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Sexual Dimorphism, the Aging Kidney, and Involvement of Nitric Oxide Deficiency

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Summary

Females develop less age-dependent loss of renal function, in part because of cardiorenal protective effects of estrogens. The low androgen level in women also may be protective, although the animal and clinical data are controversial. Both estrogen and androgens act through multiple mechanisms, sometimes beneficial, sometimes damaging, which makes it difficult to predict the impact of hormone replacement therapy in an aging population. Nitric oxide (NO) deficiency contributes to age-dependent cardiovascular risk and kidney damage in animal models. The increased oxidative stress of aging impacts at multiple sites in the NO biosynthetic pathway to decrease NO production/action. Endothelial dysfunction develops with aging and is delayed in women, in association with a delayed increase in asymmetric dimethylarginine. Animal data suggest that the aging kidney develops NO deficiency because of changes in the neuronal NO synthase. Relative preservation of NO production in females contributes to the better cardiovascular and renal responses to aging.

Keywords

Estrogen; androgen; asymmetric dimethylarginine; cardiovascular events; dimethylarginine dimethylaminohydrolase

With advancing age the glomerular filtration rate (GFR) decreases and structural damage develops.[1,2] The contribution of normal aging is difficult to separate from undocumented comorbidities such as hypertension, atherosclerosis, glucose intolerance/diabetes, obesity, dyslipidemias, and chronic kidney disease (CKD).[2-8] These factors likely contribute to the variability seen in the rate of loss of GFR with age.[1,2,9] Sex is another variable, with females being protected, and this review focuses on some aspects of this sexual dimorphism.

AGE-DEPENDENT CHANGES IN GLOMERULAR FUNCTION

The GFR usually decreases gradually in aging men (Fig. 1) owing to structural damage and to decreases in renal plasma flow (RPF) secondary to renal vasoconstriction.[10] In women, however, there is less functional decline with age (Fig. 1). This sex difference is seen in clinical and animal studies and persists irrespective of genetic background/race.[2,7,11]

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Structural changes in the aging kidney include expansion of the glomerular mesangium and extracellular matrix leading to glomerular sclerosis, glomerular ischemia, arteriolar- and atherosclerosis, loss of peritubular capillaries, and tubulointerstitial injury, all of which contribute to loss of functioning nephrons and declines in GFR.[1,2,5,12,13]

The normotensive male Munich Wistar (MW) rat develops slowly evolving structural damage, however, this is not associated with increased glomerular blood pressure[14] (Fig. 2), which develops only after the injury is established.[15] Male rats of the MWF/ZTM strain develop accelerated age-dependent kidney disease but their glomerular blood pressure remains normal.[16] Therefore, age-dependent decreases in GFR and glomerular injury can occur in the absence of systemic and glomerular hypertension. However, age-dependent injury and functional declines are accelerated by hypertension[1,14,17,18] and glomerular hypertension, as occurs in the sclerosis-prone Sprague-Dawley (SD) rat.[19] Structural damage also develops in the kidney of aging man.[1,5,13,14]

In female rats there is considerable protection against age-induced structural damage to the kidney[2] and, as shown in Figure 2, glomerular blood pressure remains similar and constant with age in both sexes of the MW rat. Constancy of glomerular blood pressure is maintained in the aging male by parallel increases in afferent and efferent renal arteriolar resistances, whereas parallel relaxation occurs in the initially vasoconstricted female kidney (Fig. 2). In clinical studies Neugarten et al[13] reported no sex difference in kidney injury, although a small study by McLachlan et al[12] reported a greater vulnerability of aging men to glomerular sclerosis. There is no direct information on what happens to glomerular blood pressure in aging human beings although the exacerbation by systemic hypertension likely reflects development of glomerular hypertension.[1,14,17,18]

In the aging male MW rat there is progressive renal vasoconstriction leading to decreases in RPF, whereas in the female MW rat preservation of GFR is associated with preserved renal plasma flow, facilitated by gradual relaxation of both afferent and efferent renal arteriolar resistances (Fig. 2). In women, RPF also is maintained[10,11] such that by age 70 the values of RPF (factored for surface area) are similar in normotensive men and women,[20] reflecting the lower values of GFR and RPF in young women versus men.[1,10]

Why are males more vulnerable to age-dependent kidney damage and dysfunction? The determinants of sexual dimorphism are complex and in part the result of the gonadal hormones (discussed later).

