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Insulin resistance is associated with urinary albumin-creatinine ratio in normal weight individuals with hypertension and diabetes: The REACTION study

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Abstract

Background: The relationship between albuminuria and insulin resistance (IR) has not been clarified in previous studies. This study was conducted to examine whether IR is associated with albuminuria in subjects with diverse blood pressure and glycometabolism statuses.

Methods: This study included 34 136 participants whose data were drawn from a cross-sectional survey named the 2011 REACTION study. The participants were divided into six groups. The urinary albumin-creatinine ratio (UACR) and glomerular filtration rate (GFR) were used as markers of chronic kidney disease (CKD). Variance tests and logistic regression models were performed for homeostatic model assessment of insulin resistance (HOMA-IR) in relation to UACR and eGFR.

Results: First, UACR levels and HOMA-IR exhibited a positive correlation among participants ($P < 0.05$), and a negative correlation existed between GFR and HOMA-IR ($P < 0.05$). Second, in the hypertension with diabetes group, in individuals whose body mass index (BMI) was 18.5-24.0 kg/m^2, age was 50-60 years old, low density lipoprotein cholesterol (LDL-C) was 2.6-3.4 mmol/L or high density lipoprotein cholesterol (HDL-C) was 0.9-1.55 mmol/L, HOMA-IR was positively associated with UACR ($P < 0.05$). However, there was a negative correlation between GFR and HOMA-IR in the hypertension with diabetes group in individuals whose BMI was 18.5-24.0 kg/m^2 or whose age was over 65 years old ($P < 0.05$).

Conclusions: In the context of different blood pressure and glycometabolism statuses, the positive correlation between UACR levels and HOMA-IR was affected by BMI, age, LDL-C, HDL-C, and GFR. In patients with hypertension and diabetes, the early detection and intervention of IR and related risk factors in patients with normal BMI may reduce the occurrence of microalbuminuria and delay the progression of CKD.

1 | INTRODUCTION

Chronic kidney disease (CKD) is a common global public health problem. In recent years, as people's dietary habits and lifestyles have changed, the intake of sugar, fat, protein, and other substances has increased significantly, which has been coupled with a lack of physical exercise; the prevalence of CKD has increased year by year, and the prevalence rate is approximately 8%-16%.[1] Diabetes and hypertension are the most common causes of CKD and can result in the worsening of the disease[2] by speeding up the progression of kidney disease, increasing cardiovascular mortality, and leading to acute kidney injury, impaired cognitive function, anemia, imbalanced bone salt metabolism, fracture, and other complications. It is estimated that by 2025, the number of people with diabetes worldwide will increase to 300 million.[3] Therefore, the prevention of diabetes- or hypertension-related kidney disease may be the key to reducing the social and economic burden of end-stage renal disease (ESRD)-induced diseases.[4]

Microalbuminuria is currently recognized as an independent risk factor for cardiovascular and cerebrovascular diseases and is also an indicator of the stability of CKD; microalbuminuria has been widely used in the clinic as the most sensitive and reliable early indicator of kidney disease. The prevalence of microalbuminuria in diabetic patients is 2-3 times higher than that in healthy people, and the prevalence rate is more than 10%.[5] The prevalence increases with increasing blood glucose levels; however, reduced insulin sensitivity may augment the risk of albuminuria.[6] Studies have shown that microalbuminuria can occur concurrently with diabetes and that microalbuminuria predicts the risk of type 2 diabetes mellitus (T2DM). Microalbuminuria and metabolic syndrome (MetS) as well as its components (including abdominal obesity, blood lipids, blood pressure, blood glucose, etc.), insulin sensitivity, and insulin resistance (IR) are closely related. Currently, this area has become a popular research focus.

IR refers to the reduced in vivo activity of insulin in the promotion of peripheral tissue uptake and utilization of glucose, decreasing the biological effects of hepatic glycogen output inhibition, thus resulting in hyperinsulinemia and/or elevated blood glucose. IR often occurs in patients with MetS and is the central component of the pathogenesis of MetS. IR is mainly caused by abdominal obesity,[7] and studies have shown that IR and obesity in individuals with diabetic renal injury are closely related.[7-10] Another study demonstrated that IgA nephropathy exists in most patients with IR as well.[11] Therefore, IR is not only a risk factor for new-onset diabetes, cardiovascular events, and all-cause mortality but is also an independent risk factor for renal damage and ultimately renal failure. Recently, research on CKD and IR has been carried out throughout the world. However, the relationship between CKD and IR is not consistent among all ethnic groups and countries.[12-14] In this regard, we conducted related research on blood pressure and glucose metabolism status based on data from China's Risk Evaluation of cAncers in Chinese diabeTic Individuals, a lONgitudinal (REACTION) study.

2 | METHODS

2.1 | Study subjects

A total of 53 639 participants from the REACTION study were investigated; the participants were recruited from 8 regional centers: Gansu, Guangdong, Guangxi, Henan, Hubei, Liaoning, Shanghai, and Sichuan. Subjects with primary kidney diseases, daily use of angiotensin converting enzyme inhibitor/angiotensin receptor blocker medicine, and unreasonable and missing data were excluded, and 34 136 participants were finally selected for baseline inclusion.

2.2 | Medical history

The participants' basic information, including their general situation, past medical history, current medication situation, lifestyle, physical exercise, smoking and alcohol consumption habits, family history and other basic information, was collected using a standardized questionnaire. All involved investigators were formally trained.

