Sex Differences in Diabetic Kidney Disease

Christine Maric-Bilkan, PhD

Abstract

While the global prevalence of both type 1 and type 2 diabetes mellitus is similar in men and women, the consequences of diabetes on associated end-organ complications, including diabetic kidney disease, appear to be more sex-specific. Particularly, women with diabetes have higher mortality rates for diabetes-related deaths, and higher prevalence of diabetic kidney disease risk factors such as hypertension, hyperglycemia, obesity, and dyslipidemia. However, the evidence for the impact of sex on diabetic kidney disease prevalence and disease progression is limited and inconsistent. Although most studies agree that the protective effect of the female sex against the development of kidney disease is diminished in the setting of diabetes, the reasons for this observation are unclear. Whether or not sex differences exist in the risk of diabetic kidney disease is also unclear, with studies reporting either higher risk in men, women, or no sex differences. Despite the remaining controversies, some of the factors that associate with sex differences in the risk of diabetic kidney disease are age at onset, and type and duration of diabetes. There is growing appreciation of the importance of sex hormones in the regulation of renal function, with estrogens generally considered to be renoprotective. Although some progress has been made towards better understanding of the mechanisms by which sex hormones play a role in the pathophysiology of diabetic kidney disease, the translational potential...
Despite improvements in management, diabetes mellitus (both type 1 [T1DM] and type 2 [T2DM]) remains the leading cause of end-stage renal disease (ESRD) worldwide.\(^1\)\(^-\)\(^3\) It is associated with significant morbidity and mortality directly by causing ESRD and indirectly by increasing cardiovascular risk.\(^4\)\(^-\)\(^5\) The Centers for Disease Control and Prevention estimates that nearly 40% of individuals living with diabetes will develop diabetic kidney disease (DKD) at some stage of their life.\(^6\) With the incidence of diabetes, especially T2DM, rising globally,\(^7\)\(^-\)\(^8\) the incidence of DKD is also projected to continue to rise.\(^3\)\(^,\)\(^9\)

Although the prevalence of diabetes (T1DM and T2DM combined) may be similar between women and men,\(^10\) the burden of diabetes appears to be sex-specific. Women with both T1DM and T2DM diabetes have a higher residual lifetime risk at all ages,\(^11\) higher mortality rate for diabetes-related deaths, including DKD,\(^12\) and a greater prevalence of DKD risk factors including hypertension, hyperglycemia, obesity, and dyslipidemia.\(^13\)\(^-\)\(^15\) However, whether DKD prevalence and disease progression varies by sex remains unclear. A large meta-analysis published in 2000, and also a more recent analysis of the Chronic Renal Insufficiency Cohort (CRIC) reported that male sex is associated with a more rapid rate of progression and a worse renal outcome in patients with nondiabetic chronic kidney disease (CKD).\(^16\)\(^,\)\(^17\) These observations suggest that the female sex is protective factor for nondiabetic CKD; however, this may only hold true in younger, premenopausal women. Indeed, after adjustment for confounding factors, a study which included mainly postmenopausal women reported that women appear to have as high, or even a higher, rate of nondiabetic CKD progression as men.\(^18\)

These observations clearly indicate that sex differences exist in the nondiabetic population and that the differences may be related to age, hormonal status of the individuals, and differences in renal hemodynamics, as well as renal mass differences between men and women.\(^19\)\(^-\)\(^21\) Unfortunately, the link between sex and DKD has not been well established with studies reporting either higher DKD risk in men,\(^22\)\(^-\)\(^26\) women,\(^27\)\(^-\)\(^30\) or no sex differences.\(^17\)\(^,\)\(^31\)\(^-\)\(^35\) The underlying reasons for these disparate findings may include different patient populations studied (including but not limited to age and T1DM vs T2DM), differences in study designs, existence of confounding factors that independently affect DKD progression in men and women, or simply because very few studies have been designed to specifically address this issue.

