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RESEARCH

The visceral fat area/subcutaneous fat area ratio is positively associated with carotid atherosclerosis in patients with type 2 diabetes mellitus

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Abstract

Background: Evidence has demonstrated that visceral fat area (VFA) and subcutaneous fat area (SFA) have different influences on cardiovascular disease (CVD) risk in patients with type 2 diabetes mellitus (T2DM). We aimed to investigate the relationship between the visceral fat area (VFA), the subcutaneous fat area (SFA) ratio (V/S), and carotid atherosclerosis (CAS) in patients with T2DM.

Methods: From January 2018 to May 2023, 1838 patients with T2DM admitted to the National Metabolic Management Centre in our hospital were assigned to two groups based on comorbid CAS. Dual bioelectrical impedance analysis was used to measure the VAF and SFA, and the V/S was calculated. Patient characteristics and serum biochemical indices were compared between groups. Factors influencing comorbid CAS were determined, and correlations between V/S and other clinical indices were analyzed.

Results: The group with comorbid CAS included 858 individuals and 980 without comorbid CAS. Those with comorbid CAS were older and had a longer disease duration, more significant systolic blood pressure, and greater V/S. The proportions of patients with comorbid hypertension increased significantly with the V/S ratio. The V/S ratio positively correlated with triglyceride (TG), low-density lipoprotein cholesterol levels, and waist circumference. According to binary logistic regression analysis, V/S was an independent risk factor for CAS.

Conclusion: Elevated V/S is an independent risk factor for CAS in patients with T2DM.

Keywords: carotid atherosclerosis; subcutaneous fat area; type 2 diabetes mellitus; visceral fat area

Introduction

In recent years, type 2 diabetes mellitus (T2DM) has become the metabolic disease with the fastest-growing prevalence in the world. Statistical data released by the International Diabetes Federation (IDF) in 2021 revealed that 537 million people aged 20 to 79 years worldwide are affected by diabetes. This number is expected to increase to 783.2 million by 2045 (1). Patients with diabetes mellitus are susceptible to a variety of serious

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complications (2), among which macrovascular diseases, including carotid atherosclerosis (CAS), are a significant cause of disability and mortality in patients with diabetes mellitus (3). Therefore, early prevention and treatment of macrovascular diseases are crucial for improving the prognosis of patients with T2DM.

Obesity is the most significant risk factor for T2DM, and approximately 86% of patients with T2DM are obese or overweight (4). Moreover, obesity is associated with insulin resistance, dyslipidemia, and hypertension, which in turn increases the risk of cardiovascular diseases (CVDs) (5, 6, 7). Body mass index (BMI) is a prevalent metric for assessing relative body weight and identifying obesity in individuals. Nonetheless, accurately evaluating the extent of visceral fat accumulation based solely on BMI remains challenging (8, 9). Compared with BMI, waist circumference, visceral fat area (VFA), and subcutaneous fat area (SFA), the VFA-to-SFA ratio (V/S) is more strongly correlated with CVD risk in patients with T2DM (7, 10, 11, 12, 13, 14). In particular, the V/S ratio is strongly associated with the severity of aortic calcification (13); however, no existing study has investigated the correlation between the V/S ratio and the incidence of CAS in patients with T2DM. Therefore, we aimed to investigate the relationship between the V/S ratio and the incidence of CAS and identify risk factors for comorbid CAS in patients with T2DM to provide a theoretical basis for the early prevention of macrovascular diseases.

Materials and methods

Study population

In this study, we randomly selected 1838 patients with T2DM who were admitted to the National Metabolic Management Centre (MMC) in our hospital between January 2018 and May 2023. The inclusion criteria for patients were as follows: (1) older than 18 years and (2) diagnosed with T2DM based on the 2010 diagnostic criteria released by the American Diabetes Association (15). The exclusion criteria were as follows: (1) had infectious diseases, active infectious diseases, severe renal impairment (estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 or undergoing renal replacement therapy), malignant tumors, hematological disorders, rheumatism, or connective tissue diseases; (2) had a history of blood transfusion or decompensated heart failure within the past three months; (3) had acute comorbid complications of diabetes mellitus, such as diabetic ketoacidosis, lactic acidosis, or hyperglycemic hyperosmolar state; (4) were pregnant and had a BMI < 18.5 kg/m^2 or abnormal thyroid function; and (5) had incomplete clinical data. All enrolled patients provided written informed consent before participation. The study protocol adhered to the principles outlined in the Declaration of Helsinki and has been approved by the ethical committee of Suzhou Municipal Hospital (NO. KL901011).

