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ORIGINAL ARTICLE

Sex differences in the association between visceral adipose tissue and atherosclerosis in type 2 diabetes patients with normal bodyweight: A study in a Chinese population

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ABSTRACT

Aims/Introduction: To investigate the impact of visceral adipose tissue (VAT) on atherosclerosis in type 2 diabetes patients with normal bodyweight (OB[–]) in the Chinese population, and to further assess the sex–age differences between them.

Materials and Methods: A total of 8,839 type 2 diabetes patients from two of the National Metabolic Management Centers in China were included in this study. Participants were classified into four groups by visceral fat area (VFA; cm^2) and body mass index (BMI; kg/m^2): VFA < 100 and BMI < 23.9 (VA[–]OB[–]), VFA < 100 and BMI ≥ 23.9 (VA[–]OB[+]), VFA ≥ 100 and BMI < 23.9 (VA[+]OB[–]), VFA ≥ 100 and BMI ≥ 23.9 (VA[+]OB[+]). Atherosclerosis was defined by brachial-ankle pulse wave velocity (baPWV; cm/s), and we analyzed the association between VFA, BMI and the tertiles of baPWV values.

Results: The VA(+)OB(–) prevalence was 3.7% among these participants. Patients with VA(+)OB(–) had the highest baPWV value ($P < 0.001$) and the highest proportion of the tertile 3 of baPWV ($P < 0.001$) among four groups, and were significantly associated with baPWV (standardized $\beta = 0.026$, $P = 0.008$). VFA was significantly related to tertile 2 to tertile 3 of baPWV in (OB[–]) type 2 diabetes patients, when compared with tertile 1 of baPWV, respectively. In sex–age stratified analysis, the association of VFA and the tertiles of baPWV showed sex differences. For the 55 years age stratification analysis, there was no age difference in the relationship between VFA and baPWV in (OB[–]) patients.

Conclusion: Increased VAT was an independent risk factor for atherosclerosis in female type 2 diabetes patients with normal weight.

INTRODUCTION

In recent decades, the number of type 2 diabetes patients with an average weight has markedly increased. Several studies have concentrated on the metabolically obese normal-weight phenotype. Body mass index (BMI) is a conventional index to measure normal weight, overweight and obesity. However, a collaborative analysis of 58 prospective studies has indicated that BMI, waist circumference and waist-to-hip ratio did not remarkably improve the prediction of cardiovascular disease (CVD) risk in developed countries. A multicenter observational study in white people showed that in newly diagnosed type 2 diabetes patients, patients with normal BMI had a higher mortality rate than those with overweight or obesity[2]. Accumulating evidence has shown that the visceral fat area (VFA) rather than BMI is closely associated with an increased risk of CVD in

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type 2 diabetes patients[3–6], because BMI might fail to differentiate the regional body fat distribution, such as visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT)[2,6,7].

Notably, increased VAT is an independent risk factor for the burden of arterial stiffness in type 2 diabetes patients with normal BMI, thus increasing atherosclerosis (AS) risk[6]. In addition, a 5-year follow-up study of 452 Japanese-Americans showed that the change in VAT was an independent predictor of AS, but not BMI, waist circumference or SAT[8]. These observations suggested that accumulation of VAT rather than SAT or BMI was independently associated with AS among Japanese patients with type 2 diabetes. Therefore, it is conceivable that increased VAT might be an independent risk factor of AS in type 2 diabetes patients with normal BMI.

However, as these studies were hospital-based, and the population was relatively small and ethnically and socially homogeneous, further studies are required to explore the impact of VFA on AS in people other than Japanese patients. We therefore designed the present cross-sectional study to investigate the association between VAT and AS in type 2 diabetes patients with normal weight in a Chinese population, and to further assess the sex and age differences between them.

MATERIALS AND METHODS

Participants

The present study was carried out at the National Metabolic Management Center (MMC), a standard nationwide and reproducible platform in China[9]. From 1 September 2017 to 7 March 2021, diabetes patients from two MMCs in China (the Second People's Hospital of Yuhuan and Sheyang diabetes specialist hospital) were collected for the present study. Patients who met the type 2 diabetes diagnostic criteria of the World Health Organization in 1999 with good follow-up compliance and could be followed up for >5 years were included. Patients with type 1 diabetes or other specific types of diabetes, history of drug-taking or drug abuse, history of AIDS, syphilis and other sexually transmitted diseases, as well as viral hepatitis, tuberculosis and other diseases in the active phase of the disease, were excluded. A total of 8,839 participants were finally included in the present study.

This study complies with the principles laid by the Declaration of Helsinki, and has been approved by the ethical committee of Ruijin Hospital, Affiliated Hospital of Shanghai Jiaotong University School of Medicine, the leading MMC center (Number 2017–42) and other participating centers subsequently. All participants in the present study provided written informed consent.

Clinical data collection

A standardized questionnaire was used to collect general information, including sex, age, height, weight, blood pressure, waist circumference, hip circumference, medical history, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, glycosylated hemoglobin (HbA1c), fasting glucose and so on. After fasting overnight for at least 12 h, study participants completed blood tests in the morning. The estimated glomerular filtration rate (eGFR) was according to the Chronic Kidney Disease Epidemiology Collaboration equation[10]. Hypertension was defined as systolic blood pressure and/or diastolic blood pressure >140 and/or 90 mmHg, respectively. Current drinking was defined as more than one 'standard drink' (refers to a 12 oz of beer, 5 oz of wine or 1.5 oz of distilled spirits) per week. Current smoking was defined as the smoking of more than one cigarette per day or seven cigarettes per week. CVD was defined as unstable angina, myocardial infarction, percutaneous coronary intervention, coronary bypass grafting, angioplasty or stroke, or major amputation due to peripheral arterial disease. All the data from the questionnaire were recorded on the MMC platform.