The intent of this review is to summarize the current knowledge on the association between sex in DKD development and progression, discuss some potential mechanisms by which sex can modulate the biological underpinnings of DKD, and highlight gaps and opportunities for future research. Although both sex and gender, as well as the interaction between the two, contribute to the differences in DKD in men and women, this review will predominantly focus on sex differences. Sex differences are being defined, according to the Institute of Medicine, as biological differences between men and women (eg, differences in sex chromosomes, sex-specific gene expression, and sex hormones) compared with gender differences (eg, differences in lifestyle, environmental influences, and nutrition).\(^36\)

**KIDNEY DISEASE ASSOCIATED WITH T1DM**

Our knowledge of sex differences in DKD, in general, is limited and inconsistent, but this is especially true for DKD associated with T1DM. Some of the contributing factors for our limited understanding of the impact of sex in DKD associated with T1DM, particularly its long-term consequences, may be that many studies in T1DM focus on either
children or patients at a young age, and that, compared with T2DM, T1DM is less prevalent so that studies often pool data from patients with both T1DM and T2DM. 27,28,31 Our limited understanding of this field is also related simply to the fact that specific studies to address sex differences have not been conducted and studies that have considered sex as a variable in DKD have reported disparate findings. In general, although most studies to date report that men with T1DM exhibit greater risk of DKD compared with women with T1DM, several studies have challenged this view reporting no sex differences or even higher risk in women. 29,30,41 Findings from these studies are discussed below and summarized in Table 1.

**Evidence for the Male Sex as a Risk Factor for DKD Associated With T1DM**

In the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, the combined

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<th>TABLE 1. Reported Sex Differences in DKD Associated With T1DMa</th>
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<tr>
<td>Reference Brief summary of findings</td>
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<tr>
<td>Greater risk in men</td>
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<tr>
<td>Hovind et al22 In patients with T1DM duration of 18 years, men have a higher relative risk of developing incipient or overt DKD compared with women (relative risk, 2.41; 95% CI, 1.43-4.06).</td>
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<tr>
<td>Raile et al23 In patients with T1DM duration of 8 years, men have a higher relative risk of developing macroalbuminuria compared with women (OR, 1.29; 95% CI, 1.003-1.658).</td>
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<tr>
<td>Mollsten et al24 During a median time of follow-up of 20 years, the highest risk of ESRD was found in men diagnosed with T1DM at ages 20-34 years (HR, 3.0; 95% CI, 1.5-5.7).</td>
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<td>Orchard et al25 In patients with T1DM duration of 30 years, the combined prevalence of micro- and macroalbuminuria was 84% in men compared with 59% in women.</td>
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<td>Harjutsalo et al26 The cumulative incidence of ESRD in patients diagnosed between 10 to 14 and ≥15 years was 17.4% (95% CI, 13.4-21.2) and 13.0% (95% CI, 9.6-16.2), respectively, in women, whereas in men it was 32.2% (95% CI, 28.0-36.1) and 24.6% (95% CI, 20.8-28.1), respectively.</td>
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<tr>
<td>Jacobsen et al27 In adult patients with T1DM, male sex is a risk factor for the decline in GFR over 5 years of patient follow-up.</td>
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<tr>
<td>Sibley et al28 In patients with T1DM duration of 16 years, male sex is a risk for development of microalbuminuria, a relationship accounted for by waist-to-hip ratio.</td>
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<tr>
<td>Skupien et al29 International study of patients with T1DM with advanced DKD reported that the risk of ESRD was associated with male sex.</td>
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<tr>
<td>Greater risk in women</td>
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<tr>
<td>Monti et al29 Greater female preponderance for diabetic complications including DKD.</td>
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<tr>
<td>Costacou et al30 In patients diagnosed with T1DM between 1965 and 1980, female protection against ESRD was lost as compared with patients diagnosed before 1965, with a slight excess of female ESRD cases.</td>
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<tr>
<td>Zhang et al31 Women have greater risk for developing DKD and a good metabolic control, whereas men are greater risk for DKD and the poor metabolic control.</td>
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<tr>
<td>Lovshin et al32 Adolescent girls with T1DM have a four-fold increase in the prevalence of hyperfiltration compared with age-matched boys.</td>
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<tr>
<td>Holl et al33 Schultz et al34 In children and adolescents with T1DM, the female sex as a risk factor for the development of microalbuminuria independent of the duration diabetes.</td>
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<tr>
<td>No sex differences</td>
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<tr>
<td>Rossing et al35 No sex differences in the progression from normoalbuminuria to microalbuminuria or macroalbuminuria were observed in patients with T1DM aged 18 years of age or older and with duration of diabetes greater than or equal to 5 years.</td>
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<tr>
<td>Finne et al36 In patients younger than 30 years, with a median duration of T1DM of 16.7 years, no sex differences in the risk of ESRD were observed, regardless of the age at onset of T1DM.</td>
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<tr>
<td>Kautzky-Willer et al37 No differences in the frequency of diabetic complications (including DKD) were observed between men and women despite more women having hyperlipidemia compared with men.</td>
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aDKD = diabetic kidney disease; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HR = hazard ratio; OR = odds ratio; T1DM = type 1 diabetes mellitus.
prevalence of micro- and macroalbuminuria in adult patients with the duration T1DM for 30 years was 84% in men compared with 59% in women. Further, the risk for microalbuminuria in this patient population decreased with the duration of diabetes in women, whereas it steadily increased in men, suggesting that diabetes duration impacts the risk for DKD in a sex-specific manner. The study concluded that the excess risk of ESRD in men was partly explained by differences in hemoglobin A1C (HbA1c), hypertension, and lipid levels between the sexes. In a group of patients with T1DM from the Steno Diabetes Center, with a median duration of diabetes of 18.0 years, men had a higher relative risk of development of incipient or overt DKD compared with women (relative risk, 2.41; 95% CI, 1.43-4.06). In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications database, the male sex was a risk for development of microalbuminuria; however, this effect was lost when adjusted for waist to hip ratio. These observations suggest a potential role for visceral adiposity in the progression of DKD associated with T1DM. In an attempt to eliminate some variation across different study cohorts, a recent international study of patients with T1DM with advanced DKD reported that the risk of ESRD was associated with male sex.

