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ORIGINAL ARTICLE

Contribution of epicardial and abdominopelvic visceral adipose tissues in Chinese adults with impaired glucose regulation and diabetes

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Abstract

Aims To quantify epicardial adipose tissue (EAT) and visceral adipose tissue (VAT) in Chinese adults with impaired glucose regulation (IGR) or diabetes and compare the contributions of EAT and VAT to the occurrence of IGR and diabetes with those of traditional obesity indices.

Methods Cardiac and abdominopelvic noncontrast computed tomographic images of 668 individuals were used to measure EAT and VAT volume. Multivariable logistic regression and area under the receiver operating characteristic (ROC) curve were used to illustrate the contributions of these tissues.

Results Patients with IGR or diabetes had larger EAT and VAT volumes than did the controls, and the VAT volume was significantly different between the IGR and diabetic groups. In multivariable models, higher EAT or VAT volume was positively associated with the presence of IGR and diabetes. After adjusting further for body mass index (BMI) and waist-to-hip ratio (WHR), a higher EAT volume was still positively associated with IGR (odds ratio (OR) = 1.46; 95% confidence interval (CI), 1.04–2.03), and a higher VAT volume was positively associated with IGR (OR = 1.86; 95% CI, 1.15–3.02) and diabetes (OR = 1.86; 95% CI, 1.16–2.99). The areas under the curve (AUCs) of the association of EAT (AUC = 0.751; 95% CI, 0.712–0.789) and VAT (AUC = 0.752; 95% CI, 0.713–0.792) with dysglycemia (IGR + diabetes) were significantly larger than those of the traditional obesity indices (all $P < 0.05$).

Conclusions High EAT or VAT volume is positively associated with IGR and diabetes in Chinese adults. With a given WHR and BMI, such an association still exists to some extent. The correlation may be stronger than those of the traditional obesity indices.

Keywords Impaired glucose regulation · Diabetes · Adipose tissue · Quantification

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Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANOVA	One-way analysis of variance
AST	Plasma aspartate transaminase
AUC	Area under the curve

BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CT	Computed tomography
CVD	Cardiovascular diseases
DBP	Diastolic blood pressure
EAT	Epicardial adipose tissue
EATHtR	EAT volume-to-height ratio
ECG	Electrocardiogram
FDR	False discovery rate
FFA	Free fatty acid
FPG	Fasting plasma glucose
HbA1c	Glycated hemoglobin A1c
HBP	High blood pressure
HDL	High-density lipoprotein
Hs-CRP	High-sensitivity C-reactive protein
HU	Hounsfield unit
IFG	Impaired fasting glucose
IGR	Impaired glucose regulation
IGT	Impaired glucose tolerance
IR	Insulin resistance
LDL	Low-density lipoprotein
MetS	Metabolic syndrome
OGTT	75-g oral glucose tolerance test
OR	Odds ratio
ROC	Receiver operating characteristic (curve)
SAT	Subcutaneous adipose tissue
SBP	Systolic blood pressure
SD	Standard deviation
TC	Total cholesterol
TG	Total triglyceride
VAT	Visceral adipose tissue
VATHtR	VAT volume-to-height ratio
VIF	Variance inflation factor
WC	Waist circumference
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio
γ-GT	Gamma-glutamyl transferase
2hPG	2 h plasma glucose

Background

The incidence of diabetes has increased rapidly in recent decades throughout the world [1]. According to the latest report in the International Diabetes Federation Diabetes Atlas [2], the overall prevalence of diabetes in adults aged 20–79 years was 8.8% in 2017. In China, diabetes has also become a major challenge to public health; in 2017, China was ranked first in the world in terms of diabetes prevalence [2].

Impaired glucose regulation (IGR), including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is a condition between normoglycemia and diabetes [3] and is associated with an increased risk of diabetes [4]. The estimated prevalence of IGR in Chinese adults was 50.1% in 2010 [5]. Each year, approximately 5–10% of people with IGR will develop diabetes, with the same proportion returning to normoglycemia [4, 6]. However, diabetes cannot be cured. Therefore, more investigations related to IGR are needed, and these investigations may benefit individuals and national medical and health systems.

There is increasing evidence that local fat depots, such as visceral adipose tissue (VAT), rather than general obesity can be linked to IGR [7, 8] as a result of insulin sensitivity deterioration, thus increasing the risk of developing metabolic disorder [9]. Furthermore, epicardial adipose tissue (EAT) has recently been recognized not only as a fat deposited around the pericardium but also as a metabolically active tissue that secretes various humoral factors [10]. The associations between increased EAT and insulin resistance (IR), metabolic syndrome (MetS) and cardiovascular diseases (CVDs) have been studied previously. Many studies have focused on the thickness of EAT or the area of VAT, whereas research on the association of total EAT or VAT volume with IGR or diabetes is rather limited.

Some traditional obesity indices, including body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR), have been researched in numerous studies regarding diabetes. These indices can reflect obesity or central obesity to some extent but cannot distinguish between muscle and fat mass or reflect the distribution of body fat [11], which may have a metabolic effect on the genesis and development of diabetes.

In conclusion, we chose EAT and VAT as our main research targets to explore their quantitative differences and potentially greater contributions to IGR and diabetes than traditional obesity indices in Chinese adults.

Methods

Protocol and subjects

Our study was a cross-sectional analysis focused on baseline data. The study was approved by the ethics committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. All patients signed written informed consent forms before the initiation of the study procedure. We selected 766 patients aged 20–60 years at the checkup center from January 2017 to June 2018. All the patients were of Chinese nationality and were East Asians. The exclusion criteria were as follows: (1) current use of steroids, immunosuppressants, contraceptives, antipsychotics or diuretics; (2) recent cardiovascular events or surgery (in the last 2 months); and (3) a history of malignant tumor or known CVD including myocardial infarction, serious coronary arterial disease, stroke and atrial fibrillation. After collecting all the data, we further excluded subjects with (1) fasting blood glucose < 3.9 mmol/L; (2) poor computed tomography (CT) image quality; and (3) missing data. Ultimately, we had 668 samples for the following analyses.