Definition of increased VAT and normal weight

VFA (cm^2) was determined by the dual bioelectrical impedance analyzer instrument (HDS 2000; Omron Co. Ltd., Kyoto, Japan). Studies have confirmed that it had a good correlation to computed tomography scan, and was cost-effective and non-invasive for estimating the VFA in patients with diabetes[11–13] VFA was measured at the umbilical level, and the cross-sectional area of visceral fat at this level in the abdomen was defined as VFA. Patients with VFA $\geq$ 100 cm^2 were considered to have increased adipose tissue[14]. BMI (kg/m^2) was equal to the weight divided by the square of height. Patients with a BMI of 18.5–23.9 kg/m^2 were regarded to have normal bodyweight, and those with BMI > 23.9 kg/m^2 were considered overweight or obese[15]. According to the definitions of the increased VAT and BMI, we assigned patients into four groups: (i) VA(−)OB(−): VFA < 100 cm^2 and BMI < 23.9 kg/m^2; (ii) VA(−)OB(+): VFA < 100 cm^2 and BMI $\geq$ 23.9 kg/m^2; (iii) VA(+)OB(−): VFA $\geq$ 100 cm^2 and BMI < 23.9 kg/m^2; and (iv) OB(+)VA(+): VFA $\geq$ 100 cm^2 and BMI $\geq$ 23.9 kg/m^2.

Definition of AS

The present study used brachial-ankle pulse wave velocity (baPWV) to show whether a patient had arteriosclerosis[16,17]. The baPWV was determined on the volume-plethysmographic apparatus (BP-203RPE II form PWV/ABI, Omron Healthcare Co. Ltd., Kyoto, Japan). The baPWV were measured both on the left and right sides, and their average value was calculated to carry out statistical analysis. A BaPWV value >1,400 cm/s was considered as AS[16,17]. The tertiles of baPWV were set to further explore the association between VFA and AS.

Statistical analysis

According to the data distribution, continuous variables were expressed as the mean ± standard deviation or median with interquartile range. Categorical variables were presented as numbers and percentages. The Pearson's χ^2-test (categorical variables) or Kruskal–Wallis test (continuous variables) were used to compare the differences between these four groups.

Pairwise comparison among these four groups was adjusted by the Bonferroni test. Multivariate linear regression analysis with an enter procedure was carried out to assess the relationship of VFA and BMI to baPWV. The following covariates were enrolled into the multivariate model: age, sex, subcutaneous fat area (SFA), HbA1c, triglycerides, HDL-C, low-density lipoprotein cholesterol, eGFR, history of CVD, history of hypertension, current smoking status and current drinking status. The selection of covariates was based on the indicators that might be clinically related to AS and previous literature studies, and the included covariates had no collinearity through the collinearity tests. Furthermore, we used multinomial logistic regression analysis to access the relationship between BMI and VFA and different tertiles of baPWV. The presence of effect modification by sex and age was examined using stratified analysis. The SPSS software (version 25.0; IBM Corp, Armonk, NY, USA) was used for statistical analysis. $P < 0.05$ was considered statistically significant.

RESULTS

General characteristics of participants

A total of 8,839 Chinese patients with type 2 diabetes were enrolled in the present study (51.7% men, 56 [50–64] years). The prevalence of VA(+)OB(−) patients was 3.7% ($n = 327$), and 24.6% ($n = 2,171$), 25.2% ($n = 2,225$) and 46.6% ($n = 4,116$) were classified as VA(−)OB(−), VA(−)OB(+) and VA(+)OB(+), respectively (Figure 1). Patients with VA(+)OB(−) had the highest baPWV value ($P < 0.001$), visceral fat area-to-subcutaneous fat area ratio ($P < 0.001$) and proportion of men ($P < 0.001$), and the lowest HbA1c ($P < 0.001$), fasting glucose ($P = 0.03$) and 2-h postprandial blood glucose ($P < 0.001$) among these four groups. Patients with VA(+)OB(+) had the highest VFA ($P < 0.001$), SFA ($P < 0.001$), WC ($P < 0.001$), hip circumference ($P < 0.001$), waist-to-hip ratio ($P < 0.001$), diastolic blood pressure ($P < 0.001$) and systolic blood pressure ($P < 0.001$), and the lowest HDL-C ($P < 0.001$) among these four groups (Table 1).

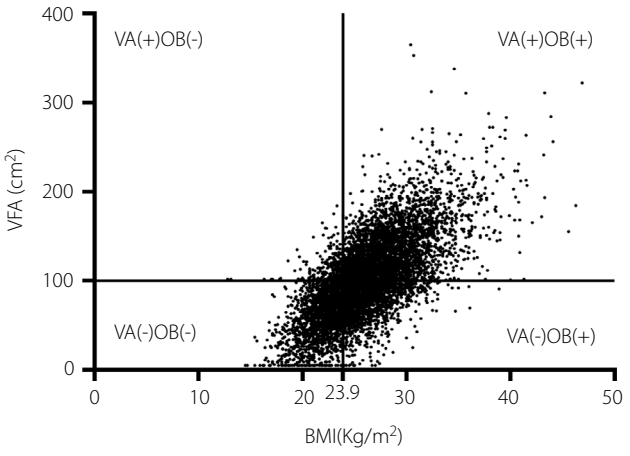

Figure 1 | The distribution of visceral fat area (VFA) and body mass index (BMI) in patients with type 2 diabetes. VA(−)OB(−), VFA < 100 and BMI < 23.9; VA(−)OB(+), VFA < 100 and BMI ≥ 23.9; VA(+)OB(−), VFA ≥ 100 and BMI < 23.9; VA(+)OB(+), VFA ≥ 100 and BMI ≥ 23.9.

