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Gender-dependent effects of aging on the kidney

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Abstract

It is well known that the kidney plays an important role in the development of cardiovascular diseases such as hypertension. The normal aging process leads to changes in kidney morphology, hemodynamics and function, which increase the incidence of cardiovascular events in the elderly population. These disturbances are influenced by several factors, including gender. In general, females are protected by the effects of estrogens on the cardiorenal system. Several studies have demonstrated the beneficial effects of estrogens on renal function in the elderly; however, the relationships between androgens and kidney health during one's lifetime are not well understood. Sex steroids have many complex actions, and the decline in their levels during aging clearly influences kidney function, decreases the renal reserve and facilitates the development of cardiovascular disorders. Therefore, in this review, we discuss the cellular, biochemical, and molecular mechanisms by which sex hormones may influence renal function during the aging process.

Key words: Sexual dimorphism; Renal function; Aging; Cardiovascular disorders; Sex hormones

Effects of sex hormones on the kidneys

The sexual dimorphism deeply reflected on renal morphology and physiology is most likely due to specific genes, to the actions of gonadal steroids and to the endocrine/paracrine pathways of the kidney. Moreover, it has also been shown that aging exerts different effects on males compared to females (1). In the past few years, studies conducted on animal models have contributed to our increased understanding of the molecular and physiological mechanisms involved in both the endocrine and aging relationships of renal function in the elderly.

Role of estrogen (E_2)

Estrogen is the main female sex hormone in both humans and animal models. It is produced in the granulosa cells of the ovarian cortex through the conversion of androgen precursors by the aromatase enzyme, which in turn is modulated by the hormonal hypothalamic-pituitary axis (2). Females also show a well-defined onset of reproductive capacity that can be used to separate somatopausal from hormonal mechanisms, enabling researchers to define the pathways responsible for any particular effects.

Evidence suggests that there are at least three distinct estrogen receptors (ER) expressed in the kidney. Two ER belong to the ligand-activated transcription factors, ERα and ERβ. The third one, GPER (also referred to as GPR 30), has been recently studied and belongs to the G-protein-coupled receptor superfamily (3).

The potential role of E_2 in regulating renal function is evident from the observation that the kidney expresses the classic ERα and ERβ, which are members of the nuclear hormone receptor superfamily. In human fetal kidneys, ERβ is the prominent renal ER expressed, whereas ERα is only marginally expressed (4). The data are controversial concerning adult renal tissue. Rogers et al. (5) showed that ERα predominates in the female rat kidney cortex, and ERβ predominates in the male rat kidney cortex, whereas Lu et al. (6) reported that male rats show greater ERα abundance than females. Because ERα and ERβ can respond differently to E_2 in mediating its transcriptional activity (7), it is possible that the differential expression of ER subtypes may be of physiological relevance.

In the kidney, E_2 suppresses collagen synthesis in the glomerular mesangial cells (GMCs) by modulating mitogen-activated protein (MAP) kinase activity and the expression

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of the transcription factor AP-1 (8-10), suggesting that E_2 may limit the progression of glomerulosclerosis. Increased generation and deposition of extracellular matrix proteins (EMP) is the initial step in the development of glomerular injury and progressive loss of renal function (11).

Clinical observations also indicate that E_2 is indirectly involved in GMC growth by modulating the synthesis of growth promoters and growth inhibitors (8,9). E_2 inhibits collagen synthesis induced by angiotensin II (ANG II) and transforming growth factor-β (TGF-β) (8,12), which are implicated in the pathophysiology of progressive renal injury in kidney disease models. Moreover, E_2 antagonizes the effects of TGF-β on collagen synthesis and inhibits proliferation (8) in GMCs. Previous investigations have also demonstrated that E_2 attenuates ANG II-induced MAP kinase activity in GMCs, thus avoiding the deleterious effects of this peptide on the kidney (12). In addition, growth within the glomerulus can be stimulated by reactive oxygen species (ROS) (13), which can contribute to the process of glomerulosclerosis in many renal diseases. The mechanisms by which ROS induce their mitogenic effects on GMCs include induction of endothelin-1 synthesis, oxidation of lipoproteins and activation of the MAP kinase pathway (7). Because E_2 is a potent antioxidant, it may protect GMCs against the growth effects of free radicals. Indeed, oxidation of low-density proteins in GMCs is inhibited by E_2 (14). Thus, there is strong evidence that E_2 protects the kidneys by abrogating the mitogenic effects of multiple growth factors that participate in the development of glomerulosclerosis.