2.3 | Physical examination

The height, weight, waist circumference (WC), and hip circumference (HC) of the subjects were measured and recorded. Participants were required to take off their shoes, hats, and coats before the measurements were taken. While the participants stood with their feet shoulder width apart, their WC was measured in the horizontal plane at the midpoint of the ligature between the anterior superior spine and the inferior margin of the 12th rib. HC was measured as the horizontal circumference of the most prominent part of the hips while the participants stood with their feet together. All data were accurate to one decimal place.

2.4 | Urinary albumin-creatinine ratio (UACR) measurement and data processing

Urine samples were collected in the morning (midstream urine) for UACR measurements. Because the kits for measuring UACR in each center and the range of normal values are different, the value of UACR divided by the median of all values in the center at which the subject was attended (UACR/median) was used to estimate albuminuria. According to the statistics, natural logarithm transformation made albuminuria normally distributed. UACR data were categorized into four groups based on quartiles of logistic regression analysis: less than 25%, 25%-50%, 50%-75%, and greater than 75%.

2.5 | Blood pressure measurement

Blood pressure was measured three times at 1 minute intervals after the subjects sat and rested for 5 minutes. The average of the three values was used for the analysis.

2.6 | Laboratory index measurement

Blood samples were drawn in the morning after subjects fasted for 8 hours the previous night. Participants without a history of diabetes underwent a 75 g oral glucose tolerance test (OGTT), and their venous blood samples were drawn at 0 and 120 minutes. The biochemical indexes, included triglycerides (TGs), cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum creatinine (Scr), blood urea nitrogen (BUN), liver function indexes (alanine transaminase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT]), fasting blood glucose (FBG), postprandial blood glucose (PBG), glycosylated hemoglobin (HbA1c),

fasting blood insulin, and postprandial blood insulin were measured by the glucose oxidase-peroxidase method. Glomerular filtration rate (GFR) was estimated from the simplified equation developed using the Modification of Diet in Renal Disease (MDRD) data: $GFR = 175 \times (Scr \text{ in } mg/dL)^{-1.154} \times age^{-0.203} \times (0.742 \text{ for women}) \times (1.212 \text{ if African American})$.[15]

2.7 | Insulin resistance index

IR was assessed using the homeostatic model of insulin resistance index (HOMA-IR) formula. HOMA-IR was calculated as fasting plasma glucose (mmol/L) × fasting insulin (mU/L) / 22.5.[16] According to the statistical requirements, natural logarithm conversion was performed to achieve a normal distribution. According to logistic regression analysis (HOMA-IR percentiles) quartiles, HOMA-IR data were divided into four groups: less than 25%, 25%-50%, 50%-75%, and more than 75%.

2.8 | Statistical analysis

Statistical analysis was performed using SPSS software, version 20.0. All continuous variables are presented as the mean values and standard deviations (SDs). Measurement data were tested by analysis of variance or t test. Enumeration data were examined by chi-square test. Pearson correlation analysis examined the relationships between two quantitative variables. The two classification variables were tested by a stepwise logistic regression analysis. $P < 0.05$ was considered statistically significant.

3 | RESULTS

1. Baseline information: A total of 34 136 participants were included in the study. According to different blood pressure and glycometabolism statuses, the participants were divided into six groups: hypertension (HT, systolic blood pressure [SBP] ≥ 140 mmHg or diastolic blood pressure [DBP] ≥ 90 mmHg) with normal glucose tolerance (NGT, according to the OGTT), HT with prediabetes (pre-DM), HT with diabetes mellitus (DM), normotension (NT) with NGT, NT with pre-DM. and NT with DM. The clinical characteristics of the study participants are presented in Table 1 and Table 2. As the data showed, there were significant differences between the groups in regard to age, sex, body mass index (BMI), WC-HC, ALT-AST, TGs, TC, LDL-C, GFR, and HOMA-IR ($P < 0.05$). In the HT with pre-DM or DM groups and the NT with pre-DM

