



ORIGINAL ARTICLE

A study on the status of normoalbuminuric renal insufficiency among type 2 diabetes mellitus patients: A multicenter study based on a Chinese population

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Abstract

Background: Patients with normoalbuminuria and a reduced estimated glomerular filtration rate (eGFR) account for a considerable proportion of type 2 diabetes patients. The aim of this research was to investigate the epidemiological and clinical characteristics of normoalbuminuric kidney disease in a Chinese population.

Methods: We included 8131 diabetic patients from a multicenter prospective study in China. Based on eGFR and urinary albumin-to-creatinine ratio (UACR), participants were stratified into four groups—normal albuminuria, albuminuria, normoalbuminuria with eGFR < 60 mL/min/1.73 m², and albuminuria with eGFR < 60 mL/min/1.73 m². Clinical parameters and characteristics of patients with normoalbuminuria and eGFR < 60 mL/min/1.73 m² were retrospectively analyzed.

Results: A total of 1060 out of 8131 individuals with diabetes had decreased eGFR (<60 mL/min/1.73 m²). Normoalbuminuria accounted for 63.3% of participants with eGFR < 60 mL/min/1.73 m², and microalbuminuria and macroalbuminuria accounted for 30.1% and 6.3%, respectively. Patients with normoalbuminuria and reduced eGFR were more frequently male, older, and had higher levels of triglycerides than patients with normal albuminuria and eGFR. We also detected a correlation between lower extremity arterial disease, newly diagnosed diabetes, and normoalbuminuria-reduced eGFR. Compared with participants with both albuminuria and eGFR decline, those with normoalbuminuria had better metabolic indicators, including systolic blood pressure and glycosylated hemoglobin, and shorter diabetes duration. Even in the normal range, UACR has a significant correlation with the risk of eGFR insufficiency.

Conclusions: Normoalbuminuric renal insufficiency, characterized by male sex, older age, a higher level of triglyceride levels, and a higher risk of lower

Xiaomeng Jia and Li Zang contributed equally to this work.

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extremity arterial disease, accounted for a dominant proportion of diabetic patients with eGFR decline.

KEYWORDS

diabetes complications, diabetic kidney disease, normoalbuminuria, type 2 diabetes

Highlights

- Approximately 63.6% of diabetes patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² have normal albuminuria.
- The factors related to normoalbuminuria and eGFR < 60 mL/min/1.73 m² were male sex, older age, higher triglyceride levels, lower extremity arterial disease, and a longer duration of diabetes.
- Compared with patients with both albuminuria and eGFR decline, those with normoalbuminuria have better control of metabolic indicators.

1 | INTRODUCTION

Diabetic kidney disease (DKD) is one of the most common microvascular complications of diabetes mellitus and the leading cause of end-stage renal disease.¹ Commonly, the onset of DKD is often accompanied by the development of microalbuminuria, progression to macroalbuminuria, and ultimately a rapid decline of estimated glomerular filtration rate (eGFR).² Therefore, in clinical practice, urinary albumin excretion has been central in the screening of diabetes with initial kidney impairment.³ Over the past decades, studies have suggested that renal dysfunction appears prior to the increase in the albumin excretion rate among diabetes patients, and a considerable proportion of DKD in the absence of albuminuria has been reported.^{4–6} The 15-year follow-up analysis of type 2 diabetes from the United Kingdom Prospective Diabetes Study (UKPDS) indicated that 67.1% of patients who progressed to renal insufficiency were identified as normoalbuminuric.⁴ The Third National Health and Nutrition Examination Survey (NHANES III) found that the prevalence of normoalbuminuria was 30% in individuals with type 2 diabetes and kidney insufficiency.⁵ In Asia, according to the data from the Japan Diabetes Clinical Data Management study (JDDM15), the percentage of normoalbuminuria and reduced eGFR was 11.4%.⁷ Epidemiological and clinical data suggest that normoalbuminuria is present in a certain proportion of diabetic patients with renal impairment, and this subtype has been defined as normoalbuminuric DKD, normoalbuminuric diabetic nephropathy, or DKD without albuminuria according to previous research.^{8–10}

Some reports suggested that normoalbuminuric renal impairment is different in clinical characteristics from

albuminuria renal dysfunction. Normoalbuminuric renal impairment is associated with obesity, lipidemia, and higher blood glucose.^{11,12} Some research also found that microangiopathy is more prevalent in albuminuria renal dysfunction^{5,11} and that macroalbuminuria is more common in normoalbuminuric renal insufficiency,¹³ indicating different pathogenesis in albuminuria and normoalbuminuria renal impairment. In contrast, some studies hold the opposite view.^{6,7,14} The prevalence of DKD is increasing rapidly in China.¹⁵ Although there have been many efforts to explore the clinical characteristics and pathogenesis of normoalbuminuric DKD, there are few Asian studies, especially in Chinese populations. The aim of this study was to investigate the clinical characteristics and related factors of normoalbuminuric renal insufficiency, providing more evidence to further understand DKD.