Role of androgens

Testosterone is the primary male sex steroid. It is produced by Leydig cells and its androgenic activity is mediated by a high-affinity androgen receptor, AR) (15). The classic action of testosterone occurs via an intracellular AR, predominantly in the nucleus in the unbound state, binding to specific DNA sequences in the target gene promoter with modification of local chromatin architecture and activation or inhibition of the target gene transcription (1). Furthermore, the presence of 5α-reductase at some locations promotes the conversion to a more potent metabolite, dihydrotestosterone (DHT) (15).

Evidence suggests that there are two analogous isoforms of AR, ARα and ARβ in mammalian kidneys (15). Testosterone is known to be profibrotic since it stimulates EMP deposition in GMCs, leading to mesangial expansion and renal dysfunction (16). Male rat mesangial cells express higher baseline fibronectin mRNA levels than female rat mesangial cells (17). This investigation also demonstrated that basal tumor necrosis factor-α (TNF-α) and interleukin-1β levels are higher in male mesangial cells compared to female mesangial cells, indicating proinflammatory and profibrotic actions of testosterone in the kidney. This sexual dimorphism in mesangial cells may play a role in the faster progression of glomerulosclerosis leading to end-stage renal disease in males.

Additionally, androgens have been shown to increase proapoptotic signaling (18). Testosterone-induced apoptosis in proximal tubule cells involves the activation of inflammatory cytokines, such as c-Jun amino terminal kinase (JNK), and can be blocked by the AR antagonist flutamide, which reduces JNK phosphorylation (19). Furthermore, testosterone activates a downstream cascade involving the up-regulation of an apoptosis-stimulating fragment and its ligands, which is blocked by JNK inhibition (19). Taken together, these data indicate that testosterone may play a crucial role in the acceleration of the tubular apoptotic process and the progression of chronic kidney disease in males.

Gender-induced differences in the aged kidney

It is well known that aging affects normal gonadal function. The most important changes include decreases in E_2 and testosterone levels in females and males, respectively, and this decline in sex hormone production is also associated with a deterioration of renal function (1). Testosterone levels decrease with normal aging as kidney function declines and decrease further in men with renal disease (20). If testosterone had renal protective actions, the gradual decline in testosterone levels that occurs in the elderly could contribute to the age-dependent renal dysfunction. However, testosterone levels are increased in most postmenopausal women as renal dysfunction develops and cardiovascular risk increases (20), suggesting that augmented testosterone levels might be damaging.

Age-related changes in renal structure and function have been extensively studied in different species (21). The decline in renal function with age in humans is well documented and is considered to be inversely related to longevity (22). Studies suggest that E_2 is responsible for the resistance of kidneys to the progression of renal disease in women (1,7). In contrast, in men, the progression of chronic renal failure occurs at a faster rate than it does in women (23), indicating that gender can be considered one of the determinants of the progression of the age-related decline in renal function (24).

Morphological changes

Several studies have extensively detailed the anatomical, histological and cytological alterations occurring in the kidney during aging. The most evident effect of aging on the kidney seems to be a decrease in renal size and weight, falling anywhere between 10 and 43% by the age of 80 years (25,26). The number of normal glomeruli is reduced with age in male Munich Wistar rats, but not in females, whereas the glomerular volume increases in both genders, but more prominently in male rats (27). Conversely, aged female C57 mice present a markedly increased renal corpuscle diameter compared to males, although glomerular damage and interstitial fibrosis are more severe in males than in females (28). Structural changes include thickening of the glomerular basement membrane, expansion of the glomerular mesangium and EMP deposition leading to glomerular sclerosis (1). The old, intact male rat develops glomerulosclerosis,

but castrated male rats are protected from such injury. The mechanism by which testosterone promotes susceptibility to the development of renal damage during aging is unrelated to glomerular hypertension or hypertrophy (27).