TABLE 1 Characteristics of study population by HOMA-IR quartiles of HT

Variable	HT with NGT group (n = 5286)					HT with pre-DM group (n = 3964)					HT with DM group (n = 4459)				
	LnHOMA-IR(1)	LnHOMA-IR(2)	LnHOMA-IR(3)	LnHOMA-IR(4)	P value	LnHOMA-IR(1)	LnHOMA-IR(2)	LnHOMA-IR(3)	LnHOMA-IR(4)	P value	LnHOMA-IR(1)	LnHOMA-IR(2)	LnHOMA-IR(3)	LnHOMA-IR(4)	P value
	n = 1339	n = 1538	n = 1516	n = 893		n = 537	n = 812	n = 1229	n = 1386		n = 318	n = 538	n = 1010	n = 2593	
Age	60.93 ± 9.45	60.43 ± 9.08	59.20 ± 9.08	58.97 ± 9.41	<0.001	63.67 ± 10.28	62.16 ± 9.09	61.62 ± 9.18	60.82 ± 9.36	<0.001	64.21 ± 9.15	64.76 ± 9.29	63.68 ± 9.06	62.69 ± 8.88	<0.001
BMI, Kg/m^2	23.31 ± 3.47	24.72 ± 3.31	25.76 ± 3.05	27.38 ± 3.17	<0.001	23.22 ± 3.00	24.87 ± 3.08	26.01 ± 3.63	27.50 ± 3.50	<0.001	23.20 ± 3.10	24.46 ± 3.05	25.47 ± 3.04	27.18 ± 3.70	<0.001
Wc-hc	0.89 ± 0.07	0.89 ± 0.07	0.90 ± 0.06	0.91 ± 0.06	<0.001	0.89 ± 0.07	0.90 ± 0.07	0.90 ± 0.07	0.91 ± 0.07	<0.001	0.89 ± 0.07	0.90 ± 0.06	0.91 ± 0.07	0.92 ± 0.06	<0.001
AST-ALT	1.65 ± 0.68	1.50 ± 0.51	1.40 ± 0.48	1.27 ± 0.50	<0.001	1.67 ± 0.57	1.51 ± 0.51	1.40 ± 0.48	1.25 ± 0.45	<0.001	1.65 ± 0.66	1.45 ± 0.53	1.37 ± 0.50	1.23 ± 0.47	<0.001
TG, mmol/L	1.22 ± 0.73	1.46 ± 0.91	1.70 ± 1.04	2.03 ± 1.37	<0.001	1.41 ± 0.97	1.64 ± 1.01	1.90 ± 1.19	2.12 ± 1.37	<0.001	1.40 ± 1.07	1.65 ± 0.99	1.91 ± 1.18	2.28 ± 1.60	<0.001
CHOL, mmol/L	4.96 ± 1.11	5.11 ± 1.15	5.21 ± 1.15	5.24 ± 1.13	<0.001	4.89 ± 1.10	5.07 ± 1.17	5.18 ± 1.20	5.15 ± 1.19	<0.001	4.83 ± 1.21	5.03 ± 1.23	5.13 ± 1.23	5.18 ± 1.23	<0.001
LDL, mmol/L	2.92 ± 0.88	3.06 ± 0.91	3.11 ± 0.90	3.13 ± 0.90	<0.001	2.82 ± 0.86	3.00 ± 0.91	3.05 ± 0.93	3.05 ± 0.92	<0.001	2.79 ± 0.97	3.00 ± 0.93	3.01 ± 0.94	3.03 ± 0.97	<0.001
HDL, mmol/L	1.42 ± 0.37	1.34 ± 0.35	1.29 ± 0.32	1.22 ± 0.29	<0.001	1.37 ± 0.38	1.28 ± 0.34	1.26 ± 0.33	1.20 ± 0.30	<0.001	1.34 ± 0.36	1.26 ± 0.34	1.24 ± 0.32	1.20 ± 0.30	<0.001
GFR(mL/min*1.73m^2)	94.80 ± 20.61	93.23 ± 19.52	91.60 ± 19.43	90.87 ± 19.43	<0.001	94.94 ± 21.81	93.75 ± 21.33	92.07 ± 20.76	91.23 ± 20.55	<0.001	95.45 ± 19.81	91.73 ± 26.17	89.86 ± 21.16	88.79 ± 20.77	<0.001
Ln(UACR/Median)	0.20 ± 1.05	0.20 ± 1.13	0.23 ± 1.16	0.31 ± 1.28	0.099	0.22 ± 1.01	0.21 ± 1.00	0.32 ± 1.05	0.37 ± 1.24	0.004	0.30 ± 1.11	0.42 ± 1.09	0.47 ± 1.22	0.70 ± 1.31	0.004
Sex(male)	41.6(557)	34.9(537)	30.1(457)	31.7(283)	<0.001	48.9(262)	41.6(338)	399(32.5)	31.5(436)	<0.001	58.2(185)	48.0(258)	40.9(413)	35.5(920)	<0.001
Smoking habits, %					<0.001					<0.001					<0.001
Never smoker	79.9(1067)	86.2(1317)	88.1(1326)	87.4(774)		79.5(427)	84.2(678)	88.1(1072)	88.9(1223)		79.0(248)	82.8(442)	86.6(869)	87.1(2245)	
Sometimes smoker	2.9(39)	2.4(37)	1.9(28)	1.8(16)		3.0(16)	2.7(22)	2.6(32)	2.2(30)		1.6(5)	2.8(15)	2.7(27)	2.5(65)	
Regular smoker	17.2(229)	11.4(174)	10.0(151)	10.8(96)		17.5(94)	13.0(105)	9.3(113)	8.9(122)		19.4(61)	14.4(77)	10.7(107)	10.4(267)	
Drinking habits, %					<0.001					<0.001					<0.001
Never drinker	71.1(949)	75.7(1155)	76.8(1159)	74.9(665)		69.6(374)	71.1(572)	77.0(936)	77.5(1067)		66.5(210)	73.9(394)	76.5(770)	78.4(2019)	
Sometimes drinker	17.2(229)	16.9(258)	16.8(254)	18.4(163)		16.2(87)	19.4(156)	14.7(179)	15.5(213)		19.6(62)	18.6(99)	16.0(161)	13.6(351)	
Regular drinker	11.7(156)	7.4(113)	6.4(97)	6.8(60)		14.2(76)	9.5(76)	8.3(101)	7.0(96)		13.9(44)	7.5(40)	7.5(76)	8.0(205)	

Note: Data were mean ± SD or median (IQR) for skewed variables or numbers (proportions) for categorical variables.

AST-ALT, aspartate aminotransferase to alanine aminotransferase rate; CHOL, cholesterol; BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hypertension (HT, SBP ≥140 mmHg or DBP ≥90 mmHg); LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; UACR, urinary albumin-creatinine ratio; Wc-hc, waist-to-height ratio.

