THE ROLE OF GENDER IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Chronic kidney disease (CKD) is a common disease worldwide and is associated with high rates of morbidity and mortality. This review discusses several aspects of the relationship between gender and CKD. While the prevalence of CKD tends to be higher in women, the disease is more severe in men, who also have a higher prevalence of end-stage renal disease. Most of the evidence in the current literature suggests a higher progression rate and mortality risk of CKD in men compared with women, except in post-menopausal women and diabetic patients. However, the decrease in glomerular filtration rate and the increase in the level of albuminuria are more prominent mortality risk factors among women. Sex hormones are thought to play a major role in the biological mechanisms associated with variability in CKD prevalence and characteristics between men and women. Animal studies have demonstrated the harmful influence of testosterone and protective influence of oestrogen on several biological processes that are involved in kidney injury. However, the role of sex hormones in explaining gender-related differences in CKD in humans has not yet been established. In summary, gender has an important influence on several aspects of CKD. Further research is needed to find additional gender-related characteristics in CKD and to identify the mechanisms of sexual dimorphism in CKD.

Keywords: Renal failure, glomerular filtration rate (GFR), sex hormones, end-stage renal disease (ESRD).

INTRODUCTION

Chronic kidney disease (CKD), defined by reduced estimated glomerular function rate (eGFR) and/or albuminuria levels, is a worldwide health problem due to the significant rate of morbidity and mortality associated with it. CKD is associated with an increased risk of all-cause mortality and cardiovascular mortality, and progression to end-stage renal disease (ESRD).1 To establish better prevention strategies and enable early detection, much effort has been made to identify risk factors associated with CKD development. In this respect, various studies have been conducted to assess the effect of gender on the prevalence, progression, and characteristics of CKD. In this review, the main aspects of gender influence on CKD are discussed.

When addressing the difference between CKD in men and women, we must take note of the fact that eGFR (commonly used in studies) is based on a patient’s sex, among other variables. The two most common equations for assessing eGFR, the MDRD (Modification of Diet in Renal Disease) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations, both use sex as a variable. They are based on the assumption that for a given creatinine level, men will have higher levels of kidney function than women due to higher muscle mass and increased creatinine generation among men.2 Thus, in the lack of studies using the gold standard measurement of glomerular filtration rate (GFR) (which is the measurement of inulin), results regarding gender influence on CKD are often biased due to the use of sex dependent equations.

PREVALENCE OF RENAL DISEASE AND END-STATE RENAL DISEASE AMONG MEN AND WOMEN

Based on the most recent US Renal Data System (USRDS) annual data report,3 the prevalence of chronic renal failure between the years 2007 and
2012 was higher in women (15.1%) than in men (12.1%). Women had a higher prevalence of high urinary albumin to creatinine ratio (9.6% versus 8.1% in men) and a higher prevalence of decreased GFR (7.6% versus 5.4% in men; decreased GFR is defined as eGFR <60 mL/min/1.73 m$^2$). It is important to mention that several previous studies have shown opposing data regarding this issue.\textsuperscript{3-8} For example, a French epidemiologic study showed a higher incidence rate of chronic renal failure in men,\textsuperscript{4} whereas a Chinese cross-sectional study\textsuperscript{5} demonstrated similar CKD prevalence among men and women. There might be a geographic variability in the effect of gender on the prevalence of CKD, as shown in Table 1. Nonetheless, the incidence of ESRD appears to be higher in men than women. Based on the most recent US Renal Data System data,\textsuperscript{3} 57.8% of the patients with a new onset ESRD were men. Furthermore, 56.3% of the prevalent dialysis patients were males, as were 59.7% of the kidney transplant recipients in the USA. Several other studies\textsuperscript{9-11} found similar results, as shown in Table 2.

