

Correlation Between Cardiometabolic Index and Microalbuminuria in Type 2 Diabetic Patients

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Research Article

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Abstract

Background: In recent years, cardiometabolic index (CMI) has been introduced to predict the risk of diabetes in the general population and is also strongly associated with cardiovascular disease, hypertension, and ischemic stroke, but the relationship between CMI and diabetic microalbuminuria remains unclear. This study intends to investigate the relationship between CMI and microalbuminuria in patients with type 2 diabetes mellitus (T2DM). **Methods:** 524 subjects (mean age 57.28 ± 10.52 years, 283 males and 241 females) from the Department of Endocrinology, Southwestern Medical University Hospital, China (data collected from June 2017 to June 2019) participated in this study. CMI was calculated by triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) multiply waist-to-height ratio (WHtR). Microalbuminuria was identified by the urinary albumin-to-creatinine ratio (UACR) when the value was between 30–300 mg/g. Multivariate logistic regression aimed to explore the association between CMI and diabetic microalbuminuria; The receiver operating characteristic (ROC) analysis was employed to evaluate the predictive value of CMI for microalbuminuria in T2DM patients. **Results:** The prevalence of microalbuminuria in all participants was 37.8% in men and 41.1% in women. Regardless of gender, CMI was significantly more unfavorable in the microalbuminuria group. The incidence of microalbuminuria increased dose-responsively with increasing CMI quartiles. Modeling CMI as a continuous variable in a multivariate-adjusted model, we observed an independent effect of each 1 SD increase in CMI on the risk of developing microalbuminuria. The relationship was more pronounced in women than in men. In women, the odds ratio (OR) for microalbuminuria was 5.666 (95% CI: 2.247–14.289) in the highest quartile of CMI compared with the lowest quartile; in men, the OR was nearly 4-fold increased (OR: 4.667, 95% CI: 1.910–11.405) in the same situation. The AUC for CMI was 0.681 (0.613 to 0.749) in women and 0.648 (0.582–0.713) in men. **Conclusion:** High levels of CMI were independently associated with diabetic microalbuminuria, and CMI, a novel index covering lipids and central obesity, explained the gender differences in obesity-related microalbuminuria excretion, an effect that was substantially increased in women. The results of this study provide important insights into the potential usefulness and clinical relevance of CMI for microalbuminuria in Chinese patients with T2DM.

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Background

Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes mellitus, the incidence of which has continued to rise in recent years and has become a significant hazard in the development of end-stage renal disease in diabetic patients. It is well known that the presence of microalbuminuria is a marker for the diagnosis of early diabetic nephropathy in T2DM. Considering that early detection of microalbuminuria is an essential factor in avoiding progressive renal function deterioration in diabetic patients. Therefore, early detection of microalbuminuria and timely and effective treatment is key to delaying the progression of diabetic nephropathy, preventing end-stage renal disease, and improving the overall prognosis. It has been widely reported in the literature that central obesity and its associated abnormal lipid metabolism in T2DM patients play an essential role in the process of renal damage, causing nonspecific low-grade inflammation and insulin resistance through the secretion of various inflammatory factors and hormones, leading to renal vascular endothelial dysfunction and the production of albuminuria [1–2]. Dyslipidemia in patients with T2DM is often manifested by high triglyceride (TG) levels and low high-density lipoprotein cholesterol (HDL-C) levels and elevated TG is positively associated with the risk of developing microalbuminuria in T2DM [3]. Also, BMI and WC have been recognized to have a clear relationship with microalbuminuria, but they are less helpful in diagnosing the disease because they do not distinguish between fat and muscle weight or fat distribution [4]. Waist height ratio (WHtR), another anthropometric indicator of central obesity, modifies the relationship between waist circumference and height, is superior to general obesity indicators in predicting the risk of microalbuminuria [5]. Cardiometabolic index (CMI) represents a combination of TG/HDL-C and WHtR, taking lipid and abdominal obesity indicators into account. As a new and widely recognized metabolic index in

recent years, it has been found to predict the risk of diabetes in the general population and is associated with cardiovascular disease, hypertension, and ischemic stroke [6–9]. In this paper, we investigated the correlation between CMI and microalbuminuria in type 2 diabetes in China and aimed to assess the diagnostic value of CMI on the occurrence of microalbuminuria in T2DM and provide a reference for clinical work. To the best of our knowledge, this has not been investigated.