Anthropometric measurements

Anthropometric measurements included height, weight, WC and hip circumference. All participants wore light clothes and removed their shoes prior to being measured for height and weight in an upright position to the nearest 0.1 cm/0.1 kg on the same height–weight scale. BMI (kg/m^2) was calculated by dividing weight (kg) by height squared (m^2). WC was measured to the nearest 0.1 cm at the level of the umbilicus at the end of a normal expiration. Hip circumference was measured to the nearest 0.1 cm at the widest point between the hip and the buttocks. The WHR and WHtR were then calculated. Blood pressure was measured twice for each patient after the patient rested for at least 5 min, and the averages of the systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated. We defined blood hypertension as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, a history of high blood pressure (HBP), or the current use of hypotensive drugs.

Laboratory examinations

All the participants' venous blood samples were collected from peripheral veins the morning after an overnight fasting period > 10 h. Plasma alanine transaminase (ALT, IU/L), aspartate transaminase (AST, IU/L), alkaline phosphatase (ALP, IU/L), gamma-glutamyl transferase (γ-GT, IU/L), blood urea nitrogen (BUN, mmol/L), serum creatinine (mmol/L), uric acid (mmol/L), total cholesterol (TC, mmol/L), total triglyceride (TG, mmol/L), high-density lipoprotein (HDL, mmol/L) and low-density lipoprotein (LDL, mmol/L) levels were measured using an autoanalyzer (Modular E170, Switzerland). Glycated hemoglobin A1c (HbA1c, mmol/mol) levels were measured using high-performance liquid chromatography on a Variant II HbA1c analyzer (Bio-Rad-10, USA). A 75-g oral glucose tolerance test (OGTT) was performed in which plasma glucose concentrations (mmol/L) were measured at 0, 30 and 120 min by venous blood using the glucose oxidase method on an autoanalyzer (Modular P800; Switzerland). High-sensitivity C-reactive protein (Hs-CRP, mg/L) levels were measured using an autoanalyzer (Olympus AU 5800, Japan).

Diabetes was defined as fasting plasma glucose (FPG) ≥ 7.0 mmol/L, 2 h plasma glucose (2hPG) ≥ 11.1 mmol/L, a history of type 2 diabetes or the current use of hypoglycemic drugs [12, 13]. IGR was defined as a condition characterized by 6.1 mmol/L ≤ FPG < 7.0 mmol/L, 7.8 mmol/L ≤ 2hPG < 11.1 mmol/L and the absence of a history of diabetes and current use of hypoglycemic drugs [13]. Normal controls were classified by the absence of either diabetes or IGR (FPG < 6.1 mmol/L and 2hPG < 11.0 mmol/L) [13].

Computed tomography scanning

Noncontrast cardiac and abdominopelvic CT scans were performed on a dual-source CT scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany). Each patient laid on the examination table with both arms stretched above the head. A standard prospectively electrocardiogram (ECG)-triggered (set to 30–80% of the R–R interval) scanning protocol was used for the cardiac CT with 128 × 0.6-mm detector configuration, 0.28-s gantry rotation time and a pitch of 3.4. The tube current and tube potential were selected automatically by CARE Dose4D and CARE kV technology. The whole heart was included. An abdominopelvic CT scan was performed with a 128 × 0.6-mm detector configuration, 0.50-s gantry rotation time, a pitch of 0.6, and 120-kV tube voltage. The scan extended from the diaphragmatic dome to the pelvic floor. Both cardiac and abdominopelvic scans were performed during a single breath-hold within 10 s.

Image processing

The images were reconstructed to a 1-mm slice thickness and copied to a semiautomated software program (CardiacRisk Prototype, Siemens Healthcare) to quantify EAT and VAT. EAT and VAT were defined as adipose tissue enclosed by the epicardium or the parietal peritoneum. Adipose tissue was defined as voxels between − 190 Hounsfield units (HU) and − 30 HU [14]. The manual operation included choosing the upper and lower limits of EAT/VAT. We defined the image in which the right pulmonary artery trunk was in the middle as the upper limit and the last image in which the heart disappeared as the lower limit of EAT; the first slice in which the diagram appeared was defined as the upper limit, and the superior margin of the symphysis pubis was defined as the lower limit of VAT. EAT was then distinguished, and its volume (cm^3) was calculated automatically (Fig. 1). To quantify VAT, we needed to draw 5–20 closed circles on the sectional images to separate VAT and subcutaneous adipose tissue (SAT) by two experienced radiologists who were familiar with the anatomical structure. After drawing the circles, a contiguous contour of each slice was generated, and the VAT volume (cm^3) was automatically calculated (Fig. 2). To eliminate the effect of height on VAT/EAT volume, we calculated the EAT volume-to-height ratio (EATHtR (EAT-to-height ratio), EAT volume (cm^3)/height (cm), cm^2) and