Glomerular sclerosis is known to occur faster and more intensely in males than in females. The androgens stimulate extracellular matrix production, leading to mesangial expansion and higher levels of glomerular procollagen mRNA levels after subtotal nephrectomy (16). In addition, glomerular metalloproteinase activity increases with age in intact females, but not in males, and castration of males restores the glomerular metalloproteinase activity and protects against glomerular injury (20). Zheng et al. (29) showed that female mice become susceptible to age-related glomerulosclerosis after menopause, and estrogen supplementation reverses glomerular sclerosis in male TGF overexpressing mice (30). Although most studies demonstrate the beneficial effect of estrogens on renal health, some studies have demonstrated their detrimental effect. Sun et al. (31) demonstrated that ERα-null mice are protected from glomerular enlargement and matrix accumulation, indicating that ERα activation, which is usually reported to be beneficial, may be injurious in some situations. Some investigators have also reported that sex hormones do not influence renal morphology during senescence. For example, Neugarten et al. (32) analyzed the glomerular histology of males and females in 250 autopsy specimens, and detected no differences between genders regarding the development of glomerulosclerosis in aging humans. As observed, the effects of gender on renal senescence reported in the literature are controversial. We have to consider that the senescence process may occur differently between species, and the beneficial and/or detrimental effects of sex hormones may not be limited by the onset of somatopause. The plasma values of sex hormones and the expression/sensitivity of the receptors to their ligands during aging may be influenced by genetic factors as well as by diverse paracrine and endocrine pathways. Further studies are thus needed to clarify the pathophysiological mechanisms underlying gender differences in the progression of age-dependent nephropathy.

Therefore, we may conclude that changes in EMP production and in cell morphology clearly trigger the loss of renal function in the elderly (25,26). The age-induced modifications in the renal structure are modifiable by sex hormones, which can be beneficial or detrimental, depending on the plasma levels of hormones and the type and location of the receptor that is activated. To illustrate the influence of gender and aging on renal morphology, Figure 1 displays typical photomicrographs of young and old male and female C57 and ApoE$^{-/-}$ mice. As observed, the aging process leads to

