



Published in final edited form as:

Am J Nephrol. 2012 ; 36(3): 245–251. doi:10.1159/000342210.

Risk factor, age and sex differences in chronic kidney disease prevalence in a diabetic cohort: The Pathways Study

Margaret K. Yu, MD^{1,2,4}, Courtney Rees Lyles, PhD³, Luis A. Bent-Shaw, MD^{1,4}, Bessie A. Young, MD, MPH^{1,3,4,5}, and the Pathways Authors

¹Division of Nephrology, University of Washington, Seattle, Washington, USA

²Department of Epidemiology, University of Washington, Seattle, Washington, USA

³Department of Health Services, University of Washington, Seattle, Washington, USA

⁴Kidney Research Institute, Seattle, Washington, USA

⁵Epidemiology Research and Information Center, Veterans Affairs Puget Sound Health Care System, Seattle, Washington, USA

Abstract

Background/Aims—Women with diabetes experience a disproportionately greater burden of diabetic kidney disease (DKD) risk factors compared to men, however sex-specific differences in DKD are not well defined. The effect of age on sex differences in DKD is unknown.

Methods—We performed a cross-sectional analysis of the prevalence of DKD (eGFR <60 ml/min/1.73m² or microalbuminuria), advanced DKD (eGFR <30 ml/min/1.73 m²), and common DKD risk factors in the Pathways Study (*N*= 4,839), a prospective cohort study of diabetic patients from a managed care setting. Subjects were stratified by age <60 and ≥60 years to examine for differences by age. Logistic regression models examined the association between sex and prevalence of DKD and risk factors.

Results—Women of all ages had 28% decreased odds of DKD (OR 0.72, 95% CI 0.62–0.83); however, they had a greater prevalence of advanced DKD (OR 1.67, 95% CI 1.05–2.64), dyslipidemia (OR 1.42 95% CI 1.16–1.74), and obesity (OR 1.87, 95% CI 1.60–2.20) compared to men. Women had similar odds of hypertension and poor glycemic control as men. Women ≥60 years had increased odds of advanced DKD, hypertension, dyslipidemia, and obesity compared to similarly aged men. Women <60 years had increased odds of obesity compared to their male counterparts.

Conclusion—Women with diabetes had an increased prevalence of advanced DKD and common DKD risk factors compared to men and these disparities were most prominent amongst the elderly.

Keywords

sex difference; gender difference; diabetic kidney disease

Corresponding Author: Bessie A. Young, MD, MPH, 1660 S. Columbian Way RDU 111A, Seattle, WA 98108, Phone (206) 277-3586; Fax (206) 543-2346; youngb@u.washington.edu.

Disclosure: All the authors declared no competing interests.

Introduction

Diabetes mellitus is the leading cause of kidney failure in the United States and is associated with substantial morbidity, mortality, and health care [1]. The lifetime risk of diabetes is greater in women than in men [2] and women with diabetes have a greater prevalence of diabetic kidney disease (DKD) risk factors including hypertension [3, 4], hyperglycemia [4, 5], dyslipidemia [3–7], and obesity [4]; however, whether women have a greater prevalence of DKD is unclear. Age appears to modify the association between sex and nondiabetic kidney disease. In a large meta-analysis of nondiabetic kidney disease, Neugarten et al. found that men had more rapid renal decline compared to women [8], however a subsequent study of older subjects of postmenopausal age found that women had a faster progression of renal disease compared to men [9]. Whether there are analogous differences by age in DKD remains unknown.

Female sex has been associated with a higher risk of retinopathy and neuropathy in type 1 diabetes [10]. The effect of sex on nephropathy is not well established, however estrogen has several effects on the kidney that may be renoprotective [11]. Estrogen deficiency accelerates the progression of glomerulosclerosis in ovariectomized mice [12] and conversely, estrogen supplementation in postmenopausal women has been shown to reduce albuminuria [13]. Furthermore, fibroblast growth factor-23 (FGF-23) levels, which predicts progression to chronic kidney disease, are higher in postmenopausal women who are not on hormone replacement compared to postmenopausal women on hormone replacement or men [14]. Women with diabetes have lower levels of estradiol compared to nondiabetic women [15] and postmenopausal women with diabetes may represent a high-risk group for DKD.