It should be noted that a natural decline in GFR with age is present in the healthy population.\textsuperscript{12}

**Table 1: Geographic variability in gender-associated prevalence of CKD.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>GFR assessment method</th>
<th>Percentage of women with CKD</th>
<th>Percentage of men with CKD</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish National Study on Ageing and Care\textsuperscript{6}</td>
<td>2014</td>
<td>Cystatin C</td>
<td>23.2</td>
<td>17.7</td>
<td>1,252</td>
</tr>
<tr>
<td>Swedish National Study on Ageing and Care\textsuperscript{6}</td>
<td>2014</td>
<td>Creatinine</td>
<td>23.08</td>
<td>15.01</td>
<td>1,252</td>
</tr>
<tr>
<td>Ile de France district (France)\textsuperscript{4}</td>
<td>1996</td>
<td>Direct level of creatinine</td>
<td>0.0179</td>
<td>0.0348</td>
<td>10,660,000</td>
</tr>
<tr>
<td>USA NHANES population\textsuperscript{3}</td>
<td>2007-2012</td>
<td>Lower estimated GFR and high urinary albumin creatinine ratio</td>
<td>15.1</td>
<td>12.1</td>
<td>No Data</td>
</tr>
<tr>
<td>Framingham (Massachusetts, USA)\textsuperscript{7}</td>
<td>1999</td>
<td>Creatinine level (gender-specific cut-off)</td>
<td>8</td>
<td>8.7</td>
<td>6,233</td>
</tr>
<tr>
<td>Beijing (China)\textsuperscript{5}</td>
<td>2008</td>
<td>Creatinine (using the MDRD equation), albuminuria</td>
<td>12.7</td>
<td>13.3</td>
<td>13,925</td>
</tr>
<tr>
<td>Middle and old-aged population of Beijing (China)\textsuperscript{6}</td>
<td>2005</td>
<td>Creatinine (using the MDRD equation)</td>
<td>12.6</td>
<td>13.2</td>
<td>2,310</td>
</tr>
</tbody>
</table>

*The reported data is the annual incidence of CKD. CKD: chronic kidney disease; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease.

**Table 2: Geographic variability in gender-associated cumulative incidence of ESRD.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>Percentage of women with ESRD</th>
<th>Percentage of men with ESRD</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors of ESRD in Finland\textsuperscript{9}</td>
<td>2010</td>
<td>0.27</td>
<td>0.46</td>
<td>25,821</td>
</tr>
<tr>
<td>Washington Country, Maryland\textsuperscript{10}</td>
<td>2003</td>
<td>0.49</td>
<td>0.78</td>
<td>23,534</td>
</tr>
<tr>
<td>Japan\textsuperscript{11}</td>
<td>1999–2000</td>
<td>0.0189</td>
<td>0.032</td>
<td>No Data</td>
</tr>
<tr>
<td>USA white people\textsuperscript{75}</td>
<td>2006</td>
<td>0.0139</td>
<td>0.0169</td>
<td>No Data</td>
</tr>
<tr>
<td>Norway\textsuperscript{75}</td>
<td>2006</td>
<td>0.0036</td>
<td>0.007</td>
<td>No Data</td>
</tr>
</tbody>
</table>

*The reported data is the incidence of CKD (but not cumulative incidence). ESRD: end-stage renal disease.
In a study which used the gold standard method for assessing GFR, a significant decrease in GFR with age among men, but not among women, was observed. Furthermore, research from India showed a significantly higher mean eGFR among women aged 41–45 years, yet no significant difference between men and women in the 20–30 or 30–40 year age groups. In contrast, in an Israeli longitudinal study that assessed the natural rate of decline in renal function with age, no significant effect of gender on the natural decline of GFR with age was observed.

**THE INFLUENCE OF GENDER ON DISEASE PROGRESSION**

Though the prevalence of chronic renal failure may be higher in women, the incidence of ESRD seems to be higher in men, indicating that the progression rate of renal disease may be faster in men than women. Though the literature regarding this issue is conflicting and inconclusive, most studies support this assumption.

In a large meta-analysis published in 2000, a significant correlation between male gender and disease progression of IgA nephropathy, membranous nephropathy, autosomal dominant polycystic disease, and ‘chronic renal disease of unknown aetiology’ was demonstrated. In addition, a Swedish cohort study found that the male sex is associated with a greater risk of future need of renal replacement therapy among patients with chronic renal failure, in comparison with the female sex. In another study, which examined the variation in GFR among patients with CKD Stage 3, a more rapid decline in GFR in men was demonstrated. Similar findings were observed in a large cohort of patients with CKD Stage 4.