Methods

Study population

A retrospective cross-sectional study was designed and conducted to describe the prevalence and risk factors for developing microalbuminuria in 524 T2DM patients (age ≥ 20 years) hospitalized in the Department of Endocrinology at the Southwestern Medical University Hospital between June 2017 and June 2019. Complete details of the study design and rationale are extensively described elsewhere. Exclusion criteria for this study were as follows: 1) other specific types of diabetes; 2) acute complications of diabetes; 3) renal disease due to primary or secondary nephritis, urinary tract infection, acute and chronic renal failure; 4) severe liver and cardiac dysfunction; 5) acute infection; 6) immunodeficiency, tumor, use of lipid-regulating drugs within the past 3 months and/or angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor antagonist (ARB) within the past 3 months. A total of 524 patients were recruited for this study. The study protocol followed the Second Declaration of Helsinki, and the Ethics Committee of Southwest Medical University (Sichuan) approved the study protocol. We obtained written informed consent from each participant before enrollment, and the entire data and procedures were under the principles of ethical standards.

Data collection and measurements

Questionnaire: Specially trained and tested doctors and nurses at our hospital were allowed to administer the questionnaire. We used a well-designed questionnaire to collect data from all patients. A central steering committee and a subcommittee performed quality control of the information collection process. The questionnaire covered the following data: age, gender, duration of diabetes, history of hypertension and diabetes, smoking and alcohol consumption, and use of insulin and antihypertensive medication.

Anthropometric measurements: All patients had to rest quietly for 5 minutes, and then blood pressure was measured by a specially trained professional physician and nurse, and three consecutive readings were recorded and averaged. Other than that, they were asked to dress very lightly, barefoot, and measure their standard weight to the nearest 0.1 kg using a calibrated digital scale; maintain a standing position and quantify their standard height to the nearest 0.1 cm using a calibrated telemetry device, and measure their waist circumference with a flexible tape measure at the level of 1 cm above the umbilicus. All measurements were performed twice and averaged for analysis. BMI was calculated as weight per height squared (kg/m^2). WHtR was defined as WC divided by height in meters.

Measurement of experimental indicators: Fasting blood was collected by venipuncture after a brief fast (overnight for 8 hours). Fasting blood glucose (FBG) was measured by the glucose oxidase method; glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography. A fully automated biochemical analyzer (Hitachi, 7600) was used to detect blood uric acid (SUA), blood creatinine (Scr), urea nitrogen (BUN), aspartate aminotransferase (ALT), alanine aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamine transferase (λ -GGT), TG, total cholesterol (TC), HDL-C, and low-density lipoprotein cholesterol (LDL-C). The 1st-morning urine was retained, and the urinary albumin/creatinine ratio (UACR) was measured by immunoturbidimetric assay. TG/HDL-C ratio was calculated using available TG and HDL-C values. All laboratory equipment was calibrated, and double-blind samples were used.

Definitions

CMI was obtained by the following formula [6]: $CMI = TG/HDL-C \times WHtR$. lipid accumulation product (LAP) was calculated according to the gender-specific formula [10]: female LAP = $TG \text{ (mmol/L)} \times [WC \text{ (cm)} - 58]$ and male LAP = $TG \text{ (mmol/L)} \times [WC \text{ (cm)} - 65]$. Normoalbuminuria was defined as $UACR < 30 \text{ mg/g}$; microalbuminuria was defined as $30 \text{ mg/g} \leq UACR < 300 \text{ mg/g}$ [11]. Hypertension was diagnosed as mean systolic blood pressure (SBP) equal to or greater than 140 mm Hg and/or diastolic blood pressure (DBP) of at least 90 mm Hg and/or the participant was taking antihypertensive medication or self-reported previously diagnosed hypertension [12]. Diagnosis of diabetes according to the American Diabetes Association criteria: fasting plasma glucose (FPG) $\geq 7.0 \text{ mmol/L}$ and/or self-reported history of previous diagnosis or treatment with plasma glucose-lowering [13].

Statistical analyses

Analyses were performed in a gender-specific manner using SPSS 25.0 software. Normally distributed measures were expressed as mean \pm standard deviation ($x \pm s$), and comparisons between the 4 groups were made using one-way ANOVA, and 2-pair comparisons between groups were made using the LSD-t-test. Non-normally distributed measures were expressed as M(Q1, Q3), and comparisons between 4 groups were made using Kruskal-Wallis H-test, and comparisons between 2 pairs of groups were made using Nemenyi's method. Categorical variables were expressed as frequencies (%), and comparisons were made using the χ^2 test. Multiple logistic regression analysis was used to explore the association between CMI (When included in the analysis as a continuous or a categorical variable, respectively) and diabetic microalbuminuria and to obtain a sex-specific dominance ratio (OR) for each SD change in CMI to determine the risk of microalbuminuria in T2DM, with results shown as ORs and 95% confidence intervals (95% CI). Finally, the optimal cut-off value for CMI was investigated using subject operating characteristic (ROC) curves to detect the presence of microalbuminuria. The area under the curve (AUC) was used to compare the ability of CMI to discriminate microalbuminuria with other indicators. Differences were considered statistically significant at $P < 0.05$.