ESTROGEN AND THE KIDNEY/CARDIOVASCULAR SYSTEM

Estrogens offer cardiovascular protection to premenopausal women, which contribute to the slower rate of progression of chronic renal disease in women versus men.[21] Loss of estrogen after menopause may lead to a late decline in renal function and development of structural damage in aging women, although it is difficult to dissociate between aging versus loss of ovarian function.

In aging rodents, injury-resistant female C57Bl6 mice develop age-related glomerulosclerosis after menopause[22] and estrogen supplementation reverses glomerular sclerosis in female sclerosis-prone ROP Os/+ mice.[23] In addition to protecting the kidney by improving cardiovascular health, estrogens also suppress glomerular mesangial cell growth and extracellular matrix accumulation, thus directly inhibiting development of glomerular sclerosis.[22,24-29]

Estrogen supplementation in rats and mice often is beneficial, but there have been unfavorable findings in clinical trials on hormone replacement therapy (HRT) in postmenopausal women.

[30,31] Animal studies routinely use the native 17-β estradiol given subcutaneously whereas clinical trials often use oral conjugated equine estrogens (containing many estrogens, progestins, androgens, and "other substances"),[30,31] which have less predictable actions.[32] Time of initiation of HRT relative to menopause also may determine outcome because older women showed less benefit and/or increased cardiovascular risk compared with women in whom HRT was initiated at, or close to, menopause.[32]

Estrogen signaling is very complex and unpredictable with many possible receptor- and non–receptor-mediated actions. The classic nuclear mechanism involves activation of the estrogen receptor (ER), which then binds to estrogen response elements in genes or interacts with transcription factors to control protein synthesis.[33] There are now known to be several membrane receptors to estrogen that activate either rapid nongenomic cellular responses or transcription. There is also cross-talk between ER and growth factor receptors and some of the estrogen metabolites exert non–ER-dependent actions.[32,33] To date, two ER subtypes, α and β, have been identified that can form homodimers or heterodimers as well as a G-protein–coupled membrane receptor (GPR30). Thus, estrogen can signal through many pathways.[33]

The kidney contains many ERs and has a large number of estrogen-regulated genes that are mainly under control of the ERα.[34] There are sparse and conflicting data on the relative role of the ER subtypes in renal and cardiovascular pathology. Studies by Lane et al[35,36] using ER knockout mice (ERKOs) suggest that ERα activation contributes to glomerular hypertrophy and sclerosis after uninephrectomy and with diabetes. Increased renal ERα and a decrease in plasma estradiol occur in type 1 diabetic female rats with evolving renal disease.[37] However, ERα is required for vascular repair from atherosclerosis in mice of both sexes,[33] ERα increases in old female (protected) mouse kidneys[38] and mesangial cells from female glomerular sclerosis-prone mice express decreased ERα and ERβ.[39] ERα depletion occurs in high-salt–induced hypertension and renal damage[40] and the αERKO female mouse develops albuminuria and glomerular damage with age.[41] In some settings ERβ is protective because the βERKO develops age-dependent hypertension[42] and βERKO females develop greater cardiac injury after ischemia/reperfusion.[43] Observations in knockout animals must be interpreted cautiously given the compensatory adaptations that can occur in nonlethal knockouts.