Study protocol

The following clinical data were collected from the entire study cohort: general characteristics, including sex, age, educational background, family history of diabetes, history of smoking, history of alcohol consumption, blood pressure, BMI, and serum biochemical indices, including fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Carotid ultrasonography: Ultrasonography was performed according to the corresponding guidelines by an experienced ultrasonographer using the IU22 color Doppler ultrasound system (Philips, USA). The frequency of the probe was adjusted to 7–12 MHz. A zoomed view was obtained 1 cm from the bifurcation of the common carotid artery, and the perpendicular distance between the anterior surface of the vascular intima and the anterior side of the vascular medial-adventitial interface was measured three times. The average carotid intima-media thickness (CIMT) was calculated from these three measurements. The atherosclerotic plaque was defined as focal thickening of the vessel wall relative to neighboring vascular segments (protrusion into the lumen and/or localized surface roughening, increased echogenicity and/or focal CIMT ≥1.2 mm) (16). Alternatively, the existence of plaque was confirmed when one or more plaques were observed in any of the 12 carotid segments (proximal and distal walls of the right and left common carotid arteries, the bifurcations, and the internal and external carotid arteries) (17, 18).

VFA and SFA measurements

Abdominal VFA and SFA were measured using dual bioelectrical impedance analysis (BIA) with an Omron body fat meter (DUALSCAN HDS2000, Kyoto, Japan). Fasting patients were placed supine on an examination bed, with the skin of the abdomen, wrists, and ankles exposed. The cross-sectional area of the abdomen at the umbilicus level was measured. After applying electrode clips and electrodes to the hands, feet, and abdomen, the abdominal VFA and SFA were measured when patients held their breath after a calm expiration. The visceral to subcutaneous fat ratio (VFA/SFA, V/S) was calculated as VFA (cm^2)/SFA (cm^2).

Statistical analysis

SPSS 25.0 software was used for statistical analysis. The continuous variables are x ± s, while the categorical

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variables are numbers (percentages). Patients were categorized into two groups based on the presence or absence of atherosclerotic plaques determined by carotid ultrasonography. The groups were compared using Student's *t*-tests for continuous variables and χ^2 tests for categorical variables. Based on the V/S ratio, patients were further divided into the following three groups: the T1 group, with a V/S ratio of 0–0.472; the T2 group, with a V/S ratio of 0.472–0.587; and the T3 group, with a V/S ratio of 0.587–1.277. One-way analysis of variance (ANOVA) was used to compare the measurement data, and χ^2 tests were used to compare the categorical data among the three groups. Spearman's correlation analysis was employed to investigate the associations between the V/S ratio and other clinical variables. Variables showing statistically significant differences in the preceding analyses were incorporated into a binary logistic regression model to identify the independent influencing factors for comorbid CAS in patients with T2DM, and odds ratios (ORs) were calculated. A P value less than 0.05, based on the model's 95% confidence interval (CI), denoted statistical significance.

Results

Comparisons of general characteristics and biochemical indices between patients with T2DM with or without comorbid CAS

Compared to the group without comorbid CAS, the group with comorbid CAS was older (t = −21.813, P < 0.001) and had greater systolic blood pressure (t = −4.897, P < 0.001), a greater V/S ratio (t = −4.920, P = 0.00), and a longer disease duration (t = −11.241, P < 0.001). The proportions of patients with a history of smoking and alcohol consumption were greater in the comorbid CAS group than in the non-comorbid CAS group (P < 0.01) (Table 1).

Comparisons of indices among groups of patients with T2DM categorized based on V/S ratio tertiles

The entire study population was divided into three parts that contained equal or similar numbers of patients based on the V/S ratio tertiles, with patients having a V/S ratio ≤ 0.472 assigned to group T1, those with 0.472 < V/S ratio ≤ 0.586 assigned to group T2, and those with a V/S ratio > 0.586 assigned to group T3. The differences in age, diastolic blood pressure, BMI, waist circumference, and the levels of HDL-C and UA among the three groups were statistically significant (P < 0.005). The proportion of patients with comorbid hypertension also increased with increasing V/S ratio, and the differences among groups were statistically significant (P < 0.001) (Table 2).

