Chapter 4: Kidney Senescence

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In the United States, the elderly and the very elderly population has largely exceeded that of any other age group.[1] By 1994, the population of these demographic groups reached 36.5 million and has continued to increase over the last decade.[1] This growth parallels the increasing number of elderly persons classified with chronic kidney disease (CKD) stages III through V. Moreover, an estimated 660,000 persons in the United States will have end-stage kidney disease (ESKD) by the year 2010, with the greatest growth rate occurring in the elderly and very elderly persons.[1–3] Unfortunately, understanding of the normal biologic progression of renal disease in the elderly persons in the absence of comorbid factors[4–9] or the progression of CKD is still not clearly understood.[10]

Cross-sectional and longitudinal studies have looked at the natural progression of the kidney with aging.[4,7,8,11] A linear relationship between aging and a decline in the renal function was noted,[7,8] but elderly persons who had no underlying disease had adequate renal reserve.[12–14] The Baltimore Longitudinal study (BLS) from 1958 until 1981 studied a cohort of individuals for 8 or more yr who had a least five 24-h urine collections for creatinine clearance.[7,8] There were three groups: group 1, CKD; group 2, on anti-hypertension medications; group 3, healthy patients. The overall rate of decline in creatinine clearance was 0.87 ml/min per year beginning at age 40 and was inversely related to age.[7,8] A rise in mean arterial pressure $>$107 mmHg was positively correlated with a decline in renal function.[7] Interestingly, in the BLS, one third of the elderly population had no decrease in renal function as measured by creatinine clearance, and a small segment actually had improvement in their renal function.[8]

In humans and some animals,[14,15] the number of glomeruli present in adulthood are predetermined between weeks 32 and 36 of gestation,[14,16] whereas the number of glomeruli continue to increase in rats and mice after gestation.[15] In humans, the superficial cortex glomeruli differ in size from the juxta-arcuate glomeruli until age 2. At this time, the size of all of the glomeruli are the same, and the kidney is functioning at adult capacity.[17]The number of glomeruli among individuals is quite variable, ranging from 247,652 to 1,825,380 per kidney, and decreases with age[14,18] at a rate of approximately 6752 glomeruli/yr after the age of 18.[14]

Renal mass increases from 50 g at birth to $>$400 g during the third and fourth decades of life before decreasing to $<$300 g by the ninth decade.[5,13,14,18,19] The latter decrease correlates with the loss of the renal cortex. Radiographically, the size of the kidney has been shown to decrease in size by 10%after age 40 to 30% by age 80.[20–23] Using the Xenon washout technique, Hollenberg *et al.*[22] noted that a decrease in the size of the kidney correlated with a decrease in function and in the renal blood flow to the cortex.[22]

HISTOLOGY

The histologic changes with aging observed in humans have been obtained from information from autopsies or nephrectomies[14,19,23–26] or studies involving laboratory animals.[27,28] With aging, there are certain universal findings in the cortex, medulla, and, in most cases, in the interstitium and vessels (Table 1; Figure 1). These histologic changes correlate with functional changes observed with aging, including an inability to concentrate or dilute the urine, an increased propensity toward salt retention, dehydration, and acute kidney injury.

Glomerulus

With aging, hyaline expansion within the mesangium results in the obliteration of the glomerular

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Table 1. Histologic change in the aging kidney

Site	Changes
Glomerulus	Thickening basement membrane, increase mesangial matrix, focal global sclerosis, hypertrophy
Podocytes	Fusion intermittent, detachment, vacuoles
Interstituim	Tubular atrophy, tubular cast, monocytes infiltrates, interstitial fibrosis
Vessels	Atrophy of afferent and efferent, hyalinosis of vessels, "aglomeruls vessels"

