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Association of different obesity indexes with diabetic kidney disease in patients with type 2 diabetes mellitus: a cross-sectional study

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The objective of this study is to investigate the association between diabetic kidney disease (DKD) and various adiposity indexes, including the visceral adiposity index (VAI), lipid accumulation product index (LAPI), visceral fat area (VFA), and subcutaneous fat area (SFA) in type 2 diabetes mellitus (T2DM) patients. 1176 T2DM patients was stratified into normoalbuminuria (NO), microalbuminuria (MI), and macroalbuminuria (MA) groups based on their urinary albumin-creatinine ratio (UACR) levels. To analyse the correlation between DKD and VAI, LAPI, VFA, and SFA. Multiple linear, restricted cubic spline (RCS), subgroup analyses, and multinomial logistic regression were employed. After adjusting for confounding variables, UACR levels were positively associated with VAI, LAPI, and VFA. RCS curves demonstrated a J-shaped dose-response relationship between VAI and LAPI levels with UACR levels, while a linear correlation was observed between UACR levels and VFA. Using the NO and MI as reference groups, the MA group was analysed as the observational group. DKD severity was positively associated with VAI, LAPI and VFA. When evaluating DKD prognostic risk, with the low-risk and medium-risk groups serving as reference categories, a significant positive correlation was identified with prognostic risk and VAI, LAPI, and VFA in the high-risk or very high-risk groups. In patients with T2DM, DKD severity and prognostic risk were positively correlated with VAI, LAPI, and VFA levels.

Keywords Diabetic kidney disease, Visceral adiposity index, Lipid accumulation product index, Visceral fat area, Subcutaneous fat area

Diabetes mellitus (DM) has become a highly prevalent global metabolic disease, posing a significant threat to human health[1]. In 2021, 10.5% of the worldwide population aged 20 to 79 years was diagnosed with DM, and this percentage will increase to 12.2% by 2045, highlighting an urgent public health concern[2]. Diabetic kidney disease (DKD), a microvascular complication of DM, leads to various health impairments and significantly reduce life expectancy[3]. DKD is a major precursor to end-stage-renal-disease (ESRD) contributing substantially to the increased mortality rates observed among patients with DM[4]. Of all cases of ESRD worldwide, it has been reported that approximately 30 to 50% are attributed to DKD[5]. Furthermore, DKD may lead to an elevated risk of heart disease[6]. The pathogenesis and progression of DKD are influenced by multiple factors, incleding oxidative stress, and inflammatory processes. Current therapeutic approaches for DKD encompass a broad spectrum of strategies, such as blood pressure and glucose management through pharmacological interventions, lifestyle modifications, and the use of angiotensin-converting enzyme inhibitors. However, despite the range of treatments available, the results thus far have been less than significant[7]. DKD imposes a considerable economic burden and severely inpacts individual's llife. Therefore, early detection and prevention of DKD are imperative to mitigate its detrimental effects.

Abdominal fat can be categorised into two types: visceral adiposity and subcutaneous adiposity[8]. Increasing evidence suggests that abdominal obesity is closely linked to DM and its complications, including DKD[9], diabetic neuropathy[10] and diabetic cardiovascular diseases[11]. Research indicates that the distribution of adipose tissue plays a more crucial role in the development of diabetic complications than the total adipose tissue[12,13].

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To assess abdominal obesity, various indicators have been employed, such as the waist-to-hip ratio[14], the lipid accumulation product index (LAPI)[15], and the visceral adiposity index (VAI)[16].

VAI serves as an indicator of visceral adiposity[17]. Several studies have shown that VAI significantly predicts insulin sensitivity, which is linked to an increased incidence of cardiovascular disease[16], DM[18], and the risk of metabolic syndrome[19,20]. LAPI, is a novel indicator of central lipid accumulation calculated by serum triglyceride (TG) and waist circumference (WC). Research indicates a strong correlation between LAPI and DKD[2]. In addition, LAPI has the ability to predict cardiovascular disease[21], type 2 diabetes mellitus (T2DM)[22], and non-alcoholic fatty liver disease[23]. However, fewer studies have investigated the direct correlation between body fat distribution and DKD. Most previous research has relied on VAI and LAPI as substitutes, for direct measures of visceral adiposity, failing to assess visceral fat area (VFA) and subcutaneous fat area (SFA) directly. VFA and SFA levels, when measured using appropriate instruments, can accurately reflect abdominal obesity and adipose tissue distribution.

Therefore, in this study, the VFA, and SFA levels of the participants were directly measured and the correlation between DKD and VAI, LAPI, VFA, and SFA, were explored. Additionally, the relationships between high or very high risk for DKD and these adiposity indexes were explored to provide a more comprehensive understanding of the factors influencing DKD risk.

Study population and methods

This study included 1241 T2DM patients hospitalized at the First Hospital of Lanzhou University between April 2016 and December 2020. After screening based on specific criteria, 1,176 patients were classified into the three groups: the normoalbuminuria (NO) group (urine albumin-to-creatinine ratio [UACR]<30 mg/g) with 628 patients, the microalbuminuria (MI) group (30 ≤ UACR<300 mg/g) with 436 patients, and the macroalbuminuria (MA) group (UACR ≥ 300 mg/g) with 112 patients. Figure 1 displays a STROBE flowchart illustrating the patient selection process.

