Editorial Commentary

The role of gender disparities in kidney injury

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The incidence of end stage kidney disease (ESRD) is 50% higher in adult men than in women, even though there is a higher prevalence of chronic kidney disease (CKD) in women. The increased prevalence of CKD in females has not varied in the past 30 years (from 13.7% versus 9.8% in 1988–1994 to 15.4% versus 12.8% in 2011–2012). Previous studies have reported that there is a lower incidence of CKD and a slower progression in premenopausal women (1), but these earlier studies were limited by certain factors such as a lower percentage of minorities sampled. A recent study in The Journal of the American Society of Nephrology, "Sex-Related Disparities in CKD Progression" by Ricardo and colleagues (2) addressed the question of sex-related disparities in progression of CKD by examining data in the Chronic Renal Insufficiency Cohort (CRIC) Study, which follows a cohort of patients with CKD that is representative of the population of patients with CKD in the US.

There were 3,939 study participants in the Ricardo study (1,778 women and 2,161 men). The participants in the study averaged 58 years at study entry with 42% non-Hispanic black, and 13% of Hispanic ancestry. At the time of entry, the average eGFR was 43.9 mL/min per 1.73 mm^2 in women and 45.7 in men, with equivalent distributions of CKD stages between the sexes. At the time of entry into the study, there were differences noted between the sexes in certain risk factors and in the therapies received. Of note, the women in the study reported less physical activity and lower socioeconomic status. There also had a higher BMI and waist circumference, higher FGF23 and serum phosphorus, and higher LDL cholesterol and lower HDL cholesterol. They were also less likely to take cardioprotective medications. In contrast, there was lower proteinuria and less tendency to abuse tobacco.

The investigators documented the number of patients who had new onset ESRD, (indicated as the need for dialysis or the receipt of a kidney transplant), 50% eGFR decline from baseline), development of stage 5 CKD (eGFR, 15 mL/min per 1.73 m^2), the slope of decline eGFR, and all-cause death. During a median follow-up of 6.9 years, 844 of the study participants developed ESRD, and 853 died. The unadjusted eGFR slope was –1.09 mL/min per 1.73 m^2 per year in women and –1.43 mL/min per 1.73 m^2 per year in men. After multivariable adjustment, this difference was not significant. However, even though the women in the study had more potential risk factors for progression of CKD, in multivariable regression models, the investigators noted that the risk for development of ESRD, a decline in eGFR by half or the development of stage 5 CKD was significantly lower in women than men.

These results are compelling and are consistent with previous epidemiologic studies indicating that premenopausal women have a decreased incidence of hypertension, less diabetic microvasculopathy, decreased prevalence of CKD and slower decline in renal function with nondiabetic CKD (3-6). Given the observational nature of this study, the investigators were not able to determine mechanisms underlying these observed differences between the sexes. However, in experimental animals there is a clear sexual dimorphism with males having a greater propensity to develop chronic renal injury in experimental animals.

There have been a number of studies in experimental animals indicating a potential role for sex hormones in this sexual disparity. Development of kidney injury in males may be at least partially the result of detrimental effects of testosterone (7-9). Furthermore, bodybuilders who abused anabolic steroids were reported to develop focal glomerulosclerosis and tubulointerstitial disease (10). A recent study by Zhang *et al.* indicated that sex hormone-dependent differences in expression of the epidermal growth factor receptor (EGFR) could be a factor in the predisposition of males to have progression of CKD since expression of EGFR was lower in kidneys of adult females, both mice and humans. Ovariectomy in mice did not alter expression levels of EGFR but castration protected male mice and testosterone directly stimulated expression of EGFR in the kidney *in vivo* and in cultured renal cells (11). Other studies have also suggested a potentially important role for estrogen as a protective factor in females. A recent study indicated that in murine models of acute kidney injury, estrogen was protective, due in part to control of mitochondrial biogenesis and function and to inhibition of generation of reactive oxygen species (12).

Therefore, there is increasing evidence for gender differences in development and progression of CKD. Although previous experimental studies had most often utilized a single sex for studies involving experimental animals in order to decrease variability of responses, funding agencies are now correctly requiring that studies investigate responses in both sexes. Similarly, clinical and epidemiologic studies are now taking gender differences into account in investigations of responses to therapy. It is clear that we still have much to learn about the underlying mechanisms mediating differences in gender responses to kidney injury, and this should be a fertile area for both future preclinical and clinical research.

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Footnote

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