Although estrogen has many beneficial actions on the kidney[21-28] there are a number of experimental situations in which estrogen seems to be damaging. ER-independent actions of estrogen lead to net prosclerotic actions in the db/db (type 2 diabetic) mouse kidney.[44] Estrogens worsen renal injury in the stroke-prone SHR,[45] and with both chronic NO synthase (NOS) inhibition and ANGII infusion.[46] Also, the progression of CKD is faster in the female analbuminemic rat and the Zucker obese rat versus males in association with more severe hypertriglyceridemia.[47,48] Given the variety and heterogeneity of signaling mechanisms it is not surprising that the renal/cardiovascular actions of estrogen are complex and variable.

ANDROGENS AND THE KIDNEY/CARDIOVASCULAR SYSTEM

Animal studies suggest that androgens may be damaging. For example, castration of the young adult male prevents age-dependent glomerular sclerosis whereas both intact and ovariectomized females are protected.[14] Androgens stimulate mesangial extracellular matrix production and mesangial expansion after subtotal nephrectomy,[49] and inhibit glomerular metalloprotease activity,[50] and thus are profibrotic. The presence of androgens is associated with greater kidney damage and higher blood pressure (BP) in several hypertensive rat models, perhaps related to enhanced tubular sodium reabsorption and activation of the renin/angiotensin/aldosterone and endothelin systems.[51]

In normal men the reverse seems true because higher androgen levels correlate with lower BP and overall cardiovascular risk whereas low androgen levels are associated with increased

cardiovascular risk and insulin resistance.[52,53] Although men with nondiabetic CKD progress more rapidly toward end stage, compared with women[21] androgen levels decrease in men with hypertension and renal disease.[51] Perhaps the gradual decline in testosterone levels with aging may contribute to age-dependent renal dysfunction in men?

In women the impact of androgen level on cardiovascular risk is controversial. Testosterone levels increase in most postmenopausal women, with aging as cardiovascular risk increases.[51] Women with polycystic ovary syndrome have increased androgen levels and increased cardiovascular risk,[53] although this may be more related to insulin sensitivity than androgen level.[54] However, a low testosterone to bioavailable estrogen ratio correlates with a pro-atherogenic adipocytokine profile,[55] and a recent review concluded that there is no clear link between increased testosterone levels and cardiovascular disease in women.[56]

The classic action of the androgens is via the intracellular androgen receptor (AR), which controls gene transcription. Only one AR gene has been characterized although multiple AR co-regulators can modify responses to testosterone.[57] Conversion of testosterone to the more potent dihydrotestosterone (via 5α- reductase) also enhances androgen actions.[57] Chronic antagonism of AR lowers BP in the male SHR[51] and protects the kidney of the female REN2 rat.[58]

Androgens also are aromatized to estrogen and the location of aromatase and ERs therefore will impact on actions of testosterone. In fact, vascular and endothelial protection seen with testosterone supplementation is dependent on aromatization to estrogen.[59,60] There are also nongenomic actions of androgens including a rapidly occurring vasodilation that does not require AR.[53]

SUMMARY AND RECOMMENDATIONS

Endogenous estrogens certainly have many positive effects on the cardiovascular system and kidney but estrogen acts via multiple pathways, not all of which are beneficial. There are little data available to allow the development of recommendations for use of HRT. There are 2 clinical studies that suggest that HRT may worsen proteinuria and accelerate the age-dependent decline in renal function in postmenopausal women.[61,62] In contrast, Agarwal et al[63] reported no deleterious actions of HRT and in fact observed reductions in proteinuria. Both major clinical trials that suggested that HRT increases cardiovascular risk used oral-conjugated equine estrogens, which have less predictable actions than estradiol.[30-32,64] Importantly, only oral HRT was associated with accelerated loss of renal function in the study by Ahmed et al.[62] Thus, it seems reasonable to favor transdermal or transvaginal administration of 17β-estradiol and to avoid the oral administration route and the use of conjugated equine estrogens. Also, the timing of beginning HRT is important[32] and it is wise to avoid beginning HRT in women who are many years postmenopausal.

Androgens often cause cardiovascular risk and exacerbate kidney damage in experimental animals, but in clinical studies higher androgen levels seem to associate with better cardiovascular health in men; the association still is controversial in women. There are likely to be both beneficial and damaging actions of androgens on the cardiovascular system. There are little clinical data on the actions of androgens on the kidney.

