Structural and Functional Changes With the Aging Kidney

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Senescence or normal physiologic aging portrays the expected age-related changes in the kidney as compared to a disease that occurs in some but not all individuals. The microanatomical structural changes of the kidney with older age include a decreased number of functional glomeruli from an increased prevalence of nephrosclerosis (arteriosclerosis, glomerulosclerosis, and tubular atrophy with interstitial fibrosis), and to some extent, compensatory hypertrophy of remaining nephrons. Among the macroanatomical structural changes, older age associates with smaller cortical volume, larger medullary volume until middle age, and larger and more numerous kidney cysts. Among carefully screened healthy kidney donors, glomerular filtration rate (GFR) declines at a rate of 6.3 mL/min/1.73 m^2 per decade. There is reason to be concerned that the elderly are being misdiagnosed with CKD. Besides this expected kidney function decline, the lowest risk of mortality is at a GFR of ≥75 mL/min/1.73 m^2 for age <55 years but at a lower GFR of 45 to 104 mL/min/1.73 m^2 for age ≥65 years. Changes with normal aging are still of clinical significance. The elderly have less kidney functional reserve when they do actually develop CKD, and they are at higher risk for acute kidney injury.

Key Words: Aging, Nephrosclerosis, Glomerulosclerosis, Kidney function, Glomerular filtration rate

INTRODUCTION

Aging is a natural, progressive, and inevitable biological process characterized by a gradual decline of cellular function and progressive structural changes in many organ systems. These anatomic and physiological changes delineate the process of "senescence," a term that portrays more predictable age-related alterations as opposed to those induced by diseases. In general, the rate of the physiologic decline is initially difficult to perceive; however, after certain age (late maturity), it undergoes acceleration. As other organ systems, the kidneys also go through process of normal senescence, including both anatomical and physiological changes. These changes in a normal aging kidney are separate from kidney diseases that are relatively common in elderly such as diabetic nephropathy.[1] It is difficult to distinguish the 2 distinct processes: inevitable organ-based senescence and disease-mediated structural and functional changes more common in the elderly. Nevertheless, it is important to emphasize that age-related diseases when superimposed on those of normal senescence, can significantly alter the rate of functional decline, exhaust kidney functional reserve, and predispose these patients to acute kidney injury.[2]

During the past 15 years, there has been an increasing interest in the aging kidney. The likely reason is wide implementation of estimated glomerular filtration rate (eGFR) instead of serum creatinine for assessment of kidney function coupled to the adoption of an absolute (non-age calibrated) threshold for defining CKD based on eGFR values alone (<60 mL/min/1.73 m^2), which unsurprisingly led to a higher number of older adults diagnosed with CKD. This diagnostic strategy also increased nephrology referrals, especially among individuals with mild to moderately reduced eGFR (30-59 mL/min/1.73 m^2).[3] The mean eGFR among community-living individuals aged more than 70 years is at or below the accepted threshold of <60 mL/min/1.73 m^2 used to define CKD.[4] Older individuals represent a unique population in which the now "traditional" assumptions that an isolated and a persistent (over 3 months) eGFR < 60 mL/min/1.73 m^2 defines CKD are not necessarily true. The psychological aspect of labeling older patients as having CKD is also of concern.[4] Regardless of disease labeling, declining kidney function with normal aging is still of clinical relevance to medication dosing, selection of living kidney donors, and risk of CKD and acute kidney injury with loss of kidney reserves.

Masked under the complex layers of estimating glomerular filtration rate (GFR) and identifying CKD in the elderly, is the underlying structural pathology in the aged kidney. More and larger kidney cysts,[5,6] focal scars,[7] increased cortical surface roughness,[8] decreased cortical volume, increased medullary volume,[9] and more kidney artery atherosclerosis[7] are evident on computed tomography (CT) imaging of older kidneys. Likewise, global glomerulosclerosis, tubular atrophy, interstitial fibrosis, arteriosclerosis, arteriolar hyalinosis,[10] tubular diverticuli,[11] and to a lesser extent, nephron hypertrophy (increased glomerular volume)[12] become more evident on kidney biopsies of older patient's kidneys. How these structural changes relate to functional alterations of the

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kidney with aging is still being explored. In this review, we will define the key structural and functional changes (with particular emphasis on GFR) that occur in the aging kidney and discuss their clinical significance.