loops[28,29] and is associated with capillary tuft collapse, intracapsular fibrosis, and proteinuria.[14] The sclerosis in the glomeruli is primarily in the superficial cortex with sparse changes in medulla.[14,16,19] Cortical atrophy and loss of the renal parenchyma result.[18] One hundred forty-six cadaveric kidneys from medical examiner offices and autopsies from hospital patients showed an increase in cortical glomerulosclerosis with age from 5% at age 40 to 10% by the eighth decade.[30]The degree of sclerosis was found to correlate with the degree of atherosclerosis, suggesting a hemodynamic role in the aging process.[31] The remaining glomeruli are enlarged to compensate for the decrease in number of functioning cortex glomeruli.[12,18,19,32,33] Electron scans showed podocyte injury with features that including hypertrophy, intracellular uptake of protein/absorptive droplets, foot process fusion, and detachment of the podocytes from the glomerular basement membranes (GBMs).[29,34]

Glomerular Basement Membrane

The GBM increases in width with age.[27,29,35] In Sprague-Dawley rats, the GBM increased in size from 1300 Å at birth to 4800 Å at 24 mo.[29] In humans, the basement membrane increases until age 40, and after age 60, the surface area decreases with wrinkling of the basement membrane with deposition of hyaline.[29] The composition of the basement membrane also changes with aging.[36,37] In older rats, the amino acid composition shifts to a more collagen-like material marked by an increase in hydroxylysine, hydroxyproline, and glycine, and more insoluble amino acids with higher content of low molecular weight proteins.[37] These findings differ in the human GBM, where a decrease in hydroxylysine, 4- hydroxyproline, and glycosylation of collagen occurs with aging.[26] The reason for these differences is not clear.

Tubulointerstitium

With aging, tubular dilation, intratubular cast formation, thickening and splitting of the basement membrane, and fibrosis of the interstitium occurs.[18,35,38] In 24-mo-old rats, scans of the interstitium showed cellular infiltrates consisting predominantly of macrophages and lymphocytes and an increase in intracellular adhesion molecule (ICAM)-1, osteopontin, and collagen IV. Areas were marked by an increase of apoptosis. None of these findings were detected in the 3-mo-old pups.[38] After the administration of enalapril to 15-d-old CF1 mice, a decrease in the peritubular and interstitial sclerosis occurred by 18 mo of age compared with the control mice or mice treated with nifedipine. A decrease in expression of SM-actin, a cytoskeleton protein commonly found in fibrosis and repair, was also noted in the enalapril-treated group.[38]

Vessels

An early angiographic study showed changes in the arteriole-glomerulus unit with aging.[24] In the arterioles, hyaline deposition within the vessels walls leads to obliteration of the lumen and is associated with sclerotic glomeruli primarily in the cortex.[22,24,31] Two structural types associated with the afferent and efferent arterioles have been described.[24] In the first case, oblit-

