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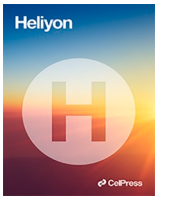

The association between obesity indicators and metabolic risk factors in type-2 diabetic patients

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ABSTRACT

Rationale and objectives: Obesity, accumulation of adipose tissue, is a global disease that can lead to cardiovascular and metabolic complications. The aim of this study was to investigate the relationship between obesity indicators and metabolic risk factors in type 2 diabetes mellitus (T2DM) patients.

Materials and methods: A total of 337 T2DM subjects were included in our study. The metabolic risk factors including diabetes duration, fast plasma glucose (FPG), height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), estimated average glucose (eAG), glycated hemoglobin (HbA1c), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), triglyceride (TG), blood urea nitrogen (BUN), serum creatinine (Scr), free fatty acid (FFA), uric acid (UA), cystatin c (cysc), albumin (Alb), urinary albumin creatinine ratio (UACR) were recorded. The obesity indicators included body surface area (BSA), body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), *para*-perirenal fat thickness (PRFT), total abdominal fat (TAF), subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT). The association between obesity indicators and metabolic risk factors was investigated by univariate and multivariate analysis.

Results: HDL-c was independently associated with WHR and PRFT ($\beta = -0.126$ vs. -0.214, both $p < 0.05$). TG and Scr were both independently associated with PRFT ($\beta = 0.173$ vs. 0.218, both $p < 0.01$, respectively). UA was independently associated with BSA ($\beta = 0.172$, $p < 0.01$) and PRFT ($\beta = 0.151$, $p < 0.01$). cysc, Alb and UACR were independently associated with WC ($\beta = 0.274$ vs. 0.204 vs. 0.182, all $p < 0.01$).

Conclusion: In T2DM patients, obesity indicators were significantly associated with metabolic risk factors.

1. Introduction

Obesity is a worldwide epidemic [1]. From 1970 to 2005, the average BMI of American population increased by 3.0 kg/m^2, and the prevalence of obesity increased gradually [2,3]. During the period from 2013 to 2014, more than 50% American adults had suffered or

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were suffering from obesity [4]. Obesity is one of the risk factors for many diseases, such as insulin resistance, diabetes, cardiovascular diseases, non-alcoholic fatty liver, immune disorders, and some cancers [5]. Obesity and its complications threaten public health, causing a serious economic burden [4,6]. Usually, such indicators as BSA, BMI, WC, and WHR were used to describe obesity, but they cannot distinguish fat from other tissue components. Moreover, they were unable to describe the distribution of fat well [7,8]. Emerging imaging techniques made it possible to assess subcutaneous fat and visceral fat quantitatively [9–12], such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Dual Energy X-ray Absorptiometry (DXA).

Excessive deposition of adipose tissue is associated with metabolic disorders. Fat deposits in the liver or skeletal muscle can increase cardiovascular metabolic risk [13], epicardial adipose tissue is closely related to myocardial metabolism [14], perirenal fat is associated with kidney disease [15].

As is mentioned above, obesity is the risk factors of diabetes. On the other hand, diabetes is one of the most common metabolic disorders, which was characterized by hyperglycemia due to insufficient insulin secretion or insulin resistance [16]. Now, diabetes can be accurately diagnosed by fasting glucose, HbA1c, and OGTT test [17]. As of 2014, 9.3% (29.1 million) of American suffered from diabetes. In addition, there was a large population in pre-diabetes [18]. It emphasized the importance of early diagnosis of metabolic dysfunction. However, to the best of our knowledge, the association between metabolic indicators and obesity indicators has not yet been assessed comprehensively in diabetics.

This study aimed to investigate the relationship between metabolic and obesity indicators, and explore the possible predictors of each metabolic indicator, which may help in early diagnosis and prevention of metabolic dysfunction in T2DM.

1.1. Methods and subjects

The study protocols were approved by the Institutional Review Board of our hospital and were performed following the Declaration of Helsinki. A written informed consent was waived as it was a retrospective study. We screened T2DM inpatients of our hospital from August 2020 to October 2021. The exclusion criteria were as follows: 1. kidney surgery and injury; 2. renal dysfunction for non-diabetic reasons, such as renal artery stenosis, renal stones, hydronephrosis, renal atrophy, renal tumor, polycystic kidney, renal developmental abnormalities, infection and inflammatory disease; 3. chronic consumptive diseases, such as tuberculosis and tumor; 4. congenital disorders of fat metabolism, such as generalized lipodystrophy and Madelung syndrome; 5. incomplete clinical or imaging data. The flowchart of the study population was shown in Fig. 1.

Patients' information was retrieved from Hospital Information System (HIS). The clinical information including age, sex, diabetes