2 | METHODS

2.1 | Participants

From 2010 to 2011, 53 639 Chinese individuals over age 40 were enrolled in Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal Study (REACTION). According to the geographical distribution and economic development, 25 communities near eight clinical centers in China were selected to perform the research, and the subjects were assessed via questionnaires, laboratory tests, and physical examinations. Biochemical detection, diabetic complications, family history, and past medical history were followed for up to 10 years. The protocols were approved by the research ethics committee at each clinical center. Written informed consent was obtained from all patients



after a full explanation of the purpose and procedures to be performed in this study.

Based on this database, subjects with normal glucose tolerance, incomplete clinical data, other diseases (congestive heart failure, urinary tract infection, and primary kidney disease), other types of diabetes, as well as pregnant women were excluded, and individuals with diabetes were enrolled. To ensure a uniform method of determining urinary albumin-to-creatinine ratio (UACR), we selected data from 8131 patients with type 2 diabetes from six of the eight clinical centers using the same chemical test kits.

2.2 | Data collection and measurements

A standardized questionnaire was administered by trained medical staff. The questionnaire included the following items: basic information (sex, age, birthplace, education status, marriage, childbirth, etc.), past medical history (covering most systems and organs in the body), family history of carcinoma and diabetes mellitus, medical treatment in the past two weeks and lifestyle (smoking, drinking, and exercise). Smoking at least one cigarette a day was defined as frequent smoking, and less than one cigarette a day or less than seven cigarettes a week was defined as occasional smoking. Drinking at least once a week in the past six months was defined as regular drinking, and drinking less than once a week was considered occasional drinking.

Systolic and diastolic blood pressure (SBP, DBP) was measured by standardized methods. Before the measurements, the subjects were told to take off their clothes and shoes. The horizontal diameter from the midpoint of the line between the upper edge of the ilium and the lower edge of the 12th rib around the abdomen was the waist circumference. The maximum circumference of the buttocks was the hip circumference. Waist-to-hip ratio (WHR) = waist circumference (cm)/hip circumference (cm). Body mass index (BMI) = weight (kg)/[height (m)]². BMI was stratified into three groups according to the criterion of the *Guidelines for Prevention and Control of Overweight and Obesity in Chinese Adults* (BMI < 24 kg/m², 24 ≤ BMI < 28 kg/m², and BMI ≥ 28 kg/m²). Blood pressure was measured by a digital meter produced by OMRON (Model HEM-725 FUZZY, OMRON Company, Dalian, China). After the participants had rested for 5 minutes, blood pressure was measured three times within 1 minute, and the average value was taken. Blood samples were collected in the morning after the participants had fasted for at least 8 hours overnight. A 75-g oral glucose tolerance test (OGTT) was administered to subjects who had not

been diagnosed with diabetes mellitus. The subjects with a history of diabetes received the steamed bread meal test. Blood and urine samples were tested and stored at each center. Fasting plasma glucose and 2-hour postload blood glucose levels were analyzed by a hexokinase method, and glycosylated hemoglobin (HbA1c) was measured by a high-pressure liquid chromatography method. High-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, triglycerides (TGs), and total cholesterol were measured using a Roche biochemical analyzer (Cobas 8000 modular analyzer series, Roche Diagnostics, Basel, Switzerland). Urine samples were collected in the morning, and each center performed UACR measurements. eGFR was calculated using the following formulas of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) for white or other races. Females: (a) serum creatinine (SCr) ≤ 0.7 mg/dL, eGFR (mL/min/1.73 m²) = 144 × [SCr (mg/dL)/0.7]^{-0.329} × (0.993)^{Age}. (b) SCr > 0.7 mg/dL, eGFR (mL/min/1.73 m²) = 144 × [SCr (mg/dL)/0.7]^{-1.209} × (0.993)^{Age}. Males: (a) SCr ≤ 0.9 mg/dL, eGFR (mL/min/1.73 m²) = 141 × [SCr (mg/dL)/0.9]^{-0.411} × (0.993)^{Age}. (b) SCr > 0.9 mg/dL, eGFR (mL/min/1.73 m²) = 141 × [SCr (mg/dL)/0.9]^{-1.209} × (0.993)^{Age}.

2.3 | Definition of variables

Subjects with a self-reported history of diabetes were considered to be diagnosed diabetic patients. For subjects who had not been diagnosed, those with a fasting plasma glucose level ≥ 7.0 mmol/L or 2-hour postload glucose level ≥ 11.1 mmol/L during the OGTT were considered to have newly diagnosed diabetes mellitus (NDDM). UACR was stratified into normal albuminuria (<30 mg/g), microalbuminuria (30-299 mg/g), and macroalbuminuria (≥300 mg/g). Reduced eGFR was defined as <60 mL/min/1.73 m². UACR and eGFR were used to evaluate renal function and divide all of the subjects into four groups: normal albuminuria, albuminuria, normoalbuminuria and eGFR <60 mL/min/1.73 m², and albuminuria and eGFR <60 mL/min/1.73 m².