In the current study, we examined the association of sex and age on the prevalence of DKD and DKD risk factors in a large cohort of outpatient diabetic patients from a vertically integrated managed care setting. We hypothesized that DKD would be more prevalent in women with diabetes compared to men and that these sex differences in DKD would be most prominent in elderly women. Additionally, we hypothesized that women with diabetes would have a higher frequency of DKD risk factors such as hypertension, dyslipidemia, and obesity compared to men with diabetes.

Methods

Study Population

We performed a cross-sectional analysis of baseline data from the Pathways Study, which has been described previously [16, 17]. In brief, the Pathways Study is a prospective epidemiologic survey of the prevalence and impact of depression on patients with diabetes at Group Health (GH), a large nonprofit health maintenance organization (HMO) in Washington and Idaho, USA, currently with over 500,000 enrollees. The study protocol was reviewed and approved by the institutional review boards at GH and the University of Washington. Nine primary care clinics were chosen for patient recruitment based on clinic size, racial/ethnic diversity, and proximity to Seattle, WA. From these selected clinics, 9,064 potential candidates for the study were identified from the GH diabetes registry. Between 2001–2002, surveys were sent to these patients regarding demographic information, diabetes history, and diabetes complications (retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, or metabolic). Of those identified, 1,222 patients were excluded from the study for the following reasons: no diabetes, gestational diabetes, cognitive impairment, severe illness, deceased, disenrollment from GH, or language/hearing problems. Of the remaining 7,842 patients eligible for the study, 4,839 (61.7%) returned the survey of which 4,467 (92.3%) gave permission to link survey data with automated data

from GH. Patients with a history of end-stage renal disease (ESRD) ($n = 67$) were excluded from these analyses, leaving a total of 4,400 subjects for this study.

Measurements

Automated data from GH provided information regarding laboratory tests, hospitalizations, and outpatient visits up to 18 months prior as well as pharmacy records regarding medication use up to 12 months prior to study enrollment. The average creatinine or albuminuria result was used if subjects had multiple measurements within this time frame. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equations [18]. Microalbuminuria was defined as urine albumin to creatinine ratio ≥ 17 mg/g for men and ≥ 25 mg/g for women, using previously defined sex-specific cutoffs [19]. Patients with hypertension were identified by *International Classification of Diseases, Ninth Revision* diagnosis codes [20]. Body mass index (BMI) was calculated from self-reported height and weight (kg/m^2).

Outcomes

The primary outcomes were sex differences in the prevalence of DKD or advanced DKD at study enrollment, amongst the subset of subjects with serum creatinine testing in the 18 months prior to study enrollment ($n = 3,024$). We defined DKD as the presence of either an eGFR <60 mL/min/1.73 m² or microalbuminuria. Since a moderate decline in eGFR is normal in the elderly, we also looked at sex differences in the prevalence of advanced DKD as defined by an eGFR <30 mL/min/1.73 m². Secondary outcomes were sex differences in the baseline prevalence of the following DKD risk factors: (1) hypertension ($n = 4,400$), (2) poor glycemic control (hemoglobin A1c $\geq 8.5\%$, $n = 4,140$), (3) dyslipidemia (low-density lipoprotein (LDL) >130 mg/dL, $n = 3,043$), and (4) obesity (BMI ≥ 30 kg/m², $n = 4,690$). The number of subjects in each analysis differs due to missing laboratory data.