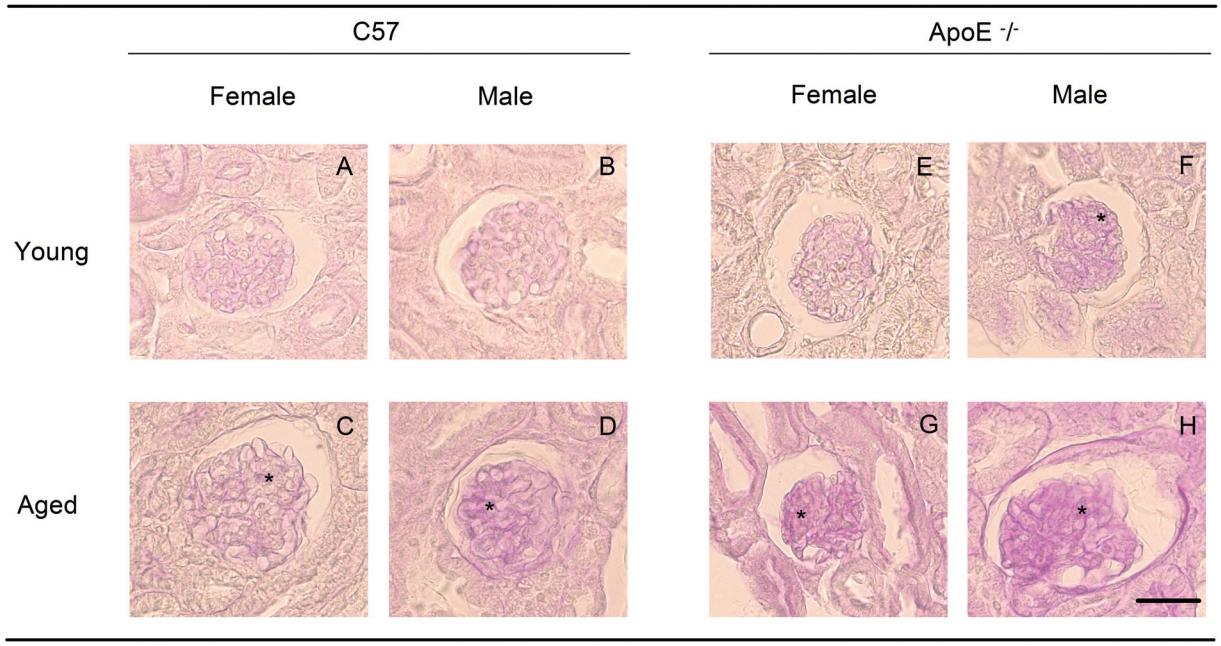

Figure 1. Renal cortex from young and aged male and female C57 and ApoE$^{-/-}$ mice. The sections were stained with periodic acid Schiff for the assessment of mesangial expansion, as indicated by asterisks. In C57 mice, young females (*A*) and males (*B*) presented similar histological features. The aging process led to mesangial expansion in both female (*C*) and male (*D)* animals; however, these alterations were more prominent in males. Young ApoE$^{-/-}$ male mice (*F*) already present expansion of the mesangial matrix compared to female ApoE$^{-/-}$ animals (*E*). Aging also exacerbates this disturbance similarly in both female (*G*) and male (*H*) ApoE$^{-/-}$ animals. Scale bar: 25 µm.

mesangial expansion in C57 mice, which is more prominent in males. Young ApoE$^{-/-}$ male mice already present an expansion of the mesangial matrix, which is aggravated in in both male and female old animals.

Changes in renal hemodynamics

The morphological changes that accompany aging result in profound functional disturbances, including alterations in renal hemodynamics (25). The renal blood flow (RBF) falls progressively at an approximate rate of 10% per decade between 30 and 60 years. Although some decrease in RBF results from reduced renal size, there is a constant decrease in RBF with age even after the correction for renal mass (25,33). Nevertheless, the relationship between the reduction in RBF and the concomitant decrease in renal mass has not been fully established (25). However, it has been suggested that if the reduction in RBF is secondary to renal parenchyma atrophy, either a proportional decrease in flow and mass or a reduction in flow less than the reduction in mass would be anticipated (33). Berg (34) demonstrated significant declines in effective renal plasma flow (ERPF) in males as early as 20 years of age, but not in females. These differences may be attributed to a differential production of and/or responsiveness to vasodilator and vasoconstrictor substances that influence renal vascular resistance (RVR). Similarly, Weinstein and Anderson (35) reported that aging-induced changes in the activity of the renin-angiotensin and nitric oxide (NO) systems may result in altered responsiveness to vasoactive stimuli, predisposing the older kidney to acute kidney injury.

In the past few years, several studies have investigated the role of NO in gender-induced changes in renal function during aging. Total NO production decreases in the aging male rat as age-dependent chronic kidney disease develops, whereas in females it remains unchanged with age, and kidney damage is delayed (24). There is also sexual dimorphism in the NO system in young adults, with premenopausal women producing more total NO than men (1), and greater abundance of constitutive NO synthases (NOS) in the kidney of young adult female rats compared to male rats (36). Additionally, increases in endogenous NOS inhibitors, such as asymmetric dimethylarginine (ADMA), have been reported in aged male rats (37), contributing to less NO production. The possible mechanisms involving sex differences in the NO system may also include estrogen actions, such as the stimulation of NO production from both endothelial and neuronal NOS isoforms and the increase in NO bioavailability by a reduced production of free radicals (38,39). Aged female mice also present a greater expression of isocitrate dehydrogenase 1, which improves cell protection against oxidation, increasing NO bioavailability (40). However, androgens have variable actions on NO production; testosterone-induced inhibition of NO-dependent vasorelaxation has been reported in some parts of the circulation, whereas stimulation has been observed in other parts of the circulation (39). Since different vascular beds may present a higher or a lower NO dependence on normal endothelial functioning, the effects of testosterone on vasorelaxation may vary between tissues. Thus, additional studies are necessary to elucidate the role of androgens in NO production and bioavailability under both normal and pathological conditions.

Among the vasoconstrictor substances, current evidence supports an important interaction between sex steroids and the renin-angiotensin-aldosterone system (RAAS). In fact, studies have reported that plasma renin levels and renin activity are higher in male than in female rodents (41). Consistent with these data, Song et al. (42) demonstrated that castration attenuates hypertension and moderates the renal vascular responses to ANG II, and chronic testosterone treatment restores the pressor and renal vascular responses, indicating that androgens play an important role in RVR and in renal sensitivity to ANG II. In aged male spontaneously hypertensive rats (SHR), RVR is increased compared to young rats, and castration attenuates this increase in RVR (43). It is important to note that, although the renal vasculature of male rats is more sensitive to the vasoconstrictor effects of ANG II, it is also more dependent on the vasodilator effects of NO compared to females, as demonstrated by the higher ANG II-induced increases in renal perfusion pressure in males compared to females, which remains the same between genders after blockade of NOS (44). Therefore, it is possible that, because the male kidneys are more dependent on NO, the reduction in NO production during the aging process may uncover the presence of more vasoconstrictors, such as ANG II, thereby accelerating the progression of renal disease. Although most studies report that RVR is increased in aged males (43), Passmore et al. (45) demonstrated a reduced response to phenylephrine in the interlobar artery of old male rats, probably due to a diminished alpha adrenergic receptor signaling for renal vasoconstriction. These data raise the question about the involvement of signaling events in declining renal vascular function during aging. We must consider that the activation and deactivation of signal transduction molecules under basal and adrenergic-induced responses may be different and influenced by both aging and gender. Because of the complexity of these factors and their interaction, contradictory data have been reported in the literature, and more studies are necessary to better elucidate this question. The results of such studies will yield the critical information needed to clarify the effects of gender on renal vascular function and to improve renal health during aging. Figure 2 summarizes the actions of sex hormones and aging on the renal hemodynamics and morphology that trigger kidney damage.

