The Other Way Around: Living With Chronic Kidney Disease From the Perspective of Men

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Summary
A wealth of evidence has suggested sex (biological) and gender (sociocultural) differences in the prevalence, progression, and outcomes of persons with chronic kidney disease. Much of this evidence tends to emphasize differences in which women are disadvantaged, and less attention is paid to findings in which women are better off or similar to men. However, gender medicine recognizes that men and women have different disease determinants, presentation, and attitudes, and it pertains to both sexes. In this review, we revisit chronic kidney disease through the perspective of men, and illustrate a population segment at need of stringent preventative and management strategies.
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The past 2 decades have evidenced the prominent role of sex (biological constructs) and gender (social constructs) as modifiers of the most common causes of death and morbidity in society.[1,2] Chronic kidney disease (CKD) is no exception because men and women, males and females, experience notable differences in its prevalence, progression, and outcomes.[3] Gender medicine represents a pivotal platform for nephrologists to better address the needs of their patients within the framework of precision medicine. However, it is a field of knowledge in which implementation practices still are not generalized.

Much of the evidence to date, as also summarized in this issue of *Seminars in Nephrology*, tends to emphasize differences in which women are disadvantaged. Identifying such gender disparity is an important area that requires both clinical and research efforts and that has been the subject of our previous work.[3-6] However, less attention is paid to findings in which women are better off or similar to men. Perhaps because of the publish or perish pressure of academia, favorable and statistically significant findings are more likely to be published.[7] This publication bias may provide a partial view of the problem.

Gender medicine recognizes that men and women have different determinants and presentation of disease, and aims to improve the disease experience of both sexes. We propose in this review to revisit various aspects of CKD through the perspective of men, illustrating a population segment at need of stringent preventative and management strategies. We recognize, however, that in many of the studies listed, it is not possible to differentiate the effects of sex from those of gender, for example, different countries, cultures, and socioeconomic positions allow for differential access to care.

FACT 1: THE PROGRESSION TO END-STAGE KIDNEY DISEASE IS FASTER IN MEN

Probably because of faster progression to kidney failure in men (discussed later), a higher risk of premature death in men, and the longer life expectancy of women, the lifetime risk of developing CKD stage 3 is reportedly higher in men than for women.[8,9] Despite wide geographic variation, there are more women than men in society with non-dialysis CKD stages 3 to 5.[3] However, the majority of individuals who progress to kidney failure or undergo maintenance dialysis/transplantation are men.[10-13]

Although not always a universal finding in historical literature,[14,15] there is agreement that the loss of kidney function over time and progression to kidney failure occurs more rapidly in men.[16-18] For example, a recent analysis from the chronic renal insufficiency cohort (CRIC)[19] showed that, compared with women, men had a 17% higher risk of starting dialysis, as well as a steeper

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mean unadjusted estimated glomerular filtration rate (eGFR) slope (-1.43 mL/min per 1.73 m^2 versus -1.09 mL/min per 1.73 m^2 per year in women). Interestingly, differences in eGFR slope disappeared after adjustment for lifestyle factors and comorbidities, which opens the hypothesis to modifiable factors haltering CKD progression in men.

Recently, and using data from 888 children, Bonneric et al[20] explored possible differences in eGFR trajectories and the risk of CKD progression between sexes. In children with nonglomerular diseases, males had a faster CKD progression, but again the sex effect was not significant after multivariable adjustment. In children with glomerular diseases, females had faster CKD progression. Thus, underlying primary kidney disease (which for some etiologies also is sex-specific) may result in different progression rates between sexes. Although historical evidence was generated previously on this phenomenon (eg, in diabetic nephropathy), it is a reminder that kidney diseases are complex and all etiologies cannot be oversimplified to a single eGFR.