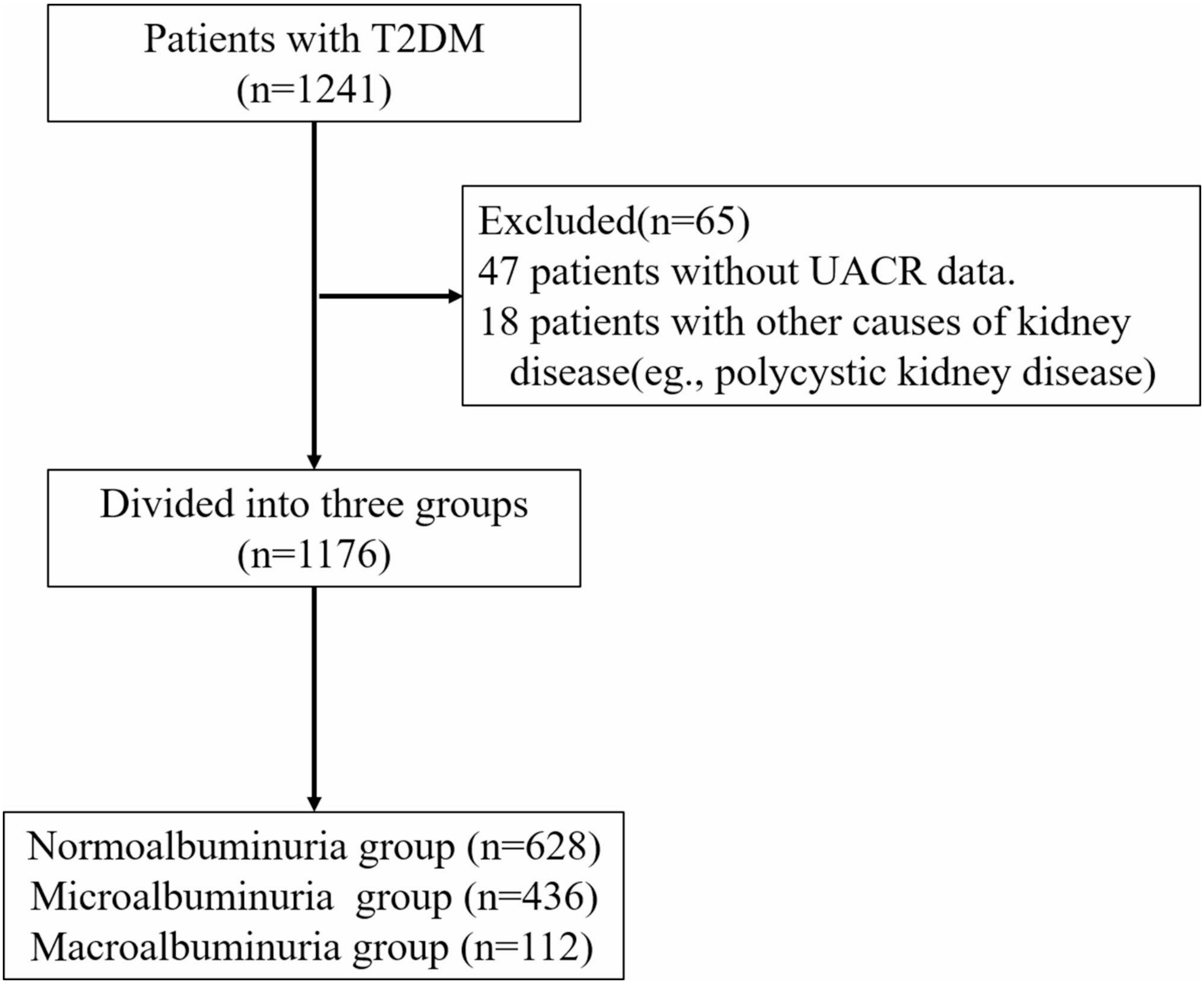


Fig. 1. Diagram of the study design.

Inclusion criteria

The study population comprised individuals aged 18 years or older who had been diagnosed with T2DM and for a minimum duration of 1 year. In addition, the diagnosis of DKD in these patients with was determined based on a UACR of ≥ 30 mg/g and/or an estimated glomerular filtration rate (eGFR) of ≤ 60 ml/min/1.73m2[24].

Exclusion criteria

T2DM patients who experience acute complications, those with type 1 DM or other type-specific DM, as well as individuals with kidney disease not induced by diabetes, were excluded, as Additionally, patients with a lack of clinical data were also excluded.

Methods

Data collection

Baseline characteristics of the study population

For each participant, the following information was reviewed: name, sex, age, height, weight, body mass index (BMI), WC, presence of hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of DM, history of smoking, drinking and other diseases were reviewed.

Laboratory examination

The data of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), TC, TG, HDL-C, LDL-C, serum uric acid (UA) and serum creatinine (SCr) were collected. As well as glycosylated haemoglobin (HbA1c), fasting plasma glucose (FPG), fasting insulin (FINS), uinary microalbumin, and urinary creatinine (CR) data were collected. VFA and SFA were determined by (Dual-Energy X-Ray Absorptiometry (EXA-3000, Osteosys, Korea).

Homeostasis model assessment of insulin resistance (HOMA-IR) = FPG × FINS/22.5.

$\text{eGFR} = 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203}$ (female × 0.742) mL/min/1.73[25].

UACR = albumin /Cr (mg/g).

Specified formulae were used to calculate the values of VAI and LAPI for every participant. For males: $\text{VAI} = \text{WC}/(39.68+(1.88\times\text{BMI}) \times(\text{TG}/1.03) \times(1.31/\text{HDL-C})$, $\text{LAPI} = (\text{WC} - 65) \times \text{TG}$; For females: $\text{VAI} = \text{WC}/(36.58+(1.89\times\text{BMI})) \times(\text{TG}/0.81) \times(1.52/\text{HDL-C})$, $\text{LAPI} = (\text{WC} - 58) \times \text{TG}$[2,16].

Statistical methods

Statistical analysis was conductedusing SPSS software (version 26.0; IMB, Armonk, New York, USA) and R software (version 4.1.0; https://www.R-project.org).Categorical variables are expressed as frequencies and percentages (%). Continuous variables were expressed as mean ± standard deviation or median (quartiles). Differences between groups were assessed using the chi-square test, one-way analysis of variance, or Kruskal-Wallis test, respectively. Post hoc two-way comparisons were performed using the Bonferroni method. Multiple linear regression was employed to evaluate the independent correlation between UACR levels and VAI, LAPI, VFA and SFA. Subgroup and interaction analyses and restricted cubic spline (RCS) analysis, were conducted to validate the nonlinear association between UACR levels and VAI, LAPI and VFA levels. The association between severity and prognostic risk of DKD and VAI, LAPI, VFA and SFA levels were evaluated by multinomial logistic regression.

Results

Baseline characteristics of the study population

1176 T2DM patients (746 men and 430 women) were enrolled.

In the MA group, SBP and UA levels were significantly higher than in the NO group. In the MI and MA groups, WC, duration of diabetes, HbA1c, and TG levels were significantly higher than the NO group, as well as significantly higher in the MA group than the MI group. SCr levels were significantly higher in the MI and MA groups compared to the NO group. Conversely, eGFR levels were significantly lower in the MI and MA groups compared to the NO group (Table 1).

Comparison of VAI, LAPI, VFA, and SFA levels among groups with different UACR levels

VAI was significantly higher in the MA [3.27(2.11, 4.98), $p < 0.001$] and MI [2.47(1.62, 3.51), $p = 0.002$] groups than the NO group [2.22(1.56, 2.98)]. Additionally, VAI was higher in the MA group compared to the MI group ($p < 0.001$) (Fig. 2A). LAPI was also were higher in the MA [48.50(25.29, 86.42), $p < 0.001$] and MI [39.89 (23.97, 56.19), $p < 0.001$] groups than the NO group [32.62(19.12, 47.02)]. Moreover, LAPI in the MA group compared to the MI group ($p = 0.007$) (Fig. 2B). VFA in the MA group [(115.74 ± 25.24) cm^2] was significantly higher than that of the NO group [(104.39 ± 30.78) cm^2, $p = 0.001$] (Fig. 2C). There was no significant difference in SFA among the NO, MI, and MA groups. (Fig. 2D).

Comparison of VAI, LAPI, VFA, and SFA among groups with different eGFR levels

Based on different eGFR levels, the study population was categorized into G1 ($\text{eGFR} \geq 90$ mL/min), G2 ($60 \leq \text{eGFR} < 90$ mL/min), and G3 ($\text{eGFR} < 60$ mL/min) groups.