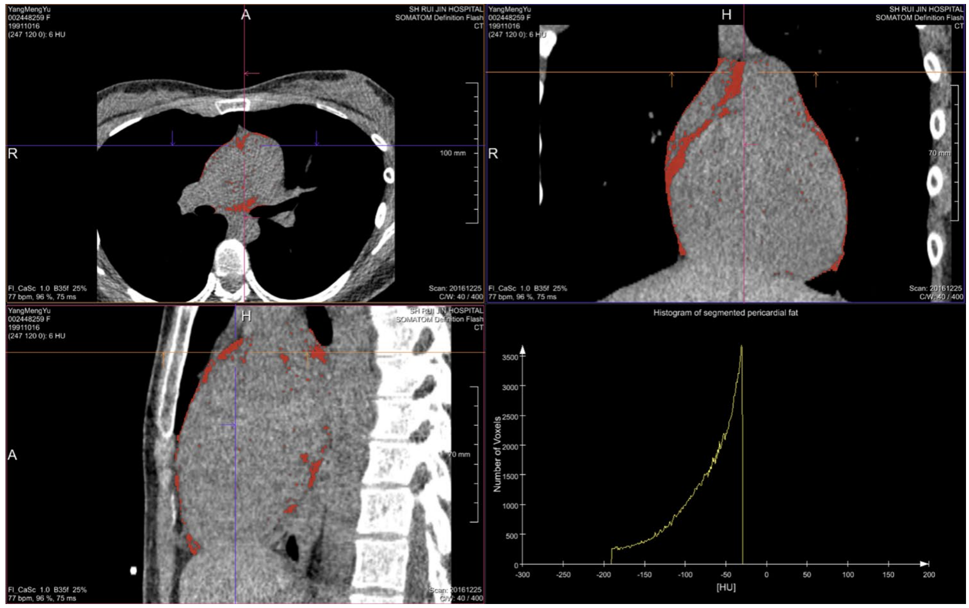

Fig. 1 Quantification of the volume of epicardial adipose tissue. The red area in this figure represents the region of epicardial adipose tissue. The volume of epicardial adipose tissue was calculated automatically by the software (color figure online)

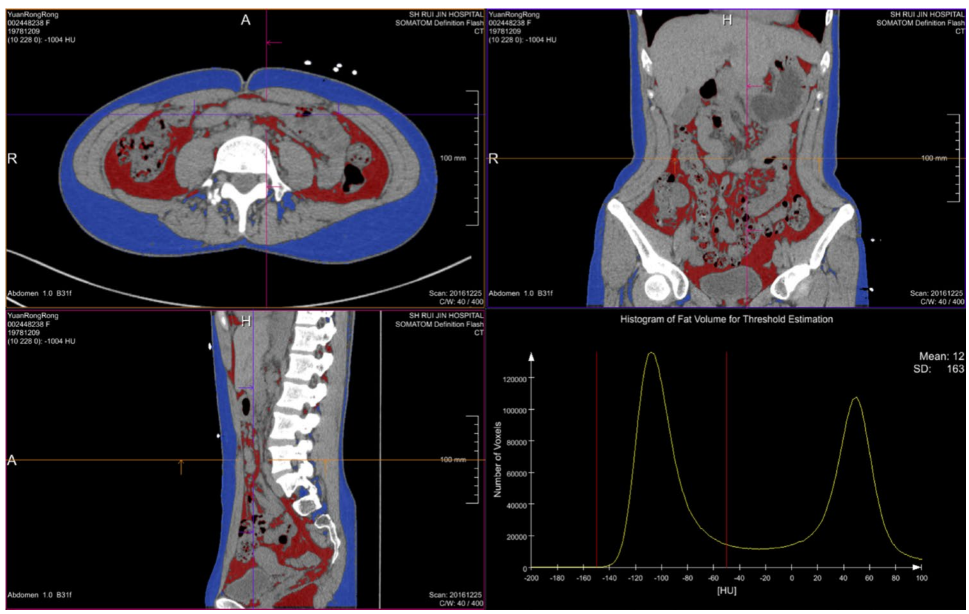

Fig. 2 Quantification of the volume of visceral adipose tissue. The red area in this figure represents the region of visceral adipose tissue, and the blue area represents the region of subcutaneous adipose tissue. The volume of visceral adipose tissue was calculated automatically by the software (color figure online)

the VAT volume-to-height ratio (VATHtR (VAT-to-height ratio), VAT volume (cm^3)/height (cm), cm^2) and used the EATHtR/VATHtR for further analyses.

Statistical analysis

All analyses were conducted in R 3.4.2 (R Development Core Team, 2008), and two-sided P values (the significance level was set at $P<0.05$), odds ratios (ORs) and 95% confidence intervals (CIs) are provided. The means ± standard deviations (SDs) for normally distributed variables and medians (25th–75th percentiles) for nonnormally distributed variables were calculated to summarize continuous variables based on Shapiro–Wilk tests. Categorical variables are presented as numbers (proportions, %). The characteristics of the participants in the various groups were compared using the Chi-square test for categorical variables and one-way analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables according to the results of the Fligner–Killeen test. The Benjamini–Hochberg procedure was applied for post hoc pairwise comparisons between groups to control the false discovery rate (FDR).

To assess the associations of adipose tissues with IGR and diabetes, several binomial logistic regressions with all covariates analyzed continuously were conducted. Similar models with all covariates analyzed categorically were assessed as well. BMI and WHR were grouped according to the China Physical Fitness Surveillance Center [15] and the Cooperative Meta-Analysis Group of China Obesity Task Force [16] for general and abdominal obesity. Adipose tissues were analyzed categorically in tertiles. The variance inflation factors (VIFs) for these models were calculated to estimate multicollinearity.

To determine the potential optimal cutoff values of age, BMI, WC, WHR, EATHtR and VATHtR, Youden's J statistic was used in conjunction with the receiver operating characteristic (ROC) analysis. The DeLong test was used to compare the area under the curve (AUC) of two ROC curves.

Results

Basic characteristics of the participants

The basic characteristics of the study population are presented in Table 1. A total of 668 individuals were included in this analysis: 468 healthy controls, 83 patients with IGR and 117 patients with diabetes. The median age was 34 years (interquartile range, 13 years); of the patients, 526 were male, 222 were current smokers, and 131 had HBP. The values of EATHtR and VATHtR were 1.00 (0.80–1.27) cm^2 and 27.60 (19.03–31.78) cm^2 in the IGR group and 1.07 (0.80–1.37) cm^2 and 29.53 (22.61–35.56) cm^2 in the diabetic group, respectively (all adjusted $P<0.001$). There were significant differences in all indices between patients with different glucose tolerance conditions. Compared with the control group, individuals with diabetes or IGR had a higher likelihood of being a current smoker, a higher prevalence of HBP and higher values of age, TG, TC, LDL, ALT, AST, Hs-CRP and fat-related indices (BMI, WC, WHR, WHtR, EATHtR and VATHtR) but lower HDL (all adjusted $P<0.05$). The pairwise post hoc analysis indicated that there were significant differences in VATHtR between the IGR and diabetic groups, whereas EATHtR did not show such significant differences.