2.4 | Statistical analysis

SPSS 20.0 (SPSS Corp, Chicago) was used for statistical analysis. Continuous variables are expressed as the mean ± SD and were compared by one-way analysis of variance (ANOVA) and Bonferroni correction for pairwise comparisons. Categorical variables are expressed as rates, and the chi-square test or Fisher's

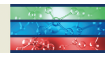


TABLE 1 Clinical characteristics of all participants stratified by eGFR and UACR

Variables	eGFR ≥ 60 mL/min/1.73 m ²		eGFR < 60 mL/min/1.73 m ²		P value
	Normoalbuminurians = 5500	Albuminurians = 1571	Normoalbuminurians = 674	Albuminurians = 386	
Age (y)	60.12 ± 8.61	62.19 ± 9.45	68.16 ± 8.80	68.97 ± 9.30	<.001
Sex, n (%)					<.001
Male	1928 (35.1)	428 (27.2)	538 (79.8)	255 (66.1)	
Female	3572 (64.9)	1143 (72.8)	136 (20.2)	131 (33.9)	
BMI (kg/m ²), n (%)					.094
≤23.9	1865 (33.9)	529 (33.7)	217 (32.2)	121 (31.4)	
24-27.9	2448 (44.5)	668 (42.5)	328 (48.7)	183 (47.5)	
≥28	1187 (21.6)	374 (23.9)	129 (19.0)	82 (21.1)	
WHR	0.90 ± 0.06	0.91 ± 0.06	0.92 ± 0.06	0.93 ± 0.06	<.001
SBP (mm Hg)	138.10 ± 20.66	145.28 ± 21.48	141.94 ± 19.722	150.05 ± 22.90	<.001
DBP (mm Hg)	78.65 ± 10.80	80.16 ± 11.83	79.13 ± 11.15	78.84 ± 12.44	<.001
HbA1c (%)	7.13 ± 1.48	7.63 ± 1.86	7.18 ± 1.51	7.82 ± 1.95	<.001
LDL-C (mmol/L)	3.01 ± 0.95	2.95 ± 0.94	3.00 ± 0.84	2.96 ± 0.97	.115
HDL-C (mmol/L)	1.24 ± 0.33	1.24 ± 0.30	1.20 ± 0.28	1.18 ± 0.30	<.001
TC (mmol/L)	5.11 ± 1.24	5.12 ± 1.23	5.08 ± 1.12	5.15 ± 1.33	.809
TGs (mmol/L)	1.91 ± 1.35	2.22 ± 1.67	2.05 ± 1.51	2.27 ± 1.73	<.001
Smoking status, n (%)					.066
No	4603 (83.7)	1338 (85.2)	545 (80.9)	313 (81.2)	
Occasional smokers	148 (2.7)	35 (2.2)	28 (4.1)	15 (3.9)	
Regular smokers	749 (13.6)	198 (12.6)	101 (15.0)	58 (14.9)	
Drinking status, n (%)					<.001
No	4213 (76.6)	1259 (80.2)	474 (70.4)	300 (77.7)	
Occasional drinkers	869 (15.8)	204 (13.0)	143 (21.3)	59 (15.2)	
Regular drinkers	418 (7.6)	108 (6.8)	57 (8.3)	27 (7.1)	
RAAS blockade, n (%)	287 (5.2)	144 (9.2)	51 (7.6)	59 (15.3)	<.001
NDDM, n (%)	2855 (51.9)	682 (43.4)	291 (43.2)	120 (31.1)	<.001
Family history of DM, n (%)	1557 (28.3)	419 (26.7)	142 (21.2)	90 (23.2)	<.001

Note: Continuous variables are expressed as mean ± SD, and categorical variables are reported for frequency (%).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NDDM, newly diagnosed diabetes mellitus; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UACR, urinary albumin-to-creatinine ratio; WHR, waist-to-hip ratio.

TABLE 2 Characteristics of patients with normoalbuminuria and eGFR < 60 mL/min/1.73 m²