TABLE 2 Characteristics of study population by HOMA-IR quartiles of NT

Variable	NT with NGT group (n=11949)					NT with pre-DM group (n=6205)					NT with DM group (n=2273)				
	LnHOMA-IR(1) n=4883	LnHOMA-IR(2) n=3825	LnHOMA-IR(3) n=2295	LnHOMA-IR(4) n=946	P value	LnHOMA-IR(1) n=1305	LnHOMA-IR(2) n=1565	LnHOMA-IR(3) n=1772	LnHOMA-IR(4) n=1563	P value	LnHOMA-IR(1) n=208	LnHOMA-IR(2) n=338	LnHOMA-IR(3) n=564	LnHOMA-IR(4) n=1163	P value
Age, years	54.60±8.17	54.33±8.13	53.89±7.83	53.98±7.96	0.002	57.96±9.76	56.88±9.02	56.53±8.59	56.07±8.37	<0.001	60.22±8.69	59.17±8.97	59.22±8.87	58.43±8.92	0.03
BMI, Kg/m²	22.10±3.07	23.55±2.96	24.69±3.23	25.95±3.40	<0.001	22.12±3.12	23.77±3.26	24.79±3.10	26.42±3.28	<0.001	22.19±2.99	23.67±3.26	24.50±3.85	25.94±3.47	<0.001
Wc-hc	0.86±0.07	0.87±0.07	0.88±0.08	0.89±0.07	<0.001	0.87±0.07	0.88±0.08	0.89±0.06	0.90±0.07	<0.001	0.88±0.06	0.89±0.06	0.90±0.07	0.91±0.06	<0.001
AST-ALT	1.61±0.52	1.50±0.50	1.38±0.47	1.26±0.46	<0.001	1.68±0.88	1.50±0.53	1.39±0.50	1.27±0.47	<0.001	1.59±0.82	1.39±0.55	1.33±0.52	1.19±0.41	<0.001
TG, mmol/L	1.12±0.74	1.33±0.84	1.55±1.04	1.91±1.27	<0.001	1.24±0.82	1.58±1.06	1.87±1.38	2.06±1.36	<0.001	1.43±1.36	1.57±1.33	1.78±1.17	2.21±1.78	<0.001
CHOL, mmol/L	4.77±1.15	4.91±1.15	4.97±1.19	5.05±1.22	<0.001	4.73±1.21	4.92±1.19	4.95±1.21	5.04±1.24	<0.001	4.69±1.10	4.81±1.12	4.87±1.22	5.02±1.23	<0.001
LDL, mmol/L	2.76±0.88	2.90±0.88	2.96±0.94	3.02±0.95	<0.001	2.72±0.89	2.89±0.90	2.88±0.90	2.98±0.97	<0.001	2.69±0.78	2.79±0.82	2.85±0.95	2.94±0.95	<0.001
HDL, mmol/L	1.41±0.37	1.35±0.36	1.29±0.33	1.22±0.34	<0.001	1.36±0.39	1.28±0.33	1.23±0.33	1.19±0.31	<0.001	1.29±0.34	1.26±0.32	1.22±0.35	1.17±0.29	<0.001
GFR(mL/min*1.73m²)	99.37±21.90	97.40±21.34	97.25±20.94	96.46±21.59	<0.001	101.28±23.58	98.29±20.77	96.43±20.28	95.37±20.40	<0.001	98.46±24.73	98.20±19.79	96.30±22.51	94.23±22.01	0.004
Ln(UACR/Median)	-0.14±1.00	-0.13±0.99	-0.17±1.04	-0.08±1.05	0.07	-0.13±0.96	-0.09±0.89	-0.05±0.88	-0.01±0.94	0.07	0.04±0.93	0.19±0.95	0.13±1.13	0.31±1.11	<0.001
Sex(male)	31.4(1531)	24.2(927)	23.4(580)	23.3(234)	<0.001	46.2(603)	30.0(469)	26.8(475)	25.8(404)	<0.001	53.8(112)	51.5(174)	44.1(249)	41.1(478)	<0.001
Smoking habits, %					<0.001					<0.001					0.0386
Never smoker	81.8(3947)	86.4(3289)	88.2(2167)	87.6(872)		77.8(1008)	85.4(1327)	88.2(1544)	87.3(1351)		76.3(158)	76.6(256)	79.9(448)	79.4(914)	
Sometimes smoker	2.2(105)	2.0(78)	2.9(72)	2.4(24)		3.7(48)	3.0(47)	2.7(47)	3.2(50)		2.9(6)	4.8(16)	4.6(26)	3.3(38)	
Regular smoker	16.1(775)	11.5(438)	8.9(219)	10.0(100)		18.5(240)	11.5(179)	9.1(160)	9.5(147)		20.8(43)	18.6(62)	15.5(87)	17.3(199)	
Drinking habits, %					<0.001					<0.001					0.483
Never drinker	70.5(3414)	73.3(2786)	75.6(1853)	75.8(755)		66.4(860)	72.5(1126)	76.4(1343)	76.3(1185)		70.7(145)	71.9(241)	75.2(422)	74.6(862)	
Sometimes drinker	22.6(1093)	22.0(834)	20.3(497)	19.6(195)		22.9(297)	21.2(329)	19.8(348)	18.9(294)		20.5(42)	22.1(74)	18.4(103)	17.9(207)	
Regular drinker	6.9(334)	4.7(179)	4.2(102)	4.6(46)		10.7(138)	6.4(99)	3.9(68)	4.8(74)		8.8(18)	6.0(20)	6.4(36)	7.5(87)	

Note: Data were mean ± SD or median (IQR) for skewed variables or numbers (proportions) for categorical variables.

AST-ALT, aspartate aminotransferase to alanine aminotransferase rate; BMI, body mass index; CHOL, cholesterol; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hypertension (HT, SBP ≥140 mmHg or DBP ≥90 mmHg); IQR, interquartile range; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; UACR, urinary albumin-creatinine ratio; Wc-hc, waist-to-height ratio.