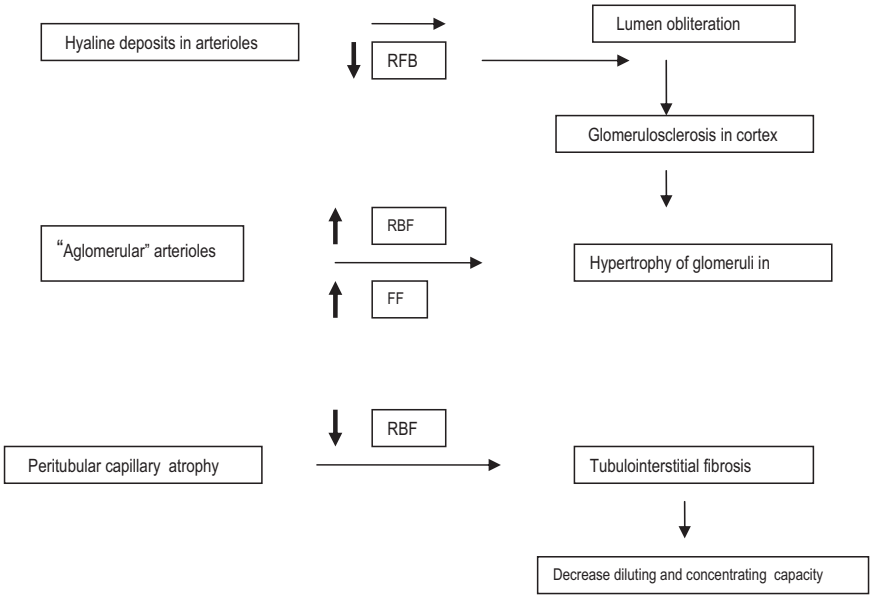

Figure 1. Histologic changes in the aging kidney. There is a decrease in the renal blood flow from hyaline deposition and obliteration of the arterioles resulting in glomerular changes such as wrinkling of the loops and noted hyaline deposition in the mesangium. The loss of these glomeruli is primarily in the cortex resulting in hypertrophy of the remaining glomeruli. In the medulla, the arterioles form " aglomerular " arterioles that results in the shunting of blood to the medulla and an increase in filtration fraction in the medulla glomeruli. The tubulointerstituim in teh area of glomerulosclerosis develop fibrosis, tubular atrophy with tubular casts, and inflammatory cell infiltrates, and increase of peritubular capillary atrophy.

eration of efferent and afferent arterioles is associated with glomerular sclerosis, whereas in the second case, a continuous channel between the afferent and efferent arterioles results in a sclerotic glomeruli, is called an "aglomerulus " arteriole, and shunts the blood to the medullary area.[19,23,24] The small arteries show some elastic duplication, fibrous intimal thickening, destructive changes in the media, narrowing of the lumen, and lamination.[24,29] The blood vessel changes play a major role in renal damage, compromising renal blood flow with subsequent loss of renal mass.[9,30]

Tubules

With aging, the length of the proximal convoluting tubule, the size of the proximal tubular epithelial cell, and the size of its respective nucleus decrease in parallel with the decrease in size of the glomerulus.[12,15,23,33] Electron micrographs of rat tubules showed nonuniform thickening of the tubular basement membrane with vacuoles in the proximal tubules, with intermittent loss of the microvilli,[28] whereas the distal tubules are dilated with diverticular formation.[28] Similar changes in the elderly may account for an increased incidence of urinary tract infections.[8]

FUNCTIONAL CHANGES

With aging, renal blood flow decreases in both human and animal populations[13,19,22,27] (Table 2). Fliser *et al.*[13] observed a marked decrease of about 10% per decade in the effective renal perfusion in healthy elderly volunteers compared with younger adults, with renal perfusion decreasing from 647 ml/min per 1.73 m^2 in younger volunteers to 339 ml/min per 1.73 m^2 in elderly volunteers. The lower renal plasma blood flow and the decrease in GFR contribute to the increase in the filtration fraction found in the elderly persons. The decrease in renal blood flow may result from an imbalance and alterations in the responsiveness to vasoactive substances, *i.e.,* acetylcholine,[22,39] or decrease in production of certain peptides with aging.[13,22,40] Hollenger *et al.*[22] performed Xenon washout studies to evaluate potential transplant donors in ages ranging from 17 to 76 yr old and found a significant decrease in renal perfusion with aging that was associated with a reduction in cortical flow rate and kidney mass. He noted that the vasodilator response to acetylcholine was blunted in the elderly but found no difference in the vasoconstrictor response to angiotensin.[22] In older rats, the vasodilator response to nitric oxide and the endothelial-derived hyperpolarizing factor pathways are attenuated.[39] This suggests the elderly may be more susceptible to acute kidney injury in a low perfusion state because of attenuated responses to vasodilators and an increase in response to vasoconstrictors.[5,22,39]

Table 2. Functional changes in the aging kidney

Decrease renal blood flow by 10%/yr after age 40
GFR decrease by 0.87 ml/min per year
Increase in RVR
Decrease diluting capacity
Decrease concentrating capacity
Normal renal reserve

The "functional reserve "of the kidney is defined as the acute rise in GFR that occurs after an infusion of amino acids.[13,41] A lack of a rise in GFR with infusion of amino acid in elderly persons with underlying renal disease may indicate that the kidney is working at maximal capacity and unable to recruit additional nephrons in response to the increase in the filtered load. However, the ability of the kidney to compensate under stress may be limited in elderly persons. Fliser *et al.*[13] found the functional reserve in healthy older volunteers to be around 15%, and this functional reserve was maintained until age 80 in both men and women. This rise in the functional reserve was not accompanied with a rise in effective renal blood flow (ERBF) or a significant decrease in renal vascular resistance. This suggests that the increase in the renal reserve is not related to vasodilatation in elderly persons as was commonly found in younger adults.