Variables	Normoalbuminuria			eGFR < 60 mL/min/1.73 m ²		
	eGFR ≥ 60 mL/min/ 1.73 m ² n = 5500	eGFR < 60 mL/min/ 1.73 m ² n = 674	P value	Albuminuria n = 386	Normoalbuminuria n = 674	P value
Age (y)	60.12 ± 8.61	68.16 ± 8.81	≤.001	68.97 ± 9.30	68.16 ± 8.81	.156
Sex, n (%)			≤.001			≤.001
Male	1928 (35.1)	538 (79.8)		255 (66.1)	538 (79.8)	
Female	3572 (64.9)	136 (20.2)		131 (33.9)	136 (20.2)	
BMI (kg/m ²)	25.53 ± 3.53	25.46 ± 3.12	.607	25.77 ± 3.43	25.46 ± 3.11	.129
WHR	0.90 ± 0.06	0.92 ± 0.06	≤.001	0.93 ± 0.06	0.92 ± 0.06	.509
SBP (mm Hg)	138.10 ± 20.66	141.90 ± 19.72	≤.001	150.10 ± 22.90	141.90 ± 19.72	≤.001
DBP (mm Hg)	78.65 ± 10.80	79.13 ± 11.14	.277	78.84 ± 12.43	79.13 ± 11.14	.694
HbA1c (%)	7.13 ± 1.48	7.18 ± 1.51	.427	7.82 ± 1.95	7.18 ± 1.51	≤.001
LDL-C (mmol/L)	3.01 ± 0.95	3.00 ± 0.84	.737	2.96 ± 0.97	3.00 ± 0.84	.578
HDL-C (mmol/L)	1.24 ± 0.33	1.20 ± 0.28	≤.001	1.18 ± 0.28	1.20 ± 0.28	.294
TC (mmol/L)	5.11 ± 1.24	5.15 ± 1.33	.466	5.10 ± 1.20	5.15 ± 1.33	.341
TGs (mmol/L)	1.91 ± 1.35	2.05 ± 1.51	.018	2.27 ± 1.73	2.05 ± 1.51	.026
Smoking status, n (%)			.074			.994
No	4549 (83.7)	539 (80.9)		310 (81.2)	539 (80.9)	
Occasional	147 (2.7)	27 (4.1)		15 (3.9)	27 (4.1)	
Regular	739 (13.6)	100 (15.0)		57 (14.9)	100 (15.0)	
Drinking status, n (%)			≤.001			.033
No	4159 (76.6)	467 (70.4)		296 (77.7)	467 (70.4)	
Occasional	857 (15.8)	141 (21.3)		58 (15.2)	141 (21.3)	
Regular	414 (7.6)	55 (8.3%)		27 (7.1)	55 (8.3)	
RAAS blockade, n (%)	287 (5.2)	51 (7.6)	.011	59 (15.3)	51 (7.6)	≤.001
NDDM, n (%)	2883 (52.4)	299 (44.4)	≤.001	122 (31.6)	299 (44.4)	≤.001
Family history of DM, n (%)	142 (21.2)	73 (22.9)		16 (24.6)	0.72901	
MI, n (%)	44 (0.8)	15 (2.3)	≤.001	14 (3.7)	15 (2.3)	.240
Stroke, n (%)	104 (1.9)	28 (4.3)	≤.001	12 (3.2)	28 (4.3)	.408
LEAD, n (%)	17 (0.3)	6 (0.9)	.032	4 (1.1)	6 (0.9)	.906
DR, n (%)	87 (1.6)	17 (2.6)	.079	13 (3.5)	17 (2.6)	.446

Note: Continuous variables are expressed as mean ± SD, and categorical variables are reported for frequency (%).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LEAD, lower extremity arterial disease; MI, myocardial infarction; NDDM, newly diagnosed diabetes mellitus; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

exact probability method were used for comparisons between groups. Multivariate regression analysis was performed to evaluate the related factors. Odds ratios (ORs) and 95% CIs were calculated. Conventional factors related to albuminuria and renal dysfunction, including age, sex, WHR, and levels of HbA1c, HDL-C, and TGs, were selected for adjustment to control the confounding effect. A value of $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of participants based on eGFR and UACR

Of the 8131 diabetic patients, 5500 (67.6%) had normal UACR and eGFR, while 1571 (19.3%) had only albuminuria. Among 1060 patients with decreased eGFR, 63.6% (674/1060) had normoalbuminuria, 30.1% (319/1060) had

TABLE 3 Independent covariates of normoalbuminuric renal insufficiency

Variables	Compared with normal albuminuria and eGFR		Compared with albuminuria and reduced eGFR	
	OR (95% CI)	P value	OR (95% CI)	P value
Male	10.03 (8.00-12.58)	≤.001	1.939 (1.40-2.67)	≤.001
Age	1.13 (1.11-1.14)	≤.001	0.99 (0.98-1.02)	.883
WHR	0.72 (0.14-3.61)	.721	0.84 (0.07-10.09)	.888
SBP	1.00 (0.99-1.01)	.787	0.98 (0.97-0.99)	≤.001
HbA1c	1.04 (0.98-1.11)	.209	0.82 (0.75-0.88)	≤.001
HDL-C	1.29 (0.93-1.77)	.126	1.49 (0.88-2.53)	.134
TGs	1.29 (1.15-1.31)	≤.001	0.95 (0.87-1.05)	.335
MI	1.78 (0.90-3.53)	.098	0.63 (0.29-1.39)	.255
Stroke	1.31 (0.77-2.19)	.314	1.70 (0.79-3.65)	.177
LEAD	3.34 (1.05-9.65)	.040	1.44 (0.35-5.86)	.614
DR	1.22 (0.63-2.34)	.553	0.79 (0.35-1.78)	.573
NDDM	0.77 (0.63-0.94)	.010	1.36 (1.01-1.83)	.041
RAAS blockade	1.10 (0.76-1.59)	.604	0.56 (0.36-0.86)	.009

Note: ORs with 95% CIs are shown for normoalbuminuric decreased eGFR (<60 mL/min/1.73 m²). Covariate factors, including age, sex, SBP, HbA1c, and use of RAAS blockade, were adjusted.

