

Gender Differences in the Incidence of Nephropathy and Changes in Renal Function in Patients with Type 2 Diabetes Mellitus: A Retrospective Cohort Study

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Purpose: This research aims to examine and scrutinize gender variations in the incidence of diabetic nephropathy (DN) and the trajectory of renal function in type 2 diabetes mellitus (T2DM) patients.

Patients and Methods: We conducted a retrospective cohort study that enrolled 1549 patients diagnosed with T2DM from May 2015 to July 2023. We separately compared the clinical characteristics of male and female participants with and without DN. We utilized the Kaplan-Meier method to examine the cumulative incidence of DN among T2DM patients of varying genders. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using univariable and multivariable Cox proportional hazards regression analysis to evaluate the correlation between various factors and the risk of DN incidence. Multiple linear regression was utilized to investigate the relationship between Δ eGFR% and each factor. Logistic regression with cubic spline function and smooth curve fitting was employed to analyze the nonlinear link between Δ eGFR% and the risk of DN among participants of different genders.

Results: The prevalence of DN was higher in female participants (17.31%) than in male participants (12.62%), with a significant cumulative risk ratio (1.33 [1.02–1.73], $P = 0.034$). Multiple linear regression analysis revealed that creatinine, female gender, blood urea nitrogen, alkaline phosphatase, and total cholesterol had a significant impact on Δ eGFR% in T2DM patients, with standardized β coefficients of -0.325 , -0.219 , -0.164 , -0.084 , and 0.071 , respectively. The restricted cubic spline analysis demonstrated a strong negative association between Δ eGFR% and the risk of developing DN ($P < 0.001$).

Conclusion: Both male and female patients with T2DM had a higher prevalence of DN over the 5-year follow-up period. However, women had a greater risk of developing DN and a faster decline in renal function compared to men.

Keywords: gender differences, type 2 diabetes mellitus, nephropathy, renal function, glomerular filtration rate estimates

Introduction

Diabetes is a significant worldwide health threat, with 529 million people living with the disease globally in 2021. Based on an analysis conducted for the Global Burden of Disease Study (GBD Study 2021), the age-standardized prevalence of diabetes is 6.1%, with 96.0% of cases being type 2 diabetes mellitus (T2DM). It is estimated that the global population of individuals with diabetes will increase to 1.31 billion by 2050.¹ The increasing prevalence of diabetes is expected to lead to complications associated with the disease. T2DM increases the risk of both macrovascular and microvascular diseases.²

Diabetic nephropathy (DN) is a frequently occurring complication of diabetes, and diabetes is a significant risk factor in the advancement of kidney disease. People diagnosed with diabetes are at an extremely high risk of developing chronic kidney disease (CKD).^{3,4} The incidence of DN increases as the prevalence of diabetes rises.^{5,6} Research suggests that approximately 20% to 40% of diabetic patients develop DN.^{7–9} DN's primary clinical features are a reduced glomerular filtration rate and persistent albuminuria.¹⁰ Increased albuminuria and decreased glomerular filtration rate may lead to

end-stage renal disease. Presently, DN is a significant contributor to CKD, renal failure, and end-stage kidney disease (ESKD).^{11–15} Additionally, DN increases the risk of developing cardiovascular disease.¹⁶ There was a trend for increasing risk of cardiovascular death with increasing nephropathy.¹⁷ Progression of DN is associated with a significant reduction in life expectancy and quality of life for patients. All patients with T2DM and CKD should be treated with a comprehensive plan.¹⁸

Evidence suggests a notable gender disparity in both the prevalence and progression of T2DM. Worldwide, rates of T2DM are rising in both men and women, although men have a higher prevalence of the condition in 140 countries.¹ There are variations in complications of T2DM among men and women. Women with T2DM have a greater relative risk of cardiovascular disease and mortality as compared to men.^{19–22} Studies on the differences in microvascular disease between the genders are limited and inconclusive. Specifically, the association between gender and the development of nephropathy in patients with T2DM has been inadequately researched, and the presence of gender differences is yet to be determined. Men with T2DM have a higher risk of nephropathy compared to normoglycemic men. This risk is not apparent in women.²³ However, women have a higher risk of kidney failure and renal insufficiency in T2DM.²⁴ It has been reported that women have a higher risk of diabetic end-stage renal disease than men.²⁵ In addition, another study found that men with newly diagnosed diabetes and pre-diabetes are at an increased risk of developing chronic kidney disease.²⁶ Existing studies suggest inconclusive results, indicating an urgent need for further research.

This study analyzed gender disparities in the prevalence of DN and renal function trends among T2DM patients. It offers proof for diabetes care customization, implementing gender-specific prevention methodologies and management guidance.

Materials and Methods

Participants

This retrospective cohort study included participants diagnosed with T2DM who received care at Changzhou Third People's Hospital from May 2015 to July 2023. Patients under 18 years of age, with a history of malignancy, acute or chronic nephritis, IgA nephropathy, or other primary renal diseases, those who underwent renal occupancy surgery, pregnant patients, had less than five years of follow-up, or had incomplete data were excluded. The study enrolled 1549 participants and was conducted in accordance with the Declaration of Helsinki. It was approved by the Ethics Committee of Changzhou Third People's Hospital. Prior to the study, all participants completed an informed consent form.

Definition of diseases

T2DM was defined as either (1) a prior diagnosis by a medical professional, (2) a fasting blood glucose level of ≥ 7.0 mmol/L, (3) a glycosylated hemoglobin (HbA1c) level of $\geq 6.5\%$, or (4) the use of diabetic medications. Obesity was defined as a body mass index (BMI) of ≥ 28.0 kg/m². Hypertension was defined as systolic blood pressure (SBP) of ≥ 140 mmHg and/or diastolic blood pressure (DBP) of ≥ 90 mmHg. Dyslipidemia was defined based on abnormal levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), or a history of treatment for dyslipidemia. The study utilized the urinary albumin/creatinine ratio (UACR) to calculate kidney function. The estimated glomerular filtration rate (eGFR) was determined through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using measures of serum creatinine and serum cystatin C. Blood samples were taken in the fasting state to measure eGFR.²⁷ DN was diagnosed based on the criteria of UACR values greater than or equal to 30 mg/g and/or eGFR less than 60 mL/min/1.73m².³ Annual reassessment was conducted for DN diagnosis during the follow-up period.