Association of adipose tissues with IGR and diabetes

Multivariable logistic regression analyses were used to evaluate the possible associations between adipose tissues and IGR or diabetes and are shown in Tables 2 and 3. The VIFs for these models were 7.5 or less, indicating that

Table 1 Basic characteristics of the participants

	Groups			*P* value
	Healthy control (*n* = 468)	IGR (*n* = 83)	Diabetes (*n* = 117)	
Sex (male/female)	(352/116)^{c}	(68/15)	(106/11)^{a}	**0.001**
Age, years	32.5(28.0–41.0)^{b,c}	37.0(29.5–45.0)^{a,c}	41.0(32.0–49.0)^{a,b}	**< 0.001**
BMI, kg/m^2	25.10(22.00–29.91)^{b,c}	29.05(25.21–31.78)^{a}	30.06(26.28–32.26)^{a}	**< 0.001**
WC, cm	90.5(63.5–128.0)^{b,c}	98.6(65.0–121.6)^{a}	101.1(70.0–131.0)^{a}	**< 0.001**
WHR	0.91(0.85–0.96)^{b,c}	0.96(0.91–1.00)^{a}	0.96(0.92–1.03)^{a}	**< 0.001**
WHtR	0.52(0.48–0.58)^{b,c}	0.58(0.52–0.62)^{a}	0.58(0.54–0.62)^{a}	**< 0.001**
EAT volume, cm^3	117.34(82.67–167.19)^{b,c}	173.21(139.67–219.53)^{a}	190.64(138.33–244.82)^{a}	**< 0.001**
VAT volume, cm^3	3003.39(1621.17–4540.21)^{b,c}	4761.21(3235.06–5434.92)^{a,c}	5015.11(3947.14–6216.62)^{a,b}	**< 0.001**
EATHtR, cm^2	0.68(0.49–0.96)^{b,c}	1.00(0.80–1.27)^{a}	1.07(0.80–1.37)^{a}	**< 0.001**
VATHtR, cm^2	17.59(9.62–26.26)^{b,c}	27.60(19.03–31.78)^{a,c}	29.53(22.61–35.56)^{a,b}	**< 0.001**
TG, mmol/L	1.22(0.85–1.82)^{b,c}	1.58(1.25–2.37)^{a}	1.86(1.44–2.70)^{a}	**< 0.001**
TC, mmol/L	4.97(4.38–5.61)^{c}	5.18(4.35–6.09)	5.30(4.69–6.00)^{a}	**0.002**
HDL, mmol/L	1.32(1.12–1.59)^{b,c}	1.20(1.08–1.37)^{a,c}	1.13(1.02–1.28)^{a,b}	**< 0.001**
LDL, mmol/L	3.01(2.53–3.62)^{b,c}	3.27(2.55–3.91)^{a}	3.41(2.96–4.04)^{a}	**< 0.001**
ALT, IU/L	24.0(16.0–37.0)^{b,c}	31.0(22.0–50.5)^{a}	36.0(24.0–54.0)^{a}	**< 0.001**
AST, IU/L	21.0(18.0–26.0)^{b,c}	22.0(20.0–29.0)^{a}	23.0(19.0–32.0)^{a}	**0.002**
Hs-CRP, mg/L	0.64(0.37–1.16)^{b,c}	0.75(0.48–1.83)^{a,c}	1.19(0.58–2.32)^{a,b}	**< 0.001**
Current smoker, n (%)	121(25.9%)^{b,c}	35(42.2%)^{a}	66(56.4%)^{a}	**< 0.001**
HBP, n (%)	62(13.2%)^{b,c}	20(24.1%)^{a,c}	49(41.9%)^{a,b}	**< 0.001**

IGR, impaired glucose regulation; *BMI*, body mass index; *WC*, waist circumference; *WHR*, waist-to-hip ratio; *WHtR*, waist-to-height ratio; *EAT*, epicardial adipose tissue; *VAT*, visceral adipose tissue; *EATHtR*, EAT volume-to-height ratio; *VATHtR*, VAT volume-to-height ratio; *TG*, total triglyceride; *TC*, total cholesterol; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *ALT*, alanine transaminase; *AST*, aspartate transaminase; *Hs-CRP*, high-sensitivity C-reactive protein; *HBP*, high blood pressure. Statistical significance ($P<0.05$) was reported by superscript letters ([a]Healthy control, [b]IGR, [c]Diabetes). If the *P* value < 0.05, it was shown in bold font (same for the table below)

Table 2 Logistic regression of continuous adipose tissue indices

Factor	IGR versus healthy control			Diabetes versus healthy control		
	OR (95% CI)	*P* value	VIF value	OR (95% CI)	*P* value	VIF value
EATHtR, cm^2						
Model 1	1.83 (1.37–2.43)	**< 0.001**	3.29	1.72 (1.30–2.27)	**< 0.001**	3.03
Model 2	1.54 (1.11–2.14)	**0.010**	3.30	1.37 (0.99–1.90)	**0.044**	3.03
Model 3	1.56 (1.15–2.12)	**0.004**	3.43	1.48 (1.10–1.97)	**0.009**	3.15
Model 4	1.46 (1.04–2.03)	**0.028**	3.50	1.35 (0.98–1.87)	0.066	3.34
VATHtR, cm^2						
Model 1	2.38 (1.68–3.37)	**< 0.001**	3.27	2.35 (1.67–3.29)	**< 0.001**	3.03
Model 2	2.14 (1.35–3.38)	**0.001**	4.09	2.05 (1.29–3.24)	**0.002**	4.32
Model 3	1.95 (1.30–2.91)	**0.001**	3.45	1.95 (1.32–2.87)	**< 0.001**	3.17
Model 4	1.86 (1.15–3.02)	**0.011**	4.41	1.86 (1.16–2.99)	**0.010**	4.51

