



# Understanding sex differences in progression and prognosis of chronic kidney disease

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Several epidemiologic studies have demonstrated that women have an increased incidence of chronic kidney disease (CKD) (1), but are less likely than their male counterparts to progress to end-stage kidney disease (ESKD) (2). Several theories have been proposed to explain this discrepancy, including that women may have slower progression of CKD, are more likely to die prior to starting dialysis, or are more likely to opt for conservative care, rather than proceed with a kidney transplant or dialysis (3). A recent study by Ricardo *et al.*, published in the *Journal of the American Society of Nephrology*, provides new insights into sex differences in CKD progression by analyzing the Chronic Renal Insufficiency Cohort (CRIC), a large, well-characterized cohort of patients with CKD that has a median of 7 years of follow-up (4). Similar to prior studies, the authors identified that women were less likely to progress to ESKD [adjusted hazard ratio (HR) 0.72, 95% confidence interval (CI): 0.59–0.87], less likely to have a decline in estimated glomerular filtration rate (eGFR) of 50% (adjusted HR 0.82, 95% CI: 0.69–0.96), and had a lower risk of death (adjusted HR 0.56, 95% CI: 0.44–0.70). This difference remained significant after extensive adjustment for clinical and socio-demographic factors, confirming what appears to be a true sex difference in the risk of ESKD. However, the study also raises interesting questions for future study, including the role of sex hormones in disease progression and what role sex differences in the complications and prognosis of CKD should play in the care of patients.

One of the most commonly cited reasons as to why there are fewer women on dialysis or with a transplant is that women have a slower progression of CKD (5,6), in part due to the protective effects of estrogen. Estrogen has been shown to have nephro-protective effects in animal models, including reducing glomerulosclerosis and preventing ischemia-reperfusion injury (7,8). There is also data supporting the hypothesis that the female sex is protective against kidney disease progression in humans, including a large meta-analysis published in 2000 by Neugarten and colleagues (9). Our recent study found that women with surgical oophorectomy prior to the natural age of menopause are at an increased risk of developing CKD as compared to women with no oophorectomy (10). Women who had their ovaries removed between ages 46 and 50 and received hormone therapy had a lower risk of developing CKD than women who had their ovaries removed when they were less than 45 years of age and did not receive hormone therapy, suggesting a dose-response relationship. When looking specifically at sex differences in CKD progression, a post-hoc analysis of the Modification of Diet and Renal Disease (MDRD) study found that women had a slower decline in GFR with time and that the difference between men and women was most pronounced in women and men <52 years of age (6). These findings suggest a potential benefit of estrogen in premenopausal women; however, after adjusting for differences in blood pressure, proteinuria and high-density lipoprotein, the difference was no longer significant. Therefore, sex hormones may modify risk factors for CKD,

rather than kidney function directly. Most of the previously mentioned studies have focused on the effects of endogenous estrogen deprivation on the kidney, and it does not follow that exogenous estrogen is necessarily beneficial for kidney function. At least one study has demonstrated that use of estrogen-containing hormone therapy in elderly women may cause a steeper decline in eGFR with time (11). On the other hand, our own meta-analysis demonstrated that estrogen-containing hormone therapy was associated with a decreased risk of albuminuria (12), though these results may be due to healthy user bias.

The current study by Ricardo *et al.* found a significant difference in eGFR decline between men and women in an unadjusted analysis ( $-1.09$  mL/min/ $1.73$  m<sup>2</sup> in women and  $-1.43$  mL/min/ $1.73$  m<sup>2</sup> in men,  $P < 0.001$ ), but after fully adjusting for age, race and baseline kidney function, the difference was no longer significant. These results are consistent with the findings of the MDRD study cited above, where the difference in GFR decline was no longer significant after adjustment (6). However, other studies have suggested that women have a slower decline in GFR as compared to men, such as a population-based study in Tromsø, Norway (13). A meta-analysis published in 2003 suggested the progression of renal disease may not be slower in women as compared to men, though the majority of the women were of post-menopausal age and the analysis was restricted to subjects that were enrolled in clinical trials of angiotensin-converting enzyme inhibitors (14). Part of the discrepancy in these results could be due to the characteristics of the populations sampled. Participants in clinical trials and prospective studies may differ from true population-based cohorts. Furthermore, residual confounding is always a concern when considering sex differences. There are several critical sex differences noted in the CRIC study, such as the fact that women were less likely to have seen a nephrologist and had lower incomes and education levels than their male counterparts. The authors in the CRIC study did adjust for various, measurable socioeconomic factors, such as education, marital status, and health insurance. However, given the multitude of clinical and societal factors that may differ between men and women, it is unlikely researchers will ever be able to truly unravel biologic sex from all of these potential confounders.