Measured Values and Variables

Demographic characteristics, socioeconomic status, lifestyle factors, disease history, and medication use were obtained from each participant's medical records. Regular exercise was defined as participating in physical activity for at least 30 minutes at least three times per week. Education attainment was categorized as high school or above versus less than high school. Postmenopausal status was defined as a most recent menstrual period more than 12 months before the assessment. Participants' height and weight were measured regularly, and the BMI was determined by dividing weight by height

squared (kg/m^2). The waist circumference (WC) was measured at the midpoint between the rib edge and the ilium's upper edge at the expiration's end. The hip circumference (HC) was measured at the most prominent buttock point. The waist-to-hip ratio (WHR) was calculated by dividing WC (cm) by HC (cm). Participants were instructed to fast for 8–10 hours before providing early morning fasting venous blood samples. The blood samples were analyzed for levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), TC, TG, HDL-c, and LDL-c. Fasting plasma glucose (FPG) was assessed using a standardized clinical auto-analyzer, along with HbA1c, blood urea nitrogen (BUN), creatinine, uric acid (UA), and eGFR. The difference in eGFR from baseline at the fifth year of subject follow-up was expressed as ΔeGFR , and $\Delta\text{eGFR}\%$ represents the percentage of the above difference from baseline eGFR. Visceral fat area (VFA) was measured using the InBody770 (Biospace, Seoul, Korea).

Triglyceride-glucose (TyG) index was calculated using the following formula: $\text{Ln} [\text{TG (mg/dL)} \times \text{fasting plasma glucose (mg/dL)} / 2]$.²⁸

Lipid accumulation product (LAP) was calculated as: $\text{LAP} = (\text{WC (cm)} - 65) \times \text{TG (mmol/L)}$ for males, and $\text{LAP} = (\text{WC (cm)} - 65) \times \text{TG (mmol/L)}$ for females.²⁹

Statistical Analysis

Continuous variables were described using mean $\pm$ standard deviation (SD) or median (25th and 75th percentile), depending on normal distribution, assessed by the Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages. Differences in continuously distributed variables were compared using independent samples *t*-test, while non-normally distributed variables were analyzed using the Mann–Whitney *U*-test. Categorical variables were compared between groups using the chi-square test. Gender-stratified cumulative risk curves for DN were depicted using the Kaplan–Meier method at baseline and after five years of follow-up. A comparison of male and female groups was conducted using the Log rank test. We conducted univariate and multivariate Cox proportional risk regression analysis to estimate hazard ratios (HRs) and associated 95% confidence intervals (CIs) for each factor's association with DN incidence in different genders. We used multiple linear regression analysis to investigate the relationship between each factor and $\Delta\text{eGFR}\%$. After adjusting for age, we used cubic spline functions and smooth curve-fitted logistic regression to investigate the nonlinear relationship between $\Delta\text{eGFR}\%$ and the risk of DN in participants of different genders. We calculated inflection points using a recursive algorithm if a nonlinear relationship was observed. *P* values were considered significant (two-tailed) if they were below 0.05. All statistical analyses were performed using SPSS version 23.0 (SPSS, IBM, Corp., Armonk, NY, USA). We used GraphPad Prism v.9.0 (GraphPad Software, USA) to plot the figures.

Results

Research Subgroups

Initially, this study included 14,236 patients diagnosed with T2DM who received medical care at the Changzhou Third People's Hospital from May 2015 to July 2023. After excluding 12,373 patients who were under 18 years old, those with a history of malignancy, those with acute or chronic nephritis, IgA nephropathy, or other primary renal diseases, or those who had undergone renal occupancy surgery, those with less than five years of follow-up, and those with incomplete data, 1863 subjects met the study criteria. An additional 314 subjects with a diagnosis of DN at baseline were further excluded, leaving a final enrollment of 1549 participants. Out of the sample size, 1006 participants were male, and 543 were female. Among the female participants, the majority (73.5%) were postmenopausal. Only a small percentage of females (1.8%) reported using oestrogen-containing medication. To conduct the study, male and female participants were classified into two groups: one with DN based on its presence during the follow-up period and one without DN (non-DN) (Figure 1).

Comparison of Clinical Characteristics Between Male and Female Participants

In this study, female participants exhibited lower values of Height, Weight, BMI, WC, FPG, ALT, GGT, TG, BUN, creatinine, UA, eGFR, ΔeGFR , $\Delta\text{eGFR}\%$, and TyG. On the other hand, they showed higher values of AGE, VFA, TC, HDL-c, and LAP compared to male participants (all $P < 0.05$). It was found that female participants had

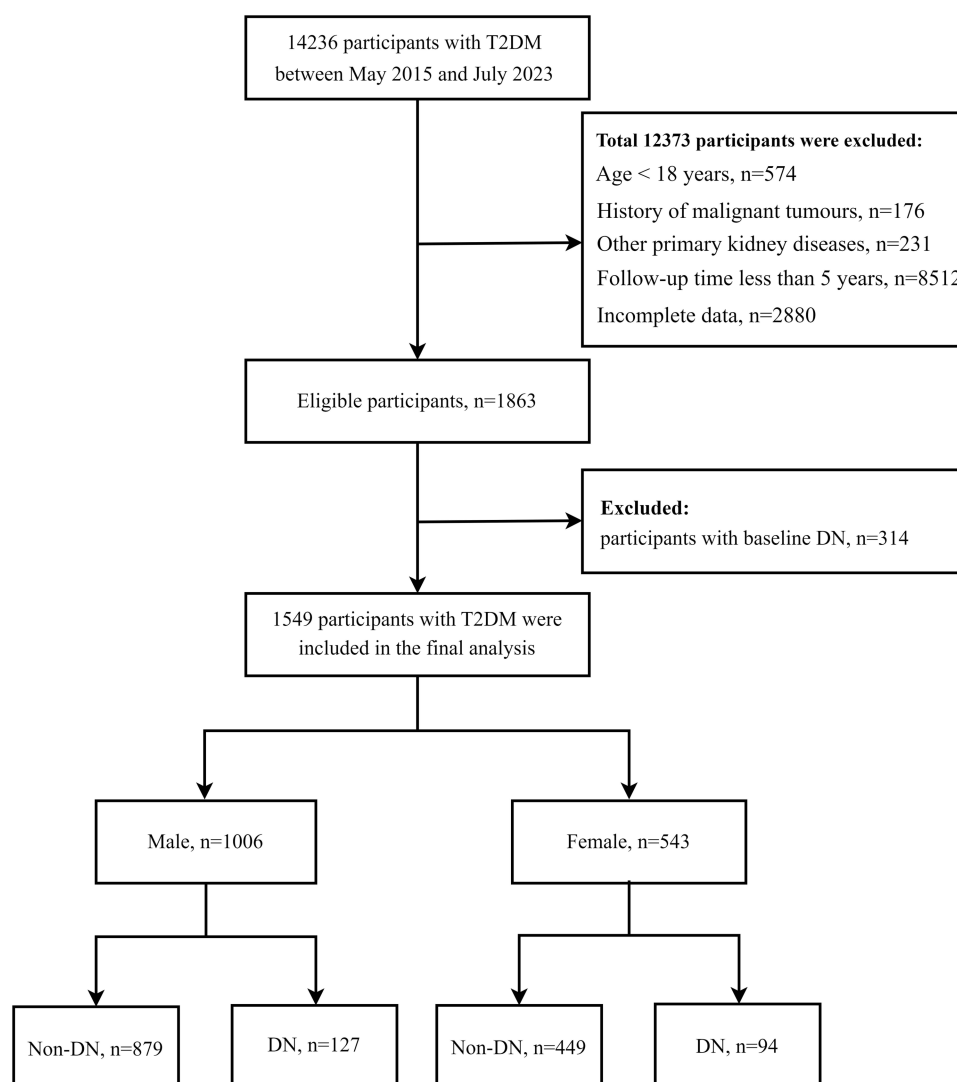


Figure 1 Study flowchart.

