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THE AGING KIDNEY: PHYSIOLOGICAL CHANGES

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Abstract

Age-associated loss of kidney function has been recognized for decades. With aging, many subjects exhibit progressive decreases in glomerular filtration rate (GFR) and renal blood flow (RBF), with wide variability among individuals. The fall in GFR is due to reductions in the glomerular capillary plasma flow rate, and the glomerular capillary ultrafiltration coefficient. In addition, a primary reduction in afferent arteriolar resistance is associated with an increase in glomerular capillary hydraulic pressure. These hemodynamic changes occur in concert with structural changes, including loss of renal mass; hyalinization of afferent arterioles and in some cases, development of aglomerular arterioles; an increase in the percentage of sclerotic glomeruli; and tubulointerstitial fibrosis. Aging is associated with altered activity and responsiveness to vasoactive stimuli, such that responses to vasoconstrictor stimuli are enhanced, while vasodilatory responses are impaired. Changes in the activity of the renin-angiotensin and nitric oxide systems appear to be particularly important, as is the modulating effect of gender. These changes may predispose the older kidney to acute kidney injury, including normotensive ischemic nephropathy, as well as progressive chronic kidney disease.

Keywords

Aging; Glomerular filtration rate; Renin-angiotensin system; Nitric oxide; Gender

The biologic price of aging includes progressive structural and functional deterioration of the kidney, and these changes are among the most dramatic of any organ system. Efforts to understand the age-related changes in kidney function, and mechanisms which underlie these changes, may help to focus future research efforts to identify potential interventions. This review considers the functional and structural changes that occur with normal aging; more detailed reviews may be found in several recent publications (1-3).

Age-Related Changes in Kidney Function and Structure

The glomerular filtration rate (GFR) is low at birth, approaches adult levels by the end of the second year of life, and is maintained at approximately 140 ml/min/1.73 m² until the fourth decade. As indicated by the classic inulin clearance studies of Davies and Shock (4), GFR declines by about 8 ml/min/1.73 m² per decade thereafter (4,5). Studies using GFR estimates

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on population-based data suggest that the decline may begin earlier, after the second decade of life (6). While clinically important in many older subjects, it should be noted that there is wide variability among individuals in the age-related fall in GFR. There is ongoing debate as to the distinction between age-related loss of GFR and the presence of chronic kidney disease (CKD) in the elderly, as is discussed elsewhere in this volume.

Epidemiologic studies suggest that acceleration of age-related loss of renal function may be associated with systemic hypertension (7,8), lead exposure (9), smoking (8,10), dyslipidemia (8), atherosclerotic disease (10), presence of inflammatory markers (11,12), increased levels of advanced glycosylation endproducts (12), and possibly obesity (13,14) and male gender (15). Recently, a history of one or more episodes of acute kidney injury has also been recognized as a risk factor for subsequent development or progression of CKD (16).

The age-related reduction in creatinine clearance (CrCl) is accompanied by a reduction in the daily urinary creatinine excretion due to reduced muscle mass. Accordingly, the relationship between serum creatinine (SCr) and CrCl changes. The net effect is near-constancy of SCr while true GFR (and CrCl) declines, and consequently, substantial reductions of GFR occur despite a relatively normal SCr level. However, as discussed elsewhere in this volume, there remains considerable controversy as to the most accurate method of estimating GFR in the elderly, and a number of alternate formulae have been proposed.

Similar changes in renal blood flow (RBF) occur, so that RBF is well maintained at about 600 ml/min until approximately the fourth decade, and then declines by about 10 percent per decade (17,18). The reduction in RBF is not entirely due to loss of renal mass, as xenon-washout studies demonstrate a progressive reduction in blood flow per unit kidney mass with advancing age. The decrease in RBF is most profound in the renal cortex; redistribution of flow from cortex to medulla may explain the slight increase in filtration fraction seen in the elderly (17, 18).