Underlying mechanisms for faster progression in men are not well elucidated. On the one hand, animal studies attribute these differences to deleterious effects of testosterone.[21-23] However, this causality is difficult to reconcile with literature regarding the association between testosterone deficiency and adverse clinical outcomes in men with CKD, and the role of testosterone replacement therapy on managing complications of CKD such as anemia or muscle wasting.[24,25] Other animal studies have reported that although nitric oxide production is lower in male compared with female animals,[26] proinflammatory mediators of kidney injury[27,28] and oxidative stress in the kidney are higher.[29]

On the other hand, faster progression rates in men may be attributed to more unhealthy behaviors. Men with CKD are described as eating more and more unhealthily than their female counterparts, thereby presenting with a higher metabolic burden that may accelerate eGFR decline.[30-32] Men tend to have a higher salt consumption,[33] and be less compliant with sodium-restricted diets.[34] Conditions such as higher body mass index and increased plasma glucose levels were associated with the acceleration of CKD progression in men to a greater extent than in women.[35] Hu et al[36] investigated the association of multiple dietary patterns with the risk of CKD progression (50% eGFR decline or kidney replacement therapy) and all-cause mortality in participants from CRIC. In three of four of the healthy dietary patterns evaluated, men scored worse than women (ie, men ate more unhealthily). Adherence to healthy dietary patterns was associated with a lower risk for CKD progression and all-cause death, independently of sex, but the study did not report analyses segregated by sex. Finally, studies also have suggested that men more often choose to start kidney replacement therapy, while women more often choose conservative care.[37] Research that elucidates why women progress more slowly than men in CKD may shed light on novel approaches to manage disease. However, efforts to tackle the rapid progression to dialysis of men also are warranted.

FACT 2: MEN WITH CKD HAVE A HIGHER RISK OF DEATH THAN WOMEN

Multiple studies coincide in that men with non−dialysis-dependent CKD have a higher mortality risk than women. The most recent study comes from the Stockholm CREAtinine Measurements project, which observed higher risk of both kidney replacement therapy and death for men, irrespective of their kidney function, CKD category, and previous eGFR slope.[38] In a nationwide study of Swedes referred to nephrology care and with CKD stages 3 to 5, men were 10% more likely to die than women of the same eGFR,[18] although this difference became less clear across more severe CKD stages. Similar observations were reported in CRIC, in addition showing higher risk of major cardiovascular events.[39] The CKD Outcomes and Practice Patterns Study[40] observed that sequential adjustment for comorbidities minimally affected the higher risk of death and kidney replacement therapy of men, arguing that the differences may not be explained by biological factors, but perhaps attributed to social factors (ie, differences in the quality of care, access to care, and so forth). As a consequence of these findings, life expectancy is reduced in men (compared with women) in all eGFR categories except for CKD stage 5.[41]

Differences in outcomes between sexes tend to disappear upon the start of dialysis, an observation initially described by Villar et al[42] as the "cancellation of the survival advantage of women in dialysis." Subsequent work from the European Renal Association register,[13,43] Dialysis Outcomes and Practice Patterns Study,[10] and others[44-46] showed that this absence of difference on death risks between sexes was attributed in part by higher noncardiovascular death risks among women (infections and cancer), but cardiovascular mortality remained higher in men.[13,43]

These worse outcomes in men with CKD occur despite a better provision of care or a more aggressive treatment of risk factors. In a recent qualitative interview study,[47] nephrologists voiced that they believed more attention was paid to men and their symptoms. Men are more likely to start dialysis at higher levels of kidney function than women and have lower rates of dialysis withdrawal.[48-51] In the United Kingdom, men are referred to nephrologists earlier and at a higher eGFR that women,[52] and men were more likely to receive a diagnostic code of CKD.[53] A Canadian cross-sectional study of people with CKD in primary care[54] reported more frequent testing of urine albumin-creatinine ratio in men, compared with women. In Sweden, men with

low eGFR were more likely to carry a diagnosis of CKD and be retested for albuminuria or creatinine than women.[55] In the United States, during the past 20 years, men have been more aware of their kidney disease than women.[56] These data come from the National Health and Nutrition Examination Survey in which participants responded to the question, "Have you ever been told by a health care professional you had weak or failing kidneys?" The response rates to this question may be interpreted, in part, as an indication that in health care more attention is attributed to CKD in men. In addition, in the United States, the likelihood of initiating renin-angiotensin inhibitors upon detection of incident albuminuria was higher in men.[57]