Results

Demographics, physical measurements values, and laboratory indices of all study participants (Table 1, Table at the end of the article)

We included a total of 524 patients with confirmed T2DM, with a mean age of 57.28 ± 10.52 years, with a higher mean age in women than in men, 46% were female, and both men and women had microalbuminuria older than their age group. Among men, 37.8% of T2DM patients had microalbuminuria, while the percentage of women with microalbuminuria was higher at 41.1%. Regarding physical measurements, regardless of gender, patients with microalbuminuria had significantly higher BMI, WC, SBP, DBP, and VFA than the group without microalbuminuria, and they had a longer duration of diabetes, substantially longer in women than in men. Laboratory index results showed that FPG, HbA1c, ALT, AST, and λ GGT were significantly higher in the male patients in the group with microalbuminuria. Regardless of gender, WHtR, TG, and TG/HDL-C were considerably higher in the microalbuminuria group, and HDL-C was significantly lower than in the regular urine albumin group. Among all subjects, smoking prevalence was significantly higher in men than in women, while female patients tended not to smoke and men showed significant differences in smoking status. Hypertension prevalence and antihypertensive medication use were more common in the group with microalbuminuria but differed significantly in female patients. Also, not surprisingly, CMI and LAP were increased dramatically in patients with microalbuminuria.

Dominance ratios (OR) and 95% confidence intervals for patients with microalbuminuria in T2DM according to sex-specific continuous variables or quartiles of CMI and LAP (Table 2, Table at the end of the article)

Multiple logistic regression analysis was performed to assess the gender-specific associations of CMI and LAP with microalbuminuria. CMI and LAP were included in the analysis as continuous variables, and the results showed that the risk of microalbuminuria increased by 48% and 59% for each SD increase in CMI level in men and women, respectively. The association between CMI and microalbuminuria was significant and robust, more pronounced in women (women, OR, 1.586;

95% CI, 1.181-2.128; men, OR, 1.480; 95% CI, 1.206-1.816). While we took CMI and LAP as categorical variables into the multiple logistic regression analysis and used age, SBP, DBP, BMI, and WC as confounding factors (model 2), then found that in female subjects, the risk of microalbuminuria in the highest quartile of CMI and LAP was 5.83 times (95% CI, 2.38 to 14.32) and 9.16 times (95%CI, 3.04 to 27.54) of those in the lowest quartile, respectively. In model 3, we further included FPG, HbA1C, history of hypertension, antihypertensive medication, and history of insulin use, and the results did not show substantial changes, and the correlation between CMI and LAP and microalbuminuria remained significant. Thus, higher CMI and LAP levels in women were independently and positively associated with the prevalence of microalbuminuria in a dose-response pattern ($P < 0.001$). Furthermore, we found a 4.67-fold increase in the OR of microalbuminuria in men with higher CMI quartile levels (95% CI, 1.910 to 11.405; $P < 0.001$), whereas LAP was not significantly associated with the prevalence of microalbuminuria after inclusion of confounding factor analysis ($P = 0.141$). Overall, the association of CMI and LAP with microalbuminuria was more prominent in female patients.

ROC curves of different metabolic indicators predicting the production of microalbuminuria in patients with T2DM (Table 3, Table at the end of the article)

ROC analysis showed that the AUC value of CMI was significant for identifying Type 2 diabetic patients with microalbuminuria, and the results are summarized in Table 3. In women, we found that CMI had the largest AUC (AUC: 0.681, 95% CI: 0.613-0.749) among the indices, statistically close to LAP (AUC: 0.676, 95% CI: 0.609-0.744) and significantly higher than BMI (AUC 0.681 vs. 0.600, $P = 0.008$) and WC (AUC 0.681 vs. 0.587, $P = 0.021$), and CMI was also superior to TG/HDL-C alone (AUC: 0.671, 95% CI: 0.601-0.740) and WHtR (AUC 0.599, 95%

CI: 0.528-0.671). Meanwhile, CMI showed a strong sensitivity of 80.8% but a specificity of only 47.9%. In men, the AUC of CMI (AUC: 0.648, 95% CI: 0.582-0.713) was higher than LAP (AUC 0.648 vs 0.645, < 0.001) and significantly greater than BMI (AUC 0.648 vs 0.599, $P = 0.005$) and WC (AUC 0.648 vs 0.582, $P = 0.021$). However, CMI showed lower sensitivity (68.0%) versus specificity (54%) in men.