Prevalence of different tertiles of baPWV

According to the tertiles of baPWV value, patients with VA(+)OB(−) had the highest proportion among these four groups in tertile 3 (T3) (30.3%, 32.0%, 36.1% and 35.5%, respectively, $P < 0.001$; Table 2). For sex-stratification, in the T3 of baPWV, women had the highest proportion ($P < 0.001$) of VA(+)OB(−) among these four groups, whereas no significant difference was seen in men (29.4%, 28.6%, 41.2% and 38.9%, respectively, $P < 0.001$; Table 3). However, for 55 years age-stratification analysis, in the T3 of baPWV, patients aged <55 years showed the highest proportion of VA(+)OB(−) (28.7%, 32.3%, 37.2% and 36.5%, respectively, $P < 0.001$) among these four groups, whereas there was no significant difference in patients aged >55 years (Table 3).

The association between VFA and baPWV in type 2 diabetes patients with OB (−)

Multivariate linear regression analysis was carried out to assess the relationship of VFA and BMI with baPWV. As shown in Table 4, the VA(+)OB(−) patients were significantly at increased risk of AS (standardized $\beta = 0.026$, $P = 0.008$). This association was not changed after adjustment for age, sex, SFA, HbA1c, triglycerides, HDL-C, low-density lipoprotein cholesterol, eGFR, history of CVD, history of hypertension, current smoking status and current drinking status. Expectedly, VA(+)OB(+) (standardized $\beta = 0.053$, $P = 0.001$) was also significantly associated with baPWV, whereas no significant association was observed between VA(−)OB(+) and baPWV. Simultaneously, we observed a significant association between age (standardized $\beta = 0.317$, $P < 0.001$), SFA (standardized $\beta = -0.047$, $P < 0.001$), HbA1c (standardized $\beta = 0.138$, $P < 0.001$), eGFR (standardized $\beta = -0.061$, $P < 0.001$), sex (standardized $\beta = -0.036$, $P = 0.003$), hypertension (standardized $\beta = 0.193$, $P < 0.001$) and baPWV, respectively (Table 4).

Association between VFA and different tertiles of baPWV in type 2 diabetes patients with OB (−)

The multinomial logistic regression analysis showed that VFA was significantly correlated with T2 and T3 of baPWV in type 2 diabetes patients with normal weight after adjustment for confounding factors, with a standard deviation increment of VFA, the odds ratios (95% confidence intervals) of T2 and T3 were 1.182 (1.042–1.341) and 1.223 (1.065–1.405), respectively, when compared with the T1 of baPWV (Table 5). However, no significant difference was obtained in the association between BMI and different tertiles of baPWV in type 2 diabetes patients with normal weight. For sex-stratification analysis, VFA was significantly associated with tertiles of baPWV in female type 2 diabetes patients with normal weight. When

Table 1 | Clinical characteristics of the total participants according to different body mass index and visceral fat area groups