Abbreviations: T2DM, Type 2 diabetes mellitus; DN, Diabetic nephropathy.

lower levels of education and a smaller percentage of smoking and drinking histories compared to male participants. However, female participants had a higher proportion of regular physical activity. Additionally, female participants had a higher prevalence of dyslipidemia and a higher rate of anti-hypertensive and lipid-modifying medications but a lower rate of insulin use. Notably, the prevalence of nephropathy among female participants was higher (17.31%) than that among male participants (12.62%) ($P = 0.012$) (Table 1).

Comparison of Clinical Characteristics Between Male and Female Participants with and without DN

Among male participants, compared to those without DN, males with DN had higher FPG, AST, ALP, GGT, BUN, Creatinine, UA, and TyG values, while eGFR, Δ eGFR, and Δ eGFR% were lower (all $P < 0.05$). Male participant with DN were also observed to be older. Participants with DN had a significantly higher prevalence of hypertension compared to those without DN. Additionally, DN participants had lower levels of education and a higher percentage of smoking history. Participants with DN were also more likely to take oral hypoglycemic medications, insulin, and anti-hypertensive medications than those without DN.

Table 1 Clinical Characteristics of Overall Participants and Separated by Gender

Variables	Overall (n=1579)	Male (n=1006)	Female (n=543)	p
AGE (years)	51.00 (41.00, 61.00)	50.00 (40.00, 58.00)	55.00 (45.00, 65.00)	<0.001
Diabetes duration (years)	8.90 (7.50, 10.50)	8.90 (7.50, 10.50)	9.00 (7.50, 10.50)	0.684
Height (cm)	168.00 (162.00, 172.50)	169.00 (163.50, 174.00)	164.50 (157.50, 170.00)	<0.001
Weight (kg)	72.60 (63.10, 81.60)	74.60 (65.80, 82.60)	68.80 (59.25, 78.90)	<0.001
BMI (kg/m ²)	26.20 (23.20, 28.30)	26.20 (23.80, 28.67)	26.10 (22.50, 28.00)	0.028
WC (cm)	91.60 (83.80, 99.20)	92.40 (85.20, 100.00)	90.10 (82.50, 96.90)	<0.001
WHR	0.93 (0.90, 0.97)	0.93 (0.90, 0.97)	0.92 (0.90, 0.97)	0.206
VFA (cm ²)	93.20 (74.20, 125.90)	92.00 (71.12, 122.25)	95.80 (78.15, 133.10)	<0.001
FPG (mmol/L)	5.50 (5.10, 6.22)	5.50 (5.10, 6.25)	5.45 (5.00, 6.20)	0.007
HbA1c (%)	7.29 (7.25, 7.33)	7.29 (7.26, 7.33)	7.29 (7.25, 7.32)	0.361
ALT (U/L)	24.20 (17.00, 36.50)	26.15 (18.50, 38.10)	21.40 (15.35, 32.75)	<0.001
AST (U/L)	23.00 (19.00, 30.00)	23.00 (19.00, 30.00)	23.00 (19.00, 32.00)	0.269
ALP (U/L)	80.00 (65.00, 101.00)	80.00 (66.00, 98.00)	82.00 (64.00, 110.00)	0.346
GGT (U/L)	26.60 (17.30, 48.00)	28.80 (19.72, 51.00)	21.10 (13.60, 43.00)	<0.001
TC (mmol/L)	4.33 (3.78, 4.94)	4.27 (3.73, 4.83)	4.41 (3.95, 5.16)	<0.001
TG (mmol/L)	1.24 (0.81, 1.59)	1.29 (0.81, 1.64)	1.14 (0.80, 1.52)	0.016
HDL-c (mmol/L)	1.17 (1.01, 1.37)	1.14 (0.96, 1.27)	1.30 (1.15, 1.55)	<0.001
LDL-c (mmol/L)	2.66 (2.17, 3.18)	2.65 (2.17, 3.12)	2.68 (2.16, 3.23)	0.163
BUN (mmol/L)	5.25 (4.37, 6.22)	5.39 (4.47, 6.35)	5.05 (4.17, 5.95)	<0.001
Creatinine (μmol/L)	70.50 (58.60, 82.50)	77.00 (68.10, 87.00)	57.00 (50.30, 65.00)	<0.001
UA (μmol/L)	327.00 (273.10, 392.50)	352.80 (299.00, 410.10)	285.70 (240.10, 330.05)	<0.001
eGFR (mL/min/1.73m ²)	97.38 (80.83, 109.73)	98.40 (81.53, 111.74)	95.62 (79.51, 106.38)	0.001
ΔeGFR (mL/min/1.73m ²)	-3.15 (-11.61, 5.31)	-2.50 (-11.43, 7.67)	-4.09 (-11.89, 2.17)	<0.001
ΔeGFR%	-3.27 (-11.59, 5.71)	-2.30 (-11.30, 8.25)	-4.28 (-12.24, 2.16)	<0.001
LAP	33.23 (20.52, 51.81)	31.77 (18.82, 51.24)	35.28 (22.97, 53.15)	0.004
TyG	8.48 (8.08, 8.84)	8.51 (8.10, 8.87)	8.39 (8.04, 8.79)	0.001
Nephropathy, n (%)	221 (14.27%)	127 (12.62%)	94 (17.31%)	0.012
Obesity, n (%)	467 (30.15%)	312 (31.01%)	155 (28.55%)	0.312
Hypertension, n (%)	447 (28.86%)	283 (28.13%)	164 (30.20%)	0.391
Dyslipidemia, n (%)	378 (24.40%)	226 (22.47%)	152 (27.99%)	0.016
Smoking history, n (%)	604 (38.99%)	567 (56.36%)	37 (6.81%)	<0.001
Alcohol history, n (%)	323 (20.85%)	289 (28.73%)	34 (6.26%)	<0.001
Regular exercise habits, n (%)	376 (24.27%)	216 (21.47%)	160 (29.47%)	<0.001
High school education or above, n (%)	757 (48.87%)	538 (53.48%)	219 (40.33%)	<0.001
Oral hypoglycemic medication use, n (%)	1249 (80.63%)	825 (82.01%)	424 (78.08%)	0.062
Insulin use, n (%)	710 (45.84%)	481 (47.81%)	229 (42.17%)	0.034
Anti-hypertensive medication use, n (%)	310 (20.01%)	186 (18.49%)	124 (22.84%)	0.041
Lipid-modifying medication use, n (%)	173 (11.17%)	97 (9.64%)	76 (14.00%)	0.009

Notes: Data is presented as median (25th, 75th percentiles) or percentages, with $p < 0.05$ considered statistically significant.