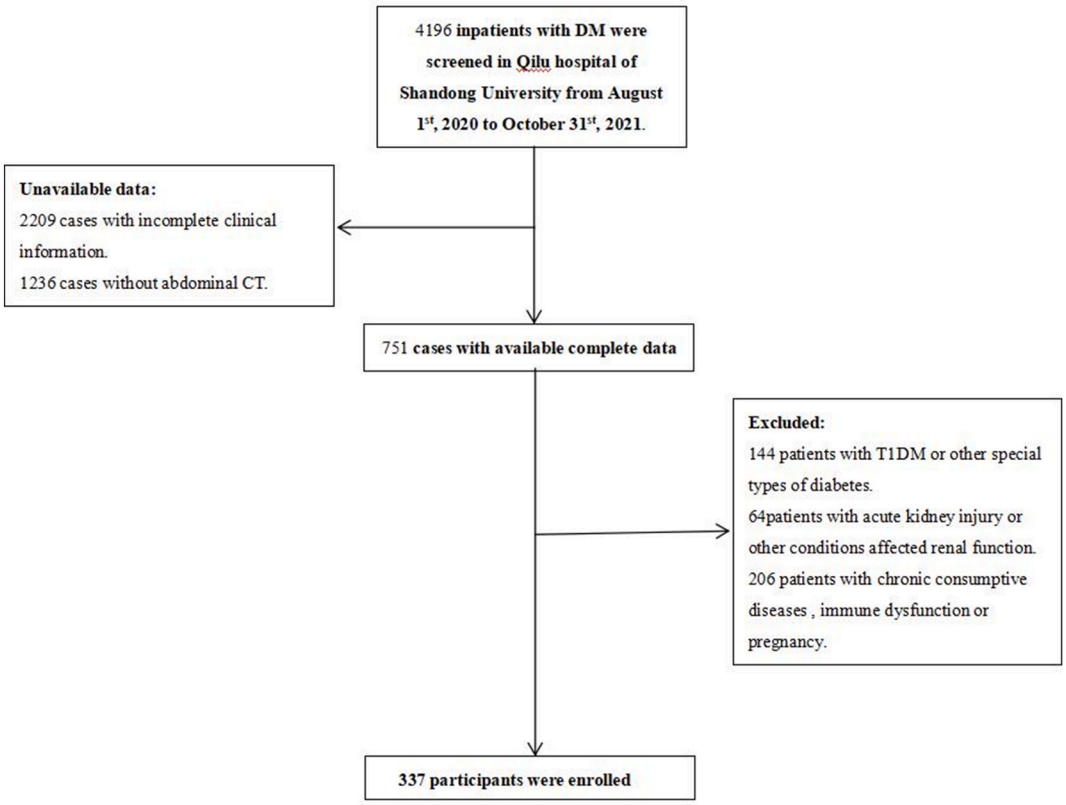

Fig. 1. Flowchart of the study population.

duration, height, weight, waist-to-hip ratio (WHR), systolic blood pressure (SBP), diastolic blood pressure (DBP) were recorded. Body surface area (BSA) was calculated according to the DuBois formula (0.20247 * height[m]0.725 * weight[kg]0.425) [10]. Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2). The blood biochemical indicators, such as fast plasma glucose (FPG), estimated average glucose (eAG), glycated hemoglobin (HbA1c), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), triglyceride (TG), blood urea nitrogen (BUN), serum creatinine (Scr), free fatty acid (FFA), uric acid (UA), cystatin c (cysc), albumin (Alb), urinary albumin creatinine ratio (UACR), were assessed by an automated analyzer (Cobas8000 c701, Roche Diagnostics GmbH, German.). The Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) was used to calculate eGFR [19]. Diabetes was diagnosed according to the American Diabetes Association's "Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes" (Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019) [20]. eGFR <60 mL/min/1.73 m^2 was considered as CKD. Metabolic syndrome (Mets) was defined according to International Diabetes Federation (IDF) in 2005 as: central obesity (waist circumference $\geq$90 cm in Chinese men and $\geq$80 cm in women) plus two of the following four items: 1. hypertension (SBP $\geq$130 mmHg, DBP $\geq$85 mmHg or antihypertensive treatments) 2. Hypertriglyceridemia (fasting plasma triglycerides $\geq$1.7 mmol/L) 3. low HDL-c (fasting HDL-c $<$ 1.0 mmol/L in men and $<$1.3 mmol/L in women) 4. high fasting glucose (fasting glucose $\geq$5.6 mmol/L or undergoing glucose-lowering treatment) [21].

Abdominal CT datasets were acquired by Force CT (SOMATOM Force, Siemens Healthcare, German). The CT scanning protocols were as follows: tube voltage: 120 kV; tube current: automatic; beam pitch: 1 mm; reconstruction thickness: 1 mm; reconstruction interval: 1 mm; window width: 260 HU; window level: 50 HU. PRFT was the distance between the outermost edge of the renal parenchyma and the inner edge of the abdominal wall muscles in the direction of the renal pedicle at the level of the renal vein (Fig. 2A, C). PRFT was measured on both sides and the average value was calculated for subsequent analysis. CT images were transferred to syngo. via semi-automated software (VB40, Siemens, German), delineated the outline of fat manually from the top of the diaphragm to the superior margin of the iliac crest, and TAF, SAT, VAT were measured automatically by the threshold method (with a fat threshold of $-200 \sim -40$ HU). The voxels within this threshold were defined as TAF, which consisted of internal VAT and external SAT (Fig. 2B). To ensure robustness of the data, the fat volume was measured by two trained radiologists (S.N.X., R.C.R.; three years and five years of work experience, respectively), who were both blinded to clinical information. Then, we calculated the average value of two measurements for analysis. The inter-classic correlation coefficients (ICC) of the average PRFT, TAF, SAT, and VAT were 0.827, 0.999, 0.998 and 0.997, respectively. The intervals of the clinical and imaging data were no more than one week.