Discussion

We found that CMI, a novel metabolic index that expresses both dyslipidemias and accurately reflects central obesity status, was significantly and independently associated with the risk of developing microalbuminuria in Chinese patients with type 2 diabetes. The findings reveal the potential of CMI as a screening marker for microalbuminuria in patients with T2DM, demonstrating that CMI is a crucial independent determinant of early diabetic nephropathy and has important implications for exploring potential areas of research targeting CMI in the future, especially for delaying the progression of diabetic nephropathy and reducing the risk of developing end-stage renal disease. Patients with T2DM are often associated with dyslipidemia and central obesity. Previous studies have shown that individuals with abnormal lipid metabolism and obesity have worse metabolic profiles and poorer renal outcomes [14]. In patients with early-stage chronic kidney disease, dyslipidemia is mainly characterized by atherogenic dyslipidemia: high TG levels, low HDL-C levels, and increased concentrations of small, dense, low-density lipoprotein (sdLDL) particles [15]. Cao et al. [16] showed that high TG levels are an essential risk factor for kidney damage, and the adjusted risk of any renal event associated with increased TG levels remains high. sd-LDL is a vital lipid indicator in diabetic dyslipidemia [17], and TG/HDL-C is thought to reflect the level of "sd-LDL" particles. Because of the combination of TG and HDL-C levels, TG/HDL-C is valuable in differentiating microalbuminuria. Wen et al. [18] found that elevated TG/HDL-C was significantly associated with microalbuminuria excretion in Chinese patients with type 2 diabetes. A study of Japanese diabetic patients showed a significant decrease in LDL particle size and a considerable increase in the TG/HDL-C ratio in patients with nephropathy than subjects without nephropathy [19]. As our hypothesis in general, TG/HDL-C performed better in predicting proteinuria/chronic kidney disease compared to non-HDL-C/HDL-C, TG, and HDL-C [20].

Obesity is considered to be an essential risk factor for the development of renal damage in T2DM. Data from the Framingham Heart Study, which included more than 2600 patients without chronic kidney disease at baseline, showed that

obese patients were at increased risk of developing stage 3 chronic kidney disease ((BMI \geq 30 kg/m²)) compared to non-obese subjects [21]. Several independent studies have shown that anthropometric measures representing central obesity are superior to general obesity indicators in predicting the development of microalbuminuria in T2DM [22-25]. As tools for detecting central obesity, BMI and WC have a clear relationship with the excretion of microalbuminuria. Still, neither can distinguish between SAT and VAT, especially for Asians, as they are not suitable for diagnosing early diabetic nephropathy because Asians are more prone to visceral fat accumulation and insulin resistance [26, 27]. KB et al. found that

individuals with chronic kidney disease had higher WC and WHtR; however, only WHtR showed a relationship with reduced eGFR and albuminuria excretion, possibly due to different criteria for WC values in individuals of different heights. WHtR corrects WC for height and better reflects abdominal obesity in people of other races, ages, and genders [28-30].

Cardiometabolic index (CMI) is a new index calculated from TG/HDL-C and WHtR, which was proposed by Ichiro Wakabayashi in 2015 [6]. It can better reflect the status of diabetes mellitus and the progression of atherosclerosis [31-32]. As a new indicator of visceral adipose tissue distribution and dysfunction, CMI has been closely associated with various diseases since its introduction [33-35]. In T2DM, considering that insulin resistance, inflammatory response, and abnormal lipid metabolism are inextricably linked to microalbuminuria production, we speculate that CMI is associated with microalbuminuria excretion and may serve as a novel screening index for early diabetic nephropathy. This paper is the first to explore the predictive value of CMI and other lipid and obesity indicators for the development of microalbuminuria in diabetic patients in a Chinese type 2 diabetic population.