Micropuncture studies in aging rat models have elucidated the glomerular hemodynamic changes that occur with aging (19). In rats at the equivalent of late middle age, values for the single nephron GFR (SNGFR) and glomerular capillary plasma flow rate (Q_A) remained similar to those in younger animals. However, the older rats exhibited a significant reduction in R_A , the afferent arteriolar resistance. The fall in R_A allowed a rise in glomerular capillary hydraulic pressure (P_{GC}), despite the absence of change in systemic blood pressure. In addition, the older rats exhibited a significant reduction in K_f , the glomerular capillary ultrafiltration coefficient. The importance of loss of afferent arteriolar responsiveness was shown in studies of the Spontaneously Hypertensive Rat (SHR)(20). In young SHR rats, protective afferent arteriolar vasoconstriction prevents transmission of high pressures into the glomerular capillary network; P_{GC} is maintained at normal levels, and little injury develops despite severe systemic hypertension. With aging, the fall in R_A allows P_{GC} to rise, and this change is accompanied by the development of proteinuria and progressive glomerular sclerosis (20). Glomerular hemodynamics cannot be measured directly in humans, but can be estimated using sophisticated morphologic and physiologic techniques. In a study of healthy kidney donors of different ages, Hoang, et al (21) confirmed these patterns in older donors. As compared with subjects under the age of 40, subjects over the age of 55 demonstrated reductions in GFR and RBF, and a significant reduction in K_f . The reduction in K_f was calculated to result from reductions in both the glomerular capillary permeability, and the surface area available for filtration (21).

Animal studies suggest that another functional abnormality in aging is an increase in glomerular basement membrane (GBM) permeability, leading to an increase in urinary excretion of proteins, including albumin (22). Adaptive changes in podocyte morphology also contribute

to proteinuria in aging animals (23). Studies in aging humans demonstrate decreased sulfation of the GBM glycosaminoglycans (24), which would be expected to render the GBM more permeable to macromolecules. Population studies also indicate that the incidence of both microalbuminuria and overt proteinuria increase with advancing age (25), even in the absence of diabetes, hypertension, or CKD.

Renal mass increases from about 50 gms at birth to over 400 gms during the fourth decade, after which it declines to under 300 gms by the ninth decade. The reduced kidney weight correlates with the reduction in body surface area (26-28). Loss of renal mass is primarily cortical, with relative sparing of the medulla (28,29). Glomerular number decreases, but studies differ on the size of the remaining glomeruli (27,30,31). Glomerular shape changes as well (30), with the spherical glomerulus in the fetal kidney developing lobular indentations as it matures. With aging, lobulation tends to diminish, and the length of the glomerular tuft perimeter decreases relative to total area. The GBM undergoes progressive folding and then thickening (32,33). This stage is accompanied by glomerular simplification, with the formation of free anastomoses between a reduced number of glomerular capillary loops. Frequently, dilatation of the afferent arteriole near the hilum is seen at this stage. Though variable, substantial hyalinosis of the afferent arterioles may develop (34). Eventually, the folded and thickened GBM condenses into hyaline material with glomerular tuft collapse. Degeneration of cortical glomeruli results in atrophy of both afferent and efferent arterioles, with global sclerosis. In the juxtamedullary glomeruli, glomerular tuft sclerosis is accompanied by the formation of direct channels between the afferent and efferent arterioles, resulting in aglomerular arterioles (32,33). These aglomerular arterioles, which presumably contribute to maintenance of medullary blood flow, are rarely seen in kidneys from healthy young adults, but their frequency increases both in aging kidneys and in the presence of CKD (33).

The incidence of glomerular sclerosis increases with advancing age. Sclerotic glomeruli comprise fewer than 5% of the total under the age of 40; thereafter, the incidence increases so that sclerosis involves as much as 30% of the glomerular population by the eighth decade (35-37). Thus, both diminished glomerular lobulation and sclerosis of glomeruli tend to reduce the surface area available for filtration, and therefore contribute to the observed age-related decline in K_f and GFR. In addition, age-related changes in cardiovascular hemodynamics, such as reduced cardiac output (38) and systemic hypertension, are likely to play a role in the progressive reduction in renal perfusion and filtration. Tubulointerstitial fibrosis contributes as well. In aging rats, this process is accelerated by loss of peritubular capillary density (39), in association with a fall in vascular endothelial growth factor expression (40). Finally, it is hypothesized that increases in cellular oxidative stress that accompany aging result in endothelial cell dysfunction and changes in vasoactive mediators resulting in increased atherosclerosis, hypertension and glomerulosclerosis (41).

Mediators of age-related physiologic changes

Studies in animal models have identified several mechanisms for injury in the aging kidney. Changes in the activity and/or responsiveness to vasoactive mediators plays a role, with a propensity toward enhanced sensitivity to vasoconstrictor stimuli (42,43), and decreased vasodilatory capacity (42,44).

