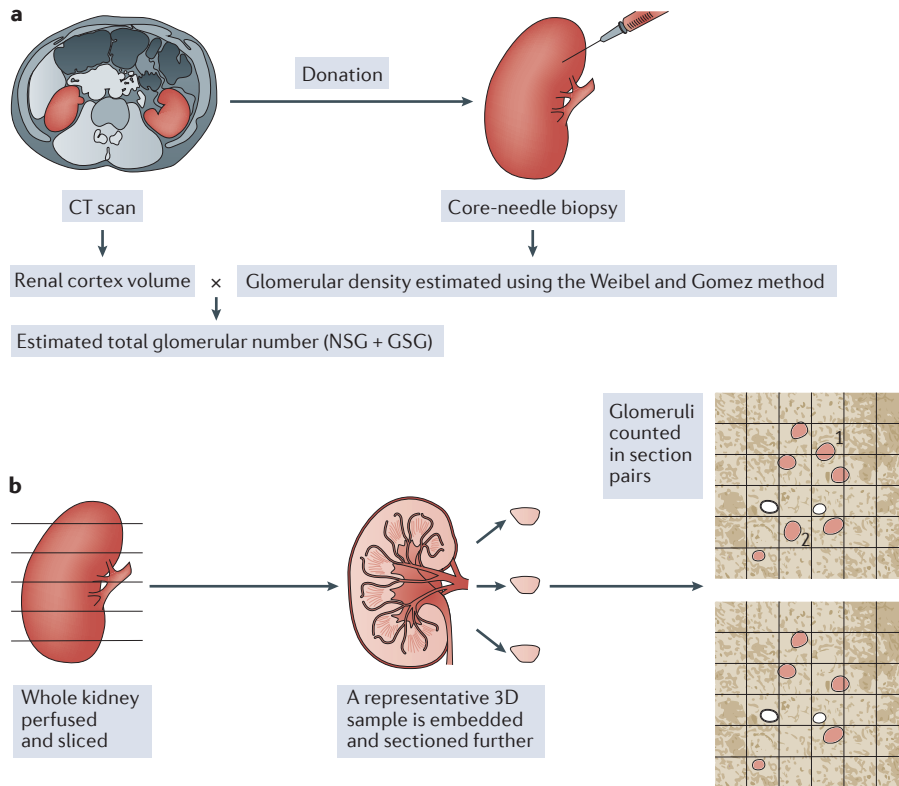
Figure 1 | **Glomerular number estimation. a** | Glomerular density (estimated using the Weibel and Gomez method on a core-needle biopsy sample obtained at the time of donation) was multiplied by cortical volume (measured on a predonation CT scan) to estimate the total number of non-sclerotic glomeruli (NSG) and globally sclerotic glomeruli (GSG). **b** | The gold-standard method to estimate glomerular number is the disector/fractionator method: the whole kidney is perfused, a known fraction of representative tissue blocks is embedded and sectioned, and glomeruli are counted using the disector principle in section pairs (the two glomeruli indicated with numbers are counted). Knowing glomerular numbers in a known fraction of kidney cortex enables calculation of the total number of glomeruli in the whole kidney.

However, although the precision of individual nephron counts was not high (reported coefficient of variation of 33%), the take-home messages from their analysis of this large sample were clear.

Other limitations of this study were the small number of individuals aged 70–75 years, variations in biopsy depth, region and angle, the assumption that those in the older age groups were born with the same nephron endowment as those in the younger age groups, and factors used to correct for tissue shrinkage. Despite these limitations, the nephron counts obtained by Denic and co-workers are remarkably similar to those reported in several previous studies[2,3,9]. In addition, these counts confirm previous estimates of the annual rate of nephron loss, gender differences in nephron number, and inverse correlations between nephron number and glomerular volume, and between nephron number and nephrosclerosis.

In conclusion, these new data[5] demonstrate an unexpectedly high loss of NSG with ageing in healthy human kidneys, as well as the disappearance of approximately one-third of all glomeruli by the age of 70–75 years. Presumably, nephron loss would be greater and tubular hypertrophy higher in individuals with renal pathophysiology than in healthy individuals. These findings support the hypothesis that nephron loss induced by overt kidney disease should be distinguished from that related to ageing in healthy kidneys. These data also call for renewed efforts to develop non-invasive methods such as MRI[10] to enumerate glomerular number and size.

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