SEX STEROIDS, AGING, AND THE NO SYSTEM

Vascular NO is vasodilatory, inhibits growth of contractile cells as well as extracellular matrix production, and also inhibits renal sodium reabsorption.[65,66] Chronic NO deficiency results in hypertension, a profibrotic state, and contributes to injury progression in many types of CKD.

[65] The contribution of NO deficiency to the development of age-dependent CKD is discussed later.

Total NO production (estimated from the urinary excretion of $NO_X = NO_2 + NO_3$; the stable oxidation products of NO from $U_{NOX}V$) decreases in the aging male SD rat as CKD develops whereas in the aging female there is little CKD and total NO production is maintained (Fig. 3).[67,68] NO production also correlates inversely with kidney damage in the aging male Fischer 344 rat; on normal protein intake, $U_{NOX}V$ decreases and kidney damage develops while protein restriction is associated with preserved $U_{NOX}V$ and structure.[69] In man $U_{NOX}V$ decreases with age,[70,71] although this effect is lost on both low or high sodium intake.[70] The decrease in $U_{NOX}V$ correlates with developing endothelial dysfunction in men[71] and although there is no clinical data on sex differences in $U_{NOX}V$ with aging, endothelial dysfunction is delayed in aging women versus men.[72] Premenopausal women make more NO than similarly aged men,[73] and young adult female rat kidney contains more NO synthase than males.[74]

Some of these sex differences are caused by estrogen, which stimulates NO directly at genomic and nongenomic levels acting on ERs, stimulation of NO indirectly by metabolites and non–ER-dependent actions, reduction of endogenous inhibitors, and probably by the antioxidant actions of estrogens, which prolong the active life of NO.[24,25,75,76] Androgens have variable actions on NO production with testosterone-induced inhibition, stimulation, and no effect on NO-dependent vasodilation being reported.[57,76] However, androgen-deficient men have enhanced NO-dependent flow-mediated dilation and testosterone supplementation reduces flow-mediated dilation to the normal male value.[57] The male rat is more vulnerable to hypertension and proteinuria produced by low-dose NOS inhibition, in part owing to androgens.[77] In addition, male rats are more susceptible to fructose feeding and hypercholesterolemia-induced vascular and kidney injury; both states associated with NO deficiency.[78,79] It is likely that the vulnerability of the male kidney to NO deficiency contributes to the sexual dimorphism of kidney aging.

POSSIBLE MECHANISMS OF AGE-DEPENDENT DECREASES IN NO PRODUCTION

There are many possible mechanisms by which NO deficiency can occur[65] and several probably contribute to the age-dependent loss of NO production (discussed later).

SUBSTRATE (L-ARGININE) AVAILABILITY AND CIRCULATING NOS INHIBITORS

L-arginine is the rate-limiting substrate for NO synthesis and in normal rodent and human beings L-arginine availability is well maintained,[65] although fasting plasma L-arginine concentration decreases in the aging male SD rat.[80] This suggests that L-arginine becomes an essential amino acid with aging, but as long as an adequate dietary source is available this should not impair NO production.

Increases in the plasma level of the endogenous NOS inhibitor, asymmetric dimethylarginine (ADMA), have been reported in healthy aging human beings, correlating with declines in renal plasma flow.[20] There is no difference between the sexes in plasma ADMA levels at 69 and 25 years of age,[20] but the increase in women is delayed until approximately 50 years of age[81] and correlates with the delayed development of endothelial dysfunction.[72] Oral arginine supplementation reverses endothelial dysfunction in healthy aged human beings,[82] which may reflect competitive inhibition of the increased ADMA.