TABLE 3 Correlation between UACR and IR in total participants or HT with DM group

	OR	LnHOMA-IR(1) (Quartile one)	LnHOMA- IR(2) (Quartile two)	LnHOMA- IR(3) (Quartile three)	LnHOMA-IR(4) (Quartile four)	P value
total	Age and sex adjusted	0.59	0.63	0.71	1	<0.001
(n = 34 136)	Multivariate adjusted	0.63	0.65	0.72	1	<0.001
HT with DM group (n = 4459)	Age and sex adjusted	0.61	0.68	0.75	1	<0.001
	Multivariate adjusted	0.65	0.75	0.79	1	<0.003

Note: Multivariate adjusted: Adjusted for sex, age, BM, Wc-hc, AST-ALT, SBP, DBP, TG, GGT, CHOL, HDL-C, LDL-C, HR, smoking, drinking, history of oncology, history of myocardial infarction, history of stroke.

AST-ALT, aspartate aminotransferase to alanine aminotransferase rate; BM, body mass; CHOL, cholesterol; DBP, diastolic blood pressure; DM, diabetes mellitus; GGT, gamma-glutamyl transpeptidase; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, heart rate; HT, hypertension; LDL-C, low density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; TG, triglycerides; UACR, urinary albumin-creatinine ratio; Wc-hc, waist-to-height ratio.

or DM groups, UACR was associated with HOMA-IR ($P < 0.05$). There was no correlation between UACR and HOMA-IR in the other two groups ($P > 0.05$). There were significant differences between smoking/alcohol consumption habits and HOMA-IR in the HT with NGT, pre-DM or DM groups and in the NT with NGT or pre-DM groups ($P < 0.05$). The other group exhibited the opposite result ($P > 0.05$).

2. Logistical correlation analysis: There was a positive correlation between HOMA-IR and UACR in the total sample of participants and in the hypertension with diabetes group ($P < 0.05$, Table 3, Figure 1), and a negative correlation existed between GFR and HOMA-IR ($P < 0.05$, Table 4, Figure 1). The correlation was adjusted for only age and sex or was fully adjusted for sex, age, BMI, WC-HC, AST-ALT, SBP, DBP, TGs, GGT, TC, HDL-C, LDL-C, heart rate (HR), tumor history, myocardial infarction history, stroke history, smoking habits, and alcohol consumption habits.

3. Diverse subgroups in the HT with DM group: Our study showed that in the HT with diabetes group, in individuals with a BMI from 18.5-24.0 kg/m², age from 50-60 years old, LDL-C from 2.6-3.4 mmol/L or HDL-C from 0.9-1.55 mmol/L, HOMA-IR was positively associated with UACR ($P < 0.05$, Table 5). The higher the IR index, the higher the UACR (Figure 2). There was also a negative correlation between GFR and HOMA-IR in the hypertension with diabetes group, in which the BMI was 18.5-24.0 kg/m² or age was over 65 years old ($P < 0.05$, Table 6, Figure 3).

4 | DISCUSSION

As early as 1974, Weisinger et al first reported that high levels of albuminuria were detected in patients with severe obesity, and the corresponding pathological biopsy suggested kidney damage. Subsequent similar cases were

FIGURE 1 Relationship between UACR and GFR and HOMA-IR in total participants; UACR, urinary albumin-creatinine ratio; GFR, glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance
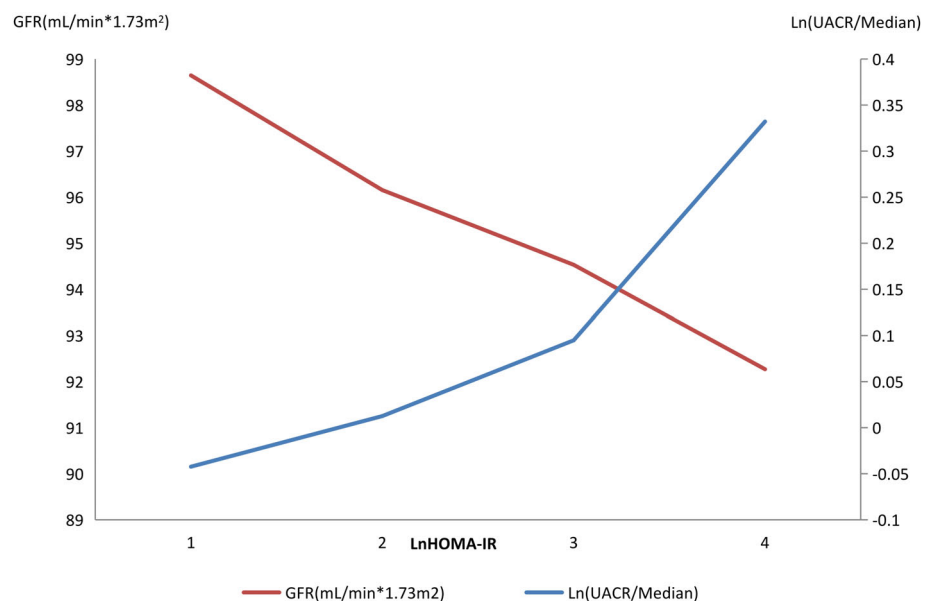
TABLE 4 Correlation between GFR and IR in total participants or HT with DM group

	OR	LnHOMA-IR(1) (Quartile one)	LnHOMA- IR(2) (Quartile two)	LnHOMA- IR(3) (Quartile three)	LnHOMA-IR(4) (Quartile four)	P value
total (n = 34 136)	Age and sex adjusted	1.5	1.28	1.15	1	<0.001
	Multivariate adjusted	1.5	1.27	1.16	1	<0.001
HT with DM group (n = 4459)	Age and sex adjusted	2.02	1.3	1.18	1	0.014
	Multivariate adjusted	2.04	1.22	1.17	1	0.047