Model 1: Adjusted for clinical variables; *Model 2:* Adjusted for clinical variables, BMI

Model 3: Adjusted for clinical variables, WHR; *Model 4:* Adjusted for clinical variables, BMI, WHR

The adjusted clinical variables including age, sex, height, smoking, HBP, AST, ALP, γ-GT, BUN, serum creatinine, uric acid, TG, HDL and LDL

OR (95% CI): The effect size is calculated based on each SD change in the variable

IGR, impaired glucose regulation; *OR*, odds ratio; *CI*, confidence interval; *EATHtR*, EAT volume-to-height ratio; *VATHtR*, VAT volume-to-height ratio; *VIF*, variance inflation factor

Table 3 Logistic regression of categorical adipose tissue indices and traditional obesity indices

Model	Factor		IGR versus healthy control		Diabetes versus healthy control	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1	EATHtR, cm^2	High versus low	4.34 (1.66–11.4)	**0.003**	3.17 (1.21–8.28)	**0.019**
		High versus middle	1.78 (0.97–3.26)	0.062	1.54 (0.87–2.71)	0.138
		Middle versus low	2.44 (1.02–5.86)	**0.046**	2.06 (0.84–5.05)	0.116
		P for trend	/	**0.003**	/	**0.020**
	BMI	High versus low	1.48 (0.49–4.47)	0.486	0.81 (0.28–2.33)	0.699
	WHR	High versus low	2.47 (1.07–5.70)	**0.034**	3.43 (1.40–8.39)	**0.007**
Model 2	VATHtR, cm^2	High versus low	5.60 (1.80–17.4)	**0.003**	2.35 (0.82–6.70)	0.110
		High versus middle	2.81 (1.43–5.50)	**0.003**	2.10 (1.13–3.93)	**0.020**
		Middle versus low	1.99 (0.76–5.25)	0.163	1.12 (0.44–2.82)	0.815
		P for trend	/	**0.003**	/	0.110
	BMI	High versus low	1.32 (0.42–4.18)	0.636	0.87 (0.29–2.64)	0.802
	WHR	High versus low	2.25 (0.97–5.26)	**0.049**	3.38 (1.37–8.36)	**0.008**

Model 1: The independent variables included categorical EATHtR, BMI, WHR

Model 2: The independent variables included categorical VATHtR, BMI, WHR

All models are also adjusted for the above-mentioned clinical variables

OR (95% CI): The effect size is calculated based on the change in the level or the tertile of the variable (shown in Table 4)

IGR, impaired glucose regulation; *OR*, odds ratio; *CI*, confidence interval; *EATHtR*, EAT volume-to-height ratio; *BMI*, body mass index; *WHR*, waist-to-hip ratio; *VATHtR*, VAT volume-to-height ratio

multicollinearity was not a significant concern. In Table 2, the adipose tissue indices were analyzed as continuous variables. After adjusting for clinical variables (including age, sex, height, smoking, HBP, AST, ALP, γ-GT, BUN, serum creatinine, uric acid, TG, HDL and LDL), EATHtR and VATHtR were positively associated with IGR and diabetes (Table 2: Model 1). After adjusting further for BMI and WHR, each SD increase in EATHtR was still associated with an increased presence of IGR (OR = 1.46; 95% CI, 1.04–2.03; $P = 0.028$), and each SD increase in VATHtR was associated with an increased presence of IGR (OR = 1.86; 95% CI, 1.15–3.02; $P = 0.011$) and diabetes (OR = 1.86; 95% CI, 1.16–2.99; $P = 0.010$) compared with that of the control group (Table 2: Model 4). Subanalysis of males was performed as shown in Table 6 in Appendix. After adjusting for clinical variables, BMI and WHR, each SD increase in EATHtR in male subjects was associated with an increased presence of IGR (OR = 1.55; 95% CI, 1.07–2.24; P = 0.019; Table 6 in Appendix: Model 4 for EATHtR). Similarly, each SD increase in VATHtR in male subjects was associated with an increased presence of IGR (OR = 2.33; 95% CI, 1.35–4.02; P = 0.002) and diabetes (OR = 2.08; 95% CI, 1.27–3.40; P = 0.003; Table 6 in Appendix: Model 4 for VATHtR).

In Table 3, when the adipose tissue indices were analyzed as categorical variables, the above-mentioned positive association still existed to some extent (detailed cutoff points are shown in Table 4). As shown in Table 3, when EATHtR was analyzed by tertiles, the adjusted ORs for IGR in the middle and highest tertiles were 2.44 (95% CI, 1.02–5.86; P = 0.046) and 4.34 (95% CI, 1.66–11.4; P = 0.003), respectively, compared with that of the lowest tertile, and the adjusted OR for diabetes in the highest tertile was 3.17 (95% CI, 1.21–8.28; P = 0.019) compared with that of the lowest tertile (Table 3: Model 1). Similarly, individuals in the highest tertile of VATHtR showed a stronger association with IGR than did those in the middle (OR = 2.81; 95% CI, 1.43–5.50; P = 0.003) or lowest (OR = 5.60; 95% CI, 1.80–17.4; P = 0.003) tertiles (Table 3: Model 2). However, the adjusted OR of VATHtR for diabetes in the highest tertile was not statistically significant (P = 0.110) compared to that of the lowest tertile, which still needs more research.