There was no significant difference in SFA among the G1, G2, and G3 groups (Fig. 3A). LAPI was higher in the G3 [43.50 (22.52, 60.01), $p = 0.018$] and G2 [38.30(22.16, 58.10), $p = 0.002$] groups than the G1 group [34.66 (19.63, 49.25)] (Fig. 3B). There were no significant difference in VFA and SFA among the G1, G2, and G3 groups (Fig. 3C and D, respectively).

Index	NO (*n* = 628)	MI (*n* = 436)	MA (*n* = 112)	*P*
Male (%) Feale (%)	402(64) 226(36)	264(60.8) 172(39.4)	80(71.4) 32(28.6)	0.093
Age(years)	59.09 ± 11.02	59.51 ± 11.23	61.54 ± 10.14	0.097
BMI(kg/m^2)	24.01 ± 4.29	24.38 ± 4.16	24.46 ± 4.12	0.297
WC(cm)	86.47 ± 11.63	88.36 ± 9.26*	94.83 ± 18.57$^{*\#}$	< 0.001
Hypertension (%)	395(62.9)	298(68.3)	79(70.5)	0.095
SBP(mmHg)	137.87 ± 15.85	139.36 ± 14.94	141.67 ± 14.63*	0.034
DBP(mmHg)	82.14 ± 13.08	83.06 ± 13.38	83.57 ± 15.72	0.405
Diabetes duration(years))	6(4.78,8)	7(5,9) **	9(8,10) $^{**\#\#}$	< 0.001
FPG(mmol/L)	8.37 ± 2.64	8.45 ± 2.76	8.83 ± 2.65	0.242
FINS(mU/L)	7.54(6.05,8.94)	7.92(5.62,10.36)	8.29(5.71,10.81))	0.019
HOMA-IR	2.61(1.91,3.46)	2.69(1.84,3.91)	2.94(1.86,4.14)	0.116
HbA1c (%)	8.36 ± 2.12	8.88 ± 2.65*	9.38 ± 2.21$^{**\#}$	< 0.001
AST(U/L)	20(17,26)	20(16,28.75)	19(17,24)	0.306
ALT(U/L)	29(19,38)	28(19,39)	33(20,42)	0.175
ALP(U/L)	77(63,97)	81(65,99.75)	80(63,99.25)	0.099
GGT(U/L)	24.8(18.75,40.90))	27.4(19.23,46.20)	25.65(17.85,40.78)	0.096
TC(mmol/L)	4.35 ± 1.10	4.24 ± 1.08	4.45 ± 1.31	0.138
TG(mmol/L)	1.43(1.21,1.65)	1.63(1.17,2.07) **	1.96(1.28,2.57) $^{**\#}$	< 0.001
HDL-C(mmol/L)	1.08 ± 0.60	1.04 ± 0.35	0.88 ± 0.25$^{**\#}$	< 0.001
LDL-C(mmol/L)	2.71 ± 0.76	2.68 ± 0.77	2.86 ± 0.86	0.078
UA(μmol/L)	322.51 ± 83.98	331.12 ± 95.76	344.60 ± 78.91*	0.031
SCr(μmol/L)	67.65 ± 16.15	71.97 ± 18.36*	103.77 ± 31.39$^{**\#\#}$	< 0.001
eGFR(ml/min)	110.47 ± 44.59	103.65 ± 46.05*	69.70 ± 27.98$^{**\#\#}$	< 0.001
Smoking (%)	171(27.2)	115(26.4)	39(35.1)	0.172
Drinking (%)	196(31.2)	154(35.3)	41(33.2)	0.274

Table 1. Clinical characteristics of study participants. *SBP*, systolic blood pressure; *DBP,* diastolic blood pressure; *BMI*, body mass index; *WC*, waist circumference; *FPG*, Fasting Plasma Glucose; *FINS*, fasting insulin; *HOMA-IR*, homeostasis model assessment of insulin resistance; *HbA1c*, glycosylated hemoglobin; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *ALP*, Alkaline phosphatase; *GGT*, gamma-glutamyl transferase; *TC*, total cholesterol; *TG*, triglycerides; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *UA*, serum uric acid; *SCr*, serum creatinine; *eGFR*, estimated glomerular filtrationrate; Compared with NO group, $^{*}p < 0.05$, $^{**}p < 0.001$; Compared with MI group $^{\#}p < 0.05$, $^{\#\#}p < 0.001$.

The relationship between UACR levels and VAI, LAPI, and VFA in patients with T2DM

The dependent variable in the study was UACR, while the independent variables included sex, age, presence of hypertension, smoking, drinking, SBP, DBP, diabetes duration, BMI, WC, FPG, FINS HOMA-IR, HbAlc, AST, ALT, ALP, GGT, TC, TG, HDL-C, LDL-C, UA, SCr, eGFR, VAI, LAPI, VFA, and SFA. The results of simple linear regression showed that UACR levels were correlated with VAI, LAPI, and VFA levels (all $p < 0.05$).

For multiple linear regression analysis, UACR-related-variables were considered as independent variables. Collinear variables, including WC and eGFR, were eliminated, and the stepwise method for the analysis. The multiple regression analysis results demonstrated a positive correlation between UACR levels and age, diabetes duration, HOMA-IR, HbA1c, TG, UA, SCr, VAI, LAPI, and VFA (Table 2).

The nonlinear correlation between UACR levels and VAI, LAPI, and VFA

The variables associated with UACR were considered independent variables, with UACR levels as the dependent variable. The RCS curves demonstrated a J-shaped dose-response relationship between VAI and UACR levels, as well as between LAPI and UACR levels. The RCS model results further indicated a nonlinear correlation between VAI and LAPI with UACR levels (both p for nonlinear relationship < 0.05) (Fig. 4A and B). Additionally, there was a linear correlation between VFA and UACR levels (p for nonlinear relationship $= 0.332$) (Fig. 4C)**.** The inflexion point analysis revealed that VAI was positively associated with UACR levels when VAI exceeded 3.18, and LAPI was positively associated with UACR levels when LAPI exceeded 63.14 (Table 3)**.**

Subgroup analysis

In order to further explore the impact of additional factors on the relationship between UACR levels and VAI, LAPI, and VFA, variables related to UACR, from the simple linear analysis were categorized into subgroups based on age, diabetes duration, FPG, HbA1c, TG, and HDL-C. Interactions between VAI and age, FPG, HbA1c, and TG (p for interaction < 0.05), with a stronger correlation observed between UACR levels and VAI in patients with TG levels (≥ 1.8 mmol/L) (Fig. 5A)**.** Interactions between LAPI and diabetes duration, TG, and HDL-C