Greater risk of developing overt DKD has also been reported in younger men with T1DM. In patients with established DKD, the male sex has been shown to be associated with a more rapid decline in glomerular filtration rate (GFR) over 5 years of patient follow-up. In a nationwide, prospective German Diabetes Documentation System survey, a cohort of patients with T1DM (average age, 21 years; mean duration of T1DM, 8 years), the male sex was found to be a risk for development of macroalbuminuria. Similarly, males aged 20 to 34 years when diagnosed with T1DM had twice as high risk of ESRD as female subjects in the same age range (hazard ratio [HR], 2.3; 95% CI, 0.99-5.3). Among males, the risk of developing ESRD was considerably higher in those that developed T1DM at 20 to 34 years of age (HR, 3.0; 95% CI, 1.5-5.7) as well as 10 to 19 years of age (HR, 2.6; 95% CI, 1.5-4.7), compared with the youngest age-at-onset group (0-9 years). In contrast, in females no difference in the risk of developing ESRD was observed if T1DM was diagnosed between ages 20 and 34 years compared with the youngest age-at-onset group (0-9 years) (HR, 1.4; 95% CI, 0.5-3.6). The highest risk was observed for the 10- to 19-year-old age group (HR, 2.8; 95% CI, 1.4-5.5). Similar observations were made in a study from the Finnish Diabetic Nephropathy Study population. These findings suggest that age at onset of T1DM is an important determinant of the risk of ESRD associated with T1DM and highlight a role for puberty and sex hormones, as will be discussed later in this review.

Evidence for the Female Sex as a Risk Factor for DKD Associated With T1DM
In contrast to the prior observation from the EDC study (patients diagnosed with T1DM before 1965) reporting the male excess of DKD associated with T1DM, a recent report from the same cohort, but with patients diagnosed with T1DM between 1965 and 1980 suggested that the female protection against ESRD was lost and that there was, in fact, a slight excess of female ESRD cases. This slight excess could not be explained by differences in modifiable risk factors, but to the contrary, such adjustments produced over a two-fold increased risk in women compared with men. In this study, although survival dramatically improved among men (HR, 0.28; 95% CI, 0.18-0.45), this was not the case in women (HR, 0.72; 95% CI, 0.45-1.14). Furthermore, if T1DM was diagnosed at or after 10 years of age, the overall incidence of ESRD was greater in women compared with men, again highlighting that the age at onset of T1DM impacts the risk of DKD in a sex-specific manner. The number of cases with ESRD in this cohort was small, suggesting the need for further follow-up to determine whether the increased risk of ESRD in women is in fact real. Most importantly, the fact that declines in the cumulative incidence of ESRD were observed between the
younger (patients diagnosed with T1DM after 1965) versus earlier cohort (patients diagnosed with T1DM before 1965) among men but not women suggests that more aggressive risk factor management may be necessary to prevent development and progression of DKD associated with T1DM, particularly in women.