Table 4 The cutoff points for adipose tissue indices and traditional obesity indices

	Low	Middle	High
Age[a]	Age ≤ 34	/	Age ≥ 35
BMI[b]	BMI < 23.0	23.0 ≤ BMI < 27.5	BMI ≥ 27.5
WC[b], cm			
Male	WC < 90	/	WC ≥ 90
Female	WC < 80	/	WC ≥ 80
WHR[b]			
Male	WHR < 0.90	/	WHR ≥ 0.90
Female	WHR < 0.85	/	WHR ≥ 0.85
WHtR[b]	WHtR < 0.50	/	WHtR ≥ 0.50
VATHtR[c]	VATHtR < 15.1	15.1 ≤ VATHtR < 27.0	VATHtR ≥ 27.0
EATHtR[c]	EATHtR < 0.62	0.62 ≤ EATHtR < 0.97	EATHtR ≥ 0.97

Superscript letters

a: Grouped in medians

b: Grouped for generalized and abdominal obesity in Chinese individuals

c: Grouped in tertiles

BMI, body mass index; *WC*, waist circumference; *WHR*, waist-to-hip ratio; *WHtR*, waist-to-height ratio; *VATHtR*, VAT volume-to-height ratio; *EATHtR*, EAT volume-to-height ratio

Multivariable logistic regression analyses of categorical traditional obesity indices are also shown in Table 3. WC and WHtR were discarded due to high collinearity (VIF > 10). The increasing categories of abdominal obesity defined by WHR were associated with an increased presence of diabetes (OR = 3.38; 95% CI, 1.37–8.36; P = 0.008) and IGR (OR = 2.25; 95% CI, 0.97–5.26; P = 0.060). However, no significant associations of BMI with IGR or diabetes were found based on increasing categories of general obesity (all P > 0.05). Subanalysis of males was also performed, as shown in Table 7 in Appendix, in which the adipose tissue indices were analyzed as categorical variables. After adjusting for clinical variables, BMI and WHR, the adjusted ORs for IGR in the middle and highest tertiles of EATHtR were 3.79 (95% CI, 1.03–13.93; P = 0.046) and 6.75 (95% CI, 1.69–26.90; P = 0.003) compared with those of the lowest tertile, and the adjusted OR for diabetes in the highest tertile was 3.30 (95% CI, 1.06–10.32; P = 0.040) compared with that of the lowest tertile (Table 7 in Appendix: Model 1). Similarly, individuals in the highest tertile of VATHtR showed a stronger association with IGR than did those in the middle (OR = 2.89; 95% CI, 1.37–6.09; P = 0.005) or lowest (OR = 19.80; 95% CI, 2.93–133.00; P = 0.002) tertiles (Table 7 in Appendix: Model 2).

ROC analysis

A summary of the ROC curve analysis of adipose tissue and traditional obesity indices is shown in Table 5. The AUCs for the association of dysglycemia with VATHtR (AUC = 0.752; 95% CI, 0.713–0.792) and EATHtR (AUC = 0.751; 95% CI, 0.712–0.789) were significantly larger than those with age, BMI, WC, WHR and WHtR (all adjusted P < 0.05). The results were similar for the AUCs of IGR and diabetes: VATHtR had the largest AUC (0.778; 95% CI, 0.731–0.823) for diabetes, followed by EATHtR. EATHtR had a significantly larger AUC (0.730; 95% CI, 0.674–0.785) for IGR than did age, BMI and WC. The optimal cutoff values determined by Youden's index for BMI, WC, WHR and WHtR (26.12, 88.20, 0.90 and 0.53, respectively), shown in Table 5, are approximately in concordance with the standards shown in Table 4. Subgroup analysis of males was also performed, and the results are shown in Table 8 in Appendix.

Discussion

Contributions of EAT and VAT to IGR and diabetes

In this study, we applied second-level imaging to characterize adipose tissue regions in a large population. We found that higher EAT or VAT volume is positively associated with IGR and diabetes, even after adjusting for BMI and WHR.

Table 5 The ROC curves of adipose tissues and traditional obesity indices

	IGR versus healthy control AUC of ROC	Diabetes versus healthy control AUC of ROC	Dysglycemia versus healthy control AUC of ROC	Cutoff value*
Age	0.605 (0.537–0.672)	0.686 (0.632–0.740)	0.652 (0.607–0.698)	39.00
BMI	0.672 (0.613–0.730)	0.710 (0.661–0.758)	0.694 (0.652–0.736)	26.12
WC, cm	0.675 (0.617–0.733)	0.723 (0.676–0.769)	0.703 (0.662–0.744)	88.20
WHR	0.683 (0.623–0.743)	0.732 (0.687–0.778)	0.712 (0.672–0.752)	0.90
WHtR	0.697 (0.640–0.753)[c]	0.724 (0.678–0.770)	0.713 (0.673–0.753)	0.53
VATHtR	0.717 (0.660–0.774)[a,c]	0.778 (0.731–0.823)[a,b,c,d,e]	0.752 (0.713–0.792)[a,b,c,d,e]	22.33
EATHtR	0.730 (0.674–0.785)[a,b,c]	0.765 (0.721–0.810)[a,b,c]	0.751 (0.712–0.789)[a,b,c,d,e]	0.87

Statistically better AUC ($P < 0.05$) was reported by superscript letters

a: Age, b: BMI, c: WC, d: WHR, e: WHtR, f: VATHtR, g: EATHtR

Cutoff value* was calculated by Youden's index based on the ROC curve

IGR, impaired glucose regulation; *AUC*, area under the curve; *ROC*, receiver operating characteristic (curve); *BMI*, body mass index; *WC*, waist circumference; *WHR*, waist-to-hip ratio; *WHtR*, waist-to-height ratio; *VATHtR*, VAT volume-to-height ratio; *EATHtR*, EAT volume-to-height ratio

EAT has been an attractive research object in recent years due to its metabolic features and pathophysiological roles in CVD and MetS [17, 18]. Adipocytes in the epicardium are able to synthesize, produce and secrete bioactive humoral factors, which are transported into the myocardium and directly impact coronary arteries and the myocardium [19]. Many patients with CVD have diabetes or IGR [20]; therefore, more attention should be paid to the effect of EAT on IGR and diabetes. Numerous articles have focused on fat distribution in diabetic patients, but relatively few studies have focused on IGR, and data about total EAT volume in patients with IGR are rather limited. To the best of our knowledge, no reports to date have studied EAT and VAT simultaneously in subgroups of both IGR and diabetes.