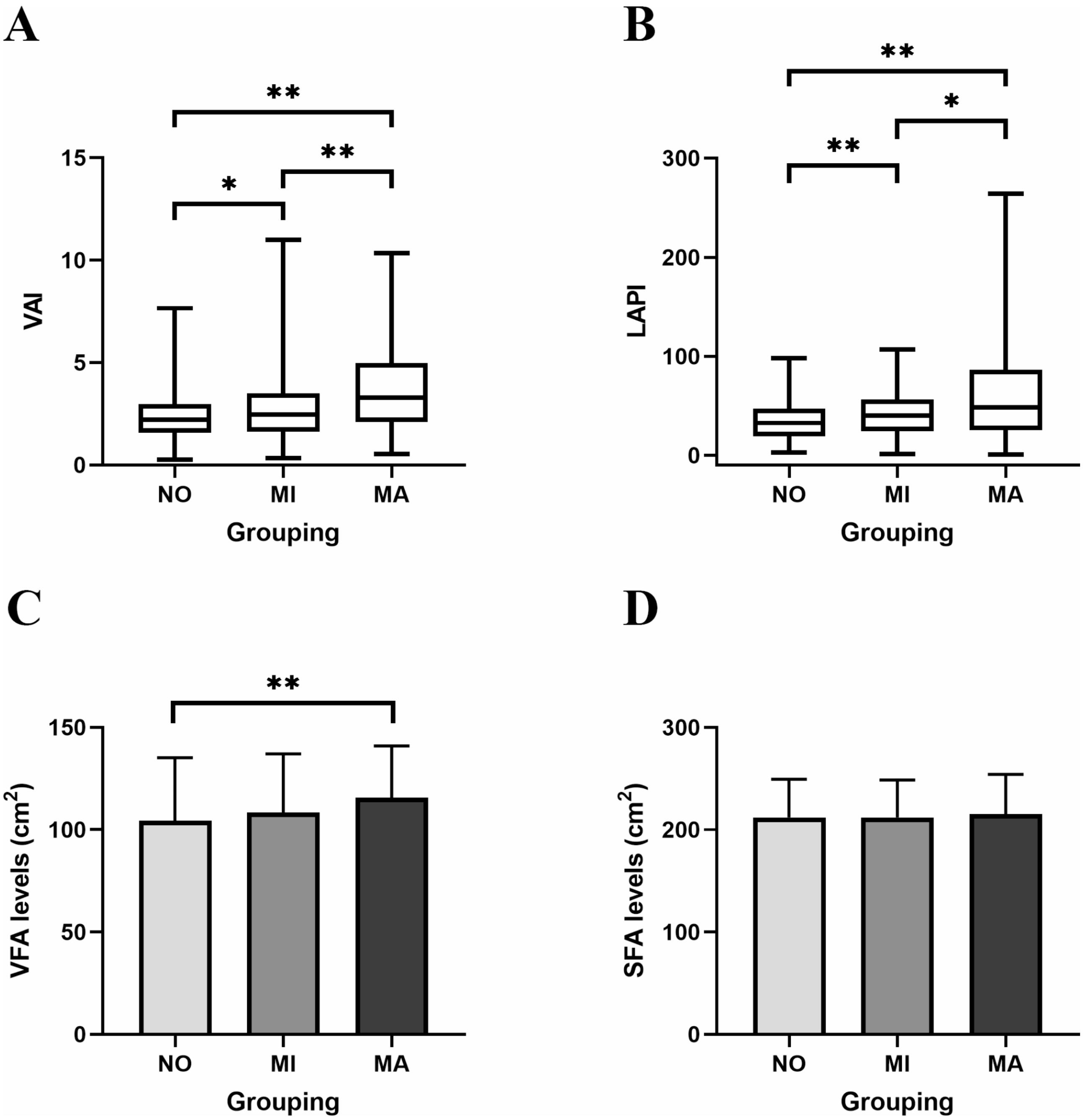


Fig. 2. Comparison of VAI, LAPI, VFA and SFA across different urinary albumin level groups. (**A**) Comparison of VAI levels; (**B**) Comparison of LAPI levels; (**C**) Comparison of VFA levels; (**D**) Comparison of SFA levels. NO: normoalbuminuria group; urinary albumin excretion rate(UACR) < 30 mg/g; MI: microalbuminuria group:30 mg/g ≤ UACR < 300 mg/g; MA: macroalbuminuriagroup, UACR ≥ 300 mg/g; VAI: visceral adiposity index; LAPI: lipid accumulation product index; VFA: visceral fat area; SFA: subcutaneous fat area; $^*p < 0.05$;$^{**}p < 0.001$.

were also examined, revealing a stronger relationship between LAPI and UACR in patients with TG levels (≥ 1.8 mmol/L) and HDL-C levels (≥ 0.8 mmol/L) (Fig. 5B). Additionally, a stronger correlation was observed between UACR levels and VFA in patients with age (≥ 50 years) (Fig. 5C).

The relationship between the severity of DKD and VAI, LAPI, VFA, and SFA analysed by multinomial logistic regression analysis in T2DM patients

Spearman's rank correlation analysis showed that DKD severity (NO = 1, MI = 2, MA = 3) was positively correlated with hypertension, SBP, diabetes duration, WC, FINS, HOMA, HbA1c, TG, UA, SCr, VAI, LAPI, and VFA (r = 0.063, 0.068, 0.242, 0.135, 0.082, 0.058, 0.118, 0.228, 0.075, 0.283, 0.189, 0.213, and 0.112, respectively,

