The aging kidney: structural changes

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ABSTRACT

A number of structural changes occur in the kidney with aging. The aging kidney is characterized by loss of renal mass, arterial sclerosis, arteriolar hyalinosis, an increased number of sclerotic glomeruli, loss of tubules and interstitial fibrosis. The pathogenesis of aging-associated structural changes is not completely understood. Both genetic background and hemodynamic factors have been associated with progression of age-related morphological changes. The structural changes of aging kidney are nonspecific and can be seen in many conditions, including diabetes and hypertension, and, as such, arterionephrosclerosis of aging is a diagnosis of exclusion.

Key words: Aging, Kidney, Pathology, Senescence

INTRODUCTION

The biological price of aging includes progressive deterioration of renal function and structure. Many general reviews describing morphological changes of the aging kidney have been written (1-5). In this review we will summarize the main histological features of aging-related renal changes and their pathogenesis.

GROSS ANATOMY

Renal mass progressively decreases with age. The average kidney weight increases from birth to the fifth decade of life, then progressively declines with age. Mass decrease amounts to about 20%-30%, especially in the 70s and 80s, with the renal cortex being affected more than the medulla, leading to thinning of cortical ribbon (1-5). Gross examination of the subcapsular surface of an aging kidney shows granularity and pitting, thought to be related to parenchymal scarring due to vascular changes (1).

VASCULAR CHANGES

Arterial sclerosis is the main feature of the aging renal vasculature. The artery walls appear thick, and the vascular lumen is narrowed. The change is due to collagen increase in the media and to intimal thickening (2, 4). Fibrointimal hyperplasia (Fig. 1) is characterized by collagenous fibrosis of arterial intima. This change is common feature in arteries of interlobular size of aging kidneys, as well other visceral organs, and it is focal in is distribution, leading to heterogeneous cortical ischemia (1, 4). Hyaline arteriolosclerosis (Fig. 2) is also a feature of age-related vasculopathy. It is caused by insudation of proteins into the vessel wall. None of these vascular changes are pathognomonic for aging, being often associated with a number of other conditions, including hypertension and diabetes. However, all have been found in the aged kidney and even in those patients who are normotensive and without diabetes (3). At the same time – and this may be as a consequence of the vascular changes – focal glomerulosclerosis, tubular atrophy and interstitial fibrosis occur in the outer cortex.

GLomerULAR CHANGES

Many morphological changes occur in the human glomerulus with aging. These include a decrease in the glomerular number, an increase of globally sclerotic glomeruli and a progressive decrease and later increase in the size of intact glomeruli (4). The number of glomeruli per kidney is extremely variable in individuals, ranging from 333,000 to 1,100,000.
Nyengaard and Bendtsen (6) reported on glomerular number and size in relation to age. They showed that the number and the size of glomeruli was inversely proportional to age. Moreover, glomerular size was inversely proportional to kidney weight. Therefore, consistent with decreases in kidney weight and thinning of cortical ribbon with increase in age, the number of glomeruli decreases with age. Furthermore, the prevalence of sclerotic glomeruli increases with aging. Kaplan et al (7) reported the age-related incidence of sclerotic glomeruli in human kidneys. The authors showed that, before the fifth decade of life, up to 10% of glomeruli might be globally sclerotic. Subsequently, the percentage of sclerotic glomeruli increases, sometimes related to comorbid conditions such as diabetes and hypertension. Smith et al (8) have suggested that, beyond 40 years of age, the percentage of “normal” sclerosed glomeruli is well represented by the formula: patient age divided by 2, minus 10.

The pathogenesis of aging-associated global glomerulosclerosis is not completely understood. Morphometric studies by Kasiske (9) showed a direct correlation between prevalence of globally sclerotic glomeruli and age, and also a correlation to intrarenal vascular disease (particularly outer cortical arterial disease). Conversely, hypertension had no independent association with glomerulosclerosis once age and intrarenal vascular disease were taken into account. Moreover, there was an inverse correlation between intrarenal arterial lumen diameter and glomerulosclerosis. However, Kasiske was unable to clarify the reason for the association between atherosclerosis and glomerulosclerosis. The association might indicate that atherosclerosis caused glomerulosclerosis, or that glomerulosclerosis and atherosclerosis shared 1 or more common pathogenic mechanisms.