FACT 3: MEN WITH CKD MORE OFTEN SUFFER FROM CARDIOVASCULAR DISEASE THAN WOMEN

Throughout all stages of CKD severity, men have a worse cardiovascular profile and more cardiovascular complications than women. In a recent study from Korea[58] including patients with nondialysis CKD, men had higher coronary artery calcium measurements at baseline, a higher risk of accelerated coronary artery calcium progression over time, and a higher risk of cardiovascular events.[58] The Korean National Health and Nutrition Examination Survey[59] also showed that men with more severe CKD had progressively higher levels of visceral adiposity, but no such association was observed for women.[59] In CRIC, men were more likely to be hospitalized for cardiovascular complications than women, although women had a higher rate of noncardiovascular complications than men.[60]

This excess cardiovascular disease (CVD) risk also is seen among patients on dialysis. In the analysis of baseline characteristics of the Dutch Netherlands Cooperative Study on the Adequacy of Dialysis trial, men who initiated dialysis had a higher cardiovascular disease prevalence (two-fold) and higher blood pressure than women, along with a higher body mass index and higher proportion of smokers.[44] In another US trial,[61] enrolled men had a higher left ventricular mass index than women. In a cohort study from Germany, male patients undergoing hemodialysis had higher calcification scores and higher CVD event rates than women.[62] Those studies are more than a decade old, and we do not believe that they represent the risk profile of patients nowadays. In the EQUAL study, including 1,479 elderly patients with incident dialysis stage 4 from five European countries during 2012 to 2018, men continued to smoke and had hypertension or cardiovascular disease comorbidity more often than women.[63]

The excess CVD risk in men with CKD compared with women resembles the differences in the general population, which are attributed in part to the cardioprotective effect of estrogen in women and, as alluded earlier, a more unhealthy lifestyle in men. There are, however, several CKD-specific risk factors that operate differently in men and women.

Hyperphosphatemia

Hyperphosphatemia is lower in men with CKD, but associated more strongly with CVD outcomes than in women. Maintenance of phosphate levels in the normal range through dietary and pharmacologic strategies is recommended by all major nephrology guidelines, suggesting ranges of normality that do not make a distinction between sexes. Thus, we find it intriguing to say the least, that a wealth of community-based studies, as well as studies of patients with CKD, have reported serum phosphate levels being significantly lower, not higher, in men compared with women.[64-68] The underlying reasons are not clear,[5] but it is even more interesting that despite men having lower levels, hyperphosphatemia is associated with subclinical atherosclerosis, cardiovascular events, and death only in men.[65-69] Each 1 mg/dL increase in serum phosphate level in men with stable CVD was associated with a 4.52 g/m^2 increase in left ventricular mass, whereas no significant association between higher serum phosphorus level and left ventricular mass was noted in women.[70] Whether more stringent phosphate control would benefit men with CKD warrants further study.

Uncontrolled Blood Pressure

Uncontrolled blood pressure is more common in men with CKD and possibly a greater risk factor for CKD progression than in women. Hypertension is a well-known risk factor for developing CKD,[71] progressing to end-stage kidney disease,[72] and suffering from cardiovascular disease,[73] or premature death.[74] Hypertension is generally more common among men than among women.[75] Weldegiorgis and Woodward[76] conducted a systematic review and meta-analysis to evaluate whether women and men with hypertension are at a similar risk of developing CKD outcomes. Their analysis showed that the effect of hypertension on the composite end point of incident CKD or end-stage kidney disease (ESKD) was different between sexes. Specifically, the risk ratio of hypertension compared with ideal blood pressure was 1.56 (95% confidence interval [CI], 1.39-1.75) in women and 2.06 (95% CI, 1.64-2.60) in men.[76] This result means that, compared with men, hypertension in women conferred a 23% lower kidney risk (relative risk, 0.77; 95% CI, 0.63-0.95) with no significant heterogeneity between studies (I^2 = 17.7%). Two possible explanations are proposed to explain why hypertension conferred approximately a fifth lower excess risk of