	Total (n = 8,839)	VFA <100 cm^2		VFA ≥100 cm^2		P-value
		BMI < 23.9 kg/m^2 VA(–)OB(–) (n = 2,171)	BMI ≥ 23.9 kg/m^2 VA(–)OB(+) (n = 2,225)	BMI < 23.9 kg/m^2 VA(+)OB(–) (n = 327)	BMI ≥ 23.9 kg/m^2 VA(+)OB(+) (n = 4,116)	
Age (years)	56 (50–64)	56 (49–64)	56 (49–64)	58 (50–65)	57 (50-65)[b]	0.001
Sex (% male)	4,567 (51.7)	1,018 (46.9)	971 (43.6)	208 (63.6)	2,370 (57.6)	<0.001*
Weight (kg)	68.2 (60.4–76.4)	56.9 (52.1–62.2)	67.5 (62.3–73.2)	61.3 (56.4–67.3)	75.2 (68.9–82.6)	<0.001*
BMI (kg/m^2)	25.85 (23.6–28.2)	22.2 (21–23.2)	25.8 (24.8–27.2)[a]	23 (22.2–23.5)[b]	28 (26.3–30.1)[abc]	<0.001
Waist circumference (cm)	91 (85–98)	81 (77–85)	90 (86–94)	87 (83–90)	97 (92–102)	<0.001*
Hip circumference (cm)	96 (92–101)	90 (87–93.5)	96 (93–100)	92.5 (90–96)	100 (96–104)	<0.001*
W/H ratio	0.943 (0.9–0.984)	0.896 (0.861–0.937)	0.934 (0.899–0.97)[a]	0.931 (0.892–0.967)[a]	0.969 (0.932–1.009)[abc]	<0.001
Visceral fat area (cm^2)	100 (73.5–126.5)	62 (42.9–77.8)	81.7 (68–91.5)	109.4 (102.9–120.7)	128.3 (112–151.8)	<0.001*
Subcutaneous fat area (cm^2)	178.1 (140.4–220.7)	120 (97.2–144.6)	174.4 (150.8–205.4)	153.6 (129–179)	210.55 (182–251.175)	<0.001*
V/S ratio	0.549 (0.438–0.669)	0.491 (0.363–0.605)	0.446 (0.361–0.531)	0.736 (0.612–0.884)	0.619 (0.531–0.728)	<0.001*
baPWW (cm/s)	1606.5 (1424–1850.5)	1571.5 (1391.5–1819.5)	1592.5 (1415–1824.5)	1652.5 (1437.5-1877)[a]	1629.5 (1443–1868.5)[ab]	<0.001
Diastolic blood pressure (mmHg)	77 (69–85)	73 (65–80)	77 (70-84)[a]	75 (68-82)[a]	80 (72-88)[abc]	<0.001
Systolic blood pressure (mmHg)	134 (122–149)	126 (114–139)	134 (122-148)[a]	131 (120-144)[a]	139 (126-153)[abc]	<0.001
Heart rate (b.p.m.)	80 (73–89)	81 (73–90)	80 (72-89)[a]	81 (73–89)	80 (73–89)	0.004
Duration of diabetes (months)	80 (24–135)	81 (23–138)	85 (27–144)	86 (32–131)	76 (23–133)	0.053
Fasting glucose (mmol/L)	9.41 (7.12–12.65)	9.43 (6.92–13.41)	9.59 (7.095–13.07)	8.74 (6.85–11.78)[ab]	9.375 (7.273–12.29)	0.03
Glucose (2H) (mmol/L)	16.5 (12.1–19.85)	16.552 (12.05–20.94)	16.552 (12.2–19.8)	15.38 (10.7–19.86)[a]	16.165 (12.23–19.3)[a]	<0.001
Glycosylated hemoglobin (%)	8.6 (7–10.2)	8.8 (7–10.9)	8.6 (7–10.3)[a]	8.3 (6.9–10.1)	8.4 (7.1–9.9)[a]	<0.001
Liver function						
ALT (IU/L)	22 (15–33)	18 (12–28)	20 (14-30)[a]	22 (14-33)[a]	26 (18-39)[abc]	<0.001
AST (IU/L)	20 (16–26)	18 (14–24)	20 (16-25)[a]	19 (15–25)	21 (17-28)[abc]	<0.001
ALP (IU/L)	77 (62–91)	79 (64–94)	76 (63-91)[a]	76 (63–89)	75 (62-90)[a]	<0.001
γ-GT (IU/L)	31 (20–49)	24 (16–40)	28 (19–45)	32 (21–53)	38 (25–58)	<0.001*
Kidney function						
BUN (mmol/L)	5.56 (4.52–6.65)	5.56 (4.53–6.66)	5.59 (4.52–6.615)	5.61 (4.61–6.69)	5.54 (4.51–6.65)	0.791
Cr (μmol/L)	63.1 (52–75.6)	60.2 (50.1–72.1)	63 (51–74.7)[a]	64 (52-79)[a]	65 (53–77.6)[ab]	<0.001
UA (μmol/L)	319 (258–382)	288 (234–347)	307 (251–370)	325 (266–388)	336 (279–402.75)	<0.001*
eGFR (mL/min/1.73 m^2)	99.778 (87.948–109.119)	101.099 (89.45–110.618)	99.69 (87.292–109.026)[a]	100.229 (89.189–109.443)	99.021 (87.11–108.354)[a]	<0.001
TG (mmol/L)	1.51 (1.04–2.32)	1.14 (0.81–1.75)	1.48 (1.05–2.21)[a]	1.51 (1.08–2.2)[a]	1.73 (1.22–2.55)[abc]	<0.001
TC (mmol/L)	5.12 (4.37–5.92)	5.04 (4.28–5.81)	5.11 (4.34–5.89)	5.309 (4.51–6.15)[ab]	5.16 (4.43–5.98)[a]	<0.001
HDL-C (mmol/L)	1.18 (0.99–1.41)	1.26 (1.06–1.55)	1.19 (0.99–1.41)[a]	1.18 (1–1.37)[a]	1.14 (0.97–1.34)[ab]	<0.001
LDL-C (mmol/L)	3.13 (2.43–3.82)	3.04 (2.39–3.7)	3.15 (2.44–3.815)	3.21 (2.39–3.94)	3.16 (2.44–3.88)[a]	0.001
Current drinking, n (%)	2,629 (29.7)	543 (25)	555 (24.9)	119 (36.4)[ab]	1,412 (34.3)[ab]	<0.001
Current smoking, n (%)	2,280 (25.8)	532 (24.5)	484 (21.8)[a]	101 (30.9)[ab]	1,163 (28.3)[ab]	<0.001
Hypertension, n (%)	4,550 (51.5)	722 (33.3)	1,100 (49.4)	142 (43.4)	2,586 (62.8)	<0.001*
Hyperlipemia, n (%)	2,515 (28.5)	353 (16.3)	596 (26.8)[a]	65 (19.9)[b]	1,501 (36.5)[abc]	<0.001
History of CVD, n (%)	907 (10.3)	162 (7.5)	220 (9.9)[a]	33 (10.1)	492 (12)[ab]	<0.001
Administration of, n (%)						

Table 1. (*Continued*)