Plasma ADMA level probably increases with age owing in part to reduced renal clearance. However, the predominant method of ADMA removal is by metabolism by dimethylarginine dimethylaminohydrolase (DDAH), and the kidney has the highest levels of DDAH of any organ. It is possible that renal and extrarenal DDAH activity decreases with age. This would explain the delayed increase in plasma ADMA in women because estrogen stimulates DDAH activity[83] and oral 17-β estradiol replacement in postmenopausal women reduces plasma ADMA.[84]

NOS PROTEIN ACTIVITY/ABUNDANCE

Reactive oxygen species are a prime determinant of NOS activity, and oxidative stress occurs with aging. By reducing the availability of tetrahydrobiopterin (BH4), an essential cofactor for all the NOS, oxidative stress causes the NOS to become superoxide, rather than NO generators.[85] Furthermore, increased ADMA will enhance superoxide production by the uncoupled NOS.[86]

In addition to decreased activity with age, declines occur in abundance of vascular endothelial eNOS[85] and renal cortical neuronal NOS (nNOS)α isoform.[67] This is associated with kidney injury rather than aging per se because the female SD rate shows neither age-dependent kidney damage nor a decrease in renal cortical nNOSα levels.[67]

In summary, endothelial NO production is preserved longer in aging women, probably owing to protective actions of the estrogens. The age-dependent decrease in total NO production probably is caused by increases in circulating ADMA. This causes endothelial dysfunction, which accelerates age-induced CKD. The declining abundance of the renal nNOS also may contribute to the age-dependent CKD. Delays in appearance of endothelial dysfunction and loss of renal nNOS probably protect the female kidney from age-dependent damage and dysfunction. In addition to reduction in NO production, the increased oxidative stress attenuates NO signaling and increased deposition of advanced glycation end products,[87] and also prevents access or egress of NO, further promoting the net NO deficiency.

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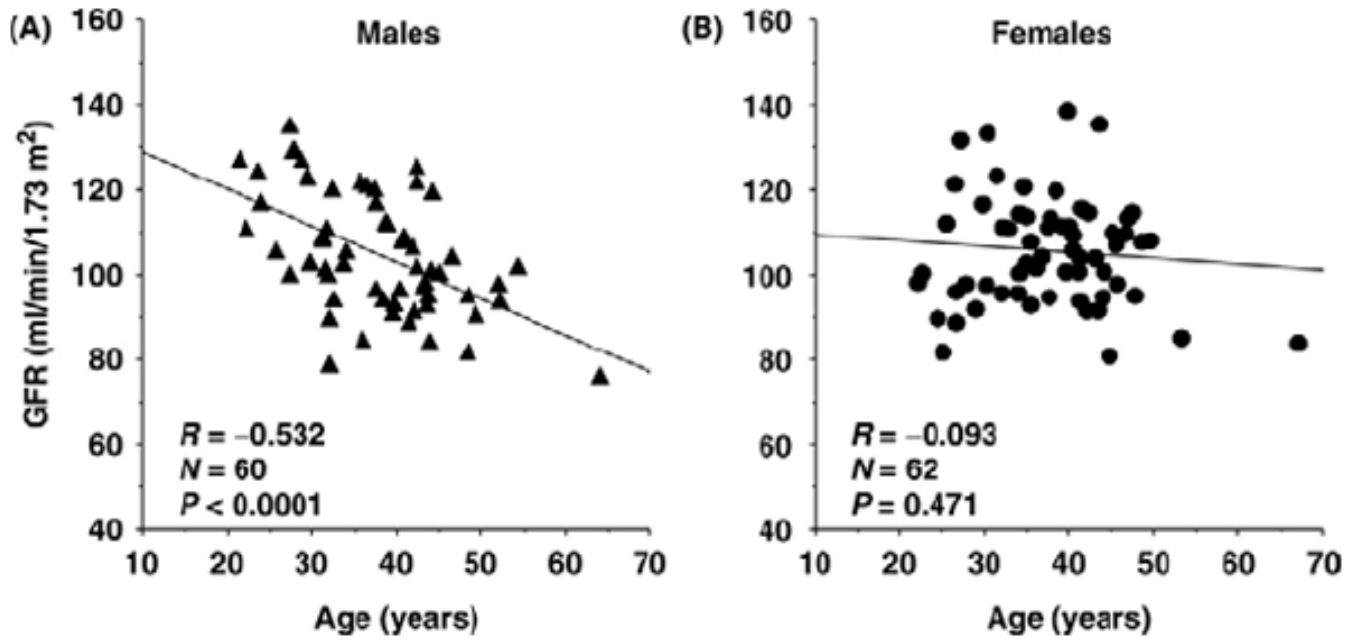