Other studies have also suggested a greater risk for DKD in women. Adolescent girls with T1DM have a four-fold increase in the prevalence of hyperfiltration compared with age-matched boys. In two large cohorts of children and adolescents with T1DM, the female sex was a risk factor for the development of microalbuminuria independent of the duration diabetes. However, no longer-term follow-up of these patients was reported to inform the sex differences in disease progression. A case-control design, nested on a cohort of T1DM families study reported greater female preponderance for diabetic complications including DKD. Further, in the Diabetes Control and Complications Trial, women have been reported to have greater risk for developing DKD even with good metabolic control, whereas men are at greater risk for DKD and poor metabolic control. These observations suggest that there may be differences in the mechanisms underlying DKD that are sex specific, and some potential mechanisms will be discussed later in this review.

**Evidence for No Sex Differences in the Risk for DKD Associated With T1DM**

In addition to studies showing sex differences in the development and progression of DKD, some studies have not observed any differences between the two sexes. In a cohort of patients from the Finnish Diabetes Register (younger than 30 years; median duration of T1DM of 16.7 years), no sex differences in the risk of ESRD were observed regardless of the age at onset of T1DM. No sex differences in the progression from normo- to micro- or macroalbuminuria were observed in a cohort of patients with T1DM aged 18 years or older and with duration of diabetes greater than or equal to 5 years. Further, in a cross-sectional study of 225 subjects with T1DM (45.3% women), no differences in the frequency of diabetic complications, including DKD, were observed between men and women despite more women having hyperlipidemia and higher total cholesterol and high-density lipoprotein cholesterol concentrations compared with men. Overall, these disparate observations regarding sex differences in the risk for the development and progression of DKD can possibly be explained by the differences in study design and analyses, duration of diabetes, and different patient populations studied. However, the fact remains that no prospective study to date has been specifically designed to directly examine sex differences in DKD associated with T1DM and capture data relevant to explain the mechanisms underlying the observed differences.

**KIDNEY DISEASE ASSOCIATED WITH T2DM**

Although not abundant, data on the impact of sex on DKD in patients with T2DM seems to be just as inconclusive and inconsistent as in patients with T1DM, with studies reporting either higher risk of DKD in men, women, or no sex differences. Findings from these studies are discussed below and summarized in Table 2. It is unfortunate that some studies reporting on sex differences in the risk of DKD often pool data from patients with both T1DM and T2DM, making data interpretation difficult and drawing definitive conclusions impossible. Further complicating the matter is the fact that T2DM clusters with obesity, which is increasingly recognized as an important risk factor for ESRD. This relationship between increasing obesity and DKD appears to be stronger for women than men. Thus, separating the effects of T2DM from obesity is often difficult. Furthermore, as T2DM is more prevalent among the older population, the effects of biological age and accompanying menopause in women from the direct effects of T2DM on DKD are often difficult to tease out. The
fact that many studies do not take into consideration the hormonal status or the use of hormone replacement in their analyses also poses a barrier to our understanding of the impact of sex on the development and progression of DKD.

### Evidence for the Male Sex as a Risk Factor for DKD Associated With T2DM

Several studies, especially earlier reports, have indicated that the male sex is a risk factor for the development of DKD in the setting of T2DM. Two prospective, observational studies have reported that the male sex is a risk factor for the development of incipient (persistent microalbuminuria) as well as overt (persistent macroalbuminuria) DKD in men with T2DM.45,46

In a study of 723 (280 women, 443 men) Japanese patients with T2DM (mean age, 63 ± 11 years) with normoalbuminuria or microalbuminuria during the mean follow-up period of 4.3 years, higher triglycerides and lower high-density lipoprotein cholesterol levels were associated with higher risk of progression to a more advanced stage of albuminuria, but only in men.47 In a prospective cohort of 1470 patients with T2DM without renal replacement therapy (60% men; age, 65 ± 11 years; median follow-up duration, 5.7 years), the male sex was found to be an independent factor associated with renal function decline.48 Specifically, the estimated GFR (eGFR) decline was greater in men compared with women (adjusted odds ratio, 1.33 [1.02-1.76]) after adjustment for age, time from diagnosis of T2DM, HbA1c, systolic blood pressure, and urinary albumin:creatinine ratio.