Tubular function

Elderly persons are not able to dilute or concentrate their urine as well as younger healthy adults. This may stem from a combination of interstitial damage, end organ resistance, or a decrease in production of various hormones.[42–44] As a consequence, elderly persons are more prone to water disorders and volume depletion than the general population. The dysnatremias are the most common electrolyte disorders recorded among elderly persons admitted to the hospital and are associated with high morbidity and mortality.[45] In older female WAG/Rij rats, aquaporin (AQP)-2 and -3 are downregulated compared with in 3-mo-old rats. This correlated with laboratory findings between the two age groups. There was a decrease in the urine output in older rats compared with younger rats (3.9 ± 0.3 *versus* 12.8 ± 0.8 ml in 24 h). Older rats also had a lower urine osmolality compared with younger rats (1042 *versus* 2511 ± 54 mosmol/kg).[44] Moreover, there was no change in the expression of AQP-1 in the proximal convoluting tubules and descending loop of Henle's or in AQP-4 in the basolateral membrane in the collecting tubules.[44] These finding are consistent with a decreased ability to concentrate urine in the elderly with normal levels of circulating vasopressin. This could result in decreased insertion of apical AQP-2 into the apical membrane and an inability to concentrate urine.

The levels of serum renin, renin activity, and aldosterone[42,43,46] are low in elderly persons, and their response in a hypovolemic state is also blunted.[12,44,47] Similarly, Sprague-Dawley adult rats were found to have a downregulation of intrarenal mRNA renin and a blunted release of the serum renin in response to hypotension compared with the younger rats.[46]

Despite a mild decline in renal function, elderly persons are capable of secreting an acid load when placed on a 70-g protein diet and maintain normal serum bicarbonate levels and an appropriate urine pH.[48] Although the serum aldosterone level is decreased in the elderly, healthy elderly volunteers and those

with CKD are able to excrete potassium to maintain normal serum potassium.[49]

MECHANISM FOR AGING

The biologic mechanisms for aging are still unknown. Various possible mechanisms for aging have been touted and included recruitment of senescence genes, changes in hormones related to gender,[27,28,50] replicative senescence,[51] damage caused by an unrestricted diet,[52] and changes in oxidative stress[53] (Figure 2). The cell cycle regulator gene regulator, $p16^{INK4a}$, a cyclin-dependent kinase inhibitor, and a possible senescence gene candidate are found in the kidney of rats, mice, and humans.[54] In the aging human kidney, there is an increase in $p16^{INK4a}$ mRNA expression in the cortex.[54] *In vitro* experiments in the aging human kidney suggested other gene candidates. Increase expression of $p16^{INK4a}$ and p^{53} was found in the sclerotic glomeruli areas, whereas $p16^{INK4a}$, p^{53}, cyclooxygenase-1 (COX-1), transforming growth factor (TGF)-β, and heat shock protein A5 (HSPA5) were found in the interstitium.[54]

Knockout mice or transgenic animals have been created to evaluate the correlation between certain proteins and aging. In transgenic male rats, the antisense growth hormone (GH) showed a suppression of the expression of GH/insulin-like growth factor-1 (IGF-1) activity.[55] The suppression of this activity prevented histologic changes normally seen in the aging rat kidney. Associated with the decrease activity of GH/IGF-1 was a decrease in macrophage infiltrates, the extracellular matrix, and collagen production. The decrease activity of GH/IGF-1 seems to be renoprotective,[55] and upregulation may contribute to sclerosis found in certain disease states such as diabetes mellitus. Another candidate gene for senescence is the SMP-30 gene, which seems to be important in anti-apoptotic function.[56] Knockout mice for the SMP-30 gene showed an increase in mortality and increase deposition of lipofuscin in the renal tubular epithelial cells, marked degeneration in the mitochondria, podocyte fusion, and an increase in apoptosis.[56]

