Gender and the Progression of Renal Disease

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The protective effect of female gender on the progression of chronic renal disease has only recently become an area of active investigation (1–4). Interestingly, the attention comes at a time of enormous controversy in light of unexpected adverse effects of combined estrogen/progestin hormone replacement therapy (HRT) on the course of cardiovascular disease.

In animal models of chronic renal disease, males show accelerated progression of renal injury compared with females (1–3). Manipulation of the hormonal milieu replicates the effects of gender on the course of experimental renal disease. These observations suggest that sex hormones per se, rather than genetically determined structural differences, determine the greater susceptibility of the male kidney to progressive renal injury. In fact, gender is not an independent determinant of glomerular size or number; rather, it is body surface area that determines these attributes (5). It remains unclear, however, whether the presence of testosterone or the absence of estrogen, or both factors combined, contribute to sexual dimorphism in renal disease progression.

Aging male rats develop spontaneous proteinuria and glomerulosclerosis, whereas females, estrogen-treated males, and orchietomized males are remarkably resistant to the development of these abnormalities (1–3). Renal injury after ablation of renal mass follows a similar pattern (1–3). Although Baylis has concluded that the presence of androgen rather than the absence of estrogen promotes glomerular injury in aging male rats, other investigators have shown that administration of estrogen to aged male rats or spontaneously hyperlipidemic Imai rats ameliorates progressive renal injury (1,6). Paradoxically, in experimental models of renal diseases associated with hypertriglyceridemia, estrogen accelerates progressive renal injury by further elevating triglyceride levels (7–10).

A larger number of variables make the issue more challenging in humans than in animal models. Individual reports that have taken gender into account in analyzing factors contributing to renal disease progression have generally included small numbers of subjects with short patient follow-up. Also, different treatment regimens may obscure any effects of gender on renal disease outcome. In light of these problems, we performed a meta-analysis involving 11,345 patients to determine the effect of gender on the progression of nondiabetic kidney disease (11). Men with autosomal dominant polycystic kidney disease, IgA nephropathy, membranous nephropathy, or chronic renal disease of unspecified etiology progressed to renal failure more rapidly than women. However, these data did not indicate whether the presence of testosterone or the absence of estrogen is the determining factor, nor whether the renoprotective effect of female gender is limited to premenopausal women, as would be expected if estrogen is critical. Moreover, our meta-analysis could not assess whether the effects of gender on renal disease progression are independent of other covariates such as diet, BP, or serum lipid levels. As to diabetic nephropathy, however, data are conflicting, and it remains to be proven that male gender accelerates progression (3).

Sex hormones have effects on mesangial cell biology that may directly influence many of the processes that contribute to renal disease progression. We have shown that estradiol reverses TGF-β1–stimulated type IV collagen gene transcription and protein synthesis via a casein kinase 2/Sp1-mediated mechanism. Estradiol also suppresses mesangial cell type I collagen gene transcription and protein synthesis via a mitogen-activated protein kinase (MAPK)/AP-1–mediated mechanism, stimulates metalloproteinase-9 activity (12–20). These actions shift the balance of matrix metabolism away from matrix accumulation and glomerulosclerosis. We also found that estradiol reverses TGF-β1–induced mesangial cell apoptosis via a casein kinase 2/p53–mediated mechanism (21). Estrogen has also been shown to activate renal nitric oxide generation and to modulate the synthesis and release of various growth factors, hormones, and cytokines (1,22). Studies investigating the influence of estrogen on the renin-angiotensin axis and on the cyclooxygenase pathway report conflicting data (1).

By contrast, the effects of testosterone on processes contributing to progressive renal injury have not been as extensively studied (1). Testosterone activates the renin-angiotensin system, increases circulating endothelin-1 levels, and modulates the cyclooxygenase pathway (1). Testosterone also stimulates collagen synthesis in nonrenal tissues and increases the accumulation of collagen and elastin in the aorta of normal and cholesterol-fed rats (1).

Conflicting data exist regarding the effect of sex hormones on renal hemodynamics in the rat (1). In humans, Miller et al. (23) found that men respond to angiotensin II infusion by maintaining their GFR at the expense of an increased filtration fraction, implying an increase in glomerular capillary pressure ($P_{GC}$). By contrast, women showed a decrease in GFR, implying no increase in $P_{GC}$. These data suggest that differences in...
glomerular hemodynamics contribute to sexual dimorphism in renal disease progression.

Reflecting the emerging interest in gender and the progression of renal disease, the current issue of the *JASN* contains two studies that greatly advance our understanding of this subject (24,25).

Tofovic *et al.* (25) have contributed a novel and important study with potentially exciting implications. These authors previously published a number of studies suggesting that the cellular effects of estradiol are mediated by nonestrogenic metabolites, particularly catecholestriadiols (2-hydroxy estradiol [2-OHE] and 4-hydroxyestriadiol) (26,27). They showed that the inhibitory effects of estradiol on cell proliferation and collagen synthesis by vascular smooth muscle cells and cardiac fibroblasts and endothelin-1 production by endothelial cells was mediated, at least in part, by the 2-OHE metabolite. In the present study, the authors show that 2-hydroxyestriadiol inhibits serum-stimulated mesangial cell proliferation and collagen synthesis *in vitro*. In a model of chronic puromycin amonucleoside-induced nephropathy, the administration of 2-OHE ameliorates the development of renal injury as reflected by preservation of renal function, reduction of proteinuria and reversal of hypertension. Glomerular collagen IV deposition and PCNA staining and glomerular and interstitial macrophage infiltration were also reduced. These effects were shown to be estrogen receptor-independent and occurred in the absence of changes in plasma cholesterol or triglyceride levels.