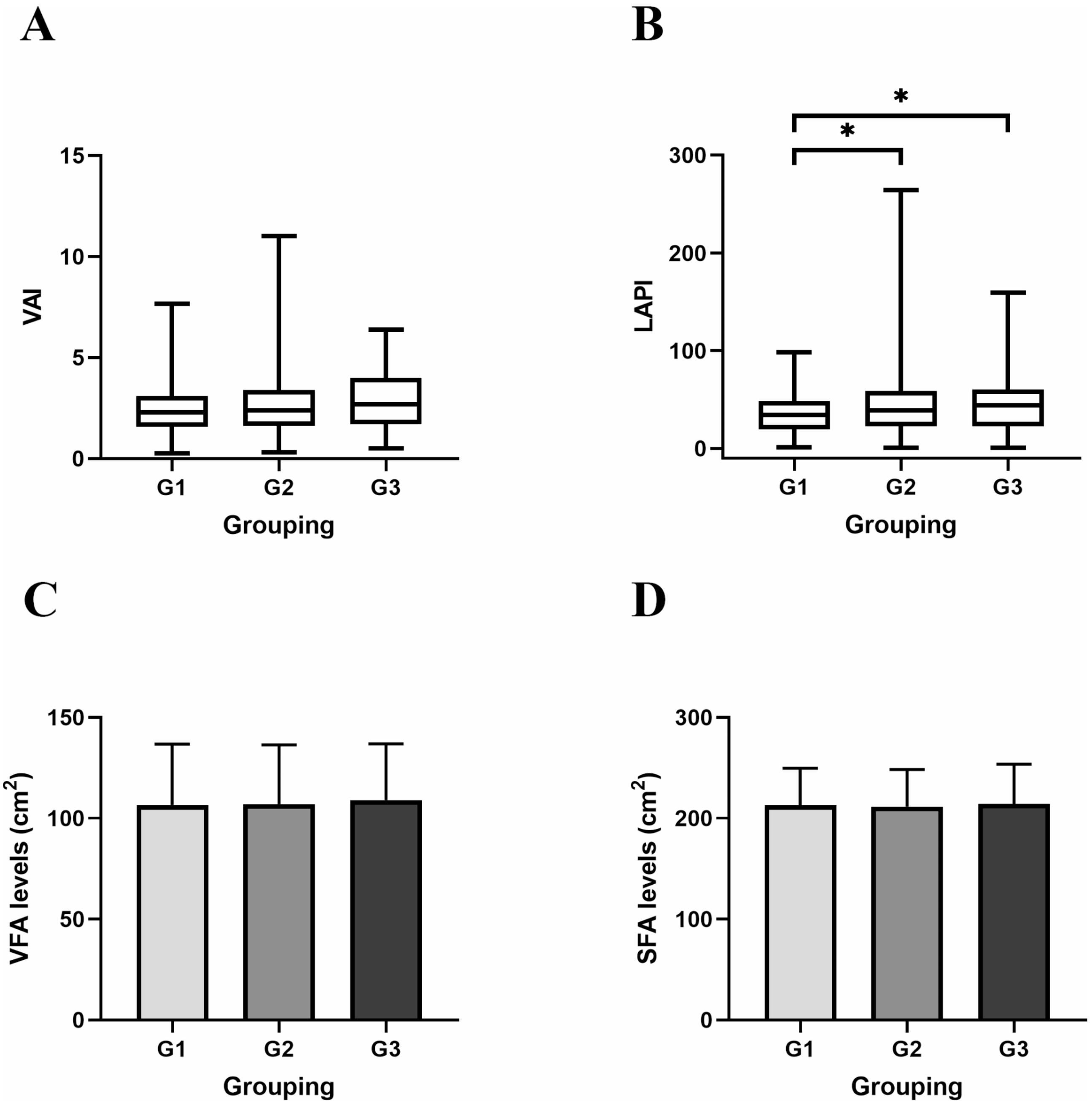


Fig. 3. Comparison of VAI, LAPI, VFA and SFA across different eGFR levels. (**A**) Comparison of VAI levels; (**B**) Comparison of LAPI levels; (**C**) Comparison of VFA levels; (**D**) Comparison of SFA levels. G1:estimated glomerular filtration rate (eGFR) ≥ 90 mL/min, G2 : 60 ≤ eGFR < 90 mL/min; G3: eGFR < 60 mL/min; VAI: visceral adiposity index; LAPI: lipid accumulation product index; VFA: visceral fat area; SFA: subcutaneous fat area; *$p < 0.05$;**$p < 0.001$.

all $p < 0.05$). Conversely, DKD severity was negatively correlated with eGFR ($r = -0.275$, $p < 0.05$). DKD severity was used as the dependent variable, with DKD severity-related variables considered independent variables. The relationship between DKD severity and VAI, LAPI, and VFA was further evaluated by multinomial logistic regression analysis.

The reference groups for this study were the NO and MI groups, while the MA group was considered an observational group. In the adjusted model, after controlling for variables such as SBP, diabetes duration, FINS, HOMA-IR, HbA1c, TGs, UA, and SCr, DKD severity was positively associated with VAI, LAPI, and VFA (Table 4).

	Simple linear regression analysis		Multiple linear regression analysis	
Index	**β (95%CI)**	***P***	**β (95%CI)**	***P***
Sex(Male = 0,Female = 1)	-8.208(-23.028,6.612)	0.277		
Age	0.974(0.329,1.619)	0.003	0.615(0.076,1.153)	0.025
Hypertension	6.454(-8.579,21.486)	0.4		
SBP	0.45(-0.012,0.912)	0.056		
DBP	0.012(-0.519,0.543)	0.965		
Diabetes duration	12.174(9.408,14.941)	< 0.001	8.376(5.984,10.767)	< 0.001
BMI	0.805(-0.885,2.494)	0.35		
WC	1.825(1.235,2.415)	< 0.001		
FPG	2.856(0.205,5.506)	0.035		
FINS	2.047(-0.560,4.653)	0.124		
HOMA-IR	5.737(0.859,10.886)	0.029	5.367(1.023,9.712)	0.016
HbAlc	5.153(2.138,8.168)	0.001	3.555(1.032,6.078)	0.006
AST	-0.389(-1.005,0.227)	0.216		
ALT	0.608(0.066,1.149)	0.028		
ALP	-0.043(-0.325,0.239)	0.766		
GGT	-0.079(-0.348,0.19)	0.565		
TC	3.356(-3.031,9.742)	0.303		
TG	65.863(53.434,78.293)	< 0.001	20.096(4.868,35.324)	0.01
HDL-C	-25.888(-40.160,-11.616)	< 0.001		
LDL-C	8.086(-1.094,17.265)	0.084		
UA	0.141(0.060,0.221)	0.001	0.115(0.048,0.183)	0.001
SCr	2.462(2.162,2.763)	< 0.001	2.108(1.828,2.389)	< 0.001
eGFR	-0.642(-0.795,-0.489)	< 0.001		
VAI	25.418(20.403,30.433)	< 0.001	8.455(1.933,14.978)	0.011
LAPI	1.550(1.276,1.823)	< 0.001	0.665(0.333,0.996)	< 0.001
VFA	0.469(0.230,0.7080	< 0.001	0.379(0.177,0.582)	< 0.001
SFA	0.041(-0.151,0.234)	0.674		
Smoking(No = 0,Yes = 1)	16.723(0.828,32.617)	0.154		
Drinking (No = 0, Yes = 1)	7.769(-7.383,22.8200	0.315		

Table 2. Simple and multiple linear regression analysis of the independent correlated factors of UACR levels in patients with T2DM. *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *BMI*, body mass index; *WC*, waist circumference; *FPG*, Fasting Plasma Glucose; *FINS*, fasting insulin; *HOMA-IR*, homeostasis model assessment of insulin resistance; *HbA1c*, glycosylated hemoglobin; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *ALP*, Alkaline phosphatase; *GGT*, gamma-glutamyl transferase; *TC*, total cholesterol; *TG*, triglycerides; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *UA*, serum uric acid; *SCr*, serum creatinine; *eGFR*, estimated glomerular filtrationrate; *VAI*, visceral adiposity index; *LAPI*, lipid accumulation product index; *VFA*, visceral fat area; *SFA*, subcutaneous fat area.

