Gender and Human Chronic Renal Disease

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ABSTRACT

Background: Gender affects the incidence, prevalence, and progression of renal disease. In animal models of the disease, female sex appears to modify the course of progression. Hormonal manipulation by male or female castration also changes the course of renal disease progression, suggesting direct effects of sex hormones in influencing the course of these maladies.

Objective: This review examines the pertinent animal and human studies assessing the role of gender, and strives to shed light on the possible physiologic mechanisms underlying the effect of gender, on renal disease progression.

Methods: A summary and evaluation of past and recent studies describing the rate of renal disease progression in animal models and humans as it pertains to gender is provided. In addition, studies elucidating the factors involved in the more modest renal progression rate in females are reviewed and conclusions drawn. Relevant English-language publications were identified by searching the PubMed database from January 1990 until November 2007 using the search terms gender, sex, renal disease, and kidney.

Results: In polycystic kidney disease, membranous nephropathy, immunoglobulin A nephropathy, and "chronic renal disease of unknown etiology," men progress at a faster rate to end-stage renal failure than do women. In type 1 diabetes mellitus, there is evidence that males are more likely to manifest signs of renal disease, such as proteinuria. The factors involved in this gender disparity may include diet, kidney and glomerular size, differences in glomerular hemodynamics, and the direct effects of sex hormones. In many, but not all, animal models of renal disease, estrogens slow progression rate. Several studies have recently evaluated the effect of selective estrogen receptor modulators on renal function in humans.

Conclusion: Further studies assessing the factors involved in the gender disparity in renal disease progression and the effects of hormonal treatments are warranted. (Gend Med. 2008;5[Suppl A]:S3–S10) © 2008 Excerpta Medica Inc.

Key words: gender, renal disease, renal disease progression, estrogen, estradiol.
INTRODUCTION
Gender affects the incidence, prevalence, and progression of many renal diseases. The mechanisms underlying these findings are not clearly identified but will be explored in this review.

The incidence of end-stage renal disease (ESRD) of all cause is higher in men than in women (55.5% vs 44.5%, respectively). Based on the most recent US Renal Data System data, the incident rate in males beginning treatment for ESRD is 1.5 times higher than the rate in females, a difference amounting to ~143 cases/million population.

The prevalence of childhood minimal change disease, adult focal segmental glomerulosclerosis, membranous nephropathy, and immunoglobulin A (IgA) nephropathy is slightly greater in males. Of all individuals in the United States receiving some mode of renal replacement therapy, 55.8% are men. The ESRD prevalence rate for males rose 14% between the years 2000 and 2005, whereas the rate for females rose 9.9%.

METHODS
In this article, we provide a summary and evaluation of past and recent studies describing the rate of renal disease progression in animal models and humans as it pertains to gender. In addition, studies elucidating the factors involved in the more modest renal progression rate in females are reviewed and conclusions drawn. Using the search terms gender, sex, renal disease, and kidney, relevant English-language publications were identified by searching the PubMed database from January 1990 until November 2007.

PROGRESSION OF RENAL DISEASE
Animal Models
Substantive data on the contribution of sex to the progression of renal disease are available from studies in rodent models. In many forms of experimental models of renal disease in animals, such as aging, renal ablation, hypertension, and polycystic kidney disease, males progress at a faster rate than do females. Hormonal manipulation in the form of male or female castration modifies the progression rate and suggests that female sex hormones, such as estradiol, may slow the progression of renal disease, whereas male hormones, such as testosterone, may promote disease progression. Naturally, there are exceptions to this generalization. In several experimental models of diabetic nephropathy and in hyperlipidemic animal models, female sex is a risk factor for renal disease progression. Moreover, in some experimental models of renal disease, it is the presence of testosterone rather than the absence of estrogen that determines gender dimorphism in disease progression. As our understanding of the actions of sex hormones has expanded, we have learned that the effects of different forms of the same sex hormone may be very different and may explain some of the disparate findings in animal studies of progressive renal disease.

Human Studies
The progression rate of many renal diseases in humans is also affected by gender. The most inclusive meta-analysis to date, comprising a total of 11,345 patients from 68 studies, reported that renal disease in women with polycystic kidney disease, IgA nephropathy, membranous glomerulopathy, and “chronic renal disease of unknown etiology” progresses at a slower rate than it does in blood pressure- and lipid level–matched men with these diseases. From the studies included in this meta-analysis, it is not possible to determine whether the women were pre- or postmenopausal. Another meta-analysis, which included 1860 non-diabetic patients from 11 randomized controlled trials evaluating the efficacy of angiotensin-converting enzyme inhibitors in slowing renal disease progression, suggested the opposite: that men may have a more moderate renal disease progression rate than do women. In the latter analysis, most women were postmenopausal, a fact that may explain the different findings in these 2 meta-analyses. The Modification of Diet in Renal Disease (MDRD) study suggested a deleterious effect of male sex on the progression of chronic renal disease. In this prospective multicenter study of 840 primarily nondiabetic patients with chronic kidney disease, loss of renal function was slower in women than in men, especially in women who were younger and predominantly premenopausal.
However, the difference in renal disease progression was no longer significant after adjusting for baseline proteinuria, mean arterial pressure, and high-density lipoprotein levels. Recently, 2 population-based studies from Scandinavia concluded that male sex was associated with a worse renal prognosis than was female sex.\textsuperscript{14,15}