Klotho is considered the anti-aging gene and has shown expression in the kidney. The klotho mouse model (KI/KI) for aging was genetically made by transgene disruption of the klotho gene locus.[57] The klotho (*kl/kl*) mouse exhibits many of the phenotypic features of aging including the following: short lifespan, growth retardation, infertility, osteoporosis, atherosclerosis, obstructive pulmonary disease, renal sclerosis, and atrophy of the skin.[57] Histologic changes in the *kl/kl* rat showed fibrosis in the renal arteries, the interstitium, and the glomeruli, as well as calcification within the cortex in the older mice.[57]

The imbalance between the accumulation and degradation of extracellular matrix (ECM) may play a role in fibrosis. A homozygote TIMP-1 transgenic mice was constructed to study the effect of TIMP-1 on ICAM-1 and fibrosis in the aging kidney.[58] TIMP-1 is a tissue inhibitor of metalloproteinase (MMP), which is known to increase the degradation of ECM and ICAM-1. In the aging rat, there was an upregulation of TIMP-1 correlating with upregulation of ICAM-1 and TGF β. Fibrosis seems to be promoted by the regulation of profibrotic proteins and inhibition of the breakdown of ECM.[58]

Besides genetic programming, there seems to be a sex dimorphism in the development of glomerulosclerosis in animals, with the female gender being protected until menopause.[27,28,59] This relationship may not hold for humans. 17β-estradiol seems to have many protective functions including inhibition of apoptosis in mesangial cells, an increase in the expression of metalloproteinase, and a decrease in collagen production, which would point to a beneficial effect on aging.[28,59] Aging female Dahl salt-sensitive rats were placed on 17β-estradiol replacement therapy after undergoing ovariec-

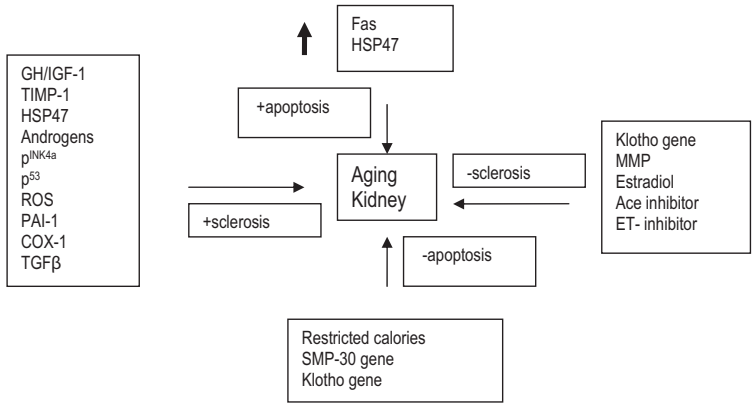

Figure 2. Aging kidney. A schematic outline of the various modulators that may be responsible for damage or reno-protection of the aging kidney. The restricted caloric intake has a reno-protective effect through modulating various proteins by suppressing GH/IGF-1 activity, Fas, and HSP47. The upregulation of MMP, downregulation of TIMP-1 and ICAM-1, and decrease in oxidative stress results in a decrease in matrix dysregulation and inflammation. The SMP-30 and klotho genes are anti-apoptotic. The klotho gene seems to be reno-protective by decreasing sclerosis. The inhibition of ET-1 and angiotensin II are known to decrease sclerosis. Areas of fibrosis are found to have an increase in PA1–1, COX-1, TGF-β, P^{INK4a}, and p^{53}. The hormones estradiol and androgen have opposite effects on aging.[35,40,50–59]

tomy at 3 mo and showed less renal scarring at 12 mo than the unsupplemented ovariectomy female rats.[59] This suggests that estradiol has a protective role in sclerosis.[59] Other studies suggest a role of androgens mediating sclerosis.[27]