	Total (n = 8,839)	VFA <100 cm^2		VFA ≥100 cm^2		*P*-value
		BMI < 23.9 kg/m^2 VA(–)OB(–) (n = 2,171)	BMI ≥ 23.9 kg/m^2 VA(–)OB(+) (n = 2,225)	BMI < 23.9 kg/m^2 VA(+)OB(–) (n = 327)	BMI ≥ 23.9 kg/m^2 VA(+)OB(+) (n = 4,116)	
Anti-diabetic medication	6,921 (78.3)	1,653 (76.1)	1760 (79.1)[a]	244 (74.6)	3,264 (79.3)[ac]	0.008
Insulin	4,097 (46.4)	1,004 (46.2)	1,134 (51)[a]	108 (33)[ab]	1851 (45)[bc]	<0.001
Anti-hypertensive medication	3,862 (43.7)	607 (28)	977 (43.9)	116 (35.5)	2,162 (52.5)	<0.001*
Anti-hyperlipidemic medication	2,803 (31.7)	589 (27.1)	703 (31.6)[a]	94 (28.7)	1,417 (34.4)[abc]	<0.001
Anti-platelet medication	1,375 (15.6)	236 (10.9)	371 (16.7)[a]	35 (10.7)[b]	733 (17.8)[ac]	<0.001

Variables are presented as median (25%–75%) or percentage. The pairwise comparison between these four groups was adjusted by the Bonferroni test. The Kruskal–Wallis tests or Pearson's χ^2-tests were used to compare differences among four groups. *P < 0.05 in any pairwise comparison. a: compared with the VA(–)OB(–), P < 0.05; b: compared with the VA(–)OB(+), P < 0.05; c: compared with the VA(+)OB(–), P < 0.05. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; CVD, cardiovascular disease.; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; UA, uric acid; V/S ratio, visceral fat area-to-subcutaneous fat area ratio; VFA, visceral fat area; W/H ratio, waist circumference-to-hip circumference ratio; γ-GT, γ-glutamyl transpeptidase.

Table 2 | Prevalence of different brachial-ankle pulse wave velocity tertiles according to different body mass index and visceral fat area groups in total type 2 diabetes patients

	baPWV Tertiles		
Tertiles	T1 (<1,484)	T2 (1,484–1,753)	T3 (≥1,753)
VA(–)OB(–), *n* (%)	824 (38.0)	690 (31.8)	657 (30.3)
VA(–)OB(+), *n* (%)	780 (35.1)[a]	733 (32.9)	712 (32.0)
VA(+)OB(–), *n* (%)	97 (29.7)[a]	112 (34.3)	118 (36.1)[a]
VA(+)OB(+), *n* (%)	1,240 (30.1)[ab]	1,415 (34.4)	1,461 (35.5)[ab]
Total	2,941 (33.3)	2,950 (33.4)	2,948 (33.4)
P-value	<0.001	0.200	<0.001

VA(–)OB(–), visceral fat area (VFA) < 100 and body mass index (BMI) < 23.9; VA(–)OB(+), VFA < 100 and BMI ≥ 23.9; VA(+)OB(–), VFA ≥ 100 and BMI < 23.9; VA(+)OB(+), VFA ≥ 100 and BMI ≥ 23.9. Tertile 1 (T1)1: brachial-ankle pulse wave velocity (baPWV) <1,484 cm/s; T2: baPWV ≥ 1,484 cm/s and < 1753 cm/s; T3: baPWV ≥ 1,753 cm/s. The Pearson's χ^2-tests were used to compare differences among the four groups. [a]Compared with the VA(–)OB(–), P < 0.05; [b]compared with the VA(–)OB(+), P < 0.05.

compared with the T1 of baPWV, the odds ratios (95% confidence intervals) of T2 and T3 were 1.244 (1.017–1.523) and 1.467 (1.170–1.838), respectively, whereas no statistical significance was obtained among male type 2 diabetes patients with normal weight (Table 5). For 55 years age-stratification analysis, no significant difference between VFA and the different tertiles of baPWV was shown in patients younger or older than 55 years.

DISCUSSION

The present cross-sectional study showed that the prevalence of VA(+)OB(−) patients was 3.7% among Chinese type 2 diabetes patients. The VA(+)OB(−) patients showed the highest value of baPWV, and had the highest proportion of T3 of baPWV. Patients with VA(+)OB(−) were significantly at increased AS risk even after adjustment for multivariable covariates. In further multinomial logistic regression analysis, a standard deviation increment of VFA was associated considerably with T2 and T3 of baPWV compared with T1 of baPWV. There were sex differences in the association between them in type 2 diabetes patients with normal weight, whereas BMI did not show a significant association with any tertiles of baPWV.

Okauchi *et al.*[18] have already investigated the prevalence of VA(+)OB(−) in a total of 2,336 general Japanese men in 2007, and found that the prevalence of VA(+)OB(−) was 17.2%. However, 14% showed severe accumulation of abdominal fat in the general population with normal weight in the general Chinese population[19]. A cross-sectional survey of 15,364 Chinese participants showed that the prevalence of VA(+)OB(−) in the general population was 7.1%[20], which is higher than those in diabetes patients, as shown in the present study. These results showed that the prevalence of VA(+)OB(−) in the general population seems to be higher than those in diabetes patients.