In the CRIC study, despite women having a significantly decreased risk of developing ESKD, there was no significant difference in the rate of progression of CKD in women as compared to men, leaving the question of why women are less likely to end up on dialysis. The authors did not find

that women were more likely to die before ending up with ESKD; on the contrary, women had lower risk of death, even after adjustment in multivariate models. The authors found similar mortality results when treating ESKD as a censoring event. Two possible explanations that remain are that (I) men may become more symptomatic at higher GFRs, and thus, are more likely to initiate dialysis, or that (II) more women may opt not to pursue dialysis. However, the authors point out that women were also less likely to reach CKD stage 5 or to have a decline in eGFR by 50%, neither or which are dependent on the choice to pursue renal replacement therapy. This discrepancy between the decline in GFR and the risk of ESKD in this study is difficult to reconcile, though it is possible that eGFR values were missing in a non-random fashion in men and women.

Another interesting finding in the CRIC study is that younger women, ages 21 to 45 years of age, had a higher risk of developing of ESKD than men in the same age group (HR 1.15, 95% CI: 0.81–1.64 *vs.* HR 0.58, 95% CI: 0.44–0.76 for ages 61 to 74). At first glance, this may undermine the idea that endogenous estrogen has beneficial effects on the kidney. However, one confounding factor is that women with the most advanced stages of CKD stop having regular menstrual periods and can have significant gonadal axis dysfunction (15). Several studies have found that amenorrhoeic women with CKD have lower systemic estradiol levels than women with CKD and regular menstrual cycles, and so these women could theoretically lose the protective benefits of estrogen (16). Gonadal axis dysfunction has long been treated as a side effect of CKD, but may instead play an important role in accelerating decline in kidney function. Reproductive factors in general are under-examined in women with CKD and may impact health in multiple ways. As another example, women in CRIC were less likely to be an angiotensin-converting enzyme inhibitor, possibly due to concerns for teratogenicity in an unplanned pregnancy for the younger age groups.

In addition to the role estrogen may play in mediating sex differences in CKD, there may be other factors that could explain the ‘apparent’ discrepancy in CKD risk and progression to ESKD between men and women. The simplest explanation may be that women and men should not have the same thresholds for CKD diagnosis and staging. Women are born with smaller kidneys and fewer nephrons (17). The impact of a declining GFR on a woman’s risk of morbidity and mortality may not be the same as for a man. The role of CKD staging is in part to identify

when certain complications develop as CKD progresses, such as anemia and disorders of bone mineral metabolism. Interestingly, the study by Ricardo *et al.* highlights that there are sex differences in these complications, as well. Women had a higher calcium, phosphorous, and FGF-23 than men in the CRIC cohort, though these were unadjusted values. Hemoglobin has sex-specific values for the normal range in the non-CKD population, but not in the CKD population. If women have different nephron endowment, different complications of CKD, and different risks of developing ESKD, why then are the stages of CKD the same? There has been more attention recently to the possibility of age-specific CKD staging, acknowledging the effects of normal aging on changes in GFR (18). Developing sex-specific criteria may be an appropriate next step.

Some interesting work has been done on the association of sex with mortality in CKD patients. The CKD Prognosis Consortium includes data from general population cohorts, cohorts at risk for cardiovascular events and cohorts with CKD, including over 2 million participants (19). In a study evaluating the risk of all cause and cardiovascular mortality by sex, they found that while women had an overall lower risk of mortality than men, women had a steeper increase in all-cause and cardiovascular mortality with declining GFR than men. The reason for this finding is unclear, but this study does highlight that it is dangerous to draw the conclusion that CKD is not as 'relevant' to a woman as to a man. The study by Ricardo and colleagues did observe a lower risk of mortality in women as compared to men, with extensive adjustment. They found no evidence of effect modification by age, race/ethnicity, diabetes or CKD stage at the time of death.

Fortunately, there has been greater attention focused on understanding the biology of sex differences, extending from animal studies and into clinical trials. However, large gaps in our knowledge remain. In the era of individualized medicine, considering something as simple as biologic sex in the diagnosis and management of CKD seems a reasonable starting point in pursuing individualized care. Ricardo *et al.* study has confirmed prior studies showing that women are less likely to progress to ESKD, after adjusting for multiple confounding factors, and had a lower risk of mortality, adding strong, credible evidence that sex differences in ESKD exist. The study highlighted differences in CKD complications and issues related to access to care between men and women. There was no significant difference in the rate of CKD progression as defined by the change in slope of eGFR, despite the significant reduction in ESKD risk.

Given the strength of the data and analysis in this study, this discrepancy does not diminish the importance of the results, but does raise questions for future study, including what role endogenous estrogen deficiency may play in accelerating disease progression in women with advanced CKD, whether sex-specific CKD criteria are needed, and how to improve CKD care for all patients, regardless of biologic sex.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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