Abbreviations: DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein; LEAD, lower extremity arterial disease; MI, myocardial infarction; NDDM, newly diagnosed diabetes mellitus; OR, odds ratio; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; TGs, triglyceride; WHR, waist-to-hip ratio.

microalbuminuria, and 6.3% (67/1060) had macroalbuminuria.

We performed a comparative analysis to investigate the differences between participants with normal eGFR and those with decreased eGFR. Compared with patients without reduced eGFR, the two groups of patients with only eGFR < 60 mL/min/1.73 m² and eGFR < 60 mL/min/1.73 m² with albuminuria were more frequently male and older and had a higher WHR, lower HDL-C, and a family history of diabetes mellitus. Moreover, the proportion of NDDM in patients with albuminuria and eGFR < 60 mL/min/1.73 m² was lower than that in the other three groups. Patients with normoalbuminuria and eGFR < 60 mL/min/1.73 m² more frequently had a habit of drinking. We then analyzed the differences between participants with normal albuminuria and albuminuria. Compared with participants with normal albuminuria, those with UACR > 30 mg/g accompanied by reduced eGFR had higher SBP, HbA1c, and TGs. Most of them underwent renin-angiotensin-aldosterone system (RAAS) blockade therapy, but a lower proportion of them had a habit of drinking (Table 1).

We then analyzed the characteristics of normoalbuminuria and eGFR < 60 mL/min/1.73 m² among participants with normal albuminuria and among those with eGFR < 60 mL/min/1.73 m². In the subgroup of normal albuminuria, compared with participants who had an eGFR ≥ 60 mL/min/1.73 m², those

with an eGFR < 60 mL/min/1.73 m² were male, older, had higher levels of WHR, SBP, and TGs, and a higher proportion of alcohol consumption, but lower HDL-C and a lower prevalence of NDDM. Regarding complications, myocardial infarction, stroke, and arterial diseases of the lower extremities were more frequent with reduced eGFR. In the subgroup of decreased eGFR, compared with those with albuminuria, normoalbuminuric patients were still more likely to be male, but the levels of SBP and TGs were lower. The proportion of NDDM and patients who had habits of drinking was higher. There was no difference in the prevalence of myocardial infarction, stroke, arterial diseases of the lower extremities, or diabetic retinopathy (Table 2).

3.2 | Independent covariates with normoalbuminuric renal insufficiency

In logistic regression analysis, considering the influence of confounding factors and to control the bias, we adjusted the differentiated factors and the factors related to renal dysfunction, including age, sex, SBP, HbA1c, and RAAS blockade. As shown in Table 3, compared with normal albuminuria and eGFR, normoalbuminuric decreased eGFR was positively related to male sex (10.03 [8.0-12.58], $P \leq .001$), older age (1.13 [1.11-1.14],



FIGURE 1 The level of UACR in eGFR stratification

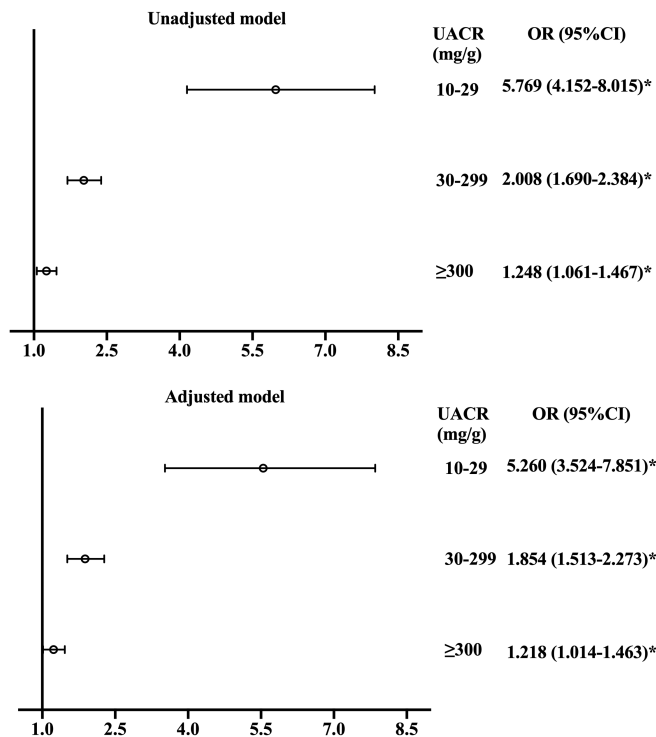
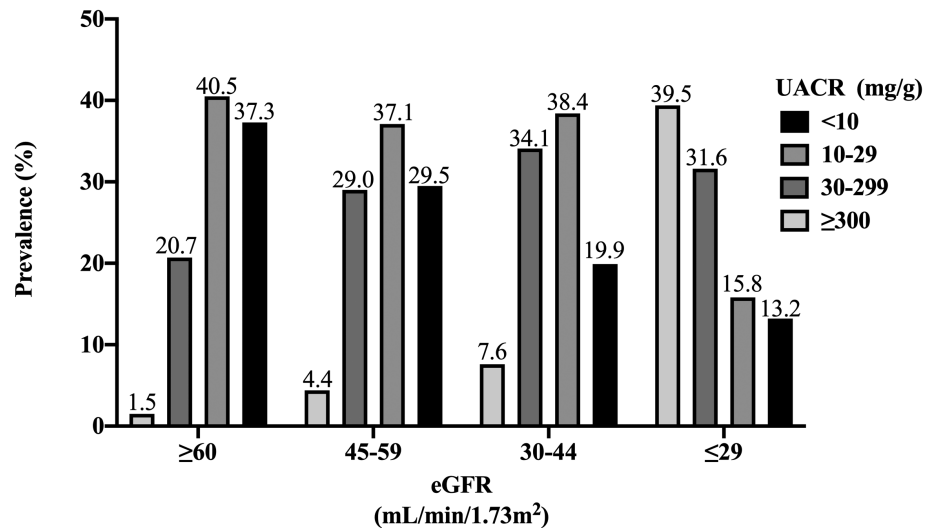