Changes in glomerular filtration rate

The measurement and/or estimation of glomerular filtration rate (GFR) are considered to be the best and most

common parameter for the determination of renal function and, consequently, the progression of chronic kidney disease. The assessment of GFR is important for several reasons: the characterization of various renal diseases, the evaluation of the effect of various therapies, the adjustment of drug doses, and the preservation of normal renal function in potential kidney donors. Most studies have shown that GFR declines steadily with age, beginning at 30-40 years, with an apparent acceleration in the rate of decline after 50-60 years (25).

The biological mechanisms underlying the decline in GFR with aging remain a subject of intense investigation. Currently, it is thought that the decrease in GFR is a manifestation of a progressive change in the vascular tree, perhaps related to the effect of oxidative stress and telomere shortening or to an effect of ANG II (26). Moreover, the percentage of individual functional glomeruli and the number of nephrons decline with age even in the absence of any co-morbidities (25,33).

It has been demonstrated that GFR is lower in young adult females compared to aged-matched males, who present a higher RVR (27). Because women start with a somewhat lower GFR, the final value of GFR in advanced age is usually lower in women than in men. In experimental studies on rats, females were found to be protected from age-dependent declines in GFR compared to males (21). The rate of progression of chronic renal disease is also faster in men than in premenopausal women (23), and this protection disappears after menopause but can be restored with estradiol replacement (7). These differences may be attributed to the protective actions of estrogen on renal morphology, such as anti-growth effects on glomerular