Abbreviations: BMI, Body mass index; WC, Waist circumference; WHR, Waist to hip ratio; VFA, Visceral fat area; FPG, Fasting plasma-glucose; HbA1c, Hemoglobin A1c; ALT, Alanine transaminase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; GGT, Glutamyl transferase; TC, Total cholesterol; TG, Triglyceride; HDL-c, High density lipoprotein cholesterol; LDL-c, Low density lipoprotein cholesterol; BUN, Blood urea nitrogen; UA, Uric acid; eGFR, Estimated glomerular filtration rate; Δ, Difference in eGFR between baseline and the fifth year of follow-up; LAP, Lipid accumulation product; TyG, Triglyceride and glucose index.

Among female participants, compared to those without DN, those with DN were older and exhibited higher levels of HbA1c, AST, ALP, GGT, BUN, creatinine, and UA values. At the same time, BMI, TC, eGFR, ΔeGFR, and ΔeGFR% were lower than those observed in female participants without DN (all $P < 0.05$). We also observed comparable trends and some distinctive characteristics. Participants with DN had a longer duration of diabetes compared to those without DN. Regarding comorbidities, the prevalence of both obesity and hypertension was significantly higher in participants with DN than in those without DN. Similar to male participants, female participants with DN had lower educational attainment and a higher rate of smoking history. Regarding medication use, female participants with DN not only had

higher rates of taking oral hypoglycemic medications and using insulin but also had significantly higher rates of using anti-hypertensive and lipid-modifying medications compared to those who did not have DN (Table 2).

Cumulative Incidence of DN

During the follow-up period, DN was diagnosed in 94 females (17.31%) and 127 males (12.62%), with incidence rates of 3.46 and 2.52 per 100 patients per year in females and males, respectively. The cumulative incidence risk for DN in females was significantly higher than in males, with a hazard ratio of 1.33 (95% CI 1.02–1.73), log-rank $P = 0.034$ (Figure 2).

Table 2 Clinical Characteristics of the Study Participants Classified by the Presence of Different Gender and Incidence of Diabetic Nephropathy

Variables	Male (n=1006)			Female (n=543)		
	Non-DN (n=879)	DN (n=127)	p	Non-DN (n=449)	DN (n=94)	p
AGE (years)	48.00 (39.00, 56.00)	61.00 (52.00, 70.00)	<0.001	53.00 (43.00, 61.00)	67.00 (61.00, 74.00)	<0.001
Diabetes duration (years)	8.90 (7.50, 10.50)	8.90 (7.55, 10.40)	0.775	8.90 (7.40, 10.40)	9.45 (7.95, 11.07)	0.009
Height (cm)	169.50 (163.50, 174.00)	168.50 (163.25, 172.50)	0.05	163.50 (157.00, 170.50)	165.75 (158.00, 168.88)	0.877
Weight (kg)	75.10 (65.80, 83.15)	71.20 (65.80, 80.30)	0.014	69.20 (59.10, 80.00)	67.10 (61.37, 73.30)	0.118
BMI (kg/m ²)	26.20 (23.90, 28.75)	26.10 (23.05, 28.10)	0.237	26.20 (22.50, 28.10)	24.90 (22.50, 27.17)	0.023
WC (cm)	93.00 (85.25, 100.70)	91.50 (84.60, 98.60)	0.139	90.10 (82.50, 98.30)	91.50 (83.93, 96.10)	0.592
WHR	0.93 (0.90, 0.97)	0.94 (0.90, 0.98)	0.873	0.92 (0.89, 0.97)	0.93 (0.91, 0.98)	0.072
VFA (cm ²)	92.00 (71.50, 122.10)	95.00 (70.00, 125.20)	0.545	95.00 (77.00, 135.10)	97.00 (78.72, 132.70)	0.798
FPG (mmol/L)	5.49 (5.10, 6.11)	6.01 (5.20, 6.91)	<0.001	5.40 (5.00, 6.01)	5.70 (5.00, 6.66)	0.148
HbA1c (%)	7.29 (7.26, 7.33)	7.30 (7.27, 7.33)	0.260	7.29 (7.25, 7.32)	7.31 (7.26, 7.33)	0.005
ALT (U/L)	26.70 (18.70, 38.00)	24.50 (16.65, 38.30)	0.234	21.50 (15.80, 33.00)	20.55 (13.77, 31.45)	0.333
AST (U/L)	23.00 (19.00, 29.00)	25.00 (19.50, 38.00)	0.017	22.00 (18.00, 30.00)	28.00 (21.00, 40.00)	<0.001
ALP (U/L)	78.00 (65.50, 96.50)	91.00 (70.00, 126.00)	<0.001	80.00 (62.00, 103.00)	92.50 (72.25, 124.75)	<0.001
GGT (U/L)	27.90 (19.30, 48.00)	40.70 (23.90, 66.80)	<0.001	20.30 (13.20, 39.90)	27.00 (16.95, 59.26)	0.002
TC (mmol/L)	4.27 (3.73, 4.83)	4.31 (3.70, 4.71)	0.648	4.52 (3.95, 5.22)	4.30 (3.96, 4.61)	0.026
TG (mmol/L)	1.27 (0.80, 1.66)	1.40 (0.93, 1.47)	0.172	1.11 (0.80, 1.57)	1.33 (0.88, 1.46)	0.698
HDL-c (mmol/L)	1.12 (0.96, 1.28)	1.16 (1.02, 1.24)	0.346	1.32 (1.15, 1.56)	1.21 (1.15, 1.46)	0.067
LDL-c (mmol/L)	2.65 (2.17, 3.15)	2.66 (2.08, 2.81)	0.310	2.70 (2.17, 3.25)	2.65 (2.09, 2.73)	0.069
BUN (mmol/L)	5.27 (4.39, 6.13)	6.68 (5.39, 9.16)	<0.001	4.92 (4.09, 5.71)	5.92 (4.86, 8.89)	<0.001
Creatinine (μmol/L)	75.40 (67.10, 83.60)	104.20 (82.85, 122.50)	<0.001	55.60 (49.20, 61.40)	73.32 (59.00, 92.75)	<0.001
UA (μmol/L)	351.50 (299.30, 405.45)	375.40 (296.25, 477.00)	0.001	278.80 (235.20, 322.70)	324.05 (269.18, 416.07)	<0.001
eGFR (mL/min/1.73m ²)	101.19 (88.19, 114.33)	58.87 (52.14, 74.62)	<0.001	99.36 (87.80, 107.99)	57.95 (51.60, 67.89)	<0.001
ΔeGFR (mL/min/1.73m ²)	-1.22 (-9.94, 8.81)	-10.05 (-21.33, -1.96)	<0.001	-2.76 (-9.11, 3.41)	-16.78 (-27.52, -6.10)	<0.001
ΔeGFR%	-1.23 (-9.49, 9.37)	-14.49 (-29.90, -3.07)	<0.001	-2.59 (-9.24, 3.14)	-22.06 (-32.64, -8.18)	<0.001
LAP	31.71 (18.72, 52.14)	32.37 (19.45, 45.66)	0.922	34.62 (22.80, 53.77)	36.04 (23.09, 49.11)	0.878
TyG	8.49 (8.09, 8.86)	8.66 (8.29, 8.99)	0.013	8.38 (8.03, 8.78)	8.46 (8.10, 8.83)	0.334
Obesity, n (%)	274 (31.17%)	38 (29.92%)	0.776	90 (20.04%)	65 (69.15%)	<0.001
Hypertension, n (%)	193 (21.96%)	90 (70.87%)	<0.001	97 (21.60%)	67 (71.28%)	<0.001
Dyslipidemia, n (%)	199 (22.64%)	27 (21.26%)	0.728	123 (27.39%)	29 (30.85%)	0.497
Smoking history, n (%)	479 (54.49%)	88 (69.29%)	0.002	25 (5.57%)	12 (12.77%)	0.012
Alcohol history, n (%)	253 (28.78%)	36 (28.35%)	0.919	29 (6.46%)	5 (5.32%)	0.678
Regular exercise habits, n (%)	184 (20.93%)	32 (25.20%)	0.274	129 (28.73%)	31 (32.98%)	0.411
High school education or above, n (%)	507 (57.68%)	31 (24.41%)	<0.001	209 (46.55%)	10 (10.64%)	<0.001
Oral hypoglycemic medication use, n (%)	712 (81.00%)	113 (88.98%)	0.029	343 (76.39%)	81 (86.17%)	0.037
Insulin use, n (%)	398 (45.28%)	83 (65.35%)	<0.001	179 (39.87%)	50 (53.19%)	0.017
Anti-hypertensive medication use, n (%)	110 (12.51%)	76 (59.84%)	<0.001	74 (16.48%)	50 (53.19%)	<0.001
Lipid-modifying medication use, n (%)	87 (9.90%)	10 (7.87%)	0.470	56 (12.47%)	20 (21.28%)	0.025