The relationship between the prognostic risk of DKD and VAI, LAPI, VFA and SFA analysed by multinomial logistic regression analysis in T2DM patients

The prognostic risk levels of patients with DKD were assessed according to the UACR and eGFR criteria defined in the guideline titled KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease[26]. Spearman's rank correlation analysis showed that the prognostic risk of DKD[26](Low-risk = 1, Medium-risk = 2, High or very high-risk = 3) was positively correlated with sex, age, SBP, diabetes duration, WC, FINS, HbA1c, GGT, TG, SCr, VAI, LAPI and VFA($r = 0.075$, 0.084, 0.068, 0.229, 0.117, 0.078, 0.105, 0.059, 0.217, 0.359, 0.190, 0.212, and 0.105, respectively, all $p < 0.05$). Conversely, it was negatively correlated with eGFR ($r =$ -0.366, $p < 0.05$). The dependent variable was DKD prognostic risk, and the independent variables were those related to DKD prognostic risk. The relationship between DKD prognostic risk and VAI, LAPI and VFA was evaluated by multinomial logistic regression analysis.

In the adjusted model, which accounted for confounders such as sex, age, SBP, diabetes duration, FINS, HbA1c, GGT, TGs, and SCr, the low-risk group served as the reference group. VAI was positively associated with DKD prognostic risk in the medium-risk group. Both LAPI and VFA were positively associated with DKD prognostic risk in the medium-risk and high or very high-risk groups. When the medium-risk group was used as the reference, VAI and LAPI were positively associated with DKD prognostic risk in the high or very high-risk group (Table 5).

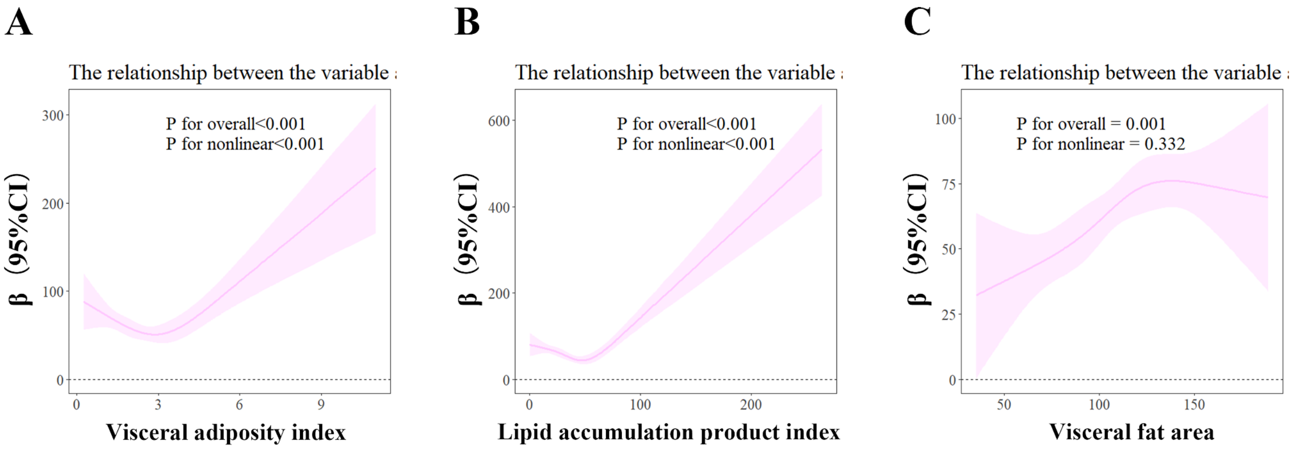


Fig. 4. The relationship of VAI, LAPI, and VFA to UACR in study population. (**A**) The relationship between VAI and UACR; (**B**) The relationship between LAPI and UACR; (**C**) The relationship between VFA and UACR. The independent variables in the model include age, duration, HOMA-IR, HbA1c, TG, UA, SCr, VAI, LAPI, and VFA.

Index	Model	Adjusted β (95%CI)	*P*
VAI	One-step linear regression	8.46(1.94,14.97)	0.011
	Two-piecewise linear regression		
	VAI < 3.18	-12.49(-22.79, -2.20)	0.018
	VAI > 3.18	23.68(14.99–32.37)	< 0.001
	Likelihood ratio test		< 0.001
LAPI	One-step linear regression	0.67(0.33, 0.10)	< 0.001
	Two-piecewise linear regression		
	LAPI < 63.14	-0.54(-0.96, 0.12)	0.012
	LAPI > 63.14	2.66(2.11, 3.21)	< 0.001
	Likelihood ratio test		< 0.001

Table 3. Threshold effect analysis of the relationship between UACR levels and VAI or LAPI in patients with T2DM.