### Greater risk in women

- **Kajiwara et al.**49 The mean decline in annual eGFR was -3.5±2.7%/year in females and -2.0±2.2%/year in males (P<0.001) and was associated with HbA1c and low-density lipoprotein cholesterol levels, but only in women.

- **Crook et al.**50 African American, Hispanic, and Pima Indian populations have shown that women are at a higher risk of DKD and greater rate of disease progression compared with age-matched men.

- **Lewis et al.**51 Proteinuria develops at a more rapid rate in women as compared with age-matched men; however, women had more severe disease at baseline.

- **Bjornstad et al.**56 Girls with T2DM are disproportionately impacted by DKD, with a three-fold greater risk of developing DKD.

### No sex differences

- **Ricardo et al.**17 There is no evidence of significant effect modification by diabetes on the association between sex and ESRD.

- **Rossing et al.**55 In 227 (60 female) patients with DKD for 6.5 years, no differences in the decline of eGFR were observed between women and men.

### TABLE 2. Reported Sex Differences in DKD Associated With T2DM

<table>
<thead>
<tr>
<th>Reference</th>
<th>Brief summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gall et al; Ravid et al.45</td>
<td>Male sex is a risk factor for the development of incipient (persistent microalbuminuria) as well as overt (persistent macroalbuminuria) DKD.</td>
</tr>
<tr>
<td>Hanai et al.47</td>
<td>Lower high-density lipoprotein cholesterol levels are associated with the progression of DKD in men but not in women.</td>
</tr>
<tr>
<td>de Hauteclercque et al.48</td>
<td>eGFR decline was greater in men compared with women (adjusted odds ratio, 1.33 [1.02-1.76]) after adjustment for age, time from diagnosis of T2DM, HbA1c, systolic blood pressure, and urinary albumin:creatinine ratio.</td>
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<td>Kajiwara et al.49</td>
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<tr>
<td>Looker et al.51</td>
<td>Proteinuria develops at a more rapid rate in women as compared with age-matched men; however, women had more severe disease at baseline.</td>
</tr>
<tr>
<td>Young et al.52</td>
<td>Both younger and older women with T2DM have higher mortality risk than diabetic men during and after first renal replacement therapy.</td>
</tr>
<tr>
<td>Bjornstad et al.56</td>
<td>Girls with T2DM are disproportionately impacted by DKD, with a three-fold greater risk of developing DKD.</td>
</tr>
<tr>
<td>Hecking et al.57</td>
<td>There is no evidence of significant effect modification by diabetes on the association between sex and ESRD.</td>
</tr>
<tr>
<td>Villar et al.58</td>
<td>In 227 (60 female) patients with DKD for 6.5 years, no differences in the decline of eGFR were observed between women and men.</td>
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</table>

*DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HbA1c = hemoglobin A1C; T2DM = type 2 diabetes mellitus.*
Evidence for the Female Sex as a Risk Factor for DKD Associated With T2DM

Girls with T2DM are disproportionally impacted by DKD, with greater propensity for hyperfiltration compared with boys and a three-fold greater risk of developing DKD. In a small (247 male, 97 female adults with T2DM) clinic-based, retrospective longitudinal study (follow-up duration, 8.1±1.4 years), the mean annual eGFR change was −3.5±2.7%/year in females and −2.0±2.2%/year in males. This eGFR decline was associated with HbA1c and low-density lipoprotein–cholesterol levels, but only in females, suggesting a need for a more aggressive therapeutic intervention to improve metabolic profiles at early stage, especially in females. Another study, conducted in women with T2DM (mean age, 61.6±6.8 years; duration of diabetes, 9.8±7.2 years) found that the early renal functional decline in these women is linked to increased vascular stiffness, which may be associated with visceral fat accumulation as determined by waist circumference.

