The Aging Kidney: More Pieces to the Puzzle

In 1973, Darmady et al[1] published a now "classic" article entitled "The Parameters of the Ageing Kidney." In this autopsy study, the authors evaluated kidney tissue samples from 105 individuals, from birth to 101 years, who had died suddenly and in whom known renal disease or hypertension was absent. The main findings included a gradual shrinking of nephron volume beginning after the third or fourth decade of life and preservation of the ratio of glomerular surface area to proximal tubule volume (ratio of about 3:1) throughout the life span. The reduction in nephron size was most marked in the juxtamedullary nephrons. An increase in elastic fiber content of small vessels associated with medial hypertrophy and intimal proliferation occurred with nephron shrinkage. Progressive increases in interstitial fibrosis and global glomerulosclerosis were also observed in a focal distribution throughout the kidneys. By the third decade of life, some degree of focal global glomerulosclerosis was observed in all individuals studied.

Almost 20 years later, in an autopsy study, Nyengaard and Bendtsen[2] examined the number and size of glomeruli in 37 apparently healthy individuals, ages 16 to 87 years; 80% of the specimens were from individuals 40 years of age or older. The investigators discovered a gradual loss of nephron number with aging, beginning after age 60 years. Interestingly, glomerular volume, measured by an unbiased stereological technique, also decreased with aging, directly proportional to a decline in kidney weight.

These autopsy studies in apparently healthy aging individuals suggest that the "senile" kidney is characterized by nephron and kidney shrinkage, an increase in globally sclerotic glomeruli (also known as obsolescent glomeruli), a progressive loss of glomeruli (presumably via absorption of obsolescent glomeruli), preservation of the glomerular tubule volume relationships, and absence of glomerular hypertrophy. These findings appear to be a "universal" consequence of aging per se, although they might be influenced by concomitant comorbidity.

None of the autopsy-based studies could correlate renal functional parameters with these anatomic changes. The advent of renal transplantation, particularly involving living donors, provided a unique opportunity to study the renal functional correlates of the anatomic changes in aging delineated by the autopsy-based studies. Functional and morphological parameters could thus be studied before transplant, using renal biopsy specimens obtained immediately before kidney implantation. In one of the first such studies, Hoang et al[3] reported on 33 kidney transplant donors (27 living, 6 deceased) in 2003. Glomerular morphometry of individual nephrons suggested a reduction in filtration surface density and filtration slit diaphragm frequency with aging. The glomerular functional parameters also suggested a decline in 2 kidney glomerular ultrafiltration coefficients (Kf) in the aging kidney. These results complement those of studies performed in the 1950s[4] in which it was reported that, with aging, whole kidney glomerular filtration rate (GFR) and renal plasma flow decreased, roughly in parallel, usually beginning after the fourth decade of life.

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These seminal studies, and others, set the stage for the next attempts to solve the puzzle of the kidney in aging. Using a unique reservoir of renal biopsy specimens obtained from living donors and routine pretransplant measurements of GFR, Rule et al[5] assembled a more complete picture of the aging kidney in 1203 apparently "healthy" individuals (those accepted for kidney donation). They reported that the frequency of *nephrosclerosis* (defined by the presence of ≥2 of the parameters of global glomerulosclerosis, interstitial fibrosis, or arteriosclerosis) increased from about 3% in donors 18 to 29 years of age to 73% in donors 70 to 77 years of age. Even more surprisingly, they discovered that GFR declined with aging *independent* of nephrosclerosis. Thus, the natural tendency for a decline in kidney function with aging does not appear to be explained simply by the appearance of nephrosclerosis per se.