Figure 1.
GFR (measured by inulin clearances) in cross-sectional studies in normal men and women of different ages who were evaluated as potential kidney transplant donors. Reprinted with permission from Berg.[10]

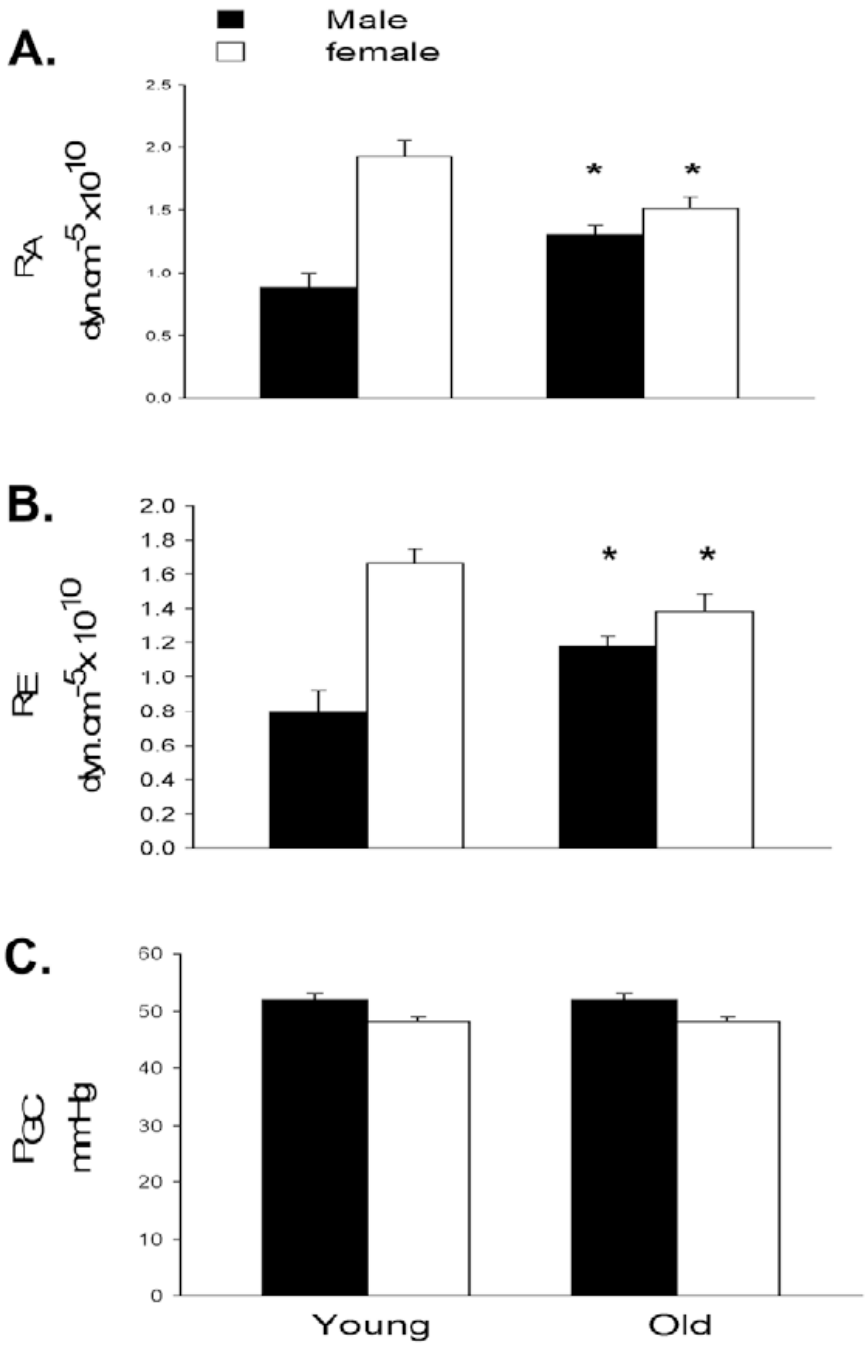

Figure 2.