Notes: Data is presented as median (25th, 75th percentiles), with $p < 0.05$ considered statistically significant.

Abbreviations: BMI, Body mass index; WC, Waist circumference; WHR, Waist to hip ratio; VFA, Visceral fat area; FPG, Fasting plasma-glucose; HbA1c, Hemoglobin A1c; ALT, Alanine transaminase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; GGT, Glutamyl transferase; TC, Total cholesterol; TG, Triglyceride; HDL-c, High density lipoprotein cholesterol; LDL-c, Low density lipoprotein cholesterol; BUN, Blood urea nitrogen; UA, Uric acid; eGFR, Estimated glomerular filtration rate; Δ, Difference in eGFR between baseline and the fifth year of follow-up; LAP, Lipid accumulation product; TyG, Triglyceride and glucose index.

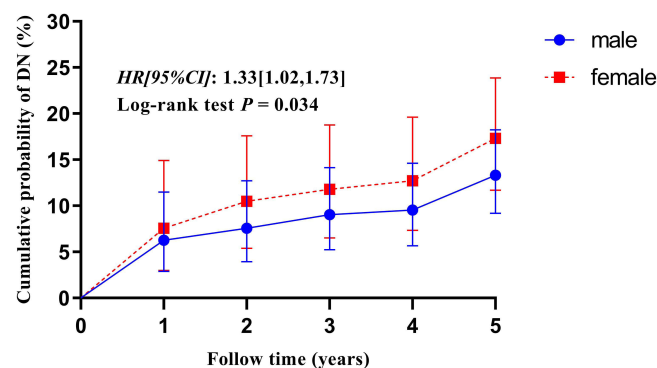


Figure 2 Cumulative prevalence of diabetic nephropathy (DN) according to different gender. The cumulative hazard curve for DN is presented through the Kaplan-Meier method, with gender stratification (using blue and red lines to represent males and females, respectively), over the course of five years. A Log rank test was used to compare the male and female groups.

Abbreviations: HR, Hazard ratios; CI, confidence interval.

Study on the Correlation of Factors in the Development of DN by Gender

Univariate and multivariate Cox proportional risk regression analyses were used to explore the association of factors with the incidence of DN in different genders. In males, AGE, Creatinine, UA, Δ eGFR%, TyG, and hypertension were significantly associated with the incidence of DN (all $P < 0.05$) as per Table 3. As per Table 4, AGE, BUN, Creatinine, Δ eGFR%, and diabetes duration were significantly associated with the incidence of DN in females (all $P < 0.05$).

Table 3 Univariate and Multivariate Cox Proportional Hazards Regression Analyses for the Association Between Various Factors and Incident Diabetic Nephropathy in Male

Variables	Univariate		Multivariate	
	HR [95% CI]	p	HR [95% CI]	p
AGE	1.07 (1.05, 1.08)	<0.001	1.03 (1.01, 1.05)	0.005
Height	0.97 (0.95, 0.99)	0.018		
Weight	0.99 (0.97, 0.99)	0.050		
BMI	0.98 (0.94, 1.02)	0.359		
WC	0.99 (0.97, 1.01)	0.210		
WHR	0.87 (0.04, 18.35)	0.928		
VFA	1.00 (1.00, 1.01)	0.337		
FPG	1.17 (1.09, 1.25)	<0.001		
HbA1C	0.99 (0.86, 1.14)	0.921		
ALT	1.00 (1.00, 1.01)	0.426		
AST	1.01 (1.01, 1.01)	<0.001		
ALP	1.01 (1.01, 1.01)	<0.001		
GGT	1.01 (1.01, 1.01)	<0.001		
TC	0.92 (0.77, 1.10)	0.369		
TG	1.05 (0.96, 1.15)	0.295		
HDL-c	0.97 (0.53, 1.76)	0.919		
LDL-c	0.84 (0.67, 1.04)	0.112		
BUN	1.11 (1.09, 1.13)	<0.001		
Creatinine	1.01 (1.01, 1.01)	<0.001	1.00 (1.00, 1.01)	<0.001
UA	1.01 (1.01, 1.01)	<0.001	1.00 (1.00, 1.00)	0.038
eGFR	0.93 (0.92, 0.94)	<0.001	0.97 (0.96, 0.98)	<0.001
Δ eGFR	0.96 (0.95, 0.97)	<0.001		
Δ eGFR%	0.95 (0.94, 0.96)	<0.001		

(Continued)

Table 3 (Continued).