Statistical Analyses

Statistical analyses were performed using Stata version 12 (StataCorp, College Station, TX, USA). Significant sex differences in primary and secondary outcomes were determined using independent t tests allowing for unequal variances and χ^2 tests. Logistic regression models were used to determine if there were associations between sex and DKD prevalence and risk factors. Given the high frequency missing LDL values (30.8%), imputed LDL (using age, sex, race, education, chronic kidney disease (CKD) stage, hypertension, hemoglobin A1c, and BMI) was used only for the purposes of adjustment in regression models. *A priori*, all models were adjusted for age, race/ethnicity, education, and smoking. Models for DKD were additionally adjusted for hemoglobin A1c, imputed LDL, and BMI; hypertension was not included as a covariate because of its collinearity with the outcome. Models for DKD risk factors were additionally adjusted for CKD stage and each of the other DKD risk factors. An interaction term between sex and age was examined in exploratory analyses of unstratified data and found to be significant ($P < 0.05$) in the models for hypertension and dyslipidemia, therefore these effects are only presented in age-stratified models. To further examine differences by age, stratified analyses by age <60 and ≥ 60 years were conducted. Age ≥ 60 was used as a cutoff since prior studies in the literature found that $>99\%$ of women were post-menopausal by the age of 57 [14]. Age-stratified analyses were adjusted for the same covariates as the unstratified analyses, with the exception of age, which was felt to be overadjustment as addition of age into these models resulted in similar point estimates but wider confidence intervals. All analyses were also repeated in the subset of patients with type 2 diabetes, which resulted in similar results as in the entire cohort; therefore, results are presented combined for all outcomes.

Results

Pathways Cohort Characteristics

Of the 4,400 subjects in the final cohort, 49.0% were women (Table 1). Men tended to be older, married, and had higher levels of education and income than women. Among enrollees, racial composition was similar between sexes and was comprised of approximately 23.3% ethnic minorities. The prevalence of smoking was similar by sex. Overall, 11.6% of participants had type 1 diabetes. Mean duration of diabetes, hemoglobin A1c, and insulin use did not differ between men and women. Men had a higher mean number of diabetic complications compared to women (1.4 vs. 1.2, $P<0.001$).

Prevalence of DKD and Advanced DKD

Compared to women, men had higher mean serum creatinine (1.17 vs. 0.92 mg/dL, $P<0.001$), lower mean eGFR (71.5 vs. 74.4 mL/min/1.73 m², $P<0.001$), and a greater prevalence of microalbuminuria (46.5% vs. 33.9%, $P<0.001$). DKD was more prevalent in men compared to women (56.9% vs. 49.6%, $P<0.001$). However, advanced DKD was more prevalent in women compared to men (3.6% vs. 2.3%, $P=0.04$). In adjusted logistic regression models, women had 28% decreased odds of DKD (OR 0.72, 95% CI 0.62–0.83) but 67% increased odds of advanced DKD (95% CI 1.05–2.64) compared to men (Table 3).

Prevalence of DKD Risk Factors

Women had a greater prevalence of hypertension compared to men (44.5% vs. 40.3%, $P=0.004$). Glycemic control was similar between men and women; approximately 25% of participants had a hemoglobin A1c $\geq 8.5\%$. Compared to men, women had higher mean LDL (116.0 vs. 108.1 mg/dL, $P<0.001$) and a greater prevalence of LDL >130 mg/dL (32.1% vs. 23.5% $P<0.001$). Moreover, women were more obese than men (mean BMI 32.4 vs. 29.7 kg/m², $P<0.001$). In multivariable logistic regression models for DKD risk factors, women had 87% greater odds of obesity (95% CI 1.60–2.20) but similar odds of poor glycemic control compared to men (OR 1.00, 95% CI 0.83–1.19).

DKD and Risk Factor Prevalence Stratified by Sex and Age

Men had a greater prevalence of DKD compared to women in both age groups (Table 2). Women ≥ 60 years old had a greater prevalence of advanced DKD (5.2% vs. 3.3%, $P=0.04$), hypertension (54.0% vs. 46.8%, $P<0.001$), and dyslipidemia (29.6% vs. 19.5%, $P<0.001$) compared to men of the same age; younger subjects had no sex differences in these factors. Women were significantly more obese than men in both age groups. Glycemic control was similar between men and women in both age groups.