Afferent and efferent arteriolar resistance (R_A and R_E, respectively) and glomerular blood pressure (P_{GC}) in young adult (~3-4 mo) and older (~18-20 mo) intact male and female MW rats. Data from Baylis.[14]

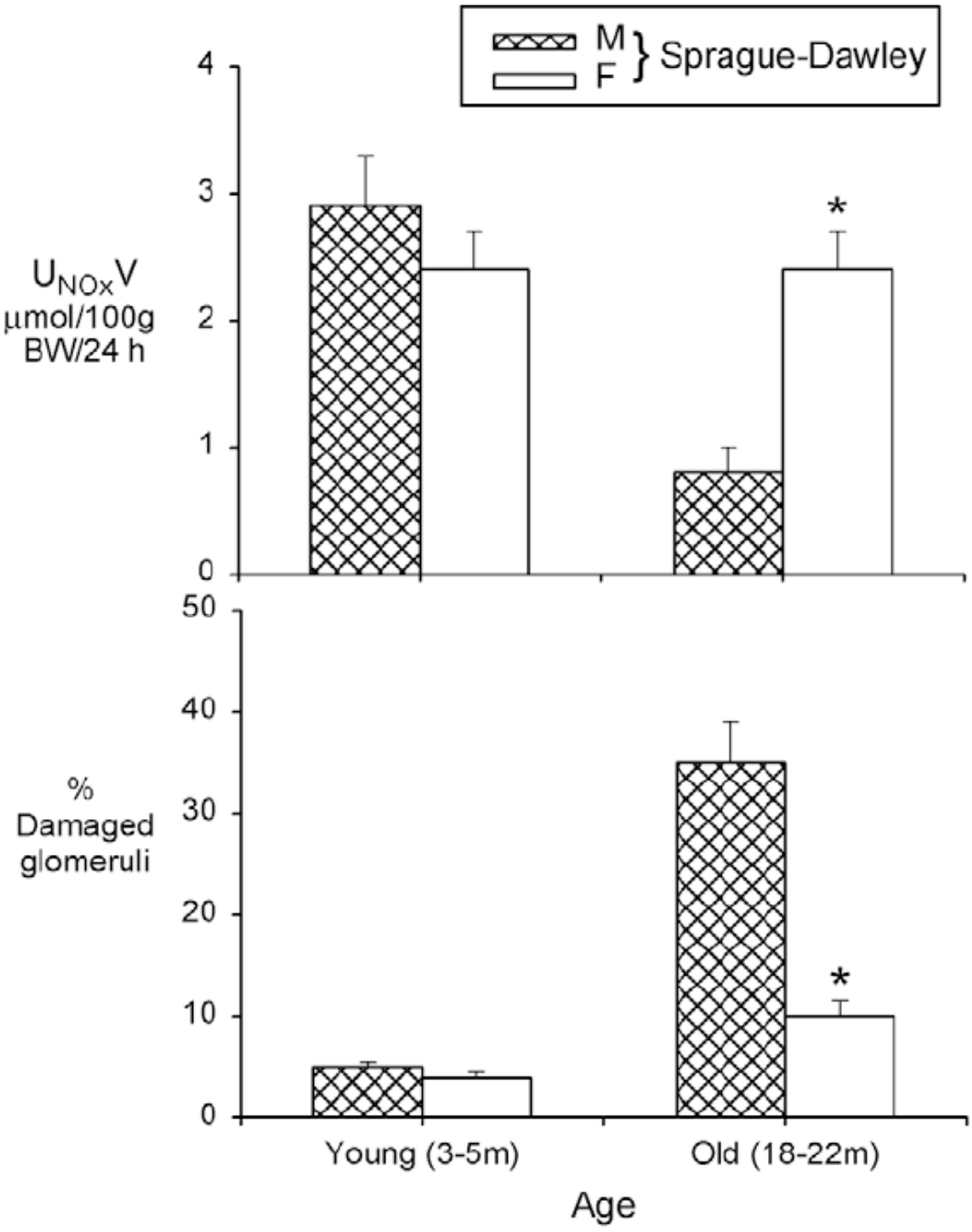

Figure 3.
The 24-hour urinary excretion of $NO_2 + NO_3$ (NO_X), $U_{NOX}V$ (upper panel) and the percentage of damaged glomeruli (ie, those showing segmental and