FIGURE 2 The risk of reduced eGFR in UACR stratification. Patients with UACR<10 mg/g were regarded as the reference. Reduced eGFR is defined as eGFR < 60 mL/min/1.73 m². Adjusted model: adjusted for age, sex, systolic blood pressure, glycated hemoglobin, and use of RAAS blockade

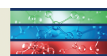
$P \leq .001$), higher levels of TGs (1.29 [1.15-1.31], $P \leq .001$), and lower extremity arterial disease (3.34 [1.05-9.65], $P = .040$), but negatively related to NDDM (0.77 [0.63-0.10], $P = .010$). There seemed to be no obvious correlation between the treatment of RAAS blockade and risk of normoalbuminuric renal dysfunction. In participants with eGFR < 60 mL/min/1.73 m², a correlation

of normoalbuminuric decreased eGFR was observed for males (1.939 [1.40-2.67], $P \leq .001$), lower SBP (0.98 [0.97-0.99], $P \leq .001$), and HbA1c (0.82 [0.75-0.88], $P \leq .001$). Furthermore, NDDM (1.36 [1.01-1.83], $P = .041$) acted as a positive factor, but RAAS blockade (0.56 [0.36-0.86], $P = .009$) as a negative one (Table 3). After stratification by sex or exclusion of those undergoing treatment with RAAS blockade, the factors related to normoalbuminuria remained significant.

3.3 | Different levels of UACR and risk of reduced eGFR

Based on the level of eGFR, the patients were divided into four subgroups (≥ 60 , 45-59, 30-44, and ≤ 29 mL/min/1.73 m²). The prevalence of different levels of UACR (<10, 10-29, 30-299, and ≥ 300 mg/g) in each subgroup was evaluated. With a decrease in eGFR, the prevalence of UACR 30-299 and ≥ 300 mg/g increased, while the proportion of UACR <10 and 10-29 mg/g decreased. Moreover, 13.2% of patients with an eGFR less than 29 mL/min/1.73 m² had a lower UACR (<10 mg/g), and 15.8% had a UACR within the normal range (10-29 mg/g). In the three subgroups with eGFR ≥ 30 mL/min/1.73 m² (30-44, 45-59, and ≥ 60 mL/min/1.73 m²), UACR 10-29 mg/g accounted for the highest proportion (38.4%, 37.1%, and 40.5%) (Figure 1).

Based on the level of UACR, participants were divided into four groups (<10, 10-29, 30-299, and ≥ 300 mg/g), and then regression analysis was used to evaluate the correlation between reduced eGFR (<60 mL/min/1.73 m²) and the level of UACR. As shown in Figure 2, compared to the group with UACR < 10 mg/g, the three groups of UACR 10-29 mg/g, UACR 30-299 mg/g, and UACR ≥ 300 mg/g had a positive relation with reduced eGFR (1.248



[1.061-1.4677], 2.008 [1.690-2.384], 5.769 [4.152-8.015], $P \leq .001$). In addition, the OR increased with UACR. The differences remained after adjusting for the confounders of age, sex, blood glucose level, blood pressure, and blood lipid levels. The results above indicate that UACR was related to the risk of decreased eGFR even within the normal range.