In multivariable logistic regression models, women had decreased odds of DKD compared to men of the same age (<60 years: OR 0.66, 95% CI 0.52–0.85; ≥ 60 years: OR 0.75, 95% CI 0.62–0.91) (Figure 1). Women ≥ 60 years had 63% greater odds of advanced DKD (95% CI 1.01–2.63), 22% greater odds of hypertension (95% CI 1.00–1.48), and 67% greater odds of dyslipidemia (95% CI 1.28–2.19) compared to men of the same age; there were no sex-specific differences in these factors in subjects <60 years. Women in both age groups had approximately 2-fold greater odds of obesity compared their male counterparts. There were no age-stratified differences in glycemic control in the regression models.

Discussion

In this analysis of patients with diabetes from a managed care setting, we found that women had a greater prevalence of advanced DKD, hypertension, dyslipidemia, and obesity than men. These sex-specific differences were primarily accounted for by subjects ≥ 60 years old.

To our knowledge, this is the first study to report the effect of age on sex-associated differences in DKD.

While it is generally accepted that women are at reduced risk of nondiabetic kidney disease, sex differences in DKD are less clear. We found that although men with diabetes had a greater prevalence of microalbuminuria, women with diabetes were at increased odds of advanced renal dysfunction. Other studies have likewise suggested that women with diabetes have a high prevalence of impaired eGFR. In a population-based study of 3,288 patients with diabetes in the United Kingdom, women had a greater prevalence of eGFR <60 ml/min/1.73 m² compared to men, based on the Modification of Diet in Renal Disease (MDRD) study equation [21]. The UK Prospective Diabetes Study 74 (UKPDS) found that although men with diabetes had a higher risk of microalbuminuria, women with diabetes were at higher risk of Cockcroft-Gault estimated creatinine clearance <60 mL/min/1.73 m² [22]. In contrast, studies from Hong Kong [23] and Japan [24] reported a greater prevalence of DKD in men versus women, although this may be related to the racial/ethnic differences in the study populations. None of these previous studies used the CKD-EPI equations for estimating GFR, which has been shown to be more accurate than the MDRD equation in patients with diabetes [18].

Our study also found sex-related disparities in the prevalence of common DKD risk factors. Women in our study had a greater prevalence of dyslipidemia and obesity compared to men. Previous studies in academic [5], HMO [3], and population-based [7] settings have reported that women with diabetes were more likely to have hypertension and dyslipidemia compared to men. A cross-sectional multicenter study found that women with diabetes had higher blood pressure and LDL compared to men with diabetes [25]. Although other studies reported worse glycemic control in diabetic women compared to men [4, 5, 7, 25], we did not find any sex differences in this risk factor.

We found that age affected the association between sex and DKD. Women over the age of 60, the majority of whom were presumably post-menopausal, had higher odds of advanced DKD compared to men of the same age. We are not aware of any other studies that examined sex differences in DKD by age. We also found that elderly women had greater odds of common DKD risk factors such as hypertension and dyslipidemia compared to their male counterparts, and these associations were not observed in the younger subjects. This is similar to the findings by Nilsson et al. who reported that women with diabetes had worse blood pressure and glycemic control than men, and these differences were most prominent amongst patients over the age of 60; sex-related differences in eGFR were not examined in this study [6].

The mechanisms behind how age modifies DKD prevalence and risk factors may be related to hormonal changes that occur with aging. Estrogen affects the kidney by reduction of mesangial cell proliferation, increased activity of metalloproteinase enzymes and nitric oxide synthesis, changes in inflammation, decreased renin-angiotensin system activity, and decreased FGF-23 levels [11, 14]. Other potential mechanisms for sex differences in kidney disease may be related to differential renal hemodynamics, diet, kidney/glomerular size, and sex-specific genetic polymorphisms [26].