global sclerosis) in young adult (3-5 mo) and old (18-22 mo) male (M) and female (F) SD rats. Data from Erdely et al[67] and reprinted with permission from Baylis.[66]

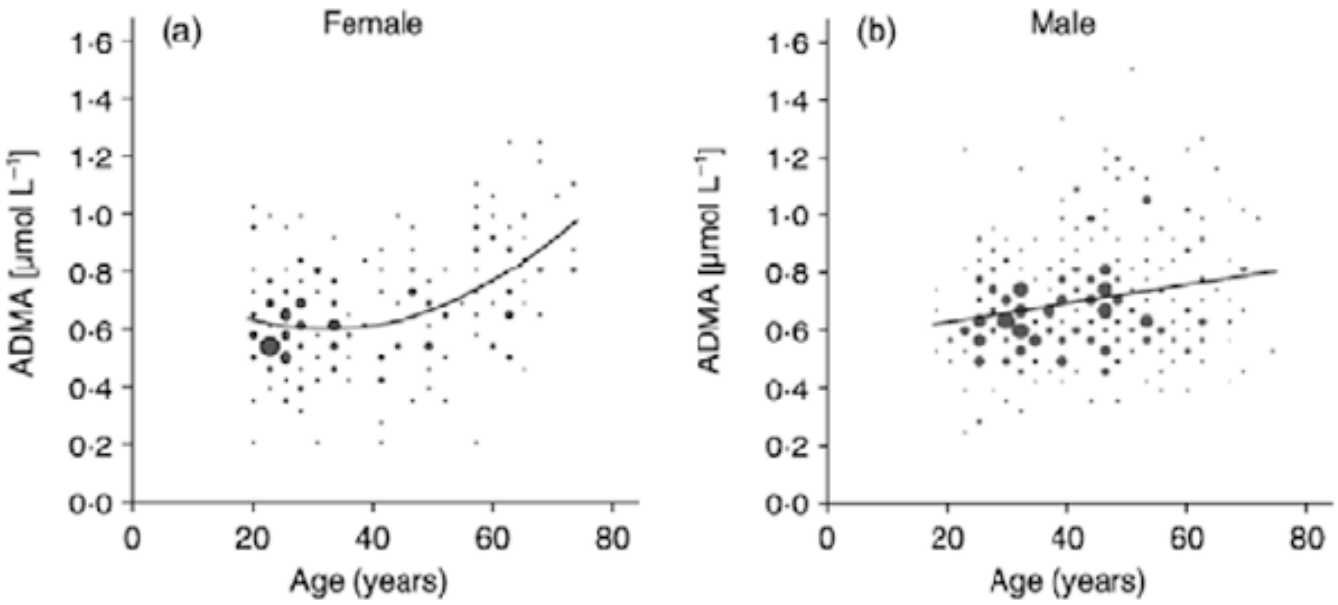

Figure 4.
A regression analysis of ADMA levels and age, based on sex, was performed on data from 500 healthy, nonsmoking, nonobese subjects ages 19 to 75 years. Reprinted with permission from Schulze et al.[81]