A smaller study performed on participants of the MDRD study indicated a slower mean GFR decline in women compared with men, particularly among younger women. However, the association between gender and the rate of GFR decline became non-significant after adjusting for differences in blood pressure, proteinuria, and high-density lipoprotein (HDL) cholesterol. In this study, women had different renal diagnoses, less proteinuria, and lower serum creatinine levels for a given GFR compared with men. Conflicting results were found in a large meta-analysis performed on a database of patients enrolled in a randomised clinical trial for evaluating the efficacy of ACE (angiotensin-converting-enzyme) inhibitors in slowing renal disease progression, in which a similar rate of progression in men and women was observed. Further, adjustment for other factors which affect the rate of renal progression suggested that progression may be faster in women. However, most of the female participants were of post-menopausal age, and therefore these findings may not extend to younger women. In a large cohort of 24,682 patients aged ≥50 years, female sex was a risk factor for developing ESRD (hazard ratio: 1.48); most of the women in this study were also of post-menopausal age. The authors suggest that as the prevalence of cardiovascular mortality increases in both men and CKD patients, mortality in men might be higher occurring before the development of ESRD. A large meta-analysis performed on a global consortium did not show a gender-related difference of eGFR with the risk of developing ESRD. For specific values of urinary albumin creatinine ratio, women showed a slightly higher risk of developing ESRD, compared with men. Results were obtained from a pooled analysis of 13 CKD cohorts containing over 38,000 participants.

The effect of gender on diabetic renal disease is much more debatable. Whilst a number of studies show that male gender is a risk factor for diabetic kidney disease (DKD), others demonstrate that women are at higher risk of developing the disorder and some found no significant difference between men and women in terms of risk. Recent research, which was designed to assess the influence of gender on the incidence of CKD among diabetic patients, concluded that diabetic women had a significantly higher incidence of CKD. Furthermore, diabetic women had a higher (but not significant) incidence of microalbuminuria. This study included both Type 1 and Type 2 diabetic patients. In another study, which was conducted using the Pathways Study database, women had a similar prevalence of DKD in comparison with men, but had an increased prevalence of advanced DKD.

In conclusion, current evidence regarding the effect of gender on DKD is contradictory, though it seems that a protective role of female sex on the kidney is lost in the case of DKD. One reason for this finding might be an imbalance in sex hormones associated with diabetes.
GENDER ASPECTS REGARDING MORTALITY

Several studies have shown a reduced risk of mortality among women with CKD, compared with men. Among CKD patients, the most common causes of death were cardiovascular disease, cancer, and infections. In a large meta-analysis performed on a global consortium of over 2 million participants, risks of all-cause mortality and cardiovascular-related mortality were higher among men for all levels of eGFR and for all levels of albuminuria. However, among participants with lower values of eGFR and participants with higher levels of albuminuria, the elevation in mortality risk was steeper for women. Thus, changes in GFR and albuminuria levels seem to be more significant risk factors for mortality (all-cause and cardiovascular-related mortality) in women. The similarity in the risk of developing ESRD for a given eGFR and level of albuminuria in both sexes leads us to speculate that the stronger correlation found between renal function and mortality among women was not due to renal disease-related mortality. It might reflect a higher risk of non-renal disease mortality. Other specific risk factors might contribute to the higher risk of cardiovascular mortality among women with low GFR. These include hypertension, serum glucose level, serum lipids (total cholesterol level, low-density lipoprotein [LDL], triglycerides), and more. Further prospective studies are needed for evaluating these risk factors in large cohorts.

THE INFLUENCE OF GENDER ON OTHER RISK FACTORS FOR DEVELOPING CHRONIC KIDNEY DISEASE

Several risk factors for developing CKD among healthy people have been defined. Hypertension, diabetes, and cardiovascular disease are considered the most important risk factors for CKD. Other considerable risk factors for CKD are hyperlipidaemia, obesity, metabolic syndrome, and smoking. Elevated levels of C-reactive protein and of homocysteine were both found to be independent risk factors for the development of CKD.