VAT also plays an important role in CVD and metabolic derangements, mainly due to the secretion of proinflammatory mediators and cytokines as a consequence of the liver releasing free fatty acids (FFAs) into portal circulation, leading to IR and systemic inflammation [21]. In our study, excess VAT, compared with that in the control group, was found in the IGR and diabetic groups; even between the IGR and diabetic groups, the difference in VAT volume was significant. Neeland et al. [7] found that in 732 obese subjects, excess visceral fat was associated with IGR and diabetes. Borel et al. [22] reported a specific abdominal fat distribution in subjects with dysglycemia. Their study included several ethnic groups, whereas ours focused on Chinese adults. Our conclusion on VAT was in line with that of the aforementioned study, which may support the conclusion made by Smith et al. [23] that VAT is associated with diabetes regardless of ethnicity; however, a difference in our study was that we extended the VAT region to the whole abdominal and pelvic cavity, which indicates that the pelvic adipose tissue volume may have the same variation trend as that of the abdominal VAT in patients with dysglycemia compared with that in normal individuals. Some studies have indicated that the area of VAT in the slice at the umbilicus level is representative of the total volume of VAT [24], but whether it can fully replace adipose tissue volume in all subjects of different ages, sexes, ethnicities or body shapes still needs more exploration. Importantly, the association between VAT and IGR or diabetes persisted after adjusting for BMI or WHR, further supporting the ideas that VAT is a unique pathogenic factor that confers a positive association with IGR and diabetes beyond its contribution to overall adiposity and that VAT may become a promising marker of systemic glycometabolic disease.

To quantify EAT and VAT, previous studies have used several methods, such as measuring the thickness of EAT by echocardiography, the area of VAT at the level of the umbilicus, the area of VAT at the level of L4–L5 or the volume of VAT with a caudal limit of the top of iliac crest. We focused on full volume-based measurements to assess the EAT surrounding the heart and the organs in the abdominopelvic cavity. However, the idea of the contribution of a certain type adipose tissue beyond its impact on overall obesity to dysglycemia has existed for a time, so the findings of this research may be more confirmative than totally novel since we have used relatively novel indices (full volume of EAT and abdominopelvic VAT) and extensive statistical approaches to further support the idea in a large Chinese population.

Strengths and limitations

In previous years, the number of studies with respect to IGR and diabetes in Asian countries was relatively smaller than the number of studies conducted in developed countries. Our study focused on Chinese adults of one ethnicity to explore adiposity levels. All CT examinations were performed on the same CT scanner, and for each person, all measurements and examinations were carried out on the same day to ensure that the outcome had good repeatability and credibility. We applied full volume-based measurements for adipose tissue and quantified them using 1-mm-thickness CT images, which made the quantification more accurate and better reflected EAT and VAT capacity since the algorithm was based on fat voxels. The relationship of VAT measured within the above-mentioned range and IGR had not been previously researched. Furthermore, each patient's CT images were acquired within 3 min. Some studies have quantified adipose tissue by MRI. Although it is nonradiative, it is time-consuming for large clinical studies and sometimes the artifacts are difficult to avoid, which may affect the quantification outcome. Finally, the study population is relatively large, which may make our results more credible.

However, there were several limitations of our study. First, since we carried out a descriptive cross-sectional study, we could not demonstrate the causal relationships between adipose tissue and IGR or diabetes. The underlying mechanism of adiposity and glucose metabolism still needs deeper investigation. Second, the numbers of female subjects and IGR subjects were relatively small in this study, which may limit the performance of subanalysis on women. Third, focusing on Chinese adults is a double-edged sword; it simultaneously diminished the confounding factors but also made our results unsuitable for extrapolation. Finally, CT scans are not used for screening purposes in some other countries. Therefore, the assessments described in this study may not be considered a novel screening strategy to be used in large populations.

Future prospects and implications

Traditional obesity indices have a great advantage in clinical work for the convenience of showing whether a patient is "obese or not" within seconds. However, these indices cannot reflect true body fat content in patients with the same BMI, and the possibility of diabetes may be underestimated in low/normal-BMI individuals if the composition and distribution of adipose tissue are not considered. In our study, the outcome indicated that EAT or VAT may possibly be used to evaluate dysglycemia in patients with the same BMI or WHR by distinguishing metabolically "healthy" obesity and unhealthy obesity. In fact, since the metabolic consequences of obesity are not clear based on simple anthropometric measurement, there remains a lack of effective tools in the clinical setting to distinguish the above-mentioned states. In addition, the trend of internal fat metabolism in the context of diabetes prevention or diabetes control can also be reflected by adipose tissues but cannot be predicted by traditional obesity indices since some people may maintain the same weight while increasing their VAT volume and decreasing their SAT volume. Therefore, monitoring the dynamic changes in different adipose tissues or a combination of adipose tissues and traditional obesity indices during the course of diabetes prevention or glucose control interventions may be a promising idea. In the future, increased specific regional fat deposits could potentially be used as additional information for cardiovascular risk stratification in the early stages of glucose dysfunction. However, although CT scans may potentially provide interesting information in the clinical research setting, we need to weigh the advantages and disadvantages of this radiological examination. Furthermore, the development of novel therapies that modify adipose tissue distribution or reduce the capacity of adipose tissue may improve metabolic and cardiovascular outcomes in individuals with IGR or diabetes in the future. Of course, more advanced image processing techniques, which can quantify different adipose tissues automatically, are urgently needed to apply this technique to larger cohorts and samples.

Finally, in the ROC analysis, the optimal cutoff values determined by Youden's index for BMI, WC, WHR and WHtR were approximately in concordance with the standard cutoff points. This agreement might imply that the cutoff values for EATHtR and VATHtR (0.885 and 22.33, respectively) may be a reference in clinical practice, although more studies are needed to confirm our findings.