Variables	Univariate		Multivariate	
	HR [95% CI]	p	HR [95% CI]	p
LAP	1.00 (1.00, 1.00)	0.747	1.57 (1.19, 2.09)	0.002
TyG	1.38 (1.08, 1.77)	0.010		
Diabetes duration	1.01 (0.92, 1.11)	0.844		
Obesity	1.02 (0.71, 1.46)	0.933		
Hypertension	6.41 (4.46, 9.21)	<0.001		
Dyslipidemia	0.90 (0.60, 1.37)	0.638		
Smoking history	0.57 (0.40, 0.82)	0.002		
Alcohol history	1.05 (0.72, 1.52)	0.802		
Regular exercise habits	1.22 (0.82, 1.81)	0.318		
High school education or above	0.29 (0.20, 0.43)	<0.001		
Oral hypoglycemic medication use	0.51 (0.30, 0.89)	0.018		
Insulin use	2.05 (1.44, 2.91)	<0.001		

Note: The bold values indicated statistical significance.

Abbreviations: HR, Hazard ratios; CI, confidence interval; BMI, Body mass index; WC, Waist circumference; WHR, Waist to hip ratio; VFA, Visceral fat area; FPG, Fasting plasma-glucose; HbA1c, Hemoglobin A1c; ALT, Alanine transaminase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; GGT, Glutamyl transferase; TC, Total cholesterol; TG, Triglyceride; HDL-c, High density lipoprotein cholesterol; LDL-c, Low density lipoprotein cholesterol; BUN, Blood urea nitrogen; UA, Uric acid; eGFR, Estimated glomerular filtration rate; Δ, Difference in eGFR between baseline and the fifth year of follow-up; LAP, Lipid accumulation product; TyG, Triglyceride and glucose index.

Table 4 Univariate and Multivariate Cox Proportional Hazards Regression Analyses for the Association Between Various Factors and Incident Diabetic Nephropathy in Female

Variables	Univariate		Multivariate	
	HR [95% CI]	p	HR [95% CI]	p
AGE	1.11 (1.08, 1.13)	<0.001	1.05 (1.01, 1.09)	0.024
Height	1.00 (0.97, 1.02)	0.841		
Weight	0.98 (0.97, 1.00)	0.058		
BMI	0.94 (0.89, 0.99)	0.042		
WC	0.99 (0.97, 1.01)	0.390		
WHR	17.51 (0.46, 669.71)	0.124		
VFA	1.00 (1.00, 1.01)	0.734		
FPG	1.15 (1.01, 1.33)	0.049		
HbA1C	1.03 (0.89, 1.20)	0.679		
ALT	1.00 (0.99, 1.00)	0.803		
AST	1.01 (1.01, 1.01)	0.041		
ALP	1.01 (1.01, 1.01)	<0.001		
GGT	1.01 (1.01, 1.01)	0.018		
TC	0.80 (0.66, 0.98)	0.033		
TG	0.95 (0.76, 1.19)	0.661		
HDL-c	0.54 (0.30, 0.98)	0.042		
LDL-c	0.85 (0.67, 1.07)	0.171		
BUN	1.13 (1.10, 1.16)	<0.001		0.027
Creatinine	1.02 (1.01, 1.02)	<0.001		
UA	1.01 (1.01, 1.01)	<0.001		
eGFR	0.93 (0.92, 0.94)	<0.001		
ΔeGFR	0.94 (0.93, 0.95)	<0.001		0.006

(Continued)

Table 4 (Continued).

Variables	Univariate		Multivariate	
	HR [95% CI]	p	HR [95% CI]	p
ΔeGFR%	0.94 (0.93, 0.95)	<0.001	0.96 (0.95, 0.97)	<0.001
LAP	1.00 (0.99, 1.01)	0.553		
TyG	1.08 (0.78, 1.51)	0.637		
Diabetes.duration	1.17 (1.04, 1.31)	0.011	1.13 (1.00, 1.29)	0.049
Obesity	0.14 (0.09, 0.22)	<0.001		
Hypertension	0.14 (0.09, 0.22)	<0.001		
Dyslipidemia	0.85 (0.55, 1.32)	0.475		
Smoking history	0.45 (0.24, 0.82)	0.009		
Alcohol history	0.80 (0.33, 1.97)	0.630		
Regular exercise habits	1.21 (0.78, 1.85)	0.392		
High school education or above	0.16 (0.08, 0.30)	<0.001		
Oral hypoglycemic medication use	0.53 (0.30, 0.96)	0.036		
Insulin use	1.66 (1.11, 2.49)	0.014		
Postmenopausal	0.14 (0.06, 0.34)	<0.001		

Note: The bold values indicated statistical significance.

Abbreviations: HR, Hazard ratios; CI, confidence interval; BMI, Body mass index; WC, Waist circumference; WHR, Waist to hip ratio; VFA, Visceral fat area; FPG, Fasting plasma-glucose; HbA1c, Hemoglobin A1c; ALT, Alanine transaminase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; GGT, Glutamyl transferase; TC, Total cholesterol; TG, Triglyceride; HDL-c, High density lipoprotein cholesterol; LDL-c, Low density lipoprotein cholesterol; BUN, Blood urea nitrogen; UA, Uric acid; eGFR, Estimated glomerular filtration rate; Δ, Difference in eGFR between baseline and the fifth year of follow-up; LAP, Lipid accumulation product; TyG, Triglyceride and glucose index.

Analysis of Factors Associated with Declining Renal Function

Multiple linear regression analysis was utilized to examine the correlation between ΔeGFR% and each associated factor in patients with T2DM. Results revealed that creatinine, female sex, BUN, ALP, and TC were the factors that influenced ΔeGFR%. The standardized β coefficients for these factors were −0.325, −0.219, −0.164, −0.084 and 0.071, respectively (Table 5).

Correlation Between Reduced Renal Function and DN Lesions

Age is a significant factor in DN lesions in male and female populations. Therefore, we examined the nonlinear correlation between ΔeGFR% and the risk of DN in gender-specific participants. We employed logistic regression with a cubic spline function and a smoothed curve fitting, adjusting for age to ensure objectivity and obtain precise results. RCS analysis indicated a negative correlation between ΔeGFR% and the risk of DN incidence in both male and female T2DM patients ($P < 0.001$). This means a smaller ΔeGFR% corresponds to a more significant decline in renal function and a higher incidence of DN. The risk of DN was also found to be negatively correlated with ΔeGFR% ($P < 0.001$), as indicated in Figure 3. The incidence of DN increased significantly in male and female patients with

Table 5 Multivariate Linear Regression Analysis Between Δegfr% and Various Factors

Dependent Variable	Independent Variable	B [95% CI]	SE	Standardized β	p
ΔeGFR%	Creatinine	−0.150[−0.177, −0.123]	0.014	−0.325	<0.001
	Female	−7.346[−8.906, −5.786]	0.795	−0.219	<0.001
	BUN	−0.918[−1.235, −0.602]	0.161	−0.164	<0.001
	ALP	−0.026[−0.039, −0.012]	0.007	−0.084	<0.001
	TC	1.117[0.417, 1.818]	0.357	0.071	0.002

Note: The bold values indicated statistical significance.