Focal segmental glomerulosclerosis is another frequent histological finding in the aging kidney, and it is ascribed to hemodynamic factors. Furthermore, morphological changes of senescent glomeruli include (i) sclerotic glomeruli with direct channels forming between the afferent and efferent arterioles bypassing the glomeruli, (ii) progressive decrease in size of intact cortical glomeruli, leading to compensatory hypertrophy of the juxtamedullary glomeruli and (iii) increase of mesangial matrix and thickening of the glomerular basement membrane (4).

**Tubulointerstitial Changes**

Localized scarring of renal cortex increases in frequency in the elderly. Tubular atrophy with thickening of the basement membrane is a common feature in scarring, as well as tubular “thyroidization,” with dilatation of the lumen, flattening of the tubular epithelium and accumulation of eosinophilic hyaline cast material within the tubular lumen (3).

In addition to tubular atrophy, other age-related tubular changes occur: the tubule number decreases, the volume decreases, length decreases and the number of diverticula increases. These diverticula in distal and collecting tubules may be precursors of simple cysts, increasingly seen in the aging kidney. Interstitial volume also increases with aging, associated with interstitial fibrosis.

**Etiopathogenesis of Renal Aging**

The pathogenesis of age-related changes in renal structure still remains a matter of debate. Genetic influences on renal aging are increasingly recognized (10). Also, gender has been identified as playing a significant role in the rate of progression.
of age-related changes both in experimental studies and in humans. Aging male rats develop progressive glomerulosclerosis, whereas females, estrogen-treated males and orchietomized males are remarkably resistant to development of these abnormalities. These data are consistent with the conclusion that sex hormones directly influence many of the processes implicated in the pathogenesis of glomerular obsolescence (11, 12). However, Neugarten et al (13), comparing the glomerular morphology of males and females ranging in age from infancy to 90 years in 250 autopsy specimens, found no difference between sexes in the development of glomerulosclerosis in aging humans. Therefore, the hypothesis that sex hormones may make an important contribution to progressive glomerulosclerosis is not confirmed in aging humans.

Genetic background, not simply sex, may have a significant role in the scale and progression of renal impairment and structural features associated with age, as discussed by Ma and Fogo (10). The control of nephron number, renal function and arterial pressure has been associated with particular genotypes in mice (3). Genes that have a role in the rate of aging have been recognized, and experimental models of accelerated senescence as well as specific knockout models have been created (3). The recent discovery of the klotho gene (14), a fundamental regulator of aging and calcium/phosphorus metabolism, and a gene predominantly expressed in the kidney, might lead to further clarification of the role of genetic background in renal aging.

Hemodynamic factors have been suggested as another pathway to glomerular sclerosis (4). Both renal blood flow and responsiveness and autoregulation of the renal arterioles decrease with increasing age. Hill et al (15) performed a morphometric study of arterioles and glomeruli in the aging kidney, showing dilatation of the afferent arterioles and glomerular capillary lumina that suggested a dysregulation between the afferent and efferent arterioles. Such a dysautoregulation may lead to increased glomerular intracapillary pressures and subsequent “hyperperfusion” glomerular injury and sclerosis. It has been suggested that hemodynamic factors first cause cortical glomerulosclerosis and subsequent juxtamedullary glomerular hypertrophy, followed by juxtamedullary glomerulosclerosis (16).

The tubulointerstitial changes also could be secondary to the aging-related vascular changes and subsequent hypoxia/ischemia in both cortex and medulla, which up-regulates both hypoxia-induced genes and the gene for collagen-1 (3). Finally, has been suggested that age-related vascular changes lead to arterial stiffness, which, in turn, increases pulse wave velocity, and therefore transmission of pulsatile energy to fragile microvessels causing tissue damage (1).

In conclusion, aging is a degenerative biological process that affects the kidney. No specific morphological findings are pathognomonic for the aging kidney, and, as such, arterionephrosclerosis of aging is a diagnosis of exclusion. Therefore, renal pathologists need to rule out hypertension, diabetes and other conditions before ascribing the morphological picture to aging. The pathogenesis of aging-associated renal structural changes is not completely understood and is likely multifactorial. A better knowledge of the mechanisms associated with renal aging may help to prevent renal failure in the elderly.

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