MOLECULAR BIOLOGY OF KIDNEY AGING

Almost 6 decades ago, Dr. Harman was the first who proposed that free radical–induced accumulation of oxidative stress, and damage at a cellular level was the primary cause of aging and a major determinant of life span.[13] This simplified theory has been one of the most popular explanations of aging. More recently, there has been an increased interest in mitochondrial theory of aging, including mitochondrial oxidative stress, mitochondrial damage, and its subsequent influences on aging and health span.[14]

Regardless of an exact molecular mechanism of aging, decline at cellular level universally leads to gradual decay of many different tissues and organs, and the kidneys are not spared. The universality of the process, present in all multicellular organisms makes it difficult to classify aging as a disease, per se. By affecting the basic structure and function of kidney cells, aging leads to GFR decline, changes in permeability of the capillary wall in glomeruli, increased susceptibility for podocyte injury, apoptosis, changes in tubular reabsorption and secretory capacities, changes in urinary concentration, and production of kidney-derived hormones and bioactive molecules.[15–18] Podocytes, cells that have crucial function to maintain normal glomerular structure and capillary permeability, certainly undergo aging-related changes. It is hypothesized that progressive reduction in number of viable and normally functioning podocytes, along with decreased capacity for their regeneration and repair, ultimately leads to glomerular obsolescence and also subtle deterioration of the integrity of slit pore membrane in glomeruli, affecting both whole kidney GFR and albumin permeability.[17–19]

CLINICAL SUMMARY

- There is a rising prevalence of nephrosclerosis with aging, from 2.7% for healthy individuals younger than 29 years up to 73% for healthy individuals aged more than 70 years.
- Total kidney volume remains stable through about age 50 years due to declining cortical volume and a compensatory medullary volume increase, but decreases with aging beyond 50 years.
- Glomerular filtration rate (GFR) declines with normal aging, and mortality data support the use of a lower range of GFR to define normal in the elderly compared to younger adults.
- There are substantial reasons to be concerned that a fixed GFR threshold of <60 mL/min/1.73 m^2 to define CKD leads to overdiagnosis in the elderly and underdiagnosis in younger adults.

STRUCTURAL CHANGES OF THE AGING KIDNEY

It is established that aging is undoubtedly associated with structural changes in the kidney, including not only glomeruli, tubules, and the interstitium but also the vasculature. Four decades ago, in one of the earliest postmortem studies, Darmady and colleagues[20] showed a decline in the number of non-sclerosed glomeruli (NSG), loss of tubules, vascular changes, and increased frequency of tubular diverticuli in apparently healthy aging individuals. Much later, studies of healthy living kidney transplant donors, with age spanning 6 decades, provided unique and ideal information on both structural and functional changes that occur with normal aging. Potential kidney donors undergo a battery of clinical evaluations, testing of kidney function, urinalyses, and kidney CT angiograms to confirm health before donation. Finally, during the surgery, preimplantational biopsy of the kidney allograft can be performed, providing material for microscopic evaluation. Of note, similar evaluation of structural changes in kidneys with aging is possible in the "sudden death" autopsy cases (suicide or accidental death) of previously healthy individuals. However, the major drawback of these autopsy studies is lack of concurrent clinical information including kidney function tests.

The structural changes in aging kidney can be divided into the 2 broad categories, "microanatomical" based on kidney biopsy findings and "macroanatomical" based on imaging studies such as CT scans.

Microanatomical Changes

The major aging-related changes observed on microscopic evaluation include nephrosclerosis and nephron hypertrophy.

Nephrosclerosis. The main features of nephrosclerosis that can be found on a kidney biopsy include glomerulosclerosis (focal and global, but not segmental), tubular atrophy, interstitial fibrosis, and arteriosclerosis (fibrointimal thickening; Supplemental Fig 1). Arteriosclerosis of small arteries in the kidneys is thought to cause an ischemic injury to nephrons, which over time progresses into global glomerulosclerosis and tubular atrophy. The main features of ischemic-related changes in the glomerulus are pericapsular fibrosis, wrinkling of capillary tufts, and progressively thicker basement membrane. In addition, Bowman's space gradually fills with a matrix-like hyaline material, most likely due to disrupted balance between formation and breakdown of the extracellular matrix in the glomerulus.[21] Finally, glomerular tufts collapse, leading to development of globally sclerotic glomeruli (GSG). These GSGs may eventually be completely reabsorbed, or atrophy to a size that is too small to be clearly identified on standard kidney biopsy sections.[22,23] In addition to the GSG, the corresponding tubule atrophies with fibrosis accumulating in the surrounding interstitium.[24,25]

This increased prevalence of GSG with aging has been consistently replicated in several studies, including both autopsy-based studies and living kidney donors.[10,22,24,26,27] In a sample of 1203 healthy living kidney donors, there was a rising prevalence of GSG with increased age.[24] For example, prevalence of GSG in the