We included CMI and LAP as categorical variables in our analysis and found that both had a more significant effect on early kidney damage in women compared to men, but the impact of LAP appeared to be more powerful. After excluding the impact of confounding factors, the risk of developing microalbuminuria in men with T2DM increased significantly with increasing quartiles of CMI, independent of LAP. In a cross-sectional study of 5398 healthy Koreans over 20 years of age, in general, the urinary albumin/creatinine ratio increased with increasing CMI levels, and that CMI was associated with increased glucose and urinary albumin/creatinine ratio increased were independently correlated [36]. Wang et al. also concluded that CMI reflects the visceral fat area and the pathological process leading to impaired renal function and can be used as a screening marker for CKD [37]. Our study confirmed that the risk of developing microalbuminuria increased proportionally with changes in CMI quartiles, and CMI showed a strong correlation with microalbuminuria excretion in T2DM. Although the ORs for the risk of developing CMI were weaker than LAP, considering that LAP does not include HDL-C, an essential indicator of dyslipidemia, in its calculations for analysis, and that people of different heights should have other WC criteria, it neglects the role of height. It, therefore, has limited value as a test indicator for combined microalbuminuria in patients with T2DM [38].

To distinguish the predictive value of CMI from lipid and obesity indicators as screening markers for diabetic microalbuminuria, we analyzed T2DM patients of both sexes separately using ROC curves. We found that CMI had the most significant AUC value in female patients. Although its discriminatory power was not significantly greater than LAP, it had a more comprehensive diagnostic significance considering that CMI covered both HDL-C and height-specific indicators. Surprisingly, CMI and LAP showed better predictive effects in women, but both TG/HDL-C and WHtR had larger AUC values than WC. This cause may be related to the smaller number of our subjects. Similarly, the AUC value of CMI was still the largest in male patients; however, the sensitivity of CMI was only 68%, and the specificity was even lower at 54.00%. Compared to men, CMI is much more sensitive than LAP in women, so CMI values are more valuable for diagnosing microalbumin excretion in women with T2DM. In conclusion, CMI has a robust discriminatory ability and high sensitivity and can be an economic screening index for screening people with T2DM combined with microalbuminuria.

Our study found that CMI and LAP are of clinical value as new metabolic indicators in assessing the risk of developing microalbuminuria in type 2 diabetes and differ by gender. The deleterious effect of CMI on early diabetic nephropathy was more significant in women compared to men. Our findings are consistent with previous clinical studies in which abnormal lipid metabolism and central obesity triggered microalbuminuria excretion, particularly in female patients with T2DM. A

study based on the Korean National Health and Nutrition Examination Survey found that obese female patients were more likely to develop microalbuminuria and that impaired fasting glucose and high triglycerides were significant correlates of microalbuminuria [39]. The interaction of increased glucose exposure with abnormal lipid metabolism associated with central obesity may be one of the leading causes of vascular endothelial dysfunction and microalbuminuria excretion in a 5398 Korean general population [40]. Based on a retrospective observational study of renal injury in elderly participants in a Chinese community, researchers hypothesized that female patients with high TG and high WC levels were significantly associated with microalbuminuria excretion[41]. In conjunction with our findings, we showed that the statistical effect of visceral fat distribution on microalbuminuria excretion in female T2DM patients manifested itself as a significant effect of CMI and LAP. The reason for this outcome may be the dysregulation of macrophage and adipocyte secretion in patients with T2DM, which produces a variety of hormones and pro-inflammatory factors, leading to a low inflammatory response, insulin resistance, dyslipidemia, and/or increased synthesis of vasoactive and fibrogenic substances [42-46]. Their complex interactions may negatively affect the vascular endothelium and impair renal function, thus causing the production of microalbuminuria. In addition, considering that most of the female patients we included were postmenopausal women with decreased sex hormones, the beneficial effects of estrogen on the kidney were inevitably lost. Estrogen is thought to reduce proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis [47-49]. Possible mechanisms are: (i) in diabetic patients, (estradiol) E2 attenuates glomerulosclerosis and tubulointerstitial fibrosis by reducing type I and type IV collagen synthesis, increasing matrix metalloproteinase expression, and inhibiting apoptosis [50-52]; (ii) E2 reduces the angiotensin type II1 receptor expression, transforming growth factor- β and endothelin-1 and regulating vascular dysfunction; (iii) E2 has also been shown to upregulate nitric oxide synthase activity and vascular endothelial growth factor expression in glomeruli and improve vascular permeability, thereby potentially reducing the loss of glomerular function in progressive chronic kidney disease, including diabetic nephropathy [53-56].

This study still has some limitations: (1) This study is a cross-sectional study, and this study can only provide evidence about the strong correlation between CMI and LAP and microalbuminuria. Still, it cannot further elucidate the causal relationship between CMI, LAP, and microalbuminuria in patients with T2DM, which needs to be further verified by a large follow-up study. (2) The sample size was small and limited by the region, and data we only collected from some patients in southwest China with a single ethnicity, so more studies are needed to investigate whether the findings apply to different regions or ethnic groups. (3) There are too many confounding factors affecting microalbuminuria excretion, and the effects of confounding factors were not eliminated when conducting the analysis, which may produce some data bias.