Note: Multivariate adjusted: Adjusted for sex, age, BM, Wc-hc, AST-ALT, SBP, DBP, TG, GGT, CHOL, HDL-C, LDL-C, HR, smoking, drinking, history of oncology, history of myocardial infarction, history of stroke.
AST-ALT, aspartate aminotransferase to alanine aminotransferase rate; BMI, body mass index; CHOL, cholesterol; DBP, diastolic blood pressure; DM, diabetes mellitus; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, heart rate; HT, hypertension; LDL-C, low density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; TG, triglycerides; UACR, urinary albumin-creatinine ratio; Wc-hc,   waist-to-height ratio.

summarized, and this disease was defined as obesity-related nephropathy (BMI > 30 kg/m^2).[17] So far, the pathogenesis of the disease remains unclear, although many investigators are committed to studying the disease. Obese patients are often associated with IR, which can damage renal podocytes and cause renal hemodynamic disturbances by affecting the podocyte insulin pathway. Numerous studies have shown that IR is an independent risk factor for kidney damage and ultimately renal failure.[18,19] Clinical studies have indicated that

TABLE 5 HT with DM group: the relationship between UACR and IR in diverse subgroup

Variable		LnHOMA-IR(1) OR	LnHOMA-IR(1) P value	LnHOMA-IR(2) OR	LnHOMA-IR(2) P value	LnHOMA-IR(3) OR	LnHOMA-IR(3) P value	LnHOMA-IR(4) OR	LnHOMA-IR(4) P value
TG(mmol/L)	<0.56	1.05	>0.05	27.22	>0.05	8.16	>0.05	1	—
	0.56-1.7	0.7	0.022	1.22	>0.05	0.82	>0.05	1	—
	>1.7	0.74	>0.05	1.46	0.015	0.81	0.048	1	—
BMI(Kg / m2)	<18.5	6.1	>0.05	8.91	>0.05	1.98	>0.05	1	—
	18.5–24.0	0.46	0	0.6	0.003	0.68	0.01	1	—
	24.0-27.9	0.81	>0.05	0.8	>0.05	0.92	>0.05	1	—
	≥28.0	0.62	>0.05	0.91	>0.05	0.68	0.02	1	—
Sex	Male	0.71	0.049	0.68	0.007	0.82	>0.05	1	—
	Female	0.68	0.041	0.89	>0.05	0.81	0.026	1	—
Age(years old)	≤50	2.22	>0.05	0.93	>0.05	0.55	0.048	1	—
	50–60	0.48	0.001	0.6	0.003	0.71	0.011	1	—
	60-70	0.97	>0.05	0.82	>0.05	0.8	>0.05	1	—
	>70	0.47	0.004	0.86	>0.05	1.04	>0.05	1	—
LDL-C(mmol/L)	<1.8	1.07	>0.05	0.92	>0.05	1.29	>0.05	1	—
	1.8-2.6	0.68	>0.05	0.67	0.05	0.76	>0.05	1	—
	2.6–3.4	0.49	0.004	0.65	0.015	0.82	>0.05	1	—
	≥3.4	0.65	>0.05	0.76	>0.05	0.7	0.05	1	—
HDL-C(mmol/L)	<0.9	0.7	>0.05	0.87	>0.05	0.95	>0.05	1	—
	0.9–1.55	0.66	0.006	0.76	0.018	0.79	0.005	1	—
	>1.55	0.66	>0.05	0.66	>0.05	0.76	>0.05	1	—
Regionalism	south	0.56	0.002	0.74	0.046	0.85	>0.05	1	—
	north	0.79	>0.05	0.76	0.037	0.79	0.012	1	—

BMI, body mass index; DM, diabetes mellitus; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol OR, odds ratio; TG, triglycerides; UACR, urinary albumin-creatinine ratio.

FIGURE 2 HT with DM group:
Association between UACR and IR in
different subgroups; UACR, urinary
albumin-creatinine ratio; HOMA-IR,
homeostatic model assessment of insulin
resistance. HT, hypertension; DM,
diabetes mellitus
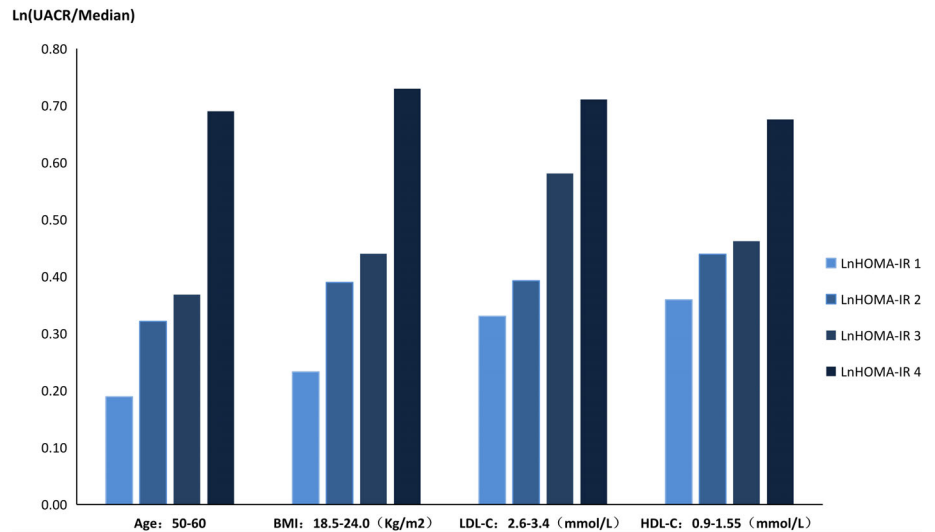
insulin sensitizers or insulin-sensitizing hypoglycemic drugs can increase the body's sensitivity to insulin while improving endothelial function, having a significant protective effect on the cardiovascular system and kidneys, but these drugs can also significantly reduce the urinary albumin excretion rate.[20] The United States Kidney Disease Outcome Quality Initiative (K/DOQI) recommended screening for microalbuminuria in people with a high risk of kidney disease and cardiovascular disease. This index has good stability. Chen et al and Srivastava et al reported that CKD was positively associated with HOMA-IR in the United States and India.[21,22] In Korean adults with or without T2DM, insulin resistance was positively associated with CKD.[23] In contrast, Satirapoj et al