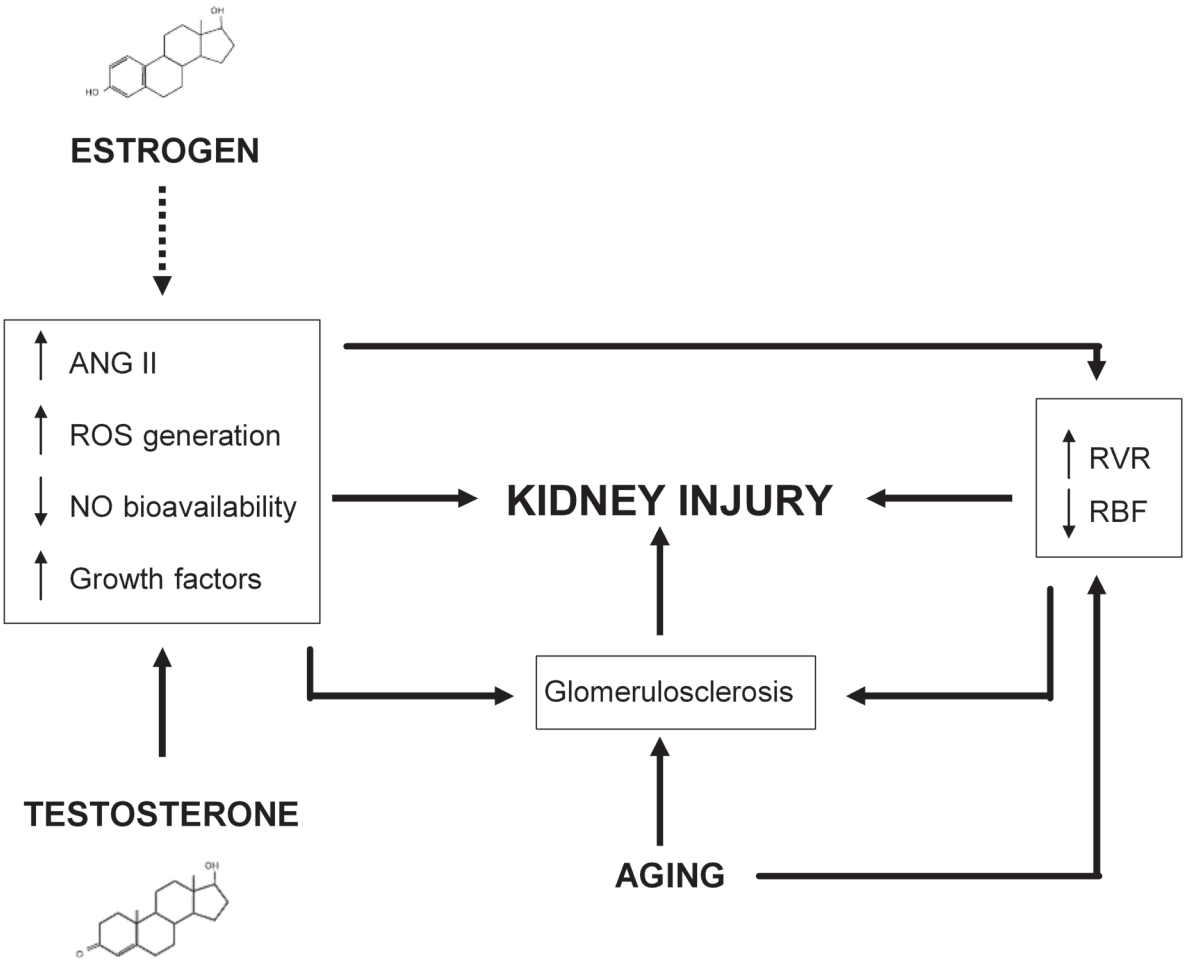

Figure 2. The role of estrogen, testosterone and aging in kidney damage. ANG II = angiotensin II; ROS = reactive oxygen species; NO = nitric oxide; RVR = renal vascular resistance; RBF = renal blood flow. The dashed arrow and the continuous arrows indicate an inhibitory and a stimulatory effect, respectively.

mesangial cells and the inhibition of mesangial extracellular matrix accumulation, which are typical events in the development of glomerular sclerosis (7,8). The deleterious effects of androgens on renal structure, such as apoptosis and increased EMP deposition (16,18) also account for a faster decline in renal function in males compared to females. In addition, castration prevents the increase in RVR found in aged male SHR (46). However, Xu et al. (47) demonstrated that low doses of DHT attenuated the development of albuminuria in streptozotocin-induced diabetic rats, indicating that the levels of plasma testosterone may play a crucial role in the progression of renal disease.

Changes in sodium and water handling

Both gender and aging influence the renal handling of water and salt. The mechanisms underlying these changes include both direct effects on renal sodium and water transporters and indirect effects through alterations in humoral systems, such as the RAAS and the antidiuretic hormone (ADH).

Androgen receptors are widely distributed along the nephron (15) and have an important influence on salt and water handling. In rats, injection of DHT directly stimulated the proximal volume reabsorptive rate and hence increased extracellular volume and blood pressure (48). These findings were also obtained in humans based on the observation that men excrete less sodium after the infusion of hypertonic saline than women and increase their systolic blood pressure with a rightward shift of the pressure-natriuresis curve to maintain sodium balance (49). However, in the elderly patient population, hyponatremia is a common disorder. This alteration in plasma sodium levels was associated with an increase in mortality in age-matched control subjects (50). Considering that testosterone may activate several mechanisms of sodium reabsorption, such as the sodium-hydrogen exchanger (48), it seems reasonable that elderly individuals may present a decline in plasma sodium levels leading to hyponatremia. In contrast, there is evidence of impaired sodium excretion of a salt load and defective conservation in the setting of sodium restriction (51) leading to accumulation of total body sodium content and development of hypertension.