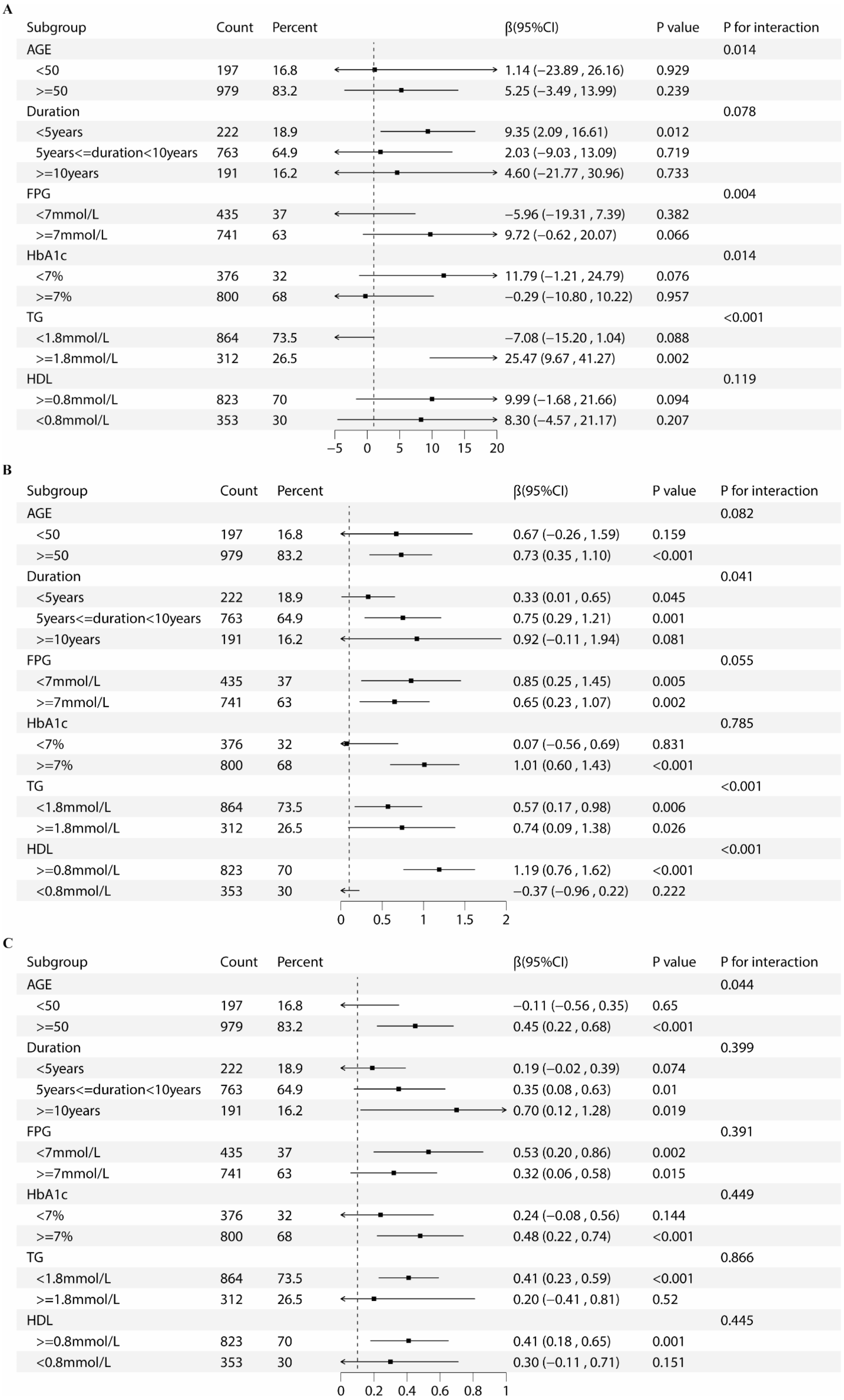
Discussion

In our study, the results indicate a significant positive association between DKD severity and prognostic risk with VAI, LAPI and VFA in patients with T2DM after adjusting for relevant confounders.

UACR is a critical marker for DKD severity, and is correlated with the onset and progression of DM and its complications in an increasing number of studies[27,28]. VAI is a quantitative measure of the distribution of visceral adipose tissue, which is strongly associated with a range of vascular diseases, including atherosclerosis and coronary heart disease[16,29]. Our research showed that UACR was positively associated with VAI, and VAI levels increasing in tandem with the DKD severity. A retrospective cohort study from Taiwan has reported similar results that VAI can be used to predict the risk of developing DKD[30]. Similarly, it has also been revealed that there is a potential positive positive relationship between VAI levels and proteinuria levels in T2DM patients[31]. In a study, the relationship between VAI and chronic kidney disease was investigated. They concluded that there is a positive relationship between VAI and kidney disease in a randomized population in rural China, although the study population in this study were T2DM patients[32].

LAPI is a new index of obesity to assess central lipid distribution and lipotoxicity[33], a positive correlation between LAPI and DKD in T2DM patients has been revealed[2,18]. In our study, LAPI was positively correlated with UACR. Similarly, a study reveals that several indicators associated with obesity, including BMI, LAPI, and VAI, are associated with DKD[34]. In addition, we further verified that there was a correlation between UACR levels and VAI, LAPI, and VFA through RCS and subgroup analyses.

As mentioned above, many prior studies have demonstrated that VAI and LAP were independently and positively associated with DKD, aligning with the findings of our study. However, a study conducted in southern China have showed that VAI and LAPI were not correlated with CKD after adjusting for confounders[35]. These differing results might arise from variations in study populations or calculation errors in VAI and LAPI, which might not fully reflect the distribution of abdominal adiposity. In our study, we not only used VAI and LAPI as visceral adiposity indexes, but also directly measured VFA and SFA in the participants. We found an independent positive correlation between VFA and DKD severity, but no correlation between SFA and DKD. In addition, we



A

Subgroup	Count	Percent	β(95%CI)	P value	P for interaction
AGE					0.014
<50	197	16.8	1.14 (−23.89 , 26.16)	0.929	
>=50	979	83.2	5.25 (−3.49 , 13.99)	0.239	
Duration					0.078
<5years	222	18.9	9.35 (2.09 , 16.61)	0.012	
5years<=duration<10years	763	64.9	2.03 (−9.03 , 13.09)	0.719	
>=10years	191	16.2	4.60 (−21.77 , 30.96)	0.733	
FPG					0.004
<7mmol/L	435	37	−5.96 (−19.31 , 7.39)	0.382	
>=7mmol/L	741	63	9.72 (−0.62 , 20.07)	0.066	
HbA1c					0.014
<7%	376	32	11.79 (−1.21 , 24.79)	0.076	
>=7%	800	68	−0.29 (−10.80 , 10.22)	0.957	
TG					<0.001
<1.8mmol/L	864	73.5	−7.08 (−15.20 , 1.04)	0.088	
>=1.8mmol/L	312	26.5	25.47 (9.67 , 41.27)	0.002	
HDL					0.119
>=0.8mmol/L	823	70	9.99 (−1.68 , 21.66)	0.094	
<0.8mmol/L	353	30	8.30 (−4.57 , 21.17)	0.207	

B

Subgroup	Count	Percent	β(95%CI)	P value	P for interaction
AGE					0.082
<50	197	16.8	0.67 (−0.26 , 1.59)	0.159	
>=50	979	83.2	0.73 (0.35 , 1.10)	<0.001	
Duration					0.041
<5years	222	18.9	0.33 (0.01 , 0.65)	0.045	
5years<=duration<10years	763	64.9	0.75 (0.29 , 1.21)	0.001	
>=10years	191	16.2	0.92 (−0.11 , 1.94)	0.081	
FPG					0.055
<7mmol/L	435	37	0.85 (0.25 , 1.45)	0.005	
>=7mmol/L	741	63	0.65 (0.23 , 1.07)	0.002	
HbA1c					0.785
<7%	376	32	0.07 (−0.56 , 0.69)	0.831	
>=7%	800	68	1.01 (0.60 , 1.43)	<0.001	
TG					<0.001
<1.8mmol/L	864	73.5	0.57 (0.17 , 0.98)	0.006	
>=1.8mmol/L	312	26.5	0.74 (0.09 , 1.38)	0.026	
HDL					<0.001
>=0.8mmol/L	823	70	1.19 (0.76 , 1.62)	<0.001	
<0.8mmol/L	353	30	−0.37 (−0.96 , 0.22)	0.222	

C

Subgroup	Count	Percent	β(95%CI)	P value	P for interaction
AGE					0.044
<50	197	16.8	−0.11 (−0.56 , 0.35)	0.65	
>=50	979	83.2	0.45 (0.22 , 0.68)	<0.001	
Duration					0.399
<5years	222	18.9	0.19 (−0.02 , 0.39)	0.074	
5years<=duration<10years	763	64.9	0.35 (0.08 , 0.63)	0.01	
>=10years	191	16.2	0.70 (0.12 , 1.28)	0.019	
FPG					0.391
<7mmol/L	435	37	0.53 (0.20 , 0.86)	0.002	
>=7mmol/L	741	63	0.32 (0.06 , 0.58)	0.015	
HbA1c					0.449
<7%	376	32	0.24 (−0.08 , 0.56)	0.144	
>=7%	800	68	0.48 (0.22 , 0.74)	<0.001	
TG					0.866
<1.8mmol/L	864	73.5	0.41 (0.23 , 0.59)	<0.001	
>=1.8mmol/L	312	26.5	0.20 (−0.41 , 0.81)	0.52	
HDL					0.445
>=0.8mmol/L	823	70	0.41 (0.18 , 0.65)	0.001	
<0.8mmol/L	353	30	0.30 (−0.11 , 0.71)	0.151	