While the systemic renin-angiotensin system (RAS) is suppressed in aging, the intrarenal RAS may not be equivalently suppressed (45,46), and pharmacologic RAS blockade has been shown to slow the progression of age-related CKD (19,47). Total body renin and aldosterone levels fall during aging, due to decreased renin production and release. Decreased responsiveness of the RAS leads to decreased renin release in response to appropriate stimuli (48). Conversely,

the prolonged low levels of renin and aldosterone may result in an exaggerated renal response to these components of the RAS when present (45).

Nitric oxide (NO) plays diverse roles impacting renal vasculature and cell growth. NO acts as a vascular vasodilator, and also inhibits mesangial cell growth and matrix production. The pathologic decrease in NO seen in aging leads to increased renal vasoconstriction, sodium retention (with resultant worsening hypertension), as well as increased matrix production and mesangial fibrosis (15). While levels of NO isoforms are higher in the medullary region, they are reduced in the renal cortex, and thereby may contribute to the reduced perfusion in the elderly (49). There are several potential mechanisms for NO reduction with age. Oxidative stress increases with age, which leads to a decrease in key co-factors for normal NO production, including tetrahydrobiopterin (50). L-Arginine is a key substrate in NO production, and the availability of this substrate may change with age. Although not classically an essential amino acid, the L-Arginine level declines with food deprivation in elderly rat models. This observation suggests that L-arginine may take on features of an essential amino acid in the aged, and additional dietary intake would be required to maintain sufficient substrate levels for NO production (15). Additionally, NO synthase is degraded by asymmetric dimethyl arginine (ADMA). ADMA levels increase with age in some rat models, suggesting that increased ADMA may result in increased NO synthase degradation and lower overall NO production in the elderly (51).

The balance of vasoconstrictor vs. vasodilatory responsiveness seems to play an important role in the kidney's response to acute injury. Impaired ability to autoregulate can lead to a fall in GFR even when the magnitude of the acquired renal insult is modest. In the context of current patterns of therapeutics in older patients – such as administration of RAS blockers and nonsteroidal anti-inflammatory drugs – the older kidney is at increased risk for development of AKI, including normotensive ischemic nephropathy (52).

Sex hormones are likely to contribute, as well. The rate of progression of CKD tends to be slower in females, both experimentally (15) and clinically (53). Gender affects the age-related changes in the RAS and NO systems, as well as metalloprotease activity. The impact of gender on the renin angiotensin system relates to the interaction between 17 β -estradiol (E2) and Ang II. E2 decreases tissue levels and activity of both Ang II and angiotensin II and angiotensin converting enzyme (ACE)(54). Conversely, testosterone tends to increase RAS activity (55). Experimentally, estrogen therapy (56) and androgen deprivation (57) are protective against progression of CKD.

Nitric oxide, as described, has an overall protective effect in kidneys due to decreased mesangial cell and matrix production (15). With advancing age, endothelial NO synthase (eNOS) abundance decreases, and oxidative stress increases, both of which contribute to impaired endothelial NO production and endothelial dysfunction (15,58). Gender differences in NO levels are likely related to the relationship between NO and E2, which stimulates release of NO synthase. Additionally, the age-related increase in ADMA is delayed in premenopausal females compared to males, which may also result in more available NO synthase in females and subsequently greater NO production (59). Indeed, the renal vasoconstrictor effect of NO synthase inhibition is considerably more pronounced in aging men than in women (60).

Discrepancy in the levels of metalloproteases may also impact gender specific renal dysfunction. Metalloproteases break down matrix, which may help prevent matrix expansion (a key element in CKD progression). Metalloprotease levels increase in aging females compared to levels seen in aging males (15,61).

While estrogens appear to have a protective effect in terms of renal aging, males may be at increased risk of renal dysfunction due to possible negative effects of androgens. Androgens

may increase fibrosis and mesangial matrix production (15). This effect may be in part related to androgen-driven inhibition of age-related increases in metalloproteases (61). Additionally, androgens may stimulate the renin-angiotensin system (55) and thereby increase sodium retention, resulting in worsening hypertension which may adversely impact CKD progression.

In addition, age-related changes in cardiovascular hemodynamics, such as reduced cardiac output and systemic hypertension, are likely to play a role in reducing renal perfusion and filtration. Finally, it is hypothesized that increases in cellular oxidative stress that accompany aging result in endothelial cell dysfunction and changes in vasoactive mediators resulting in increased atherosclerosis, hypertension and glomerulosclerosis (41).

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