4 | DISCUSSION

In this cross-sectional study in a Chinese population, we found that the subtype of renal deficiency with normoalbuminuria accounted for a considerable proportion. Normoalbuminuria with reduced eGFR was more prevalent in males, elderly patients, and those with higher TGs and lower HDLs. It also had a slight correlation with the risk of lower extremity vascular disease. Compared to diabetes with both albuminuria and reduced eGFR, those with normoalbuminuria had lower SBP, TGs, HbA1c, and shorter duration of diagnosis. After further investigation, the study suggested a positive association between UACR in the normal range and the risk of eGFR decline.

The rapid increase in diabetes has led to an increasing prevalence of diabetes-related complications. DKD, a common microvascular complication, has become a public health problem faced by various countries worldwide.¹⁶ DKD is characterized by persistent albuminuria and progressive renal dysfunction. Reductions in eGFR usually occur following macroalbuminuria. However, an increasing number of studies have indicated that eGFR decline can occur earlier than the presence of albuminuria.^{5,10,17} The reported prevalence of normoalbuminuria DKD varies in different studies. Our results showed that the prevalence of normoalbuminuria and reduced eGFR was 8.3% in all patients with diabetes and 63.3% in those who had an eGFR decline. In the UKPDS, which followed 9063 patients with type 2 diabetes for 15 years, 61% of those patients who developed renal impairment did not have albuminuria during the follow-up period,⁴ which is consistent with the current study. The NHANES III data indicated that albuminuria and retinopathy were both absent in 30% of adults with type 2 diabetes and chronic renal insufficiency among US civilians.⁵ In East Asia, Korea and Japan reported prevalence rates of 29.1% and 52.7%, respectively.^{7,18} Recently, according to a review, approximately 9.3% to 71.1% of patients with an eGFR < 60 mL/min/1.73 m² had normoalbuminuria.¹⁹ The prevalence reported in our study was higher than those reported in Korea and Japan and similar to that reported by the UK. The varying prevalence of the normoalbuminuria phenotype in DKD in different studies might be attributed to the heterogeneity and susceptibility of albuminuria in different races.¹⁷ A

study by Mather HM and Fischbacher CM showed a higher prevalence of microalbuminuria in Indian Asians than in Caucasians.^{8,20} Consistent with those results, in the review by Klimontov, the lowest prevalence of 9.3% normoalbuminuria kidney deficiency was also found in the Indian population.^{8,19,20} Although there are differences in prevalences reported in various studies, normoalbuminuria kidney deficiency still has a considerable proportion of diabetes. It is extraordinarily necessary to pay more attention to the clinical features, prognosis, and pathological mechanism of this neglected subtype.

The sex difference in susceptibility to normoalbuminuria renal insufficiency observed in this research was not consistent with previous studies. We found that normoalbuminuria eGFR decline was more prevalent in males than in females. Most previous studies have shown that women are at higher risk for normoalbuminuria renal insufficiency.^{10,11,18} The relationship between sex and impaired renal function has not yet been established. In nondiabetic conditions, men with chronic kidney disease of various etiologies show a more rapid decline in renal function than women²¹; however, a study suggested diabetic nephropathy progression to be faster in women,²¹ and the difference might be related to female hormones. A recent study published in the journal *Cells* investigated the extent to which sex hormones play a role in sex differences in both diabetes and transforming growth factor β 1 (TGF- β 1)-induced renal damage.²² They found that both genetic repertoire and sex hormones can determine sex differences in diabetic nephropathy, and hormones and sex in combination with TGF- β 1 dose determine whether TGF- β 1 exerts pro- or antifibrotic effects. In their study, neither dihydrotestosterone nor β -estradiol played a dominant role in the pathophysiology of diabetes- and/or TGF- β 1-induced renal damage, and each hormone exerted both stimulating and inhibitory effects on TGF- β 1 signaling, depending on sex and/or TGF- β 1 dosage. In our study, there was a strong correlation between males and normoalbuminuria renal insufficiency, which was rarely reported in previous studies. Whether the results are specific to the Chinese population needs to be further verified by more prospective studies.

We also found a positive relation between age and the risk of normoalbuminuria eGFR decline compared with those who did not have albuminuria and reduced eGFR. Previous research has found that age plays an important role in the progression of renal insufficiency.²³⁻²⁵ Hommos indicated that aging is associated with significant changes in the structure and function of the kidney, even in the absence of age-related comorbidities.²³ The results of our research also showed that patients who had reduced eGFR with albuminuria or not were significantly older than those who had normal albuminuria and eGFR. A review focused on aging and chronic disease suggested that the kidneys are



affected by the aging process, which results in numerous effects on the renal system. Renal mass decreases between the ages of 30 and 80 years, with the steepest decline observed after age 50. Fat and fibrosis scarring, which may replace some parenchymal tissue, occurs primarily in the renal cortex, and scarring affects the nephrons that are important for maximal urine concentration. Even in normal aging kidneys, 30% of the glomeruli are destroyed and display diffuse glomerular sclerosis by age 75, and the remaining glomeruli exhibit impaired filtering ability. The results from aging studies in animals and humans suggest that diverse factors contribute to the scarring process, such as tissue ischemia, injury, hypertension, metabolic defects, and obesity.²⁶

The results of our study showed obvious differences between high TG levels and normoalbuminuric renal dysfunction. This is not the first time such results have been reported. Ritz's study reported that high TG levels are one of the most common lipid abnormalities in chronic kidney disease and that they might be related to the alteration of the high TG fraction.²⁷ In a subsequent study, Reiss found that apolipoprotein A-I—the main protein component of high TG levels—is impaired in the progression of chronic kidney disease and enhanced in catabolism.

