MAYO CLINIC

Gender and the Progression of Chronic Kidney Disease

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More than two decades have passed since publication of the first studies suggesting that gender might influence the progression of chronic kidney disease (CKD).[1] Subsequent to these observations, numerous studies have explored the relationship between gender, sex hormones, and CKD. It has been clearly established that male animals subjected to experimental kidney injury show worse renal damage and accelerated progression compared with female animals.[2] Manipulation of the hormonal milieu replicates these effects, suggesting that sex hormones themselves rather than chromosomal differences mediate this sexual dimorphism.[2]

The role of gender in renal disease progression in humans is much more complex, and it remains a subject of controversy. This lack of clarity reflects complex interactions among biologic and nonbiologic factors. Arguably, existent data suggest that the progression of renal disease is more rapid in men than in women, mediated by differences in the actions of sex hormones on cellular processes.[2]

Numerous retrospective and prospective cohort studies suggest a protective effect of female gender on renal disease progression.[2] However, the data are far from consistent. The Chronic Kidney Disease Prognosis Consortium performed a patient-level meta-analysis that included more than 720,000 patients from 31 CKD cohorts. The study found that progression to dialysis or renal transplantation was more rapid in men than in women after adjusting for confounding factors.[3] A subsequent patient level meta-analysis from the same group, which included more than 500 million patients from 7 general population cohorts, reported that men had a 50% greater risk of progression to end-stage renal disease than women.[4] The Chronic Renal Insufficiency Cohort Study reported renal outcomes in 3939 patients followed for a median of 6.9 years. In a fully adjusted model, men were more likely to experience a 50% decline in estimated glomerular filtration rate (eGFR) or progression to the end-stage renal disease compared with women.[5] Although men also showed a more rapid decline in the slope of eGFR, this difference was no longer significant in the fully adjusted model, which accounted for differences in lifestyle factors.

Other lines of evidence also suggest more rapid progression of CKD in men than in women. CKD, defined by an eGFR less than 60 mL/min/1.73 m^2 or albuminuria, or both, is more common in women than in men.[2] In striking contrast, men are more likely than women to initiate dialysis.[2] This overrepresentation of men in the incident dialysis population, despite the underrepresentation of men in the non–dialysis-dependent CKD population, might reflect more rapid disease progression in men with CKD. Alternatively, these data could merely reflect earlier initiation of dialysis in men than in women, associated with the death of women with stage 5 CKD before they reach dialysis.

Moreover, interpretation of these observations must account for controversies concerning the criteria used to define CKD and the role of nonbiologic factors. Although the magnitude of the difference in bias of the GFR estimating equations in men versus women is a function of age and renal function, overall, the difference in bias between the sexes is small and does not alter the assertion that CKD is more common in women than in men.[2] However, it has been suggested that the use of a single eGFR threshold to define CKD might overdiagnose CKD in women, especially older women.[6] Similarly, the use of a single urinary albumin to creatinine ratio cutoff to define

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microalbuminuria might overestimate the prevalence of proteinuria in women.[7]

The use of time to dialysis or renal transplantation as an endpoint to evaluate renal disease progression is also problematic. Because of disparities in the quality of health care delivery, it has been argued that women have less access to dialysis than men do. Accordingly, women initiate dialysis later than men do, at an eGFR that is approximately 1 mL/min/1.73 m^2 lower than in men.[2,8] Moreover, women, particularly older woman, may be more likely than men to forgo dialysis and to choose conservative care. As a result, women may be more likely to die with stage 5 CKD without ever initiating dialysis; however, other data contradict these arguments. The difference in the eGFR between men and women at the initiation of dialysis is comparable to the difference in the bias of the GFR estimating equations, bringing into question the conclusion that men start dialysis at a higher GFR than women.[2] In addition, a large study of patients with stage 5 CKD from the United States found no gender disparity in the provision of renal replacement therapy.[8] No major study has been specifically designed and executed to examine the role of gender in CKD progression in humans. As a result, knowledge of menopausal status is usually lacking in existent studies. Observational cohort studies are limited in their ability to unravel complex interactions among biologic and nonbiologic factors that could affect both CKD progression and the transition to renal replacement therapy. Moreover, studies examining the influence of hormone therapy on renal function and albuminuria have yielded conflicting results.[2]

Clearly, further research in this area is indicated; however, additional observational studies may fail to provide significant new insights. Novel approaches to this issue are warranted. One such novel approach was pursued by Kattah et al.[9] These investigators matched 1653 women who underwent ovariectomy before the age of 50 with women whose ovaries were intact. They found that the cumulative incidence of CKD over 20 years was 1.4-fold greater in women who had undergone ovariectomy. The risk of CKD was also related to whether the women had received estrogen replacement therapy and the duration of therapy. These data strongly suggest a protective role for estrogen in the development of CKD.

In this issue of *Mayo Clinic Proceedings*, Kang at al[10] complement and extend the observations of Kattah et al.[9] These investigators examine the relationship between reproductive life span duration (RLD), used to estimate lifetime exposure to estrogen, and the incidence and prevalence of CKD in a population-based cohort of postmenopausal women. In a cross-sectional analysis of 50,338 women, the authors found that the odds ratio for developing CKD was lower in women with longer RLD, even after adjustment for confounding factors. The authors also performed a longitudinal analysis of a subgroup of 3155 women with a baseline eGFR exceeding 60 mL/min/1.73 m^2 and who were followed for a mean duration of 9.7 years. After adjusting for confounding factors, the risk of incident CKD was lower and the time to development of incident CKD was significantly longer in women with longer RLD. The authors attributed the inverse relationship between RLD and CKD to the protective effects of estrogen exposure on renal function. However, several significant limitations related to the study design and execution are apparent. First, the definition of CKD was based on a single measurement of eGFR or qualitative assessment of proteinuria. The failure to account for exposure to nephrotoxic agents or the use of renal protective strategies is also problematic. Furthermore, the cross-sectional analysis is flawed insofar as one cannot exclude the possibility that preexisting CKD led to earlier onset of menopause and shorter RLD. However, this criticism does not apply to their longitudinal analysis of incident CKD. In conclusion, the novel approach used by Kang et al[10] has made a significant contribution to our understanding of the influence of sex hormones on the progression of CKD, and it supports a renoprotective role for estrogen.

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