Conclusion

In summary, our study reveals for the first time an association between CMI and microalbuminuria in type 2 diabetes that is independent of prevalent CVD, medication use, and traditional cardiovascular risk factors. Thus, these data provide strong evidence for a unique, independent, and economic role of CMI in high-burden nephropathy. These findings have important implications for guiding original prevention and understanding the mechanisms of VAT-mediated kidney injury.

Abbreviations

AUC: Area under the curve; ROC: Receiver operating characteristic curve; CI: Confidence interval; SD: Standard deviation; ORs: Odds ratios; CMI: Cardiometabolic index; LAP: Lipid accumulation product; T2DM: Type 2 diabetes mellitus; UACR: Urinary albumin to creatinine ratio; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; FPG: Fasting plasma glucose; SFA: Subcutaneous fat area; VFA: Visceral fat area; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG/HDL-C: Triglyceride to high-density lipoprotein cholesterol ratio; WHtR: Waist to height ratio; WC: Waist circumference; BMI: Body mass index; HbA1c(%): Glycated hemoglobin; SUA: Serum uric acid; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; γ GGT U/L :Gammaglutamine aminotransferase;

Declarations

Ethics approval and consent to participate

This study was performed in compliance with the ethical principle of the Declaration of Helsinki. Written informed consents were acquired from all participants and all procedures were performed by the ethical standards. The Ethics Committee of Southwest Medical University(Luzhou, China) approved the study protocol. reference number 2018017.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

In this study, XY did the study design, statistical analyses, and results in interpretation. YFJ, XLH, and XLC participated in analyzing and resolving difficulties of analytic strategies and results in discussion. Finally, QW functioned as a final reviewer who gave constructional suggestions for the interpretation of data. The corresponding author was QW. All authors have read and approved the manuscript.

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Tables

Table1 Characteristics of T2DM with microalbuminuria stratified by sex

Variables	Males(n=283)			Females(n=241)		
	Normal albuminuria (n=176)	Microalbuminuria (n=107)	P value*	Normal albuminuria (n=142)	Microalbuminuria (n=99)	P value*
Age(years)	54.99±10.87	56.36±11.14	0.309	58.96±9.85	59.95±9.43	0.427
Height(cm)	165.98±5.94	165.45±6.43	0.477	154.27±5.84	153.72±5.94	0.470
Weight(cm)	68.55±11.30	71.11±10.05	0.054	57.92±9.02	61.12±11.32	0.016
BMI	24.82±3.43	25.98±3.30	0.006	24.35±3.60	25.80±4.08	0.004
WC(cm)	88.56±9.96	91.58±8.74	0.010	84.17±10.81	87.35±10.03	0.021
Hip circumference(cm)	94.32±6.84	95.21±6.55	0.278	92.11±7.00	93.31±8.39	0.226
SBP mmHg	130.44±17.42	138.42±20.82	0.001	133.24±19.13	145.70±18.35	<0.001
DBP mmHg	79.15±10.15	83.19±11.12	0.002	75.31±9.69	80.87±10.17	<0.001
VFA(cm)	88.84±41.18	105.88±46.56	0.001	84.44±43.73	98.61±46.76	0.017
SFA(cm)	154.55±58.03	167.83±49.25	0.049	167.07±66.15	181.89±70.26	0.097
Duration of diabetes (month)	40.00 2.75-98.5	62.00 2.00-147.50	0.026	48.00 1.00-114	82.00 20.50-122.75	0.028
FPG (mmol/L)	8.50 6.80-11.55	9.73 7.50-11.30	0.038	7.80 6.50-10.25	8.93 6.98-11.10	0.166
HbA1c %	8.95 7.08-11.53	9.50 8.40-11.60	0.035	8.70 7.20-11.70	9.30 7.58-11.10	0.205
SUA (μmol/L)	345.20 289.80-414.90	361.10 296.10-442.80	0.173	279.60 238.80-334.70	301.15 252.75-378.53	0.016
ALT U/L	24.50 17.60-35.40	27.70 19.28-39.83	0.049	19.50 15.75-27.65	19.90 14.90-27.60	0.732
AST U/L	19.20 16.10-24.60	21.65 17.25-30.63	0.021	19.00 16.33-23.55	19.40 14.78-26.10	0.693
ALP U/L	82.30(64.10-97.60)	89.65(65.35-106.48)	0.144	77.45(64.20-102.53)	87.40(72.10-107.60)	0.021
λGGT U/L	25.40(17.70-40.80)	36.40(23.58-69.90)	<0.001	19.20(12.70-30.28)	21.40(15.70-36.70)	0.090
TG mmol/L	1.61(1.14-2.55)	2.29(1.58-4.10)	<0.001	1.60(1.14-2.24)	2.12(1.54-3.26)	<0.001
TC mmol/L	4.56(3.73-5.23)	4.57(3.83-5.48)	0.283	4.69(3.90-5.45)	4.69(4.04-5.70)	0.297
HDL-C mmol/L	1.04(0.87-1.30)	0.97(0.84-1.19)	0.031	1.25(1.04-1.49)	1.09(0.92-1.24)	<0.001
LDL-C mmol/L	2.75 2.03-3.47	2.44 1.85-3.23	0.095	2.84 2.20-3.53	2.71 2.14-3.52	0.651
TG/HDL-C	1.61 1.02-	2.23 1.45-4.09	<0.001	1.33 0.86-	2.08 1.27-3.44	<0.001