Additionally, we found a slight correlation between lower extremity vascular disease and normoalbuminuria renal insufficiency. Notably, although there was no significant difference in logistic regression analysis, the proportion of myocardial infarction and stroke in patients with normoalbuminuria and renal insufficiency was higher than that in patients without albuminuria and reduced eGFR in one-way ANOVA. Some studies have focused on normoalbuminuric renal dysfunction and diabetic macroangiopathy. A previous research by Wing reported a higher prevalence of cardiovascular diseases in diabetic patients with renal dysfunction and normal albuminuria levels.²⁸ However, diabetic retinopathy, as a microvascular disease that is often considered to have common progress with diabetic nephropathy, has a weakened association with normoalbuminuric DKD. In the Renal Insufficiency and Cardiovascular Events (RIACE) cross-sectional study, patients with normoalbuminuric renal insufficiency also had a lower prevalence of diabetic retinopathy than those with albuminuria (10% vs 22%).¹³ The following study of Yamanouchi further provided pathological evidence. They comparatively analyzed renal biopsies of patients with type 2 diabetes and reduced renal function, with and without proteinuria, and found that patients without proteinuria had better-controlled blood pressure and fewer changes in typical diabetic nephropathy.²⁹ Hence, some researchers proposed the hypothesis that macroangiopathy, but not microangiopathy, played a more important role in the development of normoalbuminuric renal insufficiency.

In brief, the clinical characteristics of patients with normoalbuminuria and reduced eGFR analyzed above are highly consistent with the factors of eGFR decline.³⁰ Other studies suggested that renal dysfunction in normoalbuminuria is related to the use of RAAS blockade.^{31–33} In the current research, we failed to find the association between RAAS blockade and normoalbuminuric kidney insufficiency. The proportion of patients receiving angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) treatment was higher among patients with decreased eGFR. These results reflect the status of therapy at the beginning of the research but could not reflect the causal relationship between RAAS blockers and normoalbuminuria renal dysfunction. NHANES III also examined the association of ACEIs/ARBs and normoalbuminuria renal dysfunction. Their results showed that there was no significant reduction in the prevalence of normal albuminuria after excluding those undergoing ACEI/ARB treatment (33.0% vs 36.0%).⁵ Whether affected by RAAS blockade or not, we thought that albuminuria seemed inadequate for the diagnosis of renal deficiency in diabetic patients. Our results indicate that a level of 10–29 mg/g UACR, even within the reference range, is still a related risk factor for eGFR reduction. Most of the subjects with eGFR > 30 mL/min/1.73 m² performed no albuminuria and had lower levels of UACR (between 10 and 29 mg/g). It is necessary to pay more attention to this commonly overlooked phenotype of kidney dysfunction among diabetes patients.

Nevertheless, whether the prognosis of normoalbuminuria DKD is better than that of albuminuria or progression to renal dysfunction still needs more evidence. The current research was a population-based multicenter study in a Chinese population. Therefore, confounding factors such as BMI, blood pressure, blood lipids, and medical history were fully considered. The result reflects the clinical characteristics of patients with normoalbuminuria and eGFR < 60 mL/min/1.73 m² and contributes to the understanding of diabetes-related kidney diseases. However, there are some deficiencies in this study. First, the data were acquired from the physical examination of the population, and it was difficult to repeat the tests of UACR and eGFR. Consequently, we could not make a definite diagnose of DKD; so we used a more broader definition of normal albuminuria and reduced glomerular filtration rate in diabetic patients. In addition, compared with the urinary albumin excretion rate over 24 hours, the diagnostic efficiency of UACR was lower. Some interference factors of urinary protein excretion rate could not be fully considered.

In summary, normoalbuminuria accounted for a considerable proportion of diabetic renal impairment in the Chinese population. Even without albuminuria, it was still

related to a higher risk of lower extremity vascular disease. Compared with patients with both albuminuria and decreased eGFR, those with normoalbuminuria showed lower levels of SBP, TGs, and HbA1c, suggesting that normoalbuminuria might be the early stage of albuminuria renal insufficiency. In addition, a higher level of UACR within the normal range can still be related to the increased risk of eGFR decline. Regarding clinical screening and early diagnosis of renal dysfunction in diabetes, there is an urgent need to further investigate pathogenesis and prognosis of normoalbuminuric renal insufficiency.

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DISCLOSURE

The authors declare no conflicts of interest.

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