In animal models, estradiol increases sodium uptake through the luminal membranes of both proximal and distal tubules and the presence of estrogen receptors has been confirmed at both sites (52). The role of estrogen in renal salt handling was also demonstrated by Chappell et al. (53) using female mRen(2) Lewis strain rats. They reported that apart from its effects on blood pressure, estrogen manifested its protective effects only in the setting of a chronic high-salt diet, suggesting that the underlying sodium status may have an important influence on the overall effect of reduced estrogen, which also occurs in the elderly. Furthermore, oophorectomized rats presented a severe decrease in the renal functional reserve and tubular fluid output, and these events are prevented by estrogen administration, confirming the effect of estrogen on the preservation of kidney function during aging (54). In humans, some studies have also suggested a gender difference in the effects of the salt-induced blood pressure response. Young menopausal women who were not receiving hormonal replacement therapy and were subjected to a chronic salt load presented an enhanced 24-h ambulatory blood pressure and renal proximal sodium reabsorption compared to premenopausal women. Menopausal women also presented a pressure-natriuresis curve that was significantly shifted to the right compared to premenopausal women (55). Age-related alterations in salt sensitivity seem to be associated at least in part with modification of the hormonal profile that occurs in women after menopause.

Changes in humoral systems may also be influenced by gender and age. The activity of the RAAS has gender particularities regarding sodium and water balance. Men present a higher RAAS activity than pre-menopausal women (46). Androgens up-regulate several components of the RAAS system, such as expression and affinity of AT_1 receptors and intrarenal expression of angiotensinogen and renin mRNA (56). Administration of an angiotensin-converting-enzyme inhibitor or AT_1 receptor antagonist reversed the effect of androgens, indicating that the impact of male hormones on proximal tubular function is mediated by the RAAS (48).

Accumulating data indicate that estrogen regulates all known components of the RAAS. Synthesis of angiotensinogen in hepatocytes is regulated by E_2, and plasma renin levels and angiotensin-converting enzyme are higher in postmenopausal women not receiving estrogen replacement therapy (46). Additionally, 17β estradiol down-regulates AT_1 receptors (5), and these changes in the RAAS strongly reflect renal responses to ANG II. The renal microcirculation in sodium-replete women responds differently to ANG II compared to men, with the female gender showing a reduced increase of filtration fraction and a possibly blunted increase in intraglomerular pressure (57). In addition to the direct effects of ANG II on sodium reabsorption, the ANG II-induced release of aldosterone may also increase the distal tubular sodium reabsorption. Thus, estrogen-induced decreases in acute levels of ANG II-induced aldosterone secretion may contribute to the renal benefits for the sodium balance. During the aging process, the decline in plasma E_2 levels could interfere with the RAAS and contribute to disturbances in sodium handling, indicating that ANG II receptor blockers may be particularly beneficial in postmenopausal women.

There is also impaired water handling with aging, with a reduction in total body water in elderly subjects. In a young man near his ideal body weight, total body water corresponds to 60 to 65% of his body mass. By the age of 80 years, this percentage is reduced to 50% (50). A retrospective analysis of a number of clinical studies dem-

onstrated that urine osmolarity is greater in men than in women and decreases in both genders during aging (58). Experimental data demonstrated that treatment with DHT caused a reduction in water excretion in young male rats (47); however, with aging, both urine concentration and dilution were affected. Maximal urinary osmolality and thirst response to hyperosmolarity were reduced, predisposing to dehydration (26).

It is well documented that ADH plays a pivotal role in extracellular fluid volume regulation. Because men excrete a higher osmolar load through an increase in urine concentration rather than a decrease in urine volume, it may be assumed that their ADH system presents higher thresholds than those of women (58). Some studies have reported higher values for plasma and/or urinary vasopressin in men compared to women. ADH secretion seems to be more sensitive to osmotic stimuli in males than in females (49). A higher sensitivity to ADH in humans is also suggested by the higher urine osmolarity observed in men compared to women who exhibit similar plasma vasopressin levels (59). Although the data are controversial, it is generally accepted that in the elderly ADH levels are increased for any given plasma osmolarity, when compared to values of younger individuals (60); however, increases in urine osmolality in response to ADH are blunted in older individuals when compared to young subjects (26). These alterations can increase the susceptibility of the elderly to hyponatremia by interfering with the ability of their bodies to purge excess water (50).

The aging process results in profound anatomic and functional changes in renal tissue, with increased EMP accumulation, decreased RBF and GFR, augmented RVR, and disturbances in salt and water balance. These changes can contribute to the development of cardiovascular diseases. Additionally, several studies have demonstrated that sex hormones may accelerate or delay cardiorenal disturbances. Although contradictory data may be present in the literature, most studies indicate that, in general, E_2 exerts a protective effect, whereas testosterone contributes to renal injury during the aging process.

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