The effect of gender on these risk factors has also been examined. Several studies have shown that obesity (high body mass index) is a risk factor for developing CKD among women but not among men. Other studies have yielded the opposite results. Lately, it has been shown that the correlation between homocysteine and CKD is similar in men and women, in contrast to the results of a previous Japanese study in which elevated homocysteine was a risk factor for CKD only in women. An Italian study demonstrated gender differences regarding recognised risk factors for CKD: men had a higher prevalence of overweightness, having a higher waist circumference, and a higher blood pressure, whereas women had a higher prevalence of haematuria and leukocyturia, which are early manifestations of CKD.

PROTECTIVE AND PATHOGENIC MECHANISMS

Many possible mechanisms for the protective effect of female gender on CKD patients have been suggested. These include gender differences in kidney anatomy, kidney haemodynamic stress response, effect of sex hormones, diet, lipid metabolism, and blood pressure. Anatomically, the kidney is usually larger in men, due to a larger body surface area. Some studies have shown a smaller number of glomeruli in female kidneys. The haemodynamic stress response of the kidney differs between men and women; men may develop higher filtration fraction in response to angiotensin II infusion. During hyperglycaemia, women exhibited a reduction in renal blood flow and an increase in renal vascular resistance and filtration fraction, whereas males exhibited no significant renal haemodynamic changes. These findings may explain the lack of renal protection among diabetic women.

Lifestyle differences between men and women have been suggested as another possible explanation for the influence of gender on CKD. A high protein and high caloric dietary intake, which characterises men more than women, is associated with the development and the progression of kidney disease. High levels of LDL, triglycerides, and uric acid, and low levels of HDL are associated with accelerated kidney disease progression. These trends are more common in men, and are influenced by nutrition and lifestyle.

The role of sex hormones in the pathogenesis of renal injury has gained a lot of attention. Several animal studies demonstrate a harmful influence of testosterone and protective influence of oestrogen on processes involved in kidney injury. Testosterone induces podocyte apoptosis.
Testosterone deficiency is associated with several cardiovascular risk factors, including metabolic syndrome, diabetes, hypertension, obesity, and atherosclerosis. Thus, the decrease in levels of male androgens among CKD patients might play a role in the higher cardiovascular mortality rate among men with CKD.

As mentioned previously, according to many animal studies, oestrogen might have a protective role on the kidney. In humans, the higher risk of CKD progression among post-menopausal women (concluded from the fact that studies using post-menopausal women did not show a higher progression rate of CKD in men) supports the protective role of oestrogen. We would expect that hormonal therapy (either hormone replacement therapy in post-menopausal women or contraceptive use in pre-menopausal women) would improve kidney function. Clinical studies that examined this assumption yielded opposing results. Several demonstrated that post-menopausal hormonal replacement therapy was associated with a lower risk of albuminuria and a higher creatinine clearance. In contrast, one study showed a dose related association of post-menopausal oestrogen replacement therapy with loss of kidney function, whilst another found that oral contraceptives are associated with a development of macroalbuminuria among Type 1 diabetic patients. Furthermore, a case report study performed on historical data found that the use of oral contraceptives and hormone replacement therapy is associated with increased risk of microalbuminuria.

**CONCLUSIONS**

Despite conflicting data regarding the influence of gender on CKD, some conclusions can be made. The prevalence of CKD tends to be higher in women, whereas the disease in men is more severe. Much of the evidence in the current literature indicates a higher progression rate of CKD in men, with the exception of post-menopausal women and diabetic patients. Mortality rate in patients with CKD is higher among men. The findings of Nitsch et al. demonstrate that as kidney disease progresses in women, the elevation in mortality risk increases. This effect has not been shown in men, and further research is needed to understand the role of gender in the association between renal disease severity and mortality.
It seems that the influence of sex hormones on several biological processes involved in kidney injury plays a major role in creating gender differences in CKD; many animal and in vitro studies support this assumption. However, the same role has not been demonstrated in human-based research, and numerous studies refute this theory. In our opinion, as the level of sex hormones is influenced by several variables (diseases, medications, age, etc.) in addition to gender itself, it is difficult to extrapolate the findings from animal studies to the human population. Further research is therefore needed in this area.

REFERENCES

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