Table 3 | Prevalence of different brachial-ankle pulse wave velocity tertiles according to different body mass index and visceral fat area groups in total type 2 diabetes patients (sex and age stratification)

	Male (n = 4,567)			Female (n = 4,272)			<55 years (n = 3,788)			≥55 years (n = 5,051)		
	baPWV Tertiles			baPWV Tertiles			baPWV Tertiles			baPWV Tertiles		
Tertiles	T1 (<1,457)	T2 (1,457 –1,704)	T3 (≥1,704)	T1 (<1,523)	T2 (1,523 –1,801)	T3 (≥1,801)	T1 (<1,393)	T2 (1,393 –1,591)	T3 (≥1,591)	T1 (<1,586)	T2 (1,586 –1,873)	T3 (≥1,873)
VA (–)OB (–), [n (%)]	389 (38.2)	316 (31.0)	313 (30.7)	445 (38.6)	369 (32.0)	339 (29.4)	374 (38.5)	318 (32.7)	279 (28.7)	443 (36.9)	370 (30.8)	387 (32.3)
VA (–)OB (+), n (%)	315 (32.4) [a]	331 (34.1)	325 (33.5)	480 (38.3)	415 (33.1)	359 (28.6)	368 (36.4)	316 (31.3)	326 (32.3)	405 (33.3)	413 (34.0)	397 (32.7)
VA (+)OB (–), n (%)	67 (32.2)	69 (33.2)	72 (34.6)	29 (24.4)[ab]	41 (34.5)	49 (41.2)[ab]	43 (33.3)	38 (29.5)	48 (37.2)[a]	55 (27.8)[a]	71 (35.9)	72 (36.4)
VA (+)OB (+), n (%)	749 (31.6) [a]	808 (34.1)	813 (34.3)	466 (26.7)[ab]	600 (34.4)	680 (38.9)[ab]	477 (28.4)[ab]	589 (35.1)	612 (36.5)[ab]	776 (31.8)[a]	832 (34.1)	830 (34.0)
Total, n (%)	1,520 (33.3)	1,524 (33.4)	1,523 (33.3)	1,420 (33.2)	1,425 (33.4)	1,427 (33.4)	1,262 (33.3)	1,261 (33.3)	1,265 (33.4)	1,679 (33.2)	1,686 (33.4)	1,686 (33.4)
P-value	0.002	0.352	0.238	<0.001	0.604	<0.001	<0.001	0.152	<0.001	0.007	0.182	0.525

VA(–)OB(–), visceral fat area (VFA) < 100 and body mass index (BMI) < 23.9; VA(–)OB(+), VFA < 100 and BMI ≥23.9; VA(+)OB(–), VFA ≥ 100 and BMI < 23.9; VA(+)OB(+), VFA ≥ 100 and BMI ≥ 23.9. The Pearson's χ^2-tests were used to compare differences among the four groups. [a]Compared with the VA(–)OB(–), P < 0.05; [b]compared with the VA(–)OB(+), P < 0.05. baPWV, brachial-ankle pulse wave velocity.

Table 4 | Multivariate linear regression analysis for independent factors associated with pulse wave velocity in total patients with type 2 diabetes

	Standardized β	P-value
VA(–)OB(+)	0.010	0.429
VA(+)OB(–)	0.026	0.008
VA(+)OB(+)	0.053	0.001
Age	0.317	<0.001
SFA	–0.047	<0.001
HbA1c	0.138	<0.001
TG	0.001	0.879
HDL-C	–0.002	0.858
LDL-C	0.016	0.084
eGFR	–0.061	<0.001
Sex	–0.036	0.003
History of CVD	0.007	0.479
History of hypertension	0.193	<0.001
Current smoking status	–0.007	0.497
Current alcohol consumption status	0.005	0.627

VA(–)OB(–), visceral fat area (VFA) < 100 and body mass index (BMI) < 23.9; VA(–)OB(+), VFA < 100 and BMI ≥ 23.9; VA(+)OB(–), VFA ≥ 100 and BMI < 23.9; VA(+)OB(+), VFA ≥ 100 and BMI ≥ 23.9. CVD, cardiovascular disease; eGFR: estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SFA, subcutaneous fat area; TG, triglycerides.

Racial differences in the distribution of VAT were reported in the previous study[6]. It is of high interest to elucidate the prevalence of VA(+)OB(–), and the association between VA(+)OB(–) and atherosclerosis in a population other than Japanese patients with type 2 diabetes. Based on the China Health and Nutrition Survey, the prevalence of normal BMI (defined as a BMI of 18.5–23.9 kg/m^2) in the general population is 44%[21]. As we know, overweight and obesity are risk factors for diabetes, and almost 90% of type 2 diabetes can be attributed to being overweight or obese[22]. A 2013 study in China showed that the prevalence of normal BMI in type 2 diabetes patients is 34.7%[23]. The prevalence of normal BMI in the present study was 28.3%. These results show that the prevalence of normal BMI in type 2 diabetes patients seems to be lower than those in the general population. The subtle difference in the prevalence of normal BMI in the general population and diabetes population might be attributed to the lower prevalence of VA(+)OB(–) in diabetes patients.

It is noteworthy that average BMI levels between Western (29.4 kg/m^2), Chinese (25 kg/m^2) and Japanese (23.1 kg/m^2) patients with type 2 diabetes are quite different among multiracial individuals[19]. As shown in Table 1, the BMI value in the present study (mean BMI 25.85 kg/m^2) was much lower than the Western population, but higher than Japanese patients. In addition, 28.3% of type 2 diabetes patients in China had an average weight (45.2% in a previous study of 414 Japanese

Table 5 | Multinomial logistic regression analysis between different body mass index and visceral fat area and different brachial-ankle pulse wave velocity tertiles in type 2 diabetes patients with normal weight