1.2. Statistical analysis

Shapiro-Wilk test and histograms were used to detect the types of distributions of continuous variables. Continuous variables conforming to the normal distribution were described as mean $\pm$ standard deviation (SD), otherwise described as median and quartiles. Categorical variables were described as frequencies (proportions). Grouped *t*-test and Mann-Whitney *U* test were used to compare the average between two groups, as appropriate. Chi-square test was used to compare the categorical variables. Comparison of the means among multiple groups was performed by one-way ANOVA test (with LSD post hoc test), or Kruskal-Wallis H test, as appropriate. The pearson or spearman correlation analyses were performed and multivariate models were built with metabolic indicators as response variable and obesity indicators as explanatory variables. Model 1 controlled for age, sex, diabetes duration, and HbA1c. Model 2 controlled for age, sex, diabetes duration, HbA1c, SBP, LDL-c, BUN, and FFA. Model 3 controlled for age, sex, diabetes duration, HbA1c, SBP, LDL-c, BUN, FFA, and some metabolic indicators. The co-linearity of the variables in the models was assessed by calculating variance inflation factors (VIF). We built three multiple stepwise linear regression models to determine independent predictors of each metabolic indicator. The goodness-of-fit of the models were assessed by the value of R^2. Statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

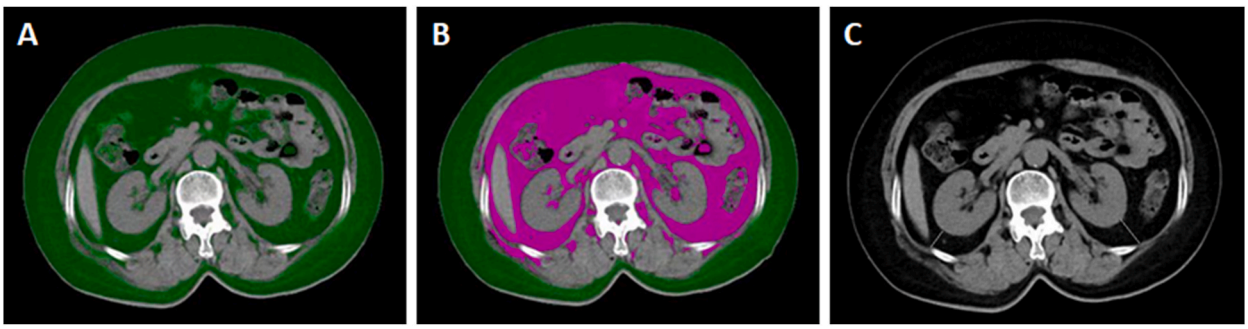

Fig. 2. Definition of the adipose tissue in CT cross-sectional image with the threshold method. A. total abdominal fat (green); B. subcutaneous adipose tissue (green) and visceral adipose tissue (purple); and c. Para-perirenal fat thickness (white line).

2. Results

337 T2DM patients were included in this study (195 men [57.9%] and 142 women [42.1%], mean age: 60.2 ± 11.6 years). The age, height, weight, BSA, WC, WHR, PRFT, DBP, BUN, Scr, UA, eGFR, TC and HDL-c levels differed significantly between men and women (all $p < 0.05$). Besides, females had more subcutaneous fat and less visceral fat (both $p < 0.01$). No significant differences were found in TAF, BMI and DBP between males and females (all $p > 0.05$) (Table 1). Moreover , kidney damage was one of the most common microvascular complications in diabetes. So subjects were further divided into CKD (chronic kidney disease) group and non-CKD group for comparisons according to the presence or absence of kidney damage. The results showed, the levels of age, diabetes duration, weight, TG, BUN, Scr, UA, cysc, Alb, UACR were higher in T2DM patients with CKD than in non-CKD patients (all $p < 0.05$). Furthermore, we found lower eAG level in CKD group (Supplementary Table 1). We also compared the metabolic indicators of patients in different CKD stage in Supplementary Table 2. Patients in CKD stage 2 and 3 were older than in stage 1 (both $p < 0.001$). Patients in CKD stage 2, 4 and 5 had longer diabetes duration than in stage 1(all $p < 0.05$). Height and eAG were lower in CKD stage 2 than those in stage 1 (both $p < 0.05$). BUN, Alb, and UACR were significantly higher in CKD stage 3, 4, and 5 than in stage 1 (all $p < 0.001$). Scr, UA, and cysc were significantly higher in CKD stages 2, 3, 4, and 5 than in stage 1 (all $p < 0.01$). According to the third National Health and Nutrition Survey (NHANES III), Mets accounted for approximately 40% of population over 20 years old in the United States [22]. So, we further compared the obesity indicators between groups divided by Mets-related indicators in Table 2. It revealed that all obesity indicator including BSA, BMI, WC, WHR, TAF, SAT, VAT, PRFT, was significantly higher in high fasting glucose group compared to low fasting glucose group (all $p < 0.001$).

Table 1
The obesity indicators and metabolic risk factors for the total population and subgroup divided by gender.