The authors had previously shown that 2-OHE retarded the progression of renal disease in obese ZSF1 rats (28). However, 2-OHE reduced food consumption and body weight and improved plasma cholesterol levels and glucose control; the authors therefore could not separate the renal protective effects of 2-OHE from the beneficial effects of improved metabolic status. They embarked on the present study to avoid this pitfall. One problem of interpreting the effects of hormonal manipulation in rats with experimental renal disease is that female rats and estrogen-treated male rats eat less food than do untreated males. Thus, the intake of salt, fat, carbohydrate, and other dietary nutrients known to influence the rate of progression of renal disease may independently affect the outcome. In the present study, the authors failed to pair-feed their animals to assure identical food consumption among the groups. Despite the fact that food intake was found to be the same when measured on three separate days during the 12-wk study, body weight was significantly less in the PAN + 2-OHE group compared with the PAN group. This observation is even more noteworthy because the PAN rats developed chronic renal disease, which might be expected to impair weight gain.

Importantly, 2-OHE therapy did not lower testosterone levels in PAN rats. This finding is significant because it has been hypothesized that the presence of testosterone rather than the absence of estrogen accounts for sexual dimorphism in renal disease progression (6). In addition, 2-OHE did not raise triglyceride levels. The lack of effect is noteworthy because exacerbation of hypertriglyceridemia is responsible for the adverse effects of estrogen in various experimental models of hyperlipidemic renal diseases (7–10).

The renoprotective effects of female gender in humans as well as the beneficial effects of estrogen on collagen metabolism and other mesangial cell processes suggest that hormonal replacement therapy might be a rational approach to chronic progressive renal disease in postmenopausal women. However, the increased risk of breast cancer and the unanticipated recent finding of an adverse effect of estrogen/progestin HRT on cardiovascular disease, effectively excludes translation of this idea into clinical practice. The next challenge is to identify compounds that confer the renoprotective effects of estrogen on the kidney but lack its undesirable effects on the breast and other organs. The excitement generated by the work of Tofovic *et al.* (25) relates to whether 2-OHE represents such a compound. Similarly, selective estrogen receptor modulators (SERMs) are compounds that bind to the estrogen receptor but have tissue-specific effects that may differ from those of estrogen itself. The promise of the SERMs lies in their ability to reproduce the beneficial effects of estrogen on bone, endothelium, and lipoprotein metabolism without reproducing the undesirable effects of estrogen on reproductive tissues. SERMs replicate the effects of estradiol on mesangial cell biology and represent another potential therapeutic agent (17). However, much additional basic scientific and clinical research is required before either of these approaches is ready for clinical testing.

In the second study appearing in this issue of *JASN*, Baltuf *et al.* (24) suggest a role for the androgen receptor in mediating renal injury in a model of renin-dependent hypertension. The authors demonstrate that androgen receptors are involved in the development of hypertension and renal damage in transgenic TGR (mREN2) 27 rats harboring the mouse Ren-2 gene. Hypertension in this model results from activation of the renin-angiotensin system (RAS). Administration of flutamide, an androgen receptor antagonist, before the development of hypertension attenuated the increase in BP. Although BP was only modestly reduced, flutamide completely reversed renal damage. Urinary albumin excretion was markedly reduced, and renal morphology was normalized. These antihypertensive and renoprotective effects were associated with a reduction in plasma renin concentration and plasma renin activity. These data suggest that the ability of flutamide to prevent renal damage in this model of renin-dependent hypertension may not merely reflect the reduction in BP, but rather, may result from inhibition of the RAS. Similarly, when these rats were crossbred with rats harboring the tfm mutation, which renders animals insensitive to androgen, hypertension was attenuated and proteinuria reduced.

Other investigators have shown that androgen receptor blockade reduces BP in models of hypertension characterized by high salt intake, and presumably a suppressed renin-angiotensin axis, as well as in renin-dependent models. This suggests that mechanisms other than suppression of the RAS may be involved in the antihypertensive effects of androgen receptor blockade in TGR (mREN2) 27 rats. Both estrogen and testosterone levels increase in flutamide-treated animals. Estrogen reduces vascular resistance by both direct and indirect mechanisms and also modulates the RAS, whereas the effects of testosterone on vascular resistance are less clear (1). Although not studied here, flutamide has been shown to modulate catecholamine levels, which may also contribute to its antihypertensive actions. In addition, increased estrogen levels may play...
a role in the preservation of renal architecture seen in flutamide-treated rats. Consequently, the relative contributions of androgen receptor blockade per se versus secondary hormonal changes may account for the antihypertensive and renoprotective effects of flutamide remains to be established.

In conclusion, the two studies presented here provide numerous avenues for further investigation. However, investigators attempting to translate these findings into the clinical arena face the challenge of reconciling the renoprotective effects of female gender and exogenous estrogen with the adverse cardiovascular consequences of estrogen/progesteron HRT in postmenopausal women.

References

See related articles, “Abolition of hypertension-induced end-organ damage by androgen receptor blockade in transgenic rats harboring the mouse Ren-2 gene” (pp. 2681–2687), and “2-Hydroxyestradiol attenuates renal disease in chronic puromycin aminonucleoside nephropathy” (pp. 2737–2747).