Abbreviations: Δ, Difference in eGFR between baseline and the fifth year of follow-up; eGFR, Estimated glomerular filtration rate; CI, confidence interval; SE, Standard error; BUN, Blood urea nitrogen; ALP, Alkaline phosphatase; TC, Total cholesterol.

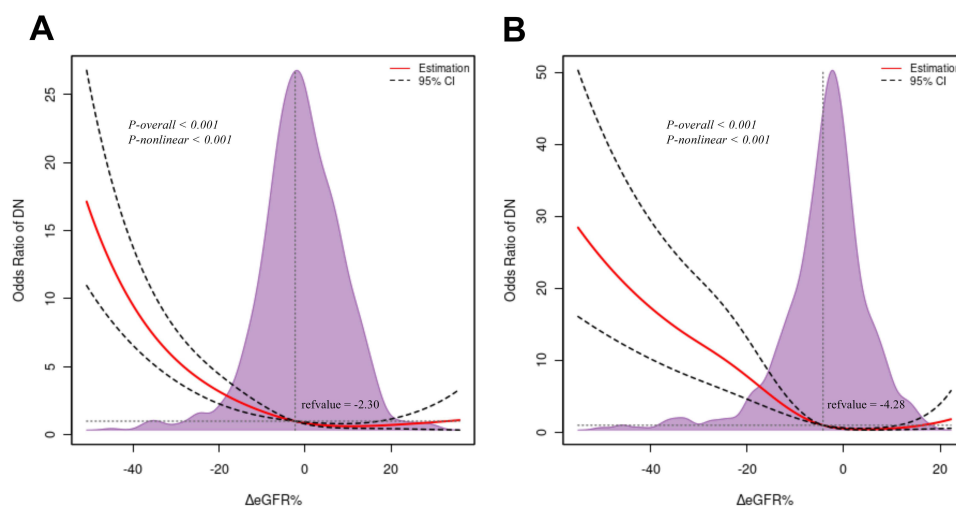


Figure 3 Restricted cubic spline analysis of $\Delta eGFR\%$ for estimating the risk of incident diabetic nephropathy in males with T2DM (A) and females with T2DM (B) after adjusting for age. The solid red line displays the odds ratio with the 95% confidence intervals represented by dashed black lines. The purple shaded area indicates the thickness of the $\Delta eGFR\%$ values.

Abbreviations: Δ , Difference in eGFR between baseline and the fifth year of follow-up; eGFR, Estimated glomerular filtration rate; DN, Diabetic nephropathy; CI, confidence interval.

T2DM when their $\Delta eGFR\%$ was less than -2.30 and -4.28 , respectively. These findings demonstrate a close correlation between $\Delta eGFR\%$ and the risk of DN in the range of closely associated.

Discussion

In this study, gender differences in the prevalence of nephropathy and changes in renal function were examined among patients with T2DM after a 5-year follow-up period. Results indicated a higher prevalence of DN among women, evidencing gender distinctions in the prevalence of nephropathy in T2DM patients. Furthermore, it was observed that as the length of follow-up increased, women exhibited a more notable decline in renal function. Upon further study, we discovered that age, insulin resistance, and hypertension significantly correlated with DN's prevalence in male T2DM patients. In female patients, age and duration of diabetes were correlated. These findings reveal the differential influence of gender on the development of DN in patients with T2DM, providing new perspectives for clinical treatment and prevention.

Gender differences were also noted in the prevalence of T2DM. Overall, diabetes is more prevalent among men worldwide, but women experience a higher T2DM rate.³⁰ This gender gap in diabetes prevalence is contrary to reproductive life stages - while young and middle-aged populations show a higher occurrence of T2DM in men,³¹ postmenopausal and older women are more likely to have the condition.³² This difference between genders is caused by genetic and hormonal influences on pathophysiology, clinical manifestations, diagnosis, and response to treatment.^{33,34} Regarding macrovascular complications of T2DM, gender differences are more clearly defined. Women with T2DM have a higher relative risk of cardiovascular disease and death than men.^{19–22} However, the incidence of microvascular complications, particularly DN, has been reported less frequently, and the results have been inconsistent. An observational study of gender differences in target organ damage in insulin-resistant patients revealed a higher prevalence of vascular and renal damage, a more tremendous increase in intima-media thickness, and a more significant number of vascular plaques in females with T2DM compared to males.³⁵ Another study indicated a greater risk of DN in women with T2DM than in men.³⁶ Studies have reported that men play an essential role in the decline of renal function in patients with T2DM and that the overall prevalence of DN is higher in men than in women.³⁷ The inconsistent results regarding gender differences may be attributed to various risk factors for diabetes prevalence and delayed diagnosis of diabetes.³⁸ In the current study, our findings indicate that the cumulative incidence of DN was significantly greater in

women diagnosed with T2DM than in their male counterparts (HR = 1.33 [95% CI 1.02–1.73]), corroborating previous research results.