TABLE 6 HT with DM group: the relationship between GFR and IR in diverse subgroup

Variable		LnHOMA-IR(1) OR	P value	LnHOMA-IR(2) OR	P value	LnHOMA-IR(3) OR	P value	LnHOMA-IR(4) OR	P value
BMI(Kg / m2)	<18.5	6515	>0.05	758	>0.05	696 623	>0.05	1	—
	18.5–24.0	3.3	0	1.48	0.02	1.34	0.046	1	—
	24.0-27.9	1.39	>0.05	1.21	>0.05	1.15	>0.05	1	—
	≥28.0	2.01	>0.05	1.06	>0.05	1.21	>0.05	1	—
Sex	Male	1.74	0.002	1.26	>0.05	0.95	>0.05	1	—
	Female	2.39	0	1.16	>0.05	0.35	0.002	1	—
Age(years old)	<45	0.87	>0.05	0.22	>0.05	0.5	>0.05	1	—
	45-55	1.28	>0.05	0.81	>0.05	1.13	>0.05	1	—
	55-65	2.09	>0.05	1.24	>0.05	1.08	>0.05	1	—
	≥65	2.28	0	1.49	0.011	1.29	0.037	1	—
LDL-C(mmol/L)	<1.8	2.47	0.026	0.92	>0.05	1.29	>0.05	1	—
	1.8–2.6	2.53	0	1.09	>0.05	0.95	>0.05	1	—
	2.6–3.4	1.51	>0.05	1.49	0.02	1.05	>0.05	1	—
	≥3.4	1.77	0.02	1.18	>0.05	1.48	0.002	1	—
HDL-C(mmol/L)	<0.9	2.86	0.032	1.02	>0.05	0.87	>0.05	1	—
	0.9–1.55	1.92	0	1.2	>0.05	1.12	>0.05	1	—
	>1.55	2.69	0.001	1.45	>0.05	1.69	0.014	1	—
Regionalism	south	2.22	0	1.21	>0.05	1.26	>0.05	1	—
	north	2.15	0	1.32	0.039	1.13	>0.05	1	—

BMI, body mass index; DM, diabetes mellitus; GFR, glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; OR, odds ratio.
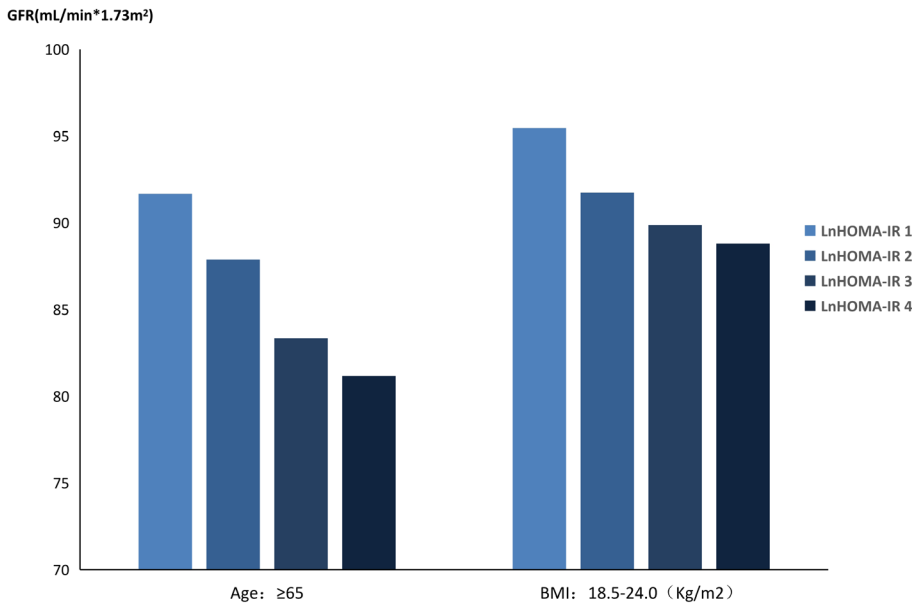
GFR(mL/min*1.73m²)

FIGURE 3 HT with DM group: Association between GFR and IR in different subgroups; GFR, glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance; HT, hypertension; DM, diabetes mellitus

and Trirogoff et al reported that HOMA-IR had no significant correlation with GFR in the United States and the United Kingdom.[24,25] It was reported that in the Indian CKD patient group, estimated GFR did not correlate with the degree of IR.[21] In the present study, the relationship between IR and microalbuminuria in groups with different blood pressure and glucose metabolism statuses was studied by grouping individuals by blood pressure (SBP ≥140 mmHg or DBP ≥90 mmHg) and glucose tolerance according to the results from a 75 g OGTT. The association between albuminuria and IR was mainly analyzed in the HT with diabetes group due to the significant correlation. Our study showed that HOMA-IR was significantly associated with age, sex, BMI, WC-HC, GFR, ALT/AST, TGs, CHOL, LDL-C, and HDL-C. In participants with prediabetes and diabetes, UACR and IR had statistically significant differences, independent of blood pressure. Thus, UACR was not associated with IR in individuals with NGT. IR most often occurs in patients with MetS and is the central component of the pathogenesis of MetS. In regard to BMI, WC-HC ratio, and blood lipids, our study's results are consistent with those of previous reports. A large prospective longitudinal survey using community-based risk of atherosclerosis (Atherosclerosis Risk in Communities, ARIC) showed that MetS and HOMA-IR quintiles were correlated with the incidence of CKD in adults without diabetes after controlling for the development of DM and HT.[26] However, our research showed no correlation between HOMA-IR and UACR in NGT patients, which is not in accordance with the conclusion of the aforementioned study. This difference may be related to the prediabetes population, that is, the population of individuals with impaired glucose tolerance and impaired fasting glucose but not meeting the criteria