	Total n = 337	Man n = 195	Woman n = 142	P
Age(years)	60.2 ± 11.6	58.5 ± 12.2	62.6 ± 10.4	0.001
Duration of diabetes(years)	11.0(6.0,20.0)	10.0(5.00,20.0)	12.5(7.00,20.0)	>0.05
FPG	7.8(6.7,8.1)	7.84(6.70,8.15)	7.84(6.39,7.88)	>0.05
Height(cm)	166.7 ± 8.2	171.8 ± 5.9	159.8 ± 5.2	<0.001
Weight(kg)	71.4 ± 11.8	75.9 ± 10.6	65.2 ± 10.5	<0.001
BSA	1.80 ± 0.17	1.88 ± 0.14	1.68 ± 0.13	<0.001
BMI(kg/m^2)	25.7 ± 3.5	25.8 ± 3.0	25.6 ± 4.1	>0.05
WC(cm)	93.7 ± 9.6	95.5 ± 8.4	91.3 ± 10.6	<0.001
WHR	0.94 ± 0.06	0.95 ± 0.60	0.92 ± 0.51	<0.01
PRFT(mm)				
LEFT	16.1(11.1,21.8)	18.20(12.80,23.80)	13.10(8.55,18.49)	<0.001
RIGHT	16.3(11.5,22.4)	18.50(13.65,24.15)	13.85(8.70,18.36)	<0.001
MEAN	16.1(11.2,22.0)	18.38(13.58,23.95)	14.04(8.50,18.39)	<0.001
TAF(cm^3)	5775.5(4085.0,7439.5)	5894.2(4095.8,7294.6)	5669.4(4081.3,7583.9)	>0.05
SAT(cm^3)	2576.9(1880.0,3627.4)	2254.2(1625.3,2977.6)	3256.8(2305.2,4243.7)	<0.001
VAT(cm^3)	2850.7(1899.5,4043.5)	3398.0(2356.7,4473.1)	2358.4(1602.9,3281.1)	<0.001
SBP(mmHg)	138.3 ± 23.5	138.8 ± 21.1	137.5 ± 26.5	>0.05
DBP(mmHg)	78.3 ± 14.1	80.3 ± 13.1	75.4 ± 14.9	0.002
eAG(mmol/L)	11.5 ± 3.8	11.3 ± 3.6	11.7 ± 4.1	>0.05
HbA1c(%)	8.3(6.8,9.5)	8.20(6.90,9.10)	8.40(6.70,10.10)	>0.05
TC(mmol/L)	4.3(3.6,5.1)	4.15(3.30,4.97)	4.43(3.85,5.12)	0.006
HDL-c(mmol/L)	1.15 ± 0.30	1.06 ± 0.26	1.26 ± 0.32	<0.001
LDL-c(mmol/L)	2.44(1.82,3.04)	2.33(1.72,2.90)	2.51(2.05,3.09)	>0.05
TG(mmol/L)	1.34(0.95,1.90)	1.24(0.90,1.87)	1.48(1.04,1.91)	>0.05
BUN	5.5(4.53,6.74)	5.76(4.70,7.10)	5.29(4.40,6.40)	0.019
Scr(umol/L)	68.0(56.0,77.5)	71.0(61.0,80.0)	60.0(48.0,73.0)	<0.001
FFA(umol/dL)	50.0(33.5,65.2)	49.0(34.5,64.0)	50.8(32.0,68.0)	>0.05
UA(umol/L)	294.2 ± 89.7	306.2 ± 88.4	277.8 ± 89.1	0.004
cysc	0.98(0.83,1.11)	0.97(0.84,1.10)	0.99(0.81,1.13)	>0.05
Alb	13.09(6.80,72.14)	12.6(6.90,79.6)	13.6(6.74,58.52)	>0.05
UACR(mg/g)	0.02(0.01,0.14)	0.02(0.01,0.12)	0.02(0.01,0.16)	>0.05
eGFR(ml/min/$1.73m^2$)-EPI	93.5(83.9104.49)	96.4(87.2105.5)	90.9(77.3101.1)	0.002
eGFR(ml/min/$1.73m^2$)-EPI	29(8.6)	16(8.2)	13(9.2)	>0.05
CKD (eGFR<60) non-CKD(eGFR≥60)	308(91.4)	179(91.8)	129(90.8)	

Note.- Continuous variables are expressed as mean ± standard deviation or median (interquartile). Categorical variables are expressed as absolute numbers (relative numbers). FPG = fast plasma glucose. BSA = body surface area. BMI = body mass index. WC = waist circumference. WHR = waist-to-hip ratio. PRFT = *para*-perirenal fat thickness. TAF = total abdominal fat. SAT = subcutaneous adipose tissue. VAT = visceral adipose tissue. SBP = systolic blood pressure. DBP = diastolic blood pressure. eAG = estimated average glucose. HbA1c = glycated hemoglobin. TC = total cholesterol. HDL-c = high-density lipoprotein-cholesterol. LDL-c = low-density lipoprotein-cholesterol. TG = triglyceride. BUN = blood urea nitrogen. Scr = serum creatinine. FFA = free fatty acid. UA = uric acid. cysc = cystatin c. Alb = albumin. UACR = urinary albumin creatinine ratio. eGFR = estimated glomerular filtration rate. CKD = chronic kidney disease.

Table 2
Comparison of obesity indicators between groups divided by metabolic syndrome diagnosis-related (Mets-related) indicators.