Advanced age, smoking, hypertension, obesity, and poor glycemic and lipid control are recognized risk factors for developing DN.³⁹ Age is an independent risk factor for both T2DM and DN.⁴⁰ The incidence of chronic renal failure increases with age in both men and women. With the aging population continuing to grow, the prevalence of older adults with chronic kidney disease is expected to rise.⁴¹ Our study found a significant association between older age and DN prevalence in male and female T2DM patients. In a prospective cohort study of 6513 patients with T2DM, smoking was identified as an independent risk factor for the development of microalbuminuria after data analysis.⁴² This finding emphasizes the negative role of smoking in diabetic complications. Furthermore, a comprehensive meta-analysis has provided compelling evidence supporting smoking as a significant causative factor for DN, with an OR of 1.70, indicating that smokers are at a significantly higher risk of developing DN.⁴³ Our study found that the proportion of male and female patients diagnosed with DN who had a smoking history was considerably higher than those without DN. This finding emphasizes the prevalence and importance of smoking in the development of diabetic nephropathy. It suggests that attention to the renal health risks of smoking is necessary for all diabetic patients, regardless of gender. In the UKPDS trial, patients with T2DM were assigned a target blood pressure of 150/85 mmHg, and the study followed them for a median of 15 years. The results demonstrated a significant 37% reduction in the incidence of microvascular complications compared to patients with a target blood pressure of 180/105 mmHg.²⁴ Our findings indicate a significantly higher prevalence of hypertension in both male and female patients with DN. Hypertension was confirmed as a significant influencing factor in the development of DN in male patients, according to a multivariate COX regression analysis. Obesity promotes the process of focal and segmental glomerulosclerosis, leading to the development of hyperproteinuria.⁴⁴ In a cohort study, obese individuals, especially those with excess central adiposity, were more likely to develop DN.⁴⁵ The prevalence of obesity was significantly higher in female patients with DN than in those without DN. Hyperglycemia is a recognized major underlying factor for the development and progression of nephropathy in diabetic patients. Oxidative stress induced by hyperglycemia activates pathways associated with inflammation and fibrosis, ultimately leading to kidney injury and dysfunction.^{46,47} In this study, male and female patients with DN were more likely to use oral hypoglycemic medication and insulin and had poorer glycemic control than patients without DN. It is worth noting that among female patients, those with DN had a significantly longer duration of diabetes. Furthermore, multivariate COX regression analysis revealed an association between the duration of diabetes and the development of DN. Insulin resistance was found to be associated with the development of DN in male patients. These findings are essential for understanding the pathogenesis of DN and developing targeted treatment programs. Dyslipidemia, comprising elevated triglycerides, low-density lipoproteins, apolipoprotein B, and decreased high-density lipoproteins, are all independently associated with the emergence of DN in a cohort of T2DM.⁴⁸ Our investigation found no evidence linking lipid management to the development of DN. This could be due to the participants receiving more consistent lipid-control therapies while under observation at the hospital and receiving regular follow-ups. Serum creatinine levels and eGFRs are commonly utilized to determine renal function. An elevated serum creatinine indicates a reduced glomerular filtration rate, while an eGFR below 60 mL/min/1.73m² indicates chronic kidney disease.⁴⁹ Consistent monitoring of alterations in renal function is critical for optimizing outcomes and reducing the effect of kidney disease on the overall health and quality of life of individuals with diabetes.⁵⁰ At least annually, urinary albumin and eGFR should be assessed in patients with T2DM regardless of treatment.⁵¹ Previous studies have debated gender differences in renal dysfunction, with some reporting a greater predisposition for renal dysfunction in male patients with T2DM,^{37,52} and others suggesting a greater predisposition for renal dysfunction in female patients.^{24,36,53} It is widely acknowledged that men with DN experience faster progression and more frequent instances of dialysis.³⁷ Conversely, women with T2DM and end-stage renal disease face a greater likelihood of mortality than men due to elevated inflammation and oxidative stress levels, as well as malleable gender-specific discrepancies in treatment modalities and accessibility.^{35,54–56} A recent meta-analysis identified a standardized mortality ratio from fatal kidney disease of 1.44 (95% CI 1.02–2.05) for females compared to males.⁵⁷ Our study found significant elevations in serum creatinine levels and significant decreases in eGFR in both male and female T2DM patients with DN. Additionally, the Cox proportional risk regression analysis results demonstrated significant associations between Creatinine and Δ eGFR%

and the prevalence of DN in both genders. Furthermore, RCS analyses indicated a negative correlation between Δ eGFR% and the risk of DN in both male and female T2DM patients. A lower decrease in estimated glomerular filtration rate (eGFR%) was associated with a higher incidence of diabetic nephropathy and a more significant decline in renal function. An analysis of factors related to changes in renal function uncovered gender disparities in the decreasing renal function of T2DM patients. Specifically, declines in renal function were more prominent in females than males ($B = -7.346 [-8.906, -5.786]$).

Sex hormones may contribute to explaining gender differences, and the hormone estrogen appears to have a protective effect on the kidneys.⁵⁸ The protection offered by estrogen may come from either a direct impact on the kidneys or an indirect result of estrogen circulating throughout the body.⁵⁹ Research has established that estrogen exhibits anti-inflammatory properties and that immune cells, such as antigen-presenting and T cells, contain estrogen receptors. These receptors modulate the immune response, potentially safeguarding the kidneys during hyperglycemia.⁶⁰ However, this protective effect is significantly reduced in postmenopausal women displaying lower endogenous estradiol levels.^{24,61,62} Our study found that 73.5% of female participants were postmenopausal, which can decrease estrogen levels. Additionally, a small number of female participants (1.8%) reported using estrogenic medications, which may also result in low estrogen levels. These factors could potentially contribute to the high prevalence of DN in female T2DM patients. Furthermore, disparities in behavior and treatment between genders can also contribute to differences in outcomes of decreased kidney function. Research has shown that men receive more intense treatment for T2DM and cardiovascular disease, which could lead to earlier diagnosis and treatment of complications.⁶³ Additional studies suggest that women have lower medication adherence than men in treating diabetes and dyslipidemia.⁶⁴ They also indicate that women tend to have poorer outcomes for dyslipidemia.⁶⁵ These differences can increase the incidence of DN in women. In this study, we observed a higher prevalence of dyslipidemia in female T2DM patients compared to males. It is important to consider the lower educational level of female patients, which may have contributed to their lesser adherence to treatment compared to men, ultimately affecting treatment outcomes. In summary, our and previous research shows that women with T2DM are at greater risk of developing renal dysfunction compared to men.

However, our study has some limitations. Firstly, this single-center study is not representative of the general population, thus impeding the provision of a comprehensive understanding of diabetic patients. To remedy this, future investigations should be multicenter and prospective, focusing on mechanisms. Secondly, our study participants were exclusively from hospitals and exhibited relatively poor glycemic control during their initial visits, potentially overestimating the prevalence of DN within the T2DM population. Generalization of these findings to other populations may be limited because all study participants were from eastern China, which may have different body composition than other regions. Additionally, the study could not standardize patient diet, exercise, and medication due to differences in treatment requirements, impeding our ability to consider these factors. Finally, it is essential to note that this study lacked specific information on participants' sex hormones. This limitation weakened our interpretation and understanding of the study results. Obtaining more detailed data on sex hormones in future studies would enhance the scientific validity and rigor of the study, allowing for a more accurate exploration of the influence of relevant factors on the results.

Conclusion

In conclusion, male and female participants with T2DM exhibited a higher prevalence of DN over the 5-year follow-up. However, women had a greater risk of developing DN and a more accelerated decline in renal function than men. Future studies should investigate the underlying mechanisms of this correlation and employ the knowledge gained to devise personalized treatment strategies to avert nephropathic complications among patients with T2DM. Special consideration should be given to vulnerable populations in research and clinical settings. Women with T2DM should pay increased attention to changes in their renal function, implementing preventive or interventional measures early to enhance renal protection and minimize the risk of DN.

Data Sharing Statement

The data utilized and analyzed in the present study are accessible from the corresponding author upon justified request.

Institutional Review Board Statement

The research adhered to the principles of the Declaration of Helsinki and received approval from the Ethics Committee of Changzhou Third People's Hospital (No. 02A-A20230023).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this study.

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