It is important to note limitations of this study. Our study population is an insured population, therefore generalizability of our results may be limited to those with similar access to health care. We had very few subjects <60 years with advanced DKD and this particular analysis was underpowered to detect sex-specific differences. Still, our study was large enough to identify sex differences in advanced DKD amongst subjects ≥ 60 years old and to perform age-stratified analyses for other outcomes. While our study did include a

small number of type 1 diabetic patients, the vast majority had type 2 diabetes, which is the largest growing population of patients developing DKD and ESRD (2). Although we did not have true GFR measurements, we used the CKD-EPI equations to estimate GFR which should be more accurate than the MDRD equation in this population.

In summary, our findings suggest that women with diabetes have an increased prevalence of advanced DKD and common DKD risk factors compared to men. These sex-related disparities were most prominent in elderly women, who represent a high-risk group for advanced stage DKD. Further studies are needed to determine whether these age and sex differences in DKD prevalence and risk factors translate into sex-specific differences in renal progression to ESRD.

Acknowledgments

Sources of Support: This work was supported by research grants by the National Institutes of Health National Institute of Diabetes, Digestive, and Kidney Diseases (DK079745, T32 007467) and National Institute of Mental Health (MH41739, MH01643). In addition, Dr. Young's contribution is supported by resources from the VA Puget Sound Health Care System, Seattle, Washington.

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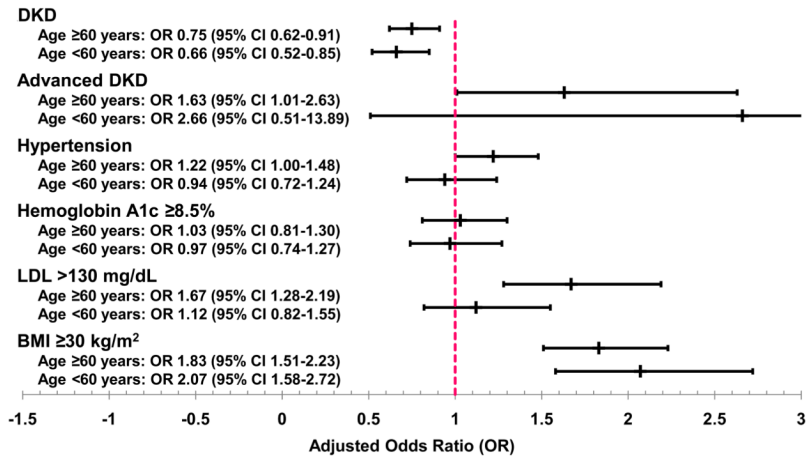


Figure 1. Adjusted odds of diabetic kidney disease (DKD) prevalence and risk factors for women compared to men, stratified by age. All models are adjusted for race/ethnicity, education, and smoking. DKD models are additionally adjusted for hemoglobin A1c, LDL, and BMI. DKD risk factor models are additionally adjusted for chronic kidney disease stage and each of the other risk factors. DKD = diabetic kidney disease; LDL = low-density lipoprotein; BMI = body mass index; OR = odds ratio; CI = confidence interval.

Table 1

Pathways cohort (n = 4,400) patient characteristics by sex.