	BSA	BMI (kg/m2)	WC(cm)	WHR	TAF	SAT	VAT	PRFT		
								LEFT	RIGHT	MEAN
central obesity[a] (n = 279)	1.79 ± 0.17	25.74 ± 3.52	93.74 ± 9.51	0.94 ± 0.06	5759.48 (4112.10,7427.58)	2616.37 (1903.57,3627.72)	2812.40 (1905.17.3973.62)	15.90 (11.15,21.35)	16.00 (11.75,21.90)	15.90 (11.30,21.48)
normal (n = 58)	1.81 ± 0.16 NS	25.53 ± 3.53 NS	93.64 ± 9.91 NS	0.94 ± 0.06 NS	5669.78 (3622.78,7776.45) NS	2295.47 (1704.28,3617.16) NS	3013.09 (1842.65,4160.91)NS	17.80 (9.04,25.84) NS	17.73 (9.75,25.89) NS	17.86 (9.53,26.88) NS
hypertension[b] (n = 218)	1.79 ± 0.17	25.59 ± 3.50	93.56 ± 9.79	0.94 ± 0.06	5594.21 (4167.95,7142.02)	2545.32 (1888.19,3517.40)	2708.63 (1893.89,3905.12)	15.10 (10.65,21.24)	16.00 (11.25,22.21)	15.53 (11.07,21.51)
Normal (n = 119)	1.80 ± 0.17 NS	25.91 ± 3.54 NS	94.01 ± 9.16 NS	0.94 ± 0.06NS	6108.49 (4034.30,7842.72) NS	2658.91 (1762.75,3703.66) NS	3246.57 (1901.93,4123.45) NS	17.65 (12.25,22.45) NS	17.15 (12.40,22.75) NS	17.68 (12.35,22.20) NS
hypertriglyceridemia[c] (n = 109)	1.81 ± 0.18	25.90 ± 3.30	94.02 ± 9.51	0.94 ± 0.06	5759.48 (4302.25,7391.50)	2558.04 (1924.49,3621.90)	2793.43 (1890.41,4081.67)	15.50 (11.45,22.70)	15.70 (11.75,22.45)	15.73 (11.33,22.53)
normal (n = 228)	1.79 ± 0.17 NS	25.61 ± 3.62 NS	93.58 ± 9.61 NS	0.94 ± 0.06NS	5706.54 (4002.31,7437.11) NS	2587.28 (1798.84,3629.16)NS	2903.40 (1902.74,3974.84)NS	16.35 (10.88,21.75) NS	16.53 (11.0,22.39) NS	16.26 (11.08,22.01) NS
low HDL-c[d] (n = 184)	1.80 ± 0.16	25.81 ± 3.01	94.43 ± 9.33	0.95 ± 0.06	6014.32 (4304.10,7476.62)	2680.56 (1994.49,3591.80)	2890.23 (1889.13,4131.80)	15.95 (11.28,21.79)	16.18 (11.51,22.00)	15.93 (11.45,21.59)
normal (n = 153)	1.79 ± 0.18 NS	25.57 ± 4.05 NS	92.87 ± 9.80NS	0.93 ± 0.06 NS	5478.85 (3725.84,7298.07) NS	2471.43 (1707.21,3659.53)NS	2770.88 (1899.48,3810.13) NS	16.55 (10.60,21.90) NS	16.30 (11.28,23.08) NS	16.13 (11.04,22.41) NS
high fasting glucose[e] (n = 290)	1.82 ± 0.17	26.45 ± 3.15	95.25 ± 8.97	0.95 ± 0.06	6180.61 (4751.83,7747.68)	2783.82 (2103.20,3746.81)	3239.39 (2182.66,4250.27)	17.38 (12.36,22.46)	17.63 (13.04,23.35)	17.56 (12.91,22.64)
normal (n = 47)	1.67 ± 0.13 ***	21.08 ± 1.60 ***	84.31 ± 7.61 ***	0.90 ± 0.05 ***	3160.51 (2240.04,3834.49) ***	1526.43 (1197.65,2104.00) ***	1310.28 (898.41,1997.58) ***	9.50 (6.40,12.35) ***	9.60 (6.95,13.10) ***	10.08 (7.00,12.98) ***

Note.- Continuous variables are expressed as mean ± standard deviation or median (interquartile).
BSA = body surface area. BMI = body mass index. WC = waist circumference. WHR = waist-to-hip ratio. PRFT = *para*-perirenal fat thickness. TAF = total abdominal fat. SAT = subcutaneous adipose tissue. VAT = visceral adipose tissue. HDL-c = high-density lipoprotein-cholesterol.
***$p < 0.001$ NS $p > 0.05$.
[a] WC ≥ 90 cm and ≥80 cm were used as the reference values for the central obesity group in men and women, respectively.
[b] SBP≥130 mmHg and (or) DBP≥85 mmHg
[c] TG ≥ 1.7 mmol/L.
[d] HDL-C levels <1.0 mmol/L and <1.3 mmol/L were used as the reference values for the low HDL-C group in men and women, respectively.
[e] FPG≥5.6 mmol/L.

Table 3
Correlation coefficient between obesity indicators and metabolic risk factors.