	2.65			1.97		
WHtR	0.53±0.06	0.55±0.06	0.004	0.55±0.07	0.57±0.07	0.015
LAP	40.00 22.30-72.88	55.80(35.25,126.72)	<0.001	37.88 22.25-70.16	63.72(41.10-94.12)	<0.001
CMI	0.85 0.54-1.48	1.15 0.81-2.36	<0.001	0.72 0.46-1.15	1.20 0.74-1.85	<0.001
hypertension (%)	58 33.0	45 42.1	0.123	53 37.3	60 60.6	<0.001
Anti-hypertensive drug (%)	50 28.4	37 32.9	0.275	47 33.1	54 54.5	0.001
history of insulin use(%)	48 27.3	38 35.5	0.144	38 26.8	37 37.4	0.080
Current smoker (%)	83 47.2	69 64.5	0.005	3 2.1	0 0	0.146
Current drinker (%)	101 57.4	65 60.7	0.578	13 9.2	6 6.1	0.381
Lipid-lowering drug (%)	17 9.7	15 14.0	0.261	13 9.2	14 14.1	1.458
<p>Data are expressed as mean ± standard deviation(SD) or median (interquartile range) and numbers (percentage) as appropriate. <i>CMI</i> cardiometabolic index, <i>LAP</i> lipid accumulation product, <i>DBP</i> diastolic blood pressure, <i>SBP</i> systolic blood pressure, <i>FPG</i> fasting plasma glucose, <i>SFA</i> subcutaneous fat area, <i>VFA</i> visceral fat area, <i>TG</i> triglyceride, <i>TC</i> total cholesterol, <i>HDL-C</i> high density lipoprotein cholesterol, <i>LDL-C</i> low-density lipoprotein cholesterol, <i>TG/HDL-C</i> triglyceride to high density lipoprotein cholesterol ratio, <i>WHtR</i> waist to height ratio, <i>WC</i> waist circumference, <i>BMI</i> body mass index, <i>HbA1c</i>(%) glycated hemoglobin, <i>SUA</i> serum uric acid, <i>ALT</i> alanine aminotransferase, <i>AST</i> aspartate aminotransferase, <i>ALP</i> alkaline phosphate, <i>γGGT</i> gammaglutamine aminotransferase</p> <p>*Comparisons of category variables between groups were tested by chi-square test or rank-sum test (ordinal category variables) and comparisons for continuous variables between groups were tested by Student's t or Mann-Whitney test</p>						