kidney disease in women, as follows: on the one hand, men may have poor adherence to antihypertensive medications, poor lifestyle choices, and more preexisting conditions that could put them at high risk of ESKD and death; on the other hand, access to timely and good-quality health care is an important modifiable factor that may cause a considerable disparity in the CKD risk profile between women and men. Limited access to medical care may result in a delayed CKD diagnosis, inadequate education in diet and self-care, insufficient access to medication or monitoring, and suboptimal treatment and follow-up evaluation. Presently, our knowledge about sex differences in the diagnosis and management of CKD is limited; not all patients may be receiving adequate guideline-recommended care, and conscious or unconscious biases could lead to fewer women having their CKD detected, monitored, and managed (discussed earlier). A cohort study of 906 patients with hypertension and CKD stages 2 to 5 attending nephrology consultation[77] investigated the association between blood pressure control and the risks of kidney replacement therapy or death. Although office blood pressure was similar in men and women, daytime and nighttime ambulatory blood pressures were higher in men. In unadjusted models, the rates of kidney replacement therapy and mortality associated with off-target blood pressure were both numerically higher in men compared with women, but interaction terms did not attain statistical significance.

FACT 4: MEN MAY REACT TO THEIR CKD WITH DENIAL

The worse clinical outcomes for men with CKD discussed earlier contrast with the recurrent finding that they score their quality of life better than women.[78-84] Men on dialysis report a lower symptom burden and less severe symptoms than women,[82,85-89] and also take less time to recover after a dialysis session than women.[88] A recent analysis from EQUAL evaluated uremic symptom burden,[63] illustrating that men and women differ in their uremic symptoms, and/or may be more concerned over certain uremic symptoms more than others. Symptoms such as bone or joint pain, leg swelling, trouble staying asleep, and shortness of breath predominantly were reported by women, while men more often reported difficulty in becoming sexually aroused and a decreased interest in sex.

Men and women may experience and react differently to ESKD and may choose to express it differently.[80] Depression is diagnosed less often in men with CKD,[10,63,81,90] and it is not well acknowledged that in the general population, although twice as many women than men are diagnosed with depression, twice as many men than women commit suicide.[91] Men more often adopt avoidance (eg, heavy drinking and smoking) as a coping strategy,[92] and they perceive themselves as better able to cope with the physical aspects of their disease.[92-95] The meaning of these findings is not necessarily that men do not care about their health issues, but that they may find it difficult to express their fears in response to the social pressure/expectation of them being tough, strong, and responsible for the economy of the household.[96] As a consequence, men use health services less often than women, are less likely than women to engage in routine checks, and arrive to the hospital often too late.[97,98] Women are more likely to seek advice from peers, magazines, books, internet, and television than men. Men tend not to rely on the experience of their peers, preferring to try to live life as normal,[99] showing "strength in silence," which might affect their desire to being informed on how to best manage their disease.[100]

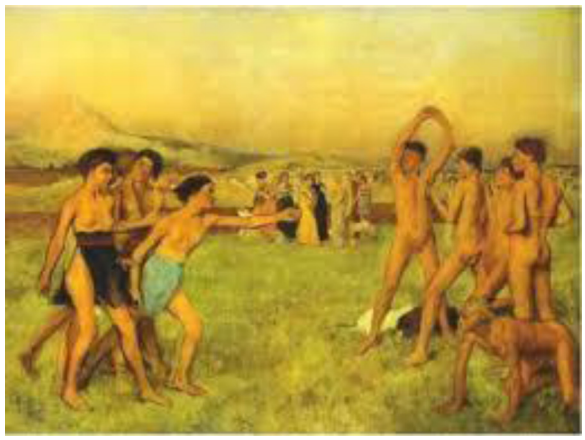

Figure 1. Edgar Degas "Young Spartans Exercising," also known as "Young Spartan Girls Challenging Boys" (~1860). National Gallery, London, UK.

SUMMARY AND CONCLUSIONS

The idea that men and women compete in society has often been the subject of art (Fig. 1).

However, if survival was the goal of human beings, then men would have to be considered as losing this battle. Notwithstanding the important gaps that may exist in the recognition and management of CKD among women, this review shows the other side of the coin, namely that men with CKD are at a consistently higher risk of worse clinical outcomes. Efforts to improve this and ensure equitable care between sexes could have important implications for justice and could reduce the burden of CKD.

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