			Tertile 1	Tertile 2		Tertile 3	
	n	SD	-	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
VFA*							
Total	2,498	30.37	Reference	1.182 (1.042–1.341)	0.010	1.223 (1.065–1.405)	0.004
Male	1,226	33.9	Reference	1.081 (0.909–1.284)	0.378	0.966 (0.805–1.158)	0.706
Female	1,272	26.54	Reference	1.244 (1.017–1.523)	0.034	1.467 (1.170–1.838)	0.001
<55 years	1,100	29.79	Reference	1.092 (0.897–1.329)	0.380	1.184 (0.966–1.452)	0.103
≥55 years	1,398	30.75	Reference	1.130 (0.963–1.327)	0.134	1.159 (0.978–1.375)	0.089
BMI*							
Total	2,498	1.61	Reference	1.017 (0.900–1.150)	0.784	0.967 (0.842–1.110)	0.631
Male	1,226	1.64	Reference	1.025 (0.867–1.213)	0.770	0.895 (0.748–1.071)	0.227
Female	1,272	1.59	Reference	1.126 (0.938–1.352)	0.204	1.031 (0.837–1.269)	0.774
<55 years	1,100	1.69	Reference	0.852 (0.711–1.021)	0.084	0.837 (0.693–1.012)	0.066
≥55 years	1,398	1.55	Reference	1.128 (0.954–1.333)	0.158	1.011 (0.848–1.206)	0.899

Covariates: age, sex, subcutaneous fat area, glycosylated hemoglobin, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, estimated glomerular filtration rate, history of cardiovascular disease, history of hypertension, current smoking status (yes/no), current alcohol consumption status (yes/no). *Parameter was calculated with a standard deviation increment used for odds ratio calculations. SD, standard deviation; VFA, visceral fat area.

participants[6]), suggesting that the prevalence of VA(+)OB(−) patients among the Chinese population has a greater potential to be lower than that in the Japanese population. This difference might stem from different definitions of BMI. The cut-off value of normal BMI in the present study was 23.9 kg/m^2, which was according to China's obesity guidelines[24]. Although the World Health Organization and previous studies defined overweight as a BMI ≥25 kg/m^2[26], we then redivided the enrolled participants into OB(−) and OB(+) groups according to a BMI = 25 kg/m^2, and carried out multiple linear regression analysis (Table S1). The result showed that VA(+)OB(−) was significantly correlated with baPWV, which was consistent with the results of multiple linear regression analysis when BMI = 23.9 kg/m^2 was taken as the cut-off value (Table 4). Considering the World Health Organization recommendation of appropriate BMI for Asian populations and the typical BMI cut-off definition by the Working Group on Obesity in China, and the previous evidence regarding ethnic differences in body composition and obesity-related risk factors in Chinese populations[25,26], we used the BMI cut-offs 18.5–23.9 kg/m^2 as a normal BMI in the follow-up statistical analysis of the present study. Further studies are required to explore the prevalence of VA(+)OB(−) among the total population of type 2 diabetes patients in China.

Several published studies have investigated the association between VAT and baPWV in type 2 diabetes patients with normal BMI[6,8]. Bouchi *et al.*[6] reported an increase in the risk of AS among type 2 diabetes patients with normal weight in Japan. However, the sample of the enrolled participants was comparatively small in the aforementioned studies, resulting in lower statistical efficiency in disclosing the association. The present study consisted of 8,839 type 2 diabetes patients from two MMCs in eastern China, the sample size of which was more significant than the previous study. As shown in Table 1, the VA(+)OB(−) patients had the highest baPWV value among the four groups, and in further analysis, those patients were at significantly increased risk of AS, which suggested that in type 2 diabetes patients with OB(−), the increased VFA was a risk factor of AS. However, the VA(−)OB(+) has no significant association with AS, which implied that in patients with normal VFA, abnormal BMI was not an independent factor of AS. The present findings were in line with the previous study[6]. Based on these observations, increased VFA was an independent risk factor of AS among type 2 diabetes patients with normal BMI in a Chinese population.

According to previous studies, in the present study, baPWV was used as the indicator of AS[17,27,28]. The multinomial logistic regression analysis showed that VFA was significantly correlated with tertiles of baPWV in OB(−) type 2 diabetes patients (Table 5). However, no significant difference was obtained in the association between BMI and different tertiles of baPWV in OB(−) type 2 diabetes patients. These observations suggested that BMI was unlikely to affect the progression of AS, and it is the increased VFA rather than BMI that is related to increased baPWV in type 2 diabetes patients with normal average weight.

Recently, the metabolically obese normal-weight phenotype was reported to be widespread and attracted much more attention. Xia *et al.* showed that normal weight, lower fat and higher muscle mass might contribute to metabolic health, and presumed that decreased skeletal muscle mass ratio accompanied by the increased fat accumulation might play a critical role in the pathological process of the metabolically unhealthy profile

in metabolically obese normal-weight phenotype[29]. It was reported that type 2 diabetes patients with visceral fat accumulation had low muscle quality, and patients with low muscle quality had a higher prevalence of cardiovascular disease than those with high muscle quality[30]. Whether decreased muscle quality is associated with increased arterial stiffness in type 2 diabetes patients with average weight remains elucidated in further study. However, we did not collect these data during baseline data entry. If these data are available, we will explore them in future research.

As body fat tissue distribution differed between women and men[3], it is essential to examine the sex-specific relationship between VFA-BMI and AS using sex subgroup analysis. Nicklas *et al.*[31] showed that VFA rather than BMI is an independent risk factor for myocardial infarction among older women, but not older men. They concluded that the area of intraabdominal adipose tissue was an independent risk factor for myocardial infarction in older women, which indicated that the sex difference association between VFA and baPWV was worth studying. In this study, subgroup analysis was carried out because of the large sample size. For the prevalence of different degrees of AS, patients with VA(+)OB(−) had the highest proportion in T3 of baPWV among female participants for sex stratification. For sex-stratification analysis, VFA was significantly associated with tertiles of baPWV in women, whereas no statistical significance was obtained among men in normal-weight type 2 diabetes patients.