for the standard diagnosis of diabetes. HOMA-IR is associated with UACR in these individuals, suggesting that IR should be observed in people with impaired glucose tolerance and diabetes. The occurrence and aggravation of IR may predict the progression of microalbuminuria. In addition, the findings also showed that there was a significant correlation between HOMA-IR and GFR in the total sample of participants, which suggested that IR may affect GFR levels in individuals with different glucose tolerance and blood pressure statuses.

Recent research has demonstrated that IR may promote the development of microalbuminuria among type 1 diabetic patients,[27] type 2 diabetic patients,[28] and hypertensive patients.[29] In this study, stratified regression analysis of hypertensive patients with DM by age, sex, BMI, TGs, LDL-C, HDL-C, and geographical region showed that in the individuals in whom BMI was 18.5-24.0 kg/m² or age ranged from 50 to 60 years old, HOMA-IR and UACR both exhibited positive correlations and regression relationships. Thus, this finding indicated that, in this part of the population, the lower the insulin sensitivity or the higher the resistance index, the higher the urine microalbumin, which is associated with kidney damage risk. In general, a HOMA-IR interquartile range greater than 75% is considered insulin resistance. This study showed that among the hypertensive population with diabetes, when the BMI remained at 18.5-24.0 kg/m², the risk of developing microalbuminuria decreased by at least 32% in the population without insulin resistance compared to the population with IR. Similarly, the risk was at least 29% lower in people aged 50-60 years. In terms of BMI, our findings were different from those of previous studies. IR was associated with the incidence of CKD in ARIC research, and this

relationship was not associated with BMI. In previous studies, all participants were of black or white race and aged 45-64.[26] Other studies have shown that, although IR and MetS are common in the Chinese population with normal weight, they are not related to CKD. IR is associated with the development of CKD in obese and overweight people.[12] However, our study demonstrated that HOMA-IR is positively associated with the occurrence of microalbuminuria in hypertensive Chinese participants with normal body mass and diabetes, and this relationship was independent of weight loss and obesity/overweight status. In the diverse subgroup analysis, GFR and IR were also affected by different BMI status. In the normal BMI participants, the more severe the IR, the lower the GFR. This finding indicated that the population with a BMI of 18.5-24 kg/m^2 could reduce or delay the progression of microalbuminuria and GFR by managing the development of IR and MetS. The differences in these studies may be related to race, age, and selected population.

Previous studies have shown that abdominal obesity, elevated triglycerides, decreased levels of HDL-C, elevated blood pressure, and elevated fasting glucose levels are risk factors for CKD.[26] Hypertensive renal blood flow in patients with automatic regulation of dysfunction leads to glomerular long-term high perfusion and reduces the charge of the filtration membrane, thus causing substantial albumin leakage and the formation of proteinuria. Hyperinsulinemia, diabetes, etc., promote the development of kidney disease through the worsening of renal hemodynamics, the release of inflammatory cytokines and the stress of the renal endoplasmic reticulum. This study attempted to find a clear and meaningful point among these risk factors that had indications for the management of CKD risk. The results showed that when the blood lipid level was controlled at 2.6 mmol/L $\leq$ LDL-C<3.4 mmol/L or 0.9 mmol/L $\leq$ HDL-C $\leq$ 1.55 mmol/L in individuals with hypertension and diabetes, HOMA-IR was positively associated with urinary microalbumin, which suggested that in this numerical range, the risk of urinary microalbumin can be reduced by decreasing IR. Urine microalbumin in the early diagnosis and prevention of CKD has important value.[30]

In conclusion, HOMA-IR was significantly associated with basic clinical parameters (BMI, WC-HC, GFR, ALT-AST, TGs, TC, LDL-C, and HDL-C) in the general population. HOMA-IR was positively associated with UACR, but this relationship was not found in the NGT group. In normotensive patients with DM, IR had no correlation with smoking habits or alcohol consumption habits. In different blood pressure and glycometabolism situations, the positive correlation between UACR and HOMA-IR was affected by BMI, age, LDL-C, and HDL-C levels.

Similarly, the negative correlation between GFR and HOMA-IR was affected by BMI and age. Above all, the IR index is associated with UACR and GFR in normal weight individuals with HT and diabetes. In the HT with DM group, the early detection and intervention of IR and its related risk factors in patients with a BMI from 18.5-24.0 kg/m^2 may reduce the occurrence of microalbuminuria and delay the progression of CKD, resulting in more clinical benefits.

AUTHORS' CONTRIBUTIONS
Shi GU analyzed the data and wrote the manuscript. Anping WANG and Linxi ZHANG performed statistical analysis. Guang NING and Yiming MU searched data. Yiming MU reviewed the manuscript. All authors read and approved the final manuscript.

DISCLOSURE OF INTEREST
The authors declare that they have no competing interests.

AVAILABILITY OF DATA AND MATERIALS
The datasets used to support this study are not freely available in view of participants' privacy protection.

CONSENT FOR PUBLICATION
Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
The study protocol was approved by the Committee on Human Research at Rui-Jin Hospital affiliated with the School of Medicine, Shanghai Jiao Tong University. Written informed consents were obtained from all participants before data collection.

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