The effect of gender on the incidence and progression rate of lupus nephritis bears mention. Compared with men, the incidence of systemic lupus erythematosus in young adults is much greater in women, but this gender disparity is less pronounced in the prepubertal and postmenopausal life stages.\textsuperscript{16} Although fewer males develop systemic lupus erythematosus, some studies show a greater prevalence and greater severity of lupus nephritis in men,\textsuperscript{16} whereas other studies have not borne out these conclusions.\textsuperscript{17}

The contribution of gender to the progression rate of diabetic nephropathy in humans is unclear, and it is confounded by interactions among gender, race, and blood sugar control. The incidence of diabetes in the US population is rising.\textsuperscript{1} Recent data suggest that the overall incidence of newly diagnosed diabetes mellitus (DM) in adult men equals that in women.\textsuperscript{1,18} Since 1990 or so, the incident rates of ESRD due to DM in males have surpassed those in females.\textsuperscript{1}

Data are accumulating to support the contention that males with type 1 DM have a poorer renal prognosis than do their female counterparts. Using urinary protein excretion as a marker of poor renal prognosis, recent studies in persons with type 1 DM show that males are more likely to exhibit this clinical abnormality, and have greater urinary protein levels once manifest.\textsuperscript{19} A recent study of 27,805 individuals with type 1 DM in Germany reported that male sex was associated with macroalbuminuria development.\textsuperscript{20} Of interest, the extent of blood sugar control in people with type 1 DM may interact with gender to determine renal prognosis. In a recent study utilizing cohort data from the Diabetes Control and Complications Trial (DCCT), investigators determined that among study participants who showed “good” metabolic control, women had a higher likelihood of developing diabetic nephropathy, whereas among participants with “poor” metabolic control, men had a higher likelihood of developing this kidney disease.\textsuperscript{21} Other studies report conflicting effects of gender and poor blood sugar control.\textsuperscript{22,23}

There is even less consistent information regarding the contribution of gender to the progression rate of type 2 diabetic nephropathy. The data that are available are contradictory—studies have either shown no difference in the progression of type 2 diabetic nephropathy,\textsuperscript{24} a worse prognosis in males,\textsuperscript{25} or a worse prognosis in females.\textsuperscript{26}

**POSSIBLE MECHANISMS RESPONSIBLE FOR GENDER DIMORPHISM IN RENAL DISEASE PROGRESSION**

The mechanisms underlying the gender disparity observed in the incidence, prevalence, and progression rate of numerous renal diseases have not been fully elucidated. Possibilities include gender-related differences in diet, renal mass or nephron number, systemic or glomerular hemodynamics, and the direct cellular effects of sex hormones. Studies in animals have contributed to our understanding of these potential factors.

**Renal Structure**

Male animals have greater kidney bulk and weight than do female animals, even when corrected for body weight. The reasons for this size and weight disparity are unclear but may be related to the direct effects of androgens, because these hormones increase kidney weight by increasing proximal tubular bulk.\textsuperscript{27} In humans, body surface area is the main predictor of kidney size. Therefore, men tend to have larger kidneys than do women.\textsuperscript{28} Some studies in humans suggest that women have fewer glomeruli than do men, but, if present, these differences have been reported to be in the 10% to 15% range.\textsuperscript{29,30}

**Systemic and Glomerular Hemodynamics**

When corrected for kidney weight or body surface area, glomerular filtration rate is no different in male or female animals or between men and women.\textsuperscript{31,32} Of interest, the glomerular hemodynamic adaptation to stress may be different
between the sexes. On receiving infused angiotensin II, healthy young men increased their glomerular filtration fraction whereas females did not, which suggests that men may manifest a higher glomerular capillary pressure in response to this hormone.³³ This finding may contribute to the gender disparity observed in progression rates of certain renal diseases. Gender-related differences in the glomerular hemodynamic response to hyperglycemia have been noted as well. In contrast to the hemodynamic response to angiotensin II, which may help explain the better prognosis of renal disease in women, the studies evaluating the hemodynamic response to hyperglycemia may help explain the lack of clear female protection in diabetic kidney disease.³⁴ Some studies have reported higher systemic blood pressures in men, and others have suggested that men are more susceptible to hypertensive renal injury.² However, the worse renal prognosis associated with male sex in such disorders as polycystic kidney disease is still evident, even after adjustment for blood pressure levels.³⁵