	BSA	BMI (kg/m^2) r	WC (cm) r	WHR r	PRFT(mm) r			TAF (cm^3) r	SAT (cm^3) r	VAT (cm^3) r
					LEFT	RIGHT	MEAN			
Age(years)	−0.257***	−0.005^{NS}	0.049^{NS}	0.035^{NS}	0.224***	0.225***	0.228***	0.054^{NS}	0.011^{NS}	0.100^{NS}
Duration of diabetes(years)	−0.073^{NS}	−0.020^{NS}	0.052^{NS}	0.064^{NS}	0.103^{NS}	0.104^{NS}	0.106^{NS}	0.061^{NS}	0.049^{NS}	0.047^{NS}
FPG	0.276***	0.631***	0.429***	0.225***	0.460***	0.476***	0.475***	0.532***	0.436***	0.477***
Height(cm)	0.812***	0.783*	0.224***	0.174**	0.137*	0.140*	0.142**	0.041^{NS}	−0.232***	0.279***
Weight(kg)	0.954***	0.754***	0.714***	0.381***	0.481***	0.494***	0.495***	0.650***	0.387***	0.705***
SBP(mmHg)	0.067^{NS}	0.105^{NS}	0.116*	0.013^{NS}	0.141*	0.149**	0.143**	0.155**	0.084^{NS}	0.186**
DBP(mmHg)	0.188**	0.091^{NS}	0.052^{NS}	0.050^{NS}	0.075^{NS}	0.083^{NS}	0.077^{NS}	0.115*	0.002^{NS}	0.183**
eAG(mmol/L)	−0.021^{NS}	−0.016^{NS}	−0.054^{NS}	−0.059^{NS}	−0.106^{NS}	−0.079^{NS}	−0.096^{NS}	−0.010^{NS}	0.038^{NS}	−0.061^{NS}
HbA1c(%)	−0.006^{NS}	−0.005^{NS}	−0.046^{NS}	−0.053^{NS}	−0.093^{NS}	−0.077^{NS}	−0.087^{NS}	−0.004^{NS}	0.043^{NS}	−0.052^{NS}
TC(mmol/L)	−0.065^{NS}	−0.053^{NS}	−0.095^{NS}	−0.074^{NS}	−0.147**	−0.133*	−0.140*	−0.009^{NS}	0.026^{NS}	−0.050^{NS}
HDL-c(mmol/L)	−0.300***	−0.200***	−0.251***	−0.255***	−0.296***	−0.296***	−0.299***	−0.250***	−0.073^{NS}	−0.371***
LDL-c(mmol/L)	−0.033^{NS}	−0.061^{NS}	−0.041^{NS}	−0.011^{NS}	−0.105^{NS}	−0.076^{NS}	−0.091^{NS}	0.034^{NS}	0.041^{NS}	0.012^{NS}
TG(mmol/L)	0.140*	0.235***	0.205***	0.189***	0.196***	0.198***	0.200***	0.330***	0.237***	0.334***
BUN(mmol/L)	0.085^{NS}	0.092^{NS}	0.062^{NS}	0.089^{NS}	0.173**	0.174**	0.177**	0.104^{NS}	−0.009^{NS}	0.162**
Scr(umol/L)	0.294***	0.173**	0.216***	0.150**	0.381***	0.387***	0.389***	0.157**	−0.038^{NS}	0.297***
FFA(umol/dL)	0.013^{NS}	0.054^{NS}	0.070^{NS}	0.025^{NS}	0.033^{NS}	0.038^{NS}	0.032^{NS}	0.109*	0.063^{NS}	0.118*
UA(umol/L)	0.238***	0.196***	0.190***	0.181**	0.202***	0.189***	0.196***	0.231***	0.072^{NS}	0.300***
cysc(mg/L)	0.064^{NS}	0.194***	0.248***	0.153**	0.309***	0.293***	0.307***	0.252***	0.168**	0.247***
Alb	0.156**	0.182**	0.191***	0.102^{NS}	0.021^{NS}	0.050^{NS}	0.035^{NS}	0.165**	0.160**	0.141*
UACR(mg/g)	0.070^{NS}	0.141**	0.167**	0.104^{NS}	−0.012^{NS}	0.020^{NS}	0.004^{NS}	0.161**	0.178**	0.099^{NS}

Note.- BSA = body surface area. BMI = body mass index. WC = waist circumference. WHR = waist-to-hip ratio. PRFT = *para*-perirenal fat thickness. TAF = total abdominal fat. SAT = subcutaneous adipose tissue. VAT = visceral adipose tissue. FPG = fast plasma glucose. SBP = systolic blood pressure. DBP = diastolic blood pressure. eAG = estimated average glucose. HbA1c = glycated hemoglobin. TC = total cholesterol. HDL-c = high-density lipoprotein-cholesterol. LDL-c = low-density lipoprotein-cholesterol. TG = triglyceride. BUN = blood urea nitrogen. Scr = serum creatinine. FFA = free fatty acid. UA = uric acid. cysc = cystatin c. Alb = albumin. UACR = urinary albumin creatinine ratio.
*p < 0.05 **p < 0.01 ***p < 0.001.

2.1. Univariate analysis of anthropometric, metabolic and obesity indicators

The univariate correlations between obesity indicators with metabolic risk factors were shown in Table 3. Age negatively correlated with BSA ($r = -0.257$, $p < 0.001$), whereas a positive correlation between age and PRFT was found ($r = 0.228$, $p < 0.001$). Height and weight were both positively correlated with BSA, BMI, WC, WHR, and PRFT (all $p < 0.05$). Besides, a positive correlation was found between height and VAT ($r = 0.279$, $p < 0.001$). Reversely, a negative correlation was found between height and SAT ($r = -0.232$,$p < 0.001$), and no correlation was found between height and TAF ($p > 0.05$). Unlike height, weight was positively correlated with TAF, SAT and VAT ($r = 0.650$ vs. 0.387 vs. 0.705, all $p < 0.001$). SBP was positively correlated with WC, PRFT, TAF, and VAT (all $p < 0.05$), while DBP was positively correlated with BSA, TAF, and VAT (all $p < 0.05$). We found that, of all the obesity indicators, TC was only correlated with PRFT ($r = -0.140$, $p = 0.010$). HDL-c, Scr, and UA were only unrelated to SAT, and they were negatively correlated with other obesity indicators, including BSA, BMI, WC, WHR, PRFT, TAF, and VAT (all $p < 0.001$). TG and FPG were positively correlated with all obesity indicators, and the strongest correlation was found with VAT and BMI, respectively ($r = 0.334$ vs. 0.631, $p < 0.001$). BUN was positively correlated with PRFT and VAT (both $p < 0.01$). FFA was positively correlated with TAF and VAT (both $p < 0.05$). cysc was found positively correlated with BMI, WC, WHR, PRFT, TAF, SAT, and VAT (all $p < 0.01$), while uncorrelated with BSA ($p > 0.05$). Alb was found positively correlated with BSA, BMI, WC, TAF, SAT, and VAT (all $p < 0.01$), while unrelated to WHR and PRFT (both $p > 0.05$). UACR was positively correlated with BMI, WC, TAF, and SAT (all $p < 0.01$).

2.2. Multivariate relationships between metabolic risk factors and obesity indicators (standardized β coefficients)

We further established three multivariate models considering each metabolic indicator as an outcome variable after adjusting for

Table 4
Standardized β coefficient of multivariate models for association between obesity indicators and metabolic risk factors.