The role of endothelin (ET) in aging was explored by treating male Wistar rats at 2 and 23 mo after treatment for 28 d with a nonpeptide endothelin A receptor antagonist.[34] There was a 50% decrease in glomerulosclerosis in the treated group at 23 mo compared with the control group, as well as a significant decrease in proteinuria in the treated group compared with the control group (51 *versus* 307 mg/kg; $P < 0.0102$).[34]

The telomeres are DNA repeat sequences of TTAAGGG $\times$ repeats that are attached to the somatic chromosome. With replication, certain base pairs are lost. There are a finite number of replicate cycles that somatic cultured cells can undergo and then replication ceases. This is termed replicative senescence (Hayflick limit).[51] In human kidneys, the cortical telomere length decreases with aging at a loss of 0.029 kbp/yr, which is greater than seen in the medulla.[51] The significance of this needs to be further evaluated.

The biology of aging is an important area with many unanswered questions. The understanding of the variability of the aging process among humans and animals may improve our fundamental knowledge of disease mechanisms and the possibility of preventing the progression of renal disease. Presently, it seems that BP control, decrease in caloric intake, and an angiotensin-converting enzyme inhibitor may delay the progression of aging in the kidney.

CONCLUSION

The elderly and the very elderly population is the fastest growing in the United States and accounts for a large percentage of those with CKD. Cross-sectional and longitudinal studies have shown a decrease in renal function with aging beginning at age 40, with the exception of a small population showing no decline with age. The comorbid problems accompanying the elderly population make it difficult to decipher the true course of aging within the kidney. Even so, there are some common histologic findings and functional changes in the kidney with aging. The biologic mechanism for the changing with age are not well known, but recent identification of senescence genes, the role of hormones, and diet may improve our understanding and slow the decline in kidney function.

TAKE HOME POINTS

- The elderly and the elderly population is the fasting growing age group in the United States, and they encompass the largest group with CKD
- The decrease in GFR begins at age 40 and is around 0.87 min/ml per year
- Gross changes with age include 30% loss in size of the kidney by the eighth decade and decrease in the renal mass to <300 g by the ninth decade
- The common histologic changes include cortical glomerular sclerosis, loss of afferent and efferent arterioles in the cortex, and shunting of the renal blood flow to the medulla
- Functional reserve and electrolyte balance are maintained under normal condition in the elderly population
- Biology of aging is not well known, but there may be an interaction between senescence genes, hormones, and diet

DISCLOSURES

None.

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REVIEW QUESTIONS: KIDNEY SENESCENCE

1. A 68-yr-old Caucasian male has been quite concerned after reading in his local newspaper about the increased incidence of chronic kidney diseases in the elderly population. He was never told by his primary care physician he had any kidney problems. He made an appointment to see a nephrologist to discuss his possible kidney disease. He presents at the clinic, and his BP is 125/70 mmHG, and there are no pertinent findings on his physical exam. He does not take any prescribed medications and only vitamins. Laboratory values show a serum creatinine of 1.2 mg/dl. Which the following is true?
   a. The rate of decline in his renal function is normal for his age group
   b. He will be on renal replacement therapy by the time he reaches 90 yr old
   c. Elevated BP has no effect on his progression
   d. The aging process affects all organs and all elderly people have progression of their renal function

2. The histologic changes in the kidney with age are the following except
   a. Glomerulosclerosis in the medulla more than the cortex
   b. The arterioles in the cortex become sclerosed leading to "aglomeruli"
   c. There is shunting of blood to the medullary region secondary arteriolar structural changes
   d. There is thickening of the glomerular membrane and change in composition with aging

3. Community-dwelling elderly persons are able to maintain electrolyte balance secondary to adequate residual renal reserve
   a. True
   b. False

4. The biologic causes of aging are unknown; however, there are certain medical interventions that may slow down renal loss in elderly person with normal renal function. The correct answer is which of the following?
   a. Controlled hypertension
   b. High caloric intake
   c. Low protein diet
   d. Testesterone