Table2 Sex-specific logistic regression models for microalbuminuria with CMI

Variables	Diabetic microalbuminuria			
			OR(95%CI)	
	Case(%)	Model1	Model2	Model3
Males				
CMI(Per 1 SD increase)		1.444(1.205-1.729)	1.473(1.208-1.798)	1.480(1.206-1.816)
<i>P</i> value for trend		<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> <0.001
Quartiles of CMI				
Q1	14(13.1)	1(reference)	1(reference)	1(reference)
Q2	26(24.3)	2.311(1.082-4.937)	2.357(1.059-5.248)	2.654(1.158-6.083)
Q3	31(29.0)	3.110(1.464-6.565)	3.198(1.415-7.228)	3.337(1.423-7.828)
Q4	36(33.6)	4.114(1.947-8.692)	4.288(1.825-10.074)	4.667(1.910-11.405)
<i>P</i> value for trend	0.001	0.002	0.008	0.008
LAP(Per 1 SD increase)		1.009 1.005-1.013	1.010 1.005-1.015	1.010 1.005-1.016
<i>P</i> value for trend		<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> <0.001
Quartiles of LAP				
q1	16 15.0	1(reference)	1(reference)	1(reference)
q2	26 24.3	1.950 0.932-4.078	1.711 0.726-4.028	1.557 0.647-3.745
q3	30 28.0	2.470 1.190-5.125	2.481 1.004-6.129	2.423(0.941-6.242)
q4	35 32.7	3.375 1.629-6.993	3.240 1.198-8.764	2.087(1.102-8.563)
<i>P</i> value for trend	0.008	<i>P</i> <0.001	0.113	0.141
Females				
CMI(Per 1 SD increase)		1.693(1.285-2.230)	1.604(1.198-2.146)	1.586(1.181-2.128)
<i>P</i> value for trend		<i>P</i> <0.001	<i>P</i> <0.001	0.002
Quartiles of CMI				
Q1	12(12.1)	1(reference)	1(reference)	1(reference)
Q2	24(24.2)	2.595(1.149-5.861)	2.725(1.137-6.535)	2.697(1.112-6.544)
Q3	27(27.3)	3.273(1.453-7.369)	3.650(1.468-9.073)	3.123(1.199-8.143)
Q4	36(36.4)	6.000(2.651-13.577)	5.831(2.375-14.318)	5.666(2.247-14.289)
<i>P</i> value for trend	<i>P</i> <0.001	<i>P</i> <0.001	0.002	0.004
LAP(Per 1 SD increase)		1.010(1.004-1.015)	1.009(1.003-1.015)	1.009(1.003-1.016)
<i>P</i> value for trend		<i>P</i> <0.001	0.003	0.004
Quartiles of LAP				
q1	10(10.1)	1(reference)	1(reference)	1(reference)
q2	26(26.3)	3.714(1.591-8.670)	4.387(1.697-11.341)	4.012(1.540-10.455)

q3	28(28.3)	4.375(1.875-10.210)	6.753(2.355-19.362)	6.361(2.188-18.490)
q4	35(35.4)	7.000(2.989-16.396)	9.156(3.044-27.541)	8.902(2.874-27.568)
<i>P</i> value for trend	<i>P</i> <0.001	<i>P</i> <0.001	0.001	0.002
Model 1: unadjusted; Model 2: adjusted for age, SBP, DBP, BMI, WC; Model 3: further adjusted for FPG, HbA1C, history of hypertension, anti-hypertensive drugs, history of insulin use Abbreviations: <i>OR</i> odd ratio; 95% <i>CI</i> 95% confidence interval, <i>CMI</i> cardiometabolic index, <i>LAP</i> lipid accumulation product, <i>SBP</i> systolic blood pressure, <i>DBP</i> diastolic blood pressure, <i>BMI</i> body mass index, <i>WC</i> waist circumference, <i>FPG</i> fasting plasma glucose, <i>HbA1c</i> (%) glycated hemoglobin				

Table3 AUC for indexes to discriminate microalbuminuria in females and males

Variables	AUC (95%CI)	<i>P</i> value	Cut-off according to Youden's index	Sensitivity (%)	Specificity (%)
Males					
CMI	0.648 0.582-0.713 abc	< 0.001	>0.89	68%	54.00%
LAP	0.645 0.579-0.711 abc	< 0.001	>32.40	82.20%	41.50%
BMI	0.599 0.532-0.666	0.005	>23.85	77.60%	39.80%
WC	0.582 0.515-0.649	0.021	>83.5	85.00%	29.50%
WHtR	0.592 0.524-0.660	0.009	>0.52	74.80%	41.50%
TG/HDL-C	0.645 0.578-0.711 abc	< 0.001	>1.71	67.30%	55.10%
Females					
CMI	0.681 0.613-0.749 abc	< 0.001	>0.64	80.80%	47.90%
LAP	0.676 0.609-0.744 abc	< 0.001	>45.26	72.70%	58.50%
BMI	0.600 0.528-0.671	0.008	>21.75	90.00%	26%
WC	0.587 0.516-0.659	0.021	>75.5	89%	26.80%
WHtR	0.599 0.528-0.671	0.009	>0.55	61.60%	57.00%
TG/HDL-C	0.671 0.601-0.740 abc	< 0.001	>1.915	55.60%	74.00%

Abbreviations: *AUC* area under the ROC curve, 95% *CI* 95% confidence interval, *CMI* cardiometabolic index, *LAP* lipid accumulation product, *BMI* body mass index, *WC* waist circumference, *WHtR* waist to height ratio, *TG/HDL-C* triglyceride to high density lipoprotein cholesterol ratio

a indicates a significant larger as compared to BMI;

b indicates a significant larger as compared to WC;

c indicates a significant larger as compared to WHtR;