Accumulating bodies of evidence have shown significant sex differences in arterial stiffness between women and men[32,33]. Sex-specific risk factors, such as the physiological estrogen withdrawal from menopause in women, might play a key role in promoting arterial stiffness. A large-scale observational study in China has found that women after menopause showed a steeper increase in baPWV[34]. Recently, the sex-specific association of baPWV with adverse cardiac remodeling and the cardiovascular outcome was shown in a large population of 11,767 patients. The detrimental effects of baPWV on adverse cardiac remodeling and cardiovascular outcomes were stronger in women than in men[35]. Unfortunately, in our present study, the data of history of menopause were incomplete, so statistical analyses could not be carried out due to large missing values.

To investigate whether postmenopausal women would affect the sex difference, we carried out analyses for the difference between VFA and baPWV among female OB(−) patients, with postmenopausal women as those aged >50 years (Table S2 and S3). The average menopausal age of Asian women ranges from 45 to 55 years, with an average of 48–50 years. Although the history of menopause was incomplete in our present study, we defined postmenopausal women as aged >50 years. Indeed, the present results showed that the baPWV was significantly higher in women than in men (1,617.0 [1428.6–1891.6] vs 545.5 [1,376.8–1,771.8], $P < 0.001$; Table S2). Postmenopausal women, compared with premenopausal women, had higher VFA (68.0 [50.7–83.7] vs 60.2 [43.4–75.8]; $P < 0.001$) and higher baPWV (1,683.0 [1,485.3–1,951.0] vs 1,421.0 [1,257.0–1,552.0]; $P < 0.001$; Table S3). We therefore speculate that the sex differences in the association between VFA and baPWV are probably explained by menopause status in women, which is worth exploring in further study.

In addition, no significant difference was detected in both younger and older than 55 years among OB(−) type 2 diabetes patients. Although, among the total type 2 diabetes patients, we found that when compared with T1, VFA was significantly associated with the T3 of baPWV both in patients aged younger and older than 55 years (Table S4). We speculated that the reason for the inconsistent results between the total type 2 diabetes patients and OB(−) patients on the age difference might be that the prevalence of OB(−) patients was small (28.3%) in the present study, which might reduce its statistical efficiency and lead to no statistically significant results shown in the OB(−)patients. Therefore, we carried out the same analysis for the OB(+) patients (Table S5). The results showed that VFA was significantly associated with the T2 and T3 of baPWV compared with T1. The relationship between them presented sex differences, whereas no age difference was found, which is the same as with total type 2 diabetes patients, showing that the relationship of VFA and baPWV in actual type 2 diabetes patients is mainly due to the more considerable prevalence of OB(+) patients. This might partly explain why there is no age difference in the relationship between VFA and baPWV in OB(−) patients. Further research should verify these results in the future.

There were several limitations to the present study. First of all, almost all of the participants enrolled were from the outpatient department, and the patients were from East China. There might be bias in the study participants; further study should expand the population. Second, VFA was measured by a dual bioelectrical impedance analyzer in the present study. Several imaging approaches, including computed tomography, magnetic resonance imaging and dual-energy X-ray absorptiometry, have been proven to measure VFA. However, accumulating evidence has confirmed that VFA measured by the dual bioelectrical impedance analyzer was more cost-effective and non-invasive than the above methods for estimating the VFA in type 2 diabetes patients[10–12]. Third, patients with VA(+)OB(−) might have an increased risk of cardiovascular events. Unfortunately, there have been few studies on the association between VA(+)OB(−) and the incidence or recurrence of cardiovascular events. Furthermore, extensive prospective studies are required to determine the impact of VFA on CVD in type 2 diabetes patients' normal weight.

The present findings confirmed that: (i) normal-weight type 2 diabetes patients with increased VFA (VA[+] OB[−]) had the highest value of baPWV in a Chinese population; (ii) increased VFA was an independent AS risk factor in type 2 diabetes patients with normal weight; and (iii) VFA was significantly related to the different tertiles of baPWV in type 2 diabetes patients with normal weight, and there were sex

differences in the relationship between them, as increased VAT was an independent risk factor for atherosclerosis in female normal-weight type 2 diabetes patients.

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DISCLOSURE

The authors declare no conflict of interest.

The study was carried out in accordance with the Declaration of Helsinki (as revised in 2013). Approval from an ethical review board of the hospitals was obtained before commencing the study.

Approval of the research protocol: 2 May 2017, No. 2017–42.

Informed consent: All participants in the present study provided written informed consent.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Tables S1 | Multivariate linear regression analysis for independent factors associated with pulse wave velocity in total patients with type 2 diabetes (patients were divided into four groups according to visceral fat area = 100 cm^2 and body mass index = 25 kg/m^2).

Table S2 | Characteristics of the type 2 diabetes patients with normal weight (OB[−]) by sex.

Table S3 | Characteristics of the type 2 diabetes patients with female normal weight (OB[−]) by age.

Table S4 | The multinomial logistic regression analysis between different body mass index and visceral fat area and different brachial-ankle pulse wave velocity tertiles in total type 2 diabetes patients.

Table S5 | The multinomial logistic regression analysis between different BMI and visceral fat area and different brachial-ankle pulse wave velocity tertiles in type 2 diabetes patients with abnormal weight (OB[+]).