In this issue of *Mayo Clinic Proceedings,* Rule et al[6] share further insights into the kidney in aging by analyzing 1046 cortical renal biopsy specimens and renal/metabolic functional parameters from healthy transplant donors. They defined glomerular density as the number of glomeruli (both normal and sclerotic) per square millimeter of cortex area and used light microscopy to analyze specimens that had at least 4 mm^2 of cortex area. Not surprisingly, glomerular density decreased with age, corroborating the autopsy findings of Nyengaard and Bendtsen.[2] Furthermore, the extent of global glomerulosclerosis was tightly correlated with decreased glomerular density, possibly suggesting absorption of obsolescent glomeruli. The extent of tubular atrophy (but not interstitial fibrosis or arteriosclerosis) was associated with *increased* glomerular density after correction for age-dependent effects, suggesting that shrinkage of the tubular component of the nephron allows glomeruli (both normal and obsolescent) to come into closer apposition. Glomerular density was inversely correlated with the

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mean glomerular area, possibly indicating some degree of compensatory hypertrophy among residual nephrons in this biopsy study. This finding differed from that of the autopsy study by Nyengaard and Bendtsen.[2] Most interestingly, the degree of glomerulosclerosis showed a dichotomous association with glomerular density—that is, there was *decreased* glomerular density with aging in the presence of less glomerulosclerosis and *increased* glomerular density with aging associated with greater glomerulosclerosis. Whether these discrepancies relate to the rate of absorption of obsolescent glomeruli (which would lower both glomerular density and glomerulosclerosis) or differences in tubular volume cannot be clearly determined by this study. It would have been of interest if the authors had tabulated the density of sclerotic and nonsclerotic (normal) glomeruli separately.

A decrease in glomerular density observed with aging was also associated with an *increase* in GFR and albumin excretion, blood pressure, serum uric acid, and body mass index—all manifestations of metabolic syndrome and worsening insulin resistance (but without frank diabetes). These phenomena might be predictors of future chronic kidney disease. The authors properly ask the main question generated by this novel study: What are the biologic events underlying decreased glomerular density and its association with metabolic factors in apparently healthy aging donors? They theorize that the decrease in glomerular density with aging is primarily the consequence of increased nephron size (glomerular and renal tubular hypertrophy). This interpretation is supported by the inverse relationship between glomerular density and glomerular size but is inconsistent with the autopsy observations of Darmady et al,[1] who found a progressive decrease in proximal tubular volume with age. The observation that decreased glomerular density (and increased glomerular size) is seen in association with features of metabolic syndrome and increased GFR is consistent with what is known about "hyperfiltration" in residual nephrons. The *paradoxical increase* in glomerular density with aging when glomerulosclerosis is more extensive (Figure 3 in accompanying article by Rule et al[6]) is intriguing. The authors explain that this phenomenon is due to concomitant tubular atrophy (bringing glomeruli into closer apposition) and a lesser degree of compensatory hypertrophy (decreasing the tendency for spreading of glomeruli further apart). To gain further insights into these issues, it would have been useful for the authors to have examined the correlations between GFR and glomerular density with and without glomerulosclerosis.

The data arising from this seminal study strongly support the notion that "hyperfiltration" (eg, GFR >120 mL/min/1.73 m^2) in "healthy" (apparently nondiabetic) individuals (transplant donors) with underlying features of metabolic syndrome may predispose to a decrease in glomerular density. Approximately 25% of the study patients had a GFR higher than 128 mL/min/1.73 m^2 (mean ± SD measured GFR, 103±18 mL/min/1.73 m^2). The anatomic phenomenon of decreasing glomerular density, closely allied to aging in the kidney, might be due to both metabolically driven glomerular hypertrophy and a progressive loss of glomeruli consequent to the aging process per se (renal senescence). This would extend the hyperfiltration theory of glomerular injury into the realm of the aging process in the kidney.[7]

Taken together, the studies by Rule et al[5,6] add pieces to the puzzle of the kidney in aging and add to the size of the puzzle itself. They also create a new dimension of concern regarding the role of metabolic risk factors in generating a milieu capable of altering the renal anatomic and functional changes consequent to normal aging. Like all good research, these studies raise as many new questions as they answer old questions.

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