Fig. 5. Subgroup analyses of associations between UACR and VAI, LAPI and VFA. (**A**) Subgroup analyses of UACR and VAI; (**B**) Subgroup analyses of UACR and LAPI; (**C**) Subgroup analyses of UACR and VFA. All variables including age, duration, FPG, HOMA-IR, HbA1c, ALT, TG, HDL-C, UA, SCr, VAI, LAPI and VFA were included in the model except when they were used as subgroups.

evaluated the correlation between high or very high risk of DKD and the levels of VAI, LAPI, and VFA, and the results demonstrated that high/very high DKD prognostic risk was independently and positively associated with the levels of VAI, LAPI, and VFA. To our knowledge, the relationships between VAI, LAPI, VFA and SFA levels and the DKD prognostic risk have been little studied to date.

Dependent variables	Independent variables	Model			
DKD		β	Wald	OR(95%CI)	*P*
NO group [a]	VAI	-0.034	0.215	0.966(0.836,1.117)	0.643
MI group	LAPI	0.010	6.012	1.010(1.002,1.018)	0.014
	VFA	0.006	7.730	1.006(1.002,1.011)	0.005
NO group [a]	VAI	0.431	11.09	1.539(1.194,1.983)	0.001
MA group	LAPI	0.024	12.80	1.025(1.011,1.039)	< 0.001
	VFA	0.017	11.54	1.017(1.007,1.028)	0.001
MI group [a]	VAI	0.465	13.66	1.593(1.244,2.038)	< 0.001
MA group	LAPI	0.014	5.147	1.014(1.002,1.027)	0.023
	VFA	0.011	4.835	1.011(1.001,1.021)	0.028

Table 4. Multinomial logistic regression analysis of the relationship between the severity of DKD and VAI, LAPI and VFA levels in patients with T2DM. *OR*, odds ratio; *CI*, confidence interval. a: reference group. Model, adjusted SBP, diabetes duration, FINS, HOMA-IR, HbA1c, TG, UA, and SCr.

Dependent variables	Independent variables	Model			
Risk for DKD		β	Wald	OR(95%CI)	*P*
Low-risk [a]	VAI	-0.056	0.531	0.945(0.813,1.100)	0.466
Medium-risk	LAPI	0.009	4.777	1.009(1.001,1.018)	0.029
	VFA	0.006	7.006	1.006(1.002,1.011)	0.008
Low-risk [a]	VAI	0.364	9.471	1.439(1.141,1.815)	0.002
High or very high-risk	LAPI	0.021	11.47	1.022(1.009,1.034)	0.001
	VFA	0.017	12.38	1.017(1.008,1.027)	< 0.001
Medium-risk [a]	VAI	0.420	13.45	1.522(1.216,1.906)	< 0.001
High or very high-risk	LAPI	0.012	4.433	1.012(1.001,1.023)	0.035
	VFA	0.011	5.327	1.011(1.002,1.021)	0.021

Table 5. Multinomial logistic regression analysis of the relationship between the prognostic risk of DKD and VAI, LAPI and VFA levels in patients with T2DM. *OR*, odds ratio; *CI*, confidence interval. a: reference group. Model, adjusted Sex, Age, SBP, diabetes duration, FINS, HbA1c, GGT, TG and SCr.

The mechanisms of obesity related DKD is incompletely understood at this time, however, possible mechanisms are as follows: Several common abnormalities in the obesity microenvironment, such as lipid accumulation, oxidative stress, and mitochondrial dysfunction, impair insulin sensitivity and negatively affect autophagy[36]. Overnutrition in obese patients inhibits autophagy, which impairs insulin signaling and promotes the development of T2DM[37]. And Obesity is hypothesized to increase glomerular filtration rate to meet metabolic demands, cause focal segmental glomerulosclerosis, and reduc renal function[38]. Excess fat deposition in the kidneys due to obesity leads to toxic substance buildup from fatty acid metabolism, leading to mitochondrial damage, apoptosis, and eventually renal damage[39]. Meanwhile, oxidative stress is a common cause of DKD[40]. In the kidney, accumulated lipids can induce oxidative stress, leading to glomerular injury and mesangial fibrosis[41,42], Dysfunction of lipid metabolism in DKD has the potential to cause a cascade of harmful effects, one of which includes direct damage to the podocytes. This type of cellular damage can hasten the progression of DKD, resulting in further deterioration of renal function and potentially leading to chronic kidney failure[43]. Overall, obesity might lead to pancreatic β-cell failure through lipid metabolism, insulin resistance, oxidative stress, and inflammation, leading to progression to T2DM and its complications[27].

Currently, VAI, BMI, and WC are primarily used as surrogates for abdominal obesity in studies examining the relationship between abdominal obesity and DKD. In this study, not only the conventional VAI was employed as a surrogate for abdominal obesity but also it was used to directly measured VFA and SFA. We found that visceral adiposity levels were independently and positively associated with DKD severity and prognostic risk. This approach more intuitively demonstrates that visceral adiposity levels correlate with DKD severity and prognostic risk rather than total abdominal adiposity levels. It further confirms that the level of visceral adiposity is independently and positively associated with the severity and prognostic risk of DKD rather than the level of total abdominal adiposity. These findings are valuable for health management in T2DM patients and hold significant clinical implications.

However, there are some limitations in our study. First, some data, such as the duration of diabetes, are based on patients' subjective descriptions and may be biased. Second, this is a cross-sectional study that could not explain the causal correlation between DKD and visceral adiposity. Third, the assessment of prognostic risk levels in patients with DKD was based on guidelines rather than follow-up results, potentially limiting the accuracy of the relationship between obesity indices and DKD prognostic risk. Validation through additional prospective studies is necessary. Fourth, our study was limited to T2DM patients in Gansu, China, and the results may have limitations. Finally, the diagnosis of DKD is based solely on clinical indicators and not on renal biopsy.

Conclusion

In the study, DKD severity and prognostic risk were positively correlated with VAI, LAPI and VFA levels in patients with T2DM, which could be beneficial for the health management and monitoring of obese diabetic patients, providing warnings about DKD occurrence and progression.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

Pingping Zhao conceived and designed the study. Pingping Zhao, Qi Zhou and Tianqi Du collected clinical and biochemical data. All authors contributed to the statistical analysis, results interpretation, drafting and revising the paper. All the authors agreed to publish this article.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards, the approval number is LDYYLL2021-317.Each participant signed the written informed consent form before taking part.

Additional information

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