Women with T2DM have also been reported to have a higher mortality risk than diabetic men during and after first renal replacement therapy. Whereas this effect was mainly observed in older women, a study from the Swedish National Diabetes Register showed that excess mortality was also observed in women with advanced renal disease who were younger than 55 years. These observations suggest that the higher risk of mortality may not be related to the age-related decline in sex hormones, although that hypothesis was not directly tested in these studies.

Several studies conducted in the African American, Hispanic, and Pima Indian populations have shown that women are at a higher risk of DKD and greater rate of disease progression compared with age-matched men, suggesting racial/ethnic disparities in the sex differences risk of DKD. However, evidence also suggests that progression of DKD may also be greater among Caucasian women compared with age-matched men. Specifically, in the Irbesartan Diabetic Nephropathy Trial (IDNT) and the Reduction of Endpoints in NIDDM With Angiotensin II Antagonist Losartan (RENAAL), proteinuria developed at a more rapid rate in women as compared with age-matched men with T2DM. In the latter study, clinical and laboratory parameters measured at baseline, including body mass index, prevalence of obesity, mean arterial pressure, and serum levels of cholesterol and triglycerides all tended to be higher in women, who also exhibited worse glycemic control compared with men. Considering the more severe disease present in women at baseline and that sex difference in DKD progression was no longer apparent in the multivariate analyses, conclusions on whether or not sex plays a role on DKD progression cannot be made directly. Given the close association between the female sex and sex hormones, it is surprising that many of these studies do not account for the potential confounding effects of menopause or hormone replacement. One potential explanation for this oversight is that relevant data are simply not available. Thus, future studies examining sex differences in DKD should consider collecting information related to hormonal status in women (eg, age at menarche, reproductive history and health, history of oral contraceptive use and hormone replacement therapy, and menopausal status).

Evidence for No Sex Differences in the Risk for DKD Associated With T2DM

Although most of the studies to date reporting on sex differences in DKD associated with T2DM show either the male or female sex being a risk for DKD, a couple of studies have reported no effect of sex on DKD risk or progression. In a prospective observational study of 227 (60 female) patients with the duration of diabetes of 6.5 years, no differences in the decline of eGFR were observed between women and men. A recent study using the CRIC cohort also reported no evidence of significant effect modification by diabetes on the association between sex and ESRD. However, this study does not make a distinction between T1DM and T2DM, which may affect the
outcome of the analysis. Given that CRIC is a clinic- rather than population-based cohort, it is conceivable that the risk for DKD progression in this population is lower compared with the patients not enrolled in the study. This may preferentially lower the overall risk in women who, in general, have a lower CKD awareness compared with men. Thus, women enrolled in CRIC may have a lower risk for DKD compared with women in general, limiting translatable findings on sex differences in DKD to the general population. Despite limitations of the study, which also include not considering hormonal status for example, it is the most recent one to report on sex differences and it provides valuable information on which future studies can only build on.

MECHANISMS UNDERLYING SEX DIFFERENCES IN DKD

Despite the recognition that sex differences exist in the risk of DKD, our understanding of the underlying mechanisms of these differences as well as disease pathophysiology are rather limited. However, accumulating evidence suggests that several biological factors are involved in the pathophysiology of DKD, many of which contribute in a sex-specific manner. As summarized in the Figure, sex hormones directly, and indirectly (as variables in menopause, puberty, and pregnancy) are thought to be one of the main drivers of sex differences in DKD. As will be discussed below, sex hormones are thought to regulate renal hemodynamics, oxidative stress, inflammation, and key biological pathways involved in the pathophysiology of DKD.62,63,66 Other general factors that lead to DKD in a sex-specific manner include: type and duration of diabetes, biological age, age at onset of diabetes, and genetic and epigenetic factors, et cetera.67,68 Classical risk factors for DKD, including glycemic control, hypertension, obesity, and dyslipidemia have also been reported to differentially contribute to disease pathophysiology according to sex.67-69 As we strive to better understand the pathophysiology of DKD, studies addressing how sex contributes to and affects disease development and progression may provide important clues.

Most of our understanding about the mechanisms underlying sex differences comes from studies in experimental models. However, it is widely acknowledged that a barrier to progress in better understanding of DKD, in general, has been a lack of appropriate animal models that fully recapitulate the main features of human DKD.70 This lack of appropriate animal models has especially hindered progress in the understanding of sex differences as females are often resistant to or develop a much milder form of the disease.71 Thus, attention to sex should be paid in future efforts to develop animal models of DKD that would fully recapitulate the human disease relevant to both sexes. Despite lack of appropriate models, our current state of knowledge of sex differences in the pathophysiology of DKD provides a good foundation and uncovers research gaps and opportunities for future research.