Conclusion

Higher EAT or VAT volume is positively associated with IGR and diabetes in Chinese adults. This correlation may be stronger than those of the traditional obesity indices.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the ethics committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Informed consent All patients signed written informed consent forms before the initiation of the study procedure.

Appendix: Subanalysis of males

See Tables 6, 7 and 8.

Table 6 Subanalysis of males of logistic regression of continuous adipose tissue indices

Factor	IGR versus healthy control		Diabetes versus healthy control	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
EATHtR, cm^2				
Model 1	1.79 (1.32–2.43)	**< 0.001**	1.72 (1.28–2.30)	**< 0.001**
Model 2	1.67 (1.16–2.39)	**0.006**	1.41 (1.00–1.98)	**0.049**
Model 3	1.48 (1.07–2.06)	**0.019**	1.49 (1.09–2.02)	**0.011**
Model 4	1.55 (1.07–2.24)	**0.019**	1.40 (0.99–1.96)	0.056
VATHtR, cm^2				
Model 1	2.41 (1.66–3.49)	**< 0.001**	2.35 (1.66–3.32)	**< 0.001**
Model 2	2.88 (1.71–4.85)	**< 0.001**	2.24 (1.39–3.61)	**0.001**
Model 3	1.88 (1.21–2.92)	**0.005**	2.05 (1.36–3.09)	**< 0.001**
Model 4	2.33 (1.35–4.02)	**0.002**	2.08 (1.27–3.40)	**0.003**

Model 1: Adjusted for clinical variables; *Model 2:* Adjusted for clinical variables, BMI

Model 3: Adjusted for clinical variables, WHR; *Model 4:* Adjusted for clinical variables, BMI, WHR

The adjusted clinical variables including age, height, smoking, HBP, AST, ALP, γ-GT, BUN, serum creatinine, uric acid, TG, HDL and LDL

OR (95% CI): The effect size is calculated based on each SD change in the variable

IGR, impaired glucose regulation; *OR*, odds ratio; *CI*, confidence interval; *EATHtR*, EAT (epicardial adipose tissue) volume-to-height ratio; *VATHtR*, VAT (visceral adipose tissue) volume-to-height ratio

Table 7 Subanalysis of males of logistic regression of categorical adipose tissue indices and traditional obesity indices

Model	Factor		IGR versus healthy control		Diabetes versus healthy control	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1	EATHtR, cm^2	High versus low	6.75 (1.69–26.90)	**0.007**	3.30 (1.06–10.32)	**0.040**
		High versus middle	1.78 (0.90–3.54)	0.099	1.75 (0.96–3.20)	0.069
		Middle versus low	3.79 (1.03–13.93)	**0.046**	1.89 (0.64–5.58)	0.251
		P for trend	/	**0.007**	/	**0.040**
Model 2	WHR	High versus low	26.40 (3.19–219.00)	**0.002**	2.23 (0.84–5.89)	0.107
	VATHtR, cm^2	High versus low	19.80 (2.93–133.00)	**0.002**	2.42 (0.73–8.03)	0.150
		High versus middle	2.89 (1.37–6.09)	**0.005**	1.91 (1.00–3.64)	**0.049**
		Middle versus low	6.85 (1.18–3.98)	**0.032**	1.26 (0.43–3.72)	0.669
		P for trend	/	**0.002**	/	0.150
	WHR	High versus low	22.10 (2.58–188.00)	**0.005**	2.21 (0.83–5.87)	0.113

Model 1: The independent variables included categorical EATHtR, BMI, WHR

Model 2: The independent variables included categorical VATHtR, BMI, WHR

All models are also adjusted for the above-mentioned clinical variables

OR (95% CI): The effect size is calculated based on the change in the level or the tertile of the variable (shown in Table 4 of the text tables)

IGR, impaired glucose regulation; *OR*, odds ratio; *CI*, confidence interval; *EATHtR*, EAT (epicardial adipose tissue) volume-to-height ratio; *VATHtR*, VAT (visceral adipose tissue) volume-to-height ratio; *WHR*, waist-to-hip ratio

Table 8 Subanalysis of males of the ROC curves of adipose tissues and traditional obesity indices

	IGR versus healthy control AUC of ROC	Diabetes versus healthy control AUC of ROC	Dysglycemia versus healthy control AUC of ROC	Cutoff value*
Age	0.618 (0.542–0.692)	0.701 (0.644–0.758)	0.668 (0.619–0.718)	39.00
BMI	0.640 (0.571–0.710)	0.668 (0.613–0.723)	0.657 (0.609–0.705)	28.38
WC, cm	0.665 (0.601–0.730)	0.682 (0.628–0.735)	0.675 (0.629–0.722)	88.60
WHR	0.694 (0.634–0.754)	0.700 (0.647–0.753)	0.698 (0.653–0.743)	0.94
WHtR	0.682 (0.618–0.746)^{b}	0.685 (0.632–0.738)	0.684 (0.638–0.730)	0.56
VATHtR	0.730 (0.670–0.789)^{a,b,c,e}	0.759 (0.709–0.809)^{b,c,d,e}	0.748 (0.705–0.790)^{a,b,c,d,e}	22.33
EATHtR	0.738 (0.680–0.797)^{a,b,c,e}	0.744 (0.694–0.794)^{b,c,e}	0.742 (0.700–0.785)^{a,b,c,e}	0.87

Statistically better AUC ($P < 0.05$) was reported by superscript letters

a: Age, b: BMI, c: WC, d: WHR, e: WHtR, f: VATHtR, g: EATHtR

Cutoff value* was calculated by Youden's index based on the ROC curve

IGR, impaired glucose regulation; *AUC*, area under the curve; *ROC*, receiver operating characteristic (curve); *BMI*, body mass index; *WC*, waist circumference; *WHR*, waist-to-hip ratio; *WHtR*, waist-to-height ratio; *VATHtR*, VAT (visceral adipose tissue) volume-to-height ratio; *EATHtR*, EAT (epicardial adipose tissue) volume-to-height ratio

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