	HDL-c	TG	Scr	UA	cysc	Alb	UACR
Model1							
BSA	−0.160*	0.127*	0.252***	0.238***	0.206***	0.294***	0.122*
BMI	−0.193***	0.162**	0.185***	0.175**	0.233***	0.190***	0.118*
WC	−0.189***	0.166**	0.172**	0.161**	0.288***	0.226***	0.196***
WHR	−0.178**	0.150**	0.151**	0.141*	0.205***	0.130*	0.168**
PRFT	−0.220***	0.188**	0.239***	0.225***	0.236***	0.057^{NS}	0.014^{NS}
TAF	-0.004^{NS}	-0.022^{NS}	0.037^{NS}	0.102^{NS}	0.028^{NS}	0.006^{NS}	-0.002^{NS}
SAT	−0.191**	0.069^{NS}	0.177**	0.179**	0.283***	0.206**	0.072^{NS}
VAT	0.007^{NS}	-0.026^{NS}	0.028^{NS}	0.093^{NS}	0.013^{NS}	-0.006^{NS}	-0.006^{NS}
Model2							
BSA	−0.158*	0.120*	0.230***	0.231***	0.179**	0.184***	0.105^{NS}
BMI	−0.184***	0.142**	0.167**	0.163**	0.213***	0.172**	0.096^{NS}
WC	−0.178**	0.147**	0.153**	0.152**	0.274***	0.204***	0.182**
WHR	−0.174**	0.145**	0.151**	0.172**	0.204***	0.133*	0.167**
PRFT	−0.248***	0.173**	0.218***	0.218***	0.216***	0.023^{NS}	0.005^{NS}
TAF	-0.010^{NS}	-0.020^{NS}	0.039^{NS}	0.114*	0.030^{NS}	-0.002^{NS}	-0.004^{NS}
SAT	−0.183**	0.045^{NS}	0.145*	0.166**	0.261***	0.187**	0.035^{NS}
VAT	0.007^{NS}	-0.023^{NS}	0.031^{NS}	0.106*	0.016^{NS}	-0.011^{NS}	0.006^{NS}
Model3							
BSA[a]	-0.022^{NS}	0.045^{NS}	0.064^{NS}	0.172**	-0.013^{NS}	0.098^{NS}	-0.009^{NS}
BMI[b]	-0.056^{NS}	0.077^{NS}	0.085^{NS}	-0.006^{NS}	0.041^{NS}	0.055^{NS}	-0.055^{NS}
WC[c]	-0.027^{NS}	0.074^{NS}	0.069^{NS}	-0.008^{NS}	0.274***	0.204***	0.182**
WHR[d]	−0.126*	0.101^{NS}	0.100^{NS}	0.076^{NS}	0.064^{NS}	0.017^{NS}	0.094^{NS}
PRFT[e]	−0.214***	0.173**	0.218***	0.151**	0.104^{NS}	-0.102^{NS}	-0.110^{NS}
TAF[f]	0.018^{NS}	-0.041^{NS}	0.016^{NS}	0.084^{NS}	0.010^{NS}	-0.019^{NS}	-0.023^{NS}
SAT[g]	-0.059^{NS}	0.007^{NS}	0.074^{NS}	0.013^{NS}	0.094^{NS}	0.050^{NS}	-0.082^{NS}
VAT[h]	0.021^{NS}	-0.042^{NS}	0.012^{NS}	0.084^{NS}	0.005^{NS}	-0.021^{NS}	-0.020^{NS}

Note.- BSA = body surface area. BMI = body mass index. WC = waist circumference. WHR = waist-to-hip ratio. PRFT = *para*-perirenal fat thickness. TAF = total abdominal fat. SAT = subcutaneous adipose tissue. VAT = visceral adipose tissue. HDL-c = high-density lipoprotein-cholesterol. TG = triglyceride. Scr = serum creatinine. UA = uric acid. cysc = cystatin c. Alb = albumin. UACR = urinary albumin creatinine ratio. Model 1 controlled for age, sex, disease duration, HbA1c. Model 2 controlled for age, sex, disease duration, HbA1c, SBP, LDL-c, BUN, FFA. Model 3 controlled for age, sex, disease duration, HbA1c, SBP, LDL-c, BUN, FFA, UACR, and other obesity indicators.
*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$ $^{NS}p>0.05$.
[a] BMI、WC、WHR、PRFT、TAF、SAT、VAT.
[b] BSA、WC、WHR、PRFT、TAF、SAT、VAT.
[c] BSA、BMI、WHR、PRFT、TAF、SAT、VAT.
[d] BSA、BMI、WC、PRFT、TAF、SAT、VAT.
[e] BSA、BMI、WC、WHR、TAF、SAT、VAT.
[f] BSA、BMI、WC、WHR、PRFT、SAT、VAT.
[g] BSA、BMI、WC、WHR、PRFT 、TAF、VAT.
[h] BSA、BMI、WC、WHR、PRFT、TAF、SAT、.

different covariates (Table 4). HDL-c levels were independently predicted by WHR and PRFT even when all obesity indicators were further added in the statistical analysis (Model 3, $R^2 = 0.193$, $\beta = -0.126$ vs. -0.214, $p < 0.05$ vs. 0.001), whereas other obesity indicators except for WHR and PRFT did not contribute independently. Similarly, TG and Scr were only independently predicted by PRFT (Model 3, $R^2 = 0.151$, $\beta = 0.173$, $p < 0.01$; $R^2 = 0.110$,$\beta = 0.218$, $p < 0.001$, respectively). UA was independently predicted by BSA and PRFT (Model 3, $R^2 = 0.130$, $\beta = 0.172$ vs. 0.151. both $p < 0.01$). cysc, Alb, UACR were only independently predicted by WC (Model 3, $R^2 = 0.168$, $\beta = 0.274$, $p < 0.001$; $R^2 = 0.144$, $\beta = 0.204$, $p < 0.001$; $R^2 = 0.084$, $\beta = 0.182$, $p < 0.01$, respectively).