Although this review predominantly focuses on sex, rather than gender differences, significant interactions between biological (sex) and psychosocial (gender) factors exist.
and play a role in disease pathophysiology.\textsuperscript{72} Our understanding of the significance of such interactions in the context of DKD remains largely unexplored and studies addressing these interactions should be encouraged.

**Contribution of Sex Hormones to DKD**

The loss of female sex as protective factor against nondiabetic CKD after menopause led to the belief that ovarian hormones are renoprotective.\textsuperscript{16} In the setting of diabetes, it is generally believed that female sex as protective factor is lost even before menopause,\textsuperscript{73} possibly due to the imbalance in sex hormone levels and activity. Indeed, studies have suggested that both T1DM and T2DM are associated with an imbalance of sex hormone levels. Specifically, men have low testosterone and high estradiol levels\textsuperscript{74-76} in contrast to women who exhibit low estradiol and higher testosterone levels.\textsuperscript{77,78} An imbalance in sex hormone levels as well as differential expression of renal estrogen and androgen receptors by sex has been reported in experimental models of DKD.\textsuperscript{79-81} Several studies have also suggested that restoring the sex hormone imbalance may be an effective treatment for DKD. In females, administration of 17β-estradiol (E\textsubscript{2}) has been shown to attenuate glomerular and tubulointerstitial injury in several rodent models of DKD.\textsuperscript{71,82-86} In a prospective, single-center clinical trial, administration of a cyclic combination of estradiol and norgestrel orally for 3.5 monthly cycles improved proteinuria and impaired creatinine clearance in postmenopausal women with T2DM.\textsuperscript{97} Furthermore, in a randomized, placebo-controlled pilot trial, raloxifene, a selective estrogen receptor modulator, has been shown to improve renal function in postmenopausal women with T2DM.\textsuperscript{98,88} Similar retrospective effects of selective estrogen receptor modulators were observed in experimental models.\textsuperscript{89,90} However, studies to investigate whether hormone replacement therapy may be additive to nephroprotective therapy in premenopausal diabetic women have thus far not been attempted.

Not all studies support the notion of a renoprotective effect of estrogens. Few studies in both experimental models and humans have suggested detrimental effects of estrogens on renal function.\textsuperscript{91,92} In particular, a prospective observational study in women with T1DM reported a strong association between use of oral contraceptives and development of macroalbuminuria.\textsuperscript{93} However, these adverse effects were absent in clinical trials using progestin-only\textsuperscript{94} or low-dose contraceptives,\textsuperscript{95} suggesting the dose, formulation, duration of treatment, and likely underlying disease state play a role in determining the overall effect of hormone use in a specific patient population.

In addition to females, treatment with E\textsubscript{2} has also been reported to be effective in males. Specifically, administration of E\textsubscript{2} in doses that adjusted the estrogen/androgen ratio to that observed in females reduced glomerulosclerosis, collagen IV deposition, and albuminuria, and prevented hyperfiltration orchiectomized cyclic adenosine monophosphate early repressor transgenic mice.\textsuperscript{71} In contrast, inhibition of estradiol synthesis using an aromatase inhibitor anastrozole partially attenuated renal injury in male streptozotocin-induced diabetic rats,\textsuperscript{96} which are characterized by increased estradiol and decreased testosterone levels.\textsuperscript{97} Interestingly, addition of dihydrotestosterone to anastrozole provided additional beneficial effects over anastrozole treatment alone, suggesting that restoring hormonal balance, rather than targeting one hormone in isolation, may be an effective strategy for the treatment of DKD.

