ISSN 1669-5402 (Print) ISSN 1669-5410 (Online)

Physiological Mini-Reviews

Edited by the Argentine Physiological Society.

Vol. 2, N° 7, February 2007.

http://www.mini.reviews.safisiol.org.ar

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[ISSN 1669-5402 (Print); ISSN 1669-5410 (Online)]

Edited by the **Argentine Physiological Society**

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http://www.mini.reviews.safisiol.org.ar

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(Resol. IGJ 763-04)

The Kidney in Aging.

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Introduction.

Aging is a slow, inflammatory biological process that affects many organs of which the kidney is one of the main targets. Aging is associated with a decline in renal function coincident with a progressive loss of nephrons, with glomerular and tubulointerstitial scarring. These changes begin in the fourth decade of life and accelerate between the 5th and 6th decade, resulting in alterations in glomerular and tubular function, systemic hemodynamics and body homeostasis. While aging-related changes begin in mid-life, most of the discussion will revolve around the management of the older population, defined as > 65 years of age.

It is important to realize that aging-associated renal disease may not be an inevitable consequence of life. Some subjects do not show age-related decline in GFR, and in some populations hypertension does not increase with aging, the latter occurring primarily in non-Westernized groups habitually on low sodium diets. This has led some to hypothesize that aging-associated renal disease may be an active process that is potentially preventable.

Functional Changes.

Glomerular filtration rate

Serum creatinine is a relatively unreliable indicator of renal function in the aging population. This is because creatinine generation reflects muscle mass, and muscle mass decreases with aging. Normally, males excrete 20-25 mg/kg body weight of creatinine in the urine each day, and women excrete 15-20 mg/kg body weight of creatinine. However, after the age of 60 years there is a progressive decrease in urinary creatinine excretion resulting in excretion rates lower than these ranges[1]

When accurate creatinine clearances are performed, there is clear evidence for a reduction in renal function with age. In one study, the mean creatinine clearance fell from 140 mL/min/1.73 M^2 at age 30 years to 97 mL/min/1.73 M^2 at age 80 years[2]. Interestingly, serum creatinine was not different between these groups due to the loss of muscle mass that occurs with aging. The decrease in renal function has been corroborated by inulin clearance studies, which show a progressive fall in GFR after the age of 40 years with a relatively greater decline in men[3].

Formulas such as the MDRD (Modification of Diet in Renal Disease) equation or the Cockcroft-Gault formula (see Chapter 3) take into account changes with age. Both have a tendency to underestimate true GFR in the aging (>65 years) population when compared to standard techniques such as ^{99m}Tc-DTPA. However, the MDRD appears to be more accurate compared to the Cockcroft-Gault formula [4,5].

In addition to the decrease in GFR with aging, there may be a reduction in 'renal reserve.' Usually, GFR increases with a protein load or with feeding. Some studies suggest that aging humans show a normal increase in GFR following amino acid infusion. However, a more profound challenge was performed in aging rats; in this study, aging rats showed a markedly blunted increase in GFR with feeding[6].

Not all individuals show a decrease in GFR with aging. In particular, in as many as one-third of subjects who remain normotensive there is no decrease in creatinine clearance with age[7].

Renal plasma flow

There is also a decrease in renal plasma flow (RPF) with aging. RPF measured by PAH clearances decrease from a mean of 650 mL/min in the fourth decade to 290 mL/min by the ninth decade, and this is associated with increasing renal vascular resistance[13]. The fall in RPF tends to be greater in males than in females, and is also greater in elderly subjects who are hypertensive[8]. Since RPF decreases relatively more than GFR, filtration fraction (defined as GFR/RPF) increases with age.

The decrease in RPF does not simply reflect a decrease in renal mass. Studies using a Xenon washout technique demonstrated there is a true reduction in renal blood flow when factored for renal mass[9]. The decrease in renal blood flow especially involves the cortex, and blood flow to the medulla is relatively preserved.

Sodium balance and hypertension

Sodium balance is also altered in aging. There is evidence for both impaired sodium excretion of a salt load[10] as well as defective conservation in the setting of sodium restriction[11]. Proximal sodium reabsorption (reflected by lithium clearances) is increased in aging, whereas distal sodium reabsorption may be reduced[12]. Studies in rats suggest that pressure natriuresis is impaired in aging[13]. As the diet of most individuals in developed countries contains excess sodium (8-10 g salt/day), there is a tendency in the elderly population for total body sodium excess.

The relative defect in sodium excretion and increased total body sodium may be a predisposing factor for the development of hypertension. Blood pressure increases with age. After the age of 60 years, the majority of the population is hypertensive[14]. The majority (> 85%) of hypertension in the aging population is sodium-sensitive, in that restricting sodium will result in a significant fall (> 10 mm Hg) in mean arterial pressure[15]. Populations that ingest low sodium diets, such as the Yanomamo Indians of Southern Venezuela, do not show an increase in blood pressure with age[16]. Other mechanisms may also be involved in aging-associated hypertension, including loss of vascular compliance due to collagen deposition in the larger arterial vessels. Endothelial dysfunction, perhaps mediated by oxidative stress, has been shown to be increased in the aging population, and may contribute to the development of increased blood pressure.