Characteristic	Women n = 2,154	Men n = 2,246	p
<i>Age (years)</i>	62.6 ± 14.0	64.0 ± 12.6	<0.001
Age ≥ 60 years	1,245 (57.8)	1,419 (63.2)	<0.001
<i>Race</i>			0.45
Non-Hispanic white	1,642 (76.2)	1,733 (77.2)	
Non-Hispanic black	183 (8.5)	165 (7.4)	
Asian	199 (9.2)	200 (8.9)	
Other	130 (6.0)	148 (6.6)	
<i>Married</i>	1,130 (53.0)	1,750 (78.3)	<0.001
<i>>High school education</i>	1,525 (71.9)	1,758 (79.1)	<0.001
<i>Income \$20,000/year</i>	872 (52.2)	1,174 (62.2)	<0.001
<i>Smoker</i>	170 (8.1)	207 (9.3)	0.14
<i>DM history</i>			
Type 1 DM	242 (11.3)	270 (12.0)	0.44
Duration of DM (years)	9.3 ± 9.0	9.5 ± 9.3	0.50
Number of DM complications	1.2 ± 1.2	1.4 ± 1.3	<0.001
Hemoglobin A1c (%)	7.8 ± 1.5	7.8 ± 1.6	0.44
Hemoglobin A1c ≥ 8.5%	510 (25.2)	522 (24.7)	0.67
Insulin	658 (30.6)	648 (28.9)	0.22
Oral diabetic medications	1,251 (58.1)	1,378 (61.4)	0.03
<i>Renal function</i>			
Creatinine (mg/dL)	0.9 ± 0.4	1.2 ± 0.4	<0.001
eGFR (ml/min/1.73 m ²)	74.4 ± 23.3	71.5 ± 20.4	<0.001
Microalbuminuria	496 (33.9)	686 (46.5)	<0.001
DKD (eGFR <60 ml/min/1.73 m ² or microalbuminuria)	799 (49.6)	992 (56.9)	<0.001
Advanced DKD (eGFR <30 ml/min/1.73 m ²)	53 (3.6)	36 (2.3)	0.04
<i>Hypertension</i>	959 (44.5)	904 (40.3)	0.004
<i>Dyslipidemia</i>			
LDL (mg/dL)	116.0 ± 36.1	108.1 ± 33.4	<0.001
LDL >130 mg/dL	449 (32.1)	386 (23.5)	<0.001
<i>Obesity</i>			
BMI (kg/m ²)	32.4 ± 8.2	29.7 ± 5.7	<0.001
BMI ≥ 30 kg/m ²	1,192 (56.6)	932 (41.9)	<0.001

Data are mean ± standard deviation or n (%). DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; DKD = diabetic kidney disease; LDL = low-density lipoprotein; BMI = body mass index.

Table 2

Diabetic kidney disease and risk factor prevalence in the Pathways cohort by age and sex.

Outcome	Women	Men	p
<i>DKD (eGFR <60 ml/min/1.73 m² or microalbuminuria)</i>			
<60 years	268 (41.6)	294 (48.4)	0.01
60 years	531 (54.9)	698 (61.4)	0.002
<i>Advanced DKD (eGFR <30 ml/min/1.73 m²)</i>			
<60 years	6 (1.0)	2 (0.4)	0.20
60 years	47 (5.2)	34 (3.3)	0.04
<i>Hypertension</i>			
<60 years	287 (31.6)	240 (29.0)	0.25
60 years	672 (54.0)	664 (46.8)	<0.001
<i>Hemoglobin A1c ≥8.5%</i>			
<60 years	268 (31.6)	237 (30.9)	0.75
60 years	242 (20.6)	285 (21.1)	0.76
<i>LDL >130 mg/dL</i>			
<60 years	201 (35.8)	182 (30.5)	0.05
60 years	248 (29.6)	204 (19.5)	<0.001
<i>BMI ≥30 kg/m²</i>			
<60 years	613 (69.0)	442 (53.8)	<0.001
60 years	579 (47.5)	490 (34.9)	<0.001

Data are number (%). DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; BMI = body mass index.

Table 3

Unadjusted and adjusted odds of diabetic kidney disease (DKD) prevalence and risk factors for women compared to men.

Outcome	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
<i>DKD (eGFR <60 ml/min/1.73 m² or microalbuminuria)</i>	0.74 (0.65–0.85)	0.72 (0.62–0.83)
<i>Advanced DKD (eGFR <30 ml/min/1.73 m²)</i>	1.55 (1.01–2.39)	1.67 (1.05–2.64)
<i>Hemoglobin A1c 8.5%</i>	1.03 (0.90–1.19)	1.00 (0.83–1.19)
<i>BMI 30 kg/m²</i>	1.81 (1.60–2.04)	1.87 (1.60–2.20)

DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; BMI = body mass index; OR = odds ratio; CI = confidence interval.

* All models are adjusted for age, race/ethnicity, education, and smoking. DKD models are additionally adjusted for hemoglobin A1c, LDL, and BMI. DKD risk factor models are additionally adjusted for chronic kidney disease stage and each of the other risk factors.