Further providing support for the association between sex hormones and DKD are observations that age at menarche and puberty play a role in determining risk of DKD. Specifically, DKD rarely occurs before puberty, and the onset of puberty accelerates DKD.\textsuperscript{98} Women with delayed menarche have a 2.30 (95% CI, 1.27-4.17) times higher risk of DKD compared with the women who undergo menarche at an earlier age.\textsuperscript{99} These data suggest that female sex as a protective factor against the development of DKD may be abolished if diabetes onset is before or during puberty, thus implicating hormonal changes in the development of DKD.
Sex Differences in the Regulation of Key Biological Pathways Associated With DKD

Several studies have shown that the activity and the expression of various components of the renin-angiotensin system in the diabetic kidney differ by sex. Specifically, renal angiotensinogen and renin levels are higher in the male streptozotocin-induced diabetic rats compared with females. Differential expression of the angiotensin-converting enzyme and angiotensin AT₁ and AT₂ receptors have also been observed in various models of DKD, however, most of these studies only provide correlative data supporting the importance of sex in the pathophysiology of DKD. Further studies are warranted to directly examine the causative relationship and physiological significance of these observations.

A study in the Zucker diabetic rat has found that males have higher levels of endothelial nitric oxide synthase protein expression in glomeruli than females, most likely an attempt to increase nitric oxide levels and vasodilation. Several other studies in experimental models of DKD have shown differential expression of the components of the transforming growth factor beta and heme oxygenase pathways and inflammatory cytokines between the sexes. Most of these studies provide evidence for the protective effect of the female sex against DKD and the role of sex hormones, estrogens mostly, in regulating pathways known to be activated in the pathophysiology of DKD. Whereas additional studies in experimental models are needed, mechanistic studies in humans are the logical next step toward fully understanding the role of sex in DKD. In addition to sex hormones, the contribution of other factors, particularly epigenetic and genetics factors, should also be explored.

Sex Differences in Renal Hemodynamics

Renal hyperperfusion and hyperfiltration are risk factors for the initiation and progression of DKD. They occur as a consequence of early changes in intrarenal hemodynamic function, including increased renal plasma flow and glomerular pressure. Adolescents with both T1DM and T2DM have greater prevalence of hyperfiltration compared with age-matched boys. A recent study examining the mechanisms behind this observation reported that normotensive, normoalbuminuric girls with T1DM with hyperfiltration had higher derived efferent arteriolar resistance and filtration fraction and lower effective renal plasma flow compared with age-matched boys with no associated sex differences in afferent arteriolar resistances. In the Treatment Options for T2DM in Adolescents and Youth (TODAY) study, girls had higher eGFR levels at baseline compared with boys, and a three-fold greater risk of developing hyperfiltration over 5 years, even after adjustment for age, ethnicity, treatment group, body mass index, HbA₁c, hypertension, glycemic control, and estimated insulin sensitivity. This evidence for the role of sex the regulation of renal hemodynamics comes from experimental models and studies in adolescents in early stages of DKD. Studies examining the impact of sex on renal hemodynamic changes associated with advanced stages of DKD are clearly needed.

CONCLUSION

It is generally acknowledged that premenopausal, nondiabetic women are relatively protected from renal disease and that this protection is lost in menopause and in the setting of diabetes. However, whether or not sex differences exist in DKD associated with either T1DM or T2DM remain unclear, with evidence to support either higher DKD risk in men, women, or no sex differences at all. Much of the discrepancies in the reports are related to differences in the patient populations studied (eg, geographic diversity, age, duration of diabetes, etc), type of diabetes (some studies do not differentiate between T1DM and T2DM), study design and analysis, and existence of confounding factors (menopause and hormone replacement) that independently affect DKD progression in men and women. The disparate observations arising from these studies highlight the need for prospective studies specifically designed to address sex differences in DKD. Such a study would take into account factors such as age, duration of diabetes, hormonal status, and history of hormone therapy use, etc, in its design. In addition, mechanistic studies addressing sex differences in the pathophysiology of DKD are also important.
needed. Although sex hormones are presumed to be the main factor underlying sex differences, genetic and epigenetic factors, among others, are also likely to contribute and warrant consideration. Understanding these mechanisms may lead to not only better understanding of disease pathophysiology, but also may lead to improved diagnosis, treatment, and overall quality of care in both women and men.

Abbreviations and Acronyms: DKD = diabetic kidney disease; E2 = 17β-estradiol; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HbA1c = hemoglobin A1C; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

Potential Competing Interests: Dr. Maric-Bilkan is an employee of the Federal Government.

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Thematic Reviews on Women’s Health will continue in an upcoming issue.

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