The observation that aging-associated renal and vascular changes may be responsible for the high frequency of hypertension in the population likely explains why correction of secondary forms of hypertension (such as primary aldosteronism, Cushing's syndrome, renovascular hypertension and hypothyroidism) is more effective at curing

hypertension in younger patients. In one study, diastolic blood pressure fell to < 90 mm Hg in 24 of 25 subjects under the age of 40 years after treating the mechanism responsible for the secondary hypertension but only 38 of 61 subjects over the age of 40 years[17].

Osmoregulation and water handling

There is also impaired water handling with aging. Both concentration and dilution are affected, and nocturia is common. There is a reduced maximal urinary osmolality and thirst response to hyperosmolality, which may be predisposing factors for the development of dehydration. Subjects respond to antidiuretic hormone (vasopressin) with an increase in urine osmolarity, but it is blunted compared to younger subjects. Total body water also decreases with age. Conversely, there is slower excretion of a water load, leading to an increased predisposition to hyponatremia.

Pathogenesis of Progressive Renal Disease in Aging.

A variety of mechanisms have been proposed for aging related renal changes. Senescence is associated with progressive telomere shortening of chromosomal DNA that may limit replicative capacity. In particular, a loss of mitochondrial DNA and total mitochondria occurs with aging[18]. A favored hypothesis is that it is due to the production of oxygen-derived free radicals that cause cumulative oxidative injury to tissues over time[19]. A loss of mitochondria interferes with mitochondrial respiration and cellular energetics and may predispose to cell injury or death. Senescence is associated with accelerated apoptosis, and increased numbers of apoptotic tubular and interstitial cells have been shown in the aging rat[20].

Glomerular number also decreases from approximately one million per kidney to 600,000 or less by the eight decade. A loss of nephrons results in hyperfiltration with increased glomerular hydrostatic pressure and glomerular hypertrophy, which are known risk factors for glomerular scarring[21]. However, studies in aging rats have shown that the initiation of renal damage with aging may occur independently of glomerular hypertension. Depending on the strain, glomerular hydrostatic pressures may be either elevated or normal with aging[13]. It is thus likely that glomerular hypertension, when it occurs with a decrease in nephron mass, is a contributor, rather than an initiator of the aging-associated decline in renal function.

The renin angiotensin system also has a role in the renal changes of aging. While aging is associated with extracellular volume expansion and a reduction in plasma renin activity, there is evidence in aging rats that renal angiotensin II levels are elevated. Furthermore, rats or mice treated with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) from shortly after birth have less glomerulosclerosis, less glomerular hypertrophy and less tubulointerstitial fibrosis with aging[22]. The renoprotection may be mediated by both hemodynamic (decreasing glomerular hydrostatic pressure and increasing renal blood flow) and non-hemodynamic (direct effect to block angiotensin II-mediated cell growth or cytokine (TGF-β) generation) mechanisms[23]. Blockade of the renin-angiotensin system also reduces aging-associated oxidative stress and preserves mitochondria in renal proximal tubules in association with upregulation of cellular antioxidant enzymes as rats age[24,25]. In addition, life-long blockade of the renin angiotensin system in rats results in less left ventricular hypertrophy and myocardial

fibrosis, improvement in learning capacity, increased sexual activity and decreased liver fibrosis[23,24,25].

Endothelial function also declines with aging, and this is greater in men than women. The decline in endothelial function is associated with a progressive reduction in nitric oxide (NO) production by endothelial cells and is reflected clinically by a reduction in brachial artery reactivity[26]. The loss of nitric oxide may be due to the accumulation of asymmetric dimethyl arginine (ADMA, an inhibitor of NO synthesis), to biologic effects of serum uric acid (which reduces endothelial NO bioavailability), or to the local generation of oxidants (which scavenge NO). There is also a loss of neuronal NO synthase in the aging kidney which is associated with renal progression. The loss of normal endothelial vasodilatory substances may account for the increased renal vasoconstrictive response observed in aging rats to agents such as angiotensin II and endothelin-1. In addition, the endothelial changes may predispose to preglomerular vascular disease resulting in impaired renal autoregulation (and glomerular hypertension) as well as inhibit renal angiogenesis with progressive capillary loss and ischemia.

Other potential mediators of aging-associated renal disease include TGF-β (an important profibrotic growth factor with increased expression in aging kidneys). Advanced glycation end-products (AGEs), while classically associated with diabetes, also accumulate in aging. Chronic administration of aminoguanidine (an inhibitor of AGE synthesis) reduces glomerulosclerosis in the aging rat.

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