Lifestyle
In animals, dietary manipulation modifies the course of renal disease. Excess dietary intake of protein, phosphorus, sodium, or calories promotes renal disease progression, whereas restriction slows progression.³⁶–³⁸ Commonly, men and women consume different amounts of calories and protein. The investigators in the MDRD study, which assessed the effect of dietary protein restriction on the progression rate of nondiabetic renal disease, have suggested that women may have less renal benefit from dietary protein reduction than do males.¹³ Although smoking has been shown to interact with estrogen deficiency to promote renal injury in an experimental model, a large epidemiologic study failed to confirm this interaction in humans.³⁹,⁴⁰

Direct Effects of Sex Hormones
Sex hormones affect many cellular processes by stimulating or inhibiting the synthesis of various cytokines, growth factors, vasoactive agents and matrix proteins, such as angiotensin, nitric oxide (NO), and collagen. In particular, estrogens act via estrogen receptor α to regulate genes involved in extracellular matrix metabolism.⁴¹,⁴² Estrogen up-regulates the expression of angiotensinogen and angiotensin type 2 receptors, but downregulates the expression of renin, angiotensin-converting enzyme, and angiotensin II.⁴³–⁴⁶ Prorenin and renin levels and plasma renin activity have been found to be higher in men than in women. These effects of estrogens may contribute to alterations in renal hemodynamics and have an impact on renal disease progression. In cultured glomerular cells, physiologic concentrations of estradiol induce release of NO, which can serve to affect glomerular filtration rate and induce apoptosis of mesangial and endothelial cells, effects that could, in vivo, influence renal disease progression.⁴⁷–⁴⁹ It also appears that there may be a gender disparity in the glomerular hemodynamic dependence on NO with aging. Males appear more NO-dependent than do females.⁵⁰ In addition, sex hormones affect serum lipid levels and their degree of oxidation. Overall, premenopausal women have lower total cholesterol levels than do age-matched men,⁵¹ and postmenopausally, when men’s cholesterol levels are less different from women’s, replacement of estrogen lowers cholesterol.⁵² In vitro, high concentrations of estradiol inhibit renal cell-mediated low-density lipoprotein oxidation, whereas low concentrations may promote oxidation.⁵³,⁵⁴ There is no information regarding the direct effect of estrogens on lipid oxidation in a renal injury model. Although, in certain animal models, lipids can induce and promote renal injury, the specific role of lipids in human renal disease is not clear.

In renal tissue culture, estrogens inhibit the synthesis of type I and type IV collagen.⁵⁵ Suppression of type IV collagen appears to occur through interference with the transforming growth factor β (TGF-β) signal.⁵⁶ In the TGF-β transgenic mouse, which develops extensive glomerulosclerosis, estradiol supplementation inhibits renal scarring.⁵⁷ Estrogens also stimulate the activity of 2 collagen-degrading enzymes, metalloproteinase-2 and metalloproteinase-9.⁵⁸,⁵⁹ Because matrix deposition and scarring contribute to the progression of renal disease, estrogens may affect progression rates by interfering with the fibrogenic process.
SELECTION ESTROGEN RECEPTOR MODULATORS

Selective estrogen receptor modulators (SERMs) are agents that mimic many of the beneficial effects of estrogen on bone and vascular tissue without reproducing estrogen’s deleterious effects on reproductive tissue. Of interest, in cultured renal cells, SERMs inhibited collagen synthesis to the same degree as estradiol. In addition, in 2 animal models of diabetes, raloxifene lessened glomerulosclerosis. The Raloxifene in Diabetic Nephropathy (RADIUS) study, a recently conducted double-blind, placebo-controlled trial in which 39 postmenopausal women with type 2 DM and evidence of renal involvement were randomized to receive either raloxifene or placebo for 6 months, reported that urinary protein excretion decreased in the patients receiving raloxifene but not in the placebo group. In nondiabetics, a recent post hoc analysis of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, a multicenter, randomized, double-masked trial of raloxifene versus placebo on the risk of fractures in postmenopausal women, found that fewer women in the group that received raloxifene reached the composite renal end point, defined as a rise in serum creatinine of ≥0.4 mg/dL, a 50% reduction in estimated glomerular filtration rate (eGFR), and an “adverse event” related to kidney disease. This is of interest, because the MORE cohort recruited only women without overt renal disease. The renal effect of raloxifene appeared more prominent in the group of women with eGFR <60 cc/min · 1.73 m². Also of note, raloxifene clearance was found to be reduced in males with impaired renal function. The direct effects of estradiol or SERM supplementation on women with documented nondiabetic renal disease is unknown.

PERSPECTIVES/CONCLUSIONS

In summary, women appear to have a more modest course of renal disease progression than do men. The reasons for this finding may stem from diet, differences in kidney structure, glomerular hemodynamic responses to stress, and the direct cellular effects of sex hormones. Recent studies suggest that SERMs, compounds that have fewer adverse effects than estradiol has, may play a role in slowing renal disease progression. Further studies will help elucidate the specific roles of estrogen and testosterone hormones in the initiation and progression of renal diseases.

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