3. Discussion

This cross-sectional study showed that HDL-c was independently and negatively correlated with WHR and PRFT. TG and Scr were both independently and positively correlated with PRFT. UA was independently and positively correlated with BSA and PRFT. cysc, Alb, and UACR were only independently and positively correlated with WC of all obesity indicators. In particular, we comprehensively advanced understanding of the independent predictors for metabolic risk factors in T2DM patients.

Numerous studies have shown that obesity indicators are associated with metabolic risk factors, while many studies have mainly focused on PRFT [23–25]. Ke J et al. showed a negative correlation between PRFT and HDL-c [26], which was consistent with our findings. It's reported that dyslipidemia is one of the risk factors for renal dysfunction [27–29]. The initial changes of lipid metabolism in CKD patients are decreased HDL-c and increased triglyceride levels [30]. Our study observed higher TG and lower HDL-c in patients with impaired renal function than those with normal renal function, which was in line with the above though no statistical difference was reached in HDL-c.

Many studies suggested that accumulation of the visceral fat was associated with increased blood uric acid [31–33]. Matsuura F et al. suggested that visceral fat was more strongly associated with hyperuricemia than subcutaneous fat in a study of male obese subjects as early as 1998 [34]. Yamada A et al. came to the same conclusion [35]. Takahashi S et al. found that the ratio of visceral fat area and body surface area was higher in patients with gout than in controls [36]. Our study showed that UA had the strongest correlation with visceral fat followed by body surface area, whereas it had no correlation with subcutaneous fat. Multivariate regression analysis further showed that UA was independently associated with PRFT and BSA, while visceral fat did not independently affect blood uric acid after adjusting for other confounding variables. This may be explained by the differences in study population, the measurement method of visceral fat and the confounding variables included in the model. Jiang M et al. concluded that PRFT was positively correlated with UA independent of other confounding factors such as BMI and WC [37], which was consistent with our research.

There are several possible mechanisms that may explain the relationship between PRFT and UA. At first, the increasement of blood uric acid levels was caused by increased production and decreased excretion of urate [38]. Several researches showed that uric acid can be produced by adipose tissue and excreted through kidneys [39,40]. Excessive accumulation of *para*-perirenal fat causes active lipid metabolism, which increases the synthesis and secretion of uric acid [33,41]. Besides, renal dysfunction in our subjects may impair uric acid excretion, which contributes to the increasement of UA. Secondly, perirenal fat is negatively correlated with lipocalin [42], and lipocalin is negatively correlated with blood uric acid [43,44]. Therefore, we speculate that lipocalin may be responsible for the phenomenon that blood uric acid levels are elevated in the presence of perirenal fat accumulation. Thirdly, inflammation may be a bridge of PRFT and UA. It's reported that visceral adipose tissue [45,46] and blood uric acid are both related to inflammation closely [47].

Weisinger et al. first linked obesity with microalbuminuria in 1974 [48]. Lamacchia O et al. showed that albuminuria was associated with WC and BMI, not PRFT [32], which was in agreement with our findings. It's reported that albuminuria mainly reflect glomerular endothelial damage [49]. Therefore, we speculate that the main mechanism of renal injury caused by perirenal fat is not glomerular endothelial injury. Visceral fat had a higher lipolytic activity than subcutaneous fat [50,51], so visceral fat can mobilize free fatty acids quickly. A positive association was found between FFA and visceral fat, whereas no association between FFA and subcutaneous fat was found, which were consistent with the previous finding.

In our study, CT was used to assess adiposity volume. CT has been reported to be the gold standard for the assessment of adipose tissue [50]. In particular, we advanced understanding of the independent predictors for Scr and cysc in T2DM patients. Scr is a common clinical indicator of renal function. Cysc, independent of gender, age, diet and muscle, can be used as a complement of Scr to measure renal function [52]. Our findings may help for early identification and prevention of renal impairment in T2DM.

Our study also has some limitations. Firstly, the study was an observational, cross-sectional study. It could not establish a causal relationship between metabolic risk factors and obesity indicators in T2DM patients. Secondly, our sample was from a single center and the results may not be representative of other populations. So further muti-centers prospective cohort studies are needed to explore their relationship. Thirdly, information that may affect obesity or metabolic indicators was not be collected, such as diet, lifestyle [53].

In conclusion, obesity indicators in T2DM patients are associated with metabolic risk factors significantly. In clinical practice, measuring the corresponding obesity indicators may help in the early recognition of metabolic complications in T2DM. In addition, it may provide new targets for prevention and treatment of metabolic diseases in T2DM patients.

Author contribution statement

Sunan Xu: Conceived and designed the experiments.
Yang Zhang: Conceived and designed the experiments.
Sunan Xu: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Ruichen Ren: Analyzed and interpreted the data.
Wenting Li: Analyzed and interpreted the data.
Yongfeng Liang: Analyzed and interpreted the data.
Junqing Ma: Contributed reagents, materials, analysis tools or data.
Yongze Zheng: Contributed reagents, materials, analysis tools or data.
Wei Zhao: Contributed reagents, materials, analysis tools or data.
Yu Ma: Contributed reagents, materials, analysis tools or data.
Tao Zhou: Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20013.

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