Correlations between essential patient characteristics and the V/S ratio

The correlations between general patient characteristics and the V/S ratio are shown in Table 3. The V/S ratio was positively correlated with TG (r = 0.118, P < 0.001), LDL-C (r = 0.057, P = 0.015), and waist circumference (r = 0.100, P < 0.001).

Table 1 Comparisons of general characteristics and biochemical indices between the groups with and without comorbid CAS.

Item	**Without comorbid CAS** (980)	**With comorbid CAS** (858)	***T***	***P***
Smoking/cases (%)	276 (28.3%)	343 (40.3%)	5.46	<0.001
Alcohol consumption/cases (%)	114 (11.7%)	149 (17.6%)	3.59	<0.001
Hypertension/cases (%)	379 (39%)	528 (62.2%)	10.17	<0.001
Disease duration (months)	63.12 ± 77.60	110.20 ± 96.50	−11.24	<0.001
Age (years)	47.82 ± 13.63	60.03 ± 10.31	−21.81	<0.001
SBP (mm Hg)	133.11 ± 17.45	137.44 ± 20.07	−4.90	<0.001
DBP (mm Hg)	79.81 ± 10.99	77.05 ± 11.29	5.29	<0.001
BMI (kg/m^2)	26.33 ± 4.14	25.23 ± 3.35	6.29	<0.001
WC (cm)	93.16 ± 10.55	92.23 ± 10.11	1.91	0.056
V/S	0.52 ± 0.14	0.55 ± 0.16	−4.92	<0.001
VFA (cm^2)	102.44 ± 39.31	99.90 ± 39.26	1.39	0.165
SFA (cm^2)	202.95 ± 77.09	181.97 ± 59.55	6.570	<0.001
Glycated haemoglobin (%)	9.37 ± 2.46	9.48 ± 2.34	−0.92	0.360
TG (mmol/L)	2.24 ± 2.51	1.97 ± 2.05	2.59	0.010
TC (mmol/L)	4.70 ± 1.25	4.67 ± 1.20	0.45	0.651
LDL-C (mmol/L)	3.03 ± 0.97	3.01 ± 1.03	0.52	0.603

BMI, body mass index; CAS, carotid atherosclerosis; DBP, Diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, Systolic blood pressure; SFA, Subcutaneous fat area; TC, total cholesterol; TG, triglyceride; VFA, Visceral fat area; V/S, ratio of visceral to fat area; WC, waist circumference.

Table 2 Comparisons of indices among groups of the 1883 patients with T2DM were categorized based on the V/S ratio.

Groups	T1 (*n* = 642)	T2 (*n* = 582)	T3 (*n* = 614)	χ^2 (*F*) value	*P*
Age (years)	52.15 ± 14.43*	53.78 ± 13.438	54.57 ± 12.892**	(5.017)	0.007
BMI (kg/m^2)	25.569 ± 4.109*	26.353 ± 3.800***	25.565 ± 3.512	(8.378)	<0.001
Disease duration (months)	82.59 ± 90.066	84.36 ± 87.661	86.10 ± 90.469	(0.227)	0.797
SBP (mm Hg)	134.10 ± 18.853	135.71 ± 19.158	135.57 ± 18.632	(1.351)	0.259
DBP (mm Hg)	77.70 ± 11.191*	79.51 ± 11.791	78.53 ± 10.672	(3.860)	0.021
WC (cm)	90.937 ± 10.587*	94.462 ± 9.868***	92.891 ± 10.306**	(17.663)	<0.001
TG (mmol/L)	1.7507 ± 1.939*	2.255 ± 2.722	2.353 ± 2.202**	(11.917)	0.051
TC (mmol/L)	4.625 ± 1.183	4.746 ± 1.393	4.678 ± 1.088	(1.455)	0.234
LDL-C (mmol/L)	2.947 ± 1.064*	3.075 ± 1.009	3.030 ± 0.901	(2.511)	0.081
HDL-C (mmol/L)	1.2071 ± 0.320*	1.1043 ± 0.285***	1.067 ± 0.261**	(37.544)	<0.001
UA (mmol/L)	317.864 ± 100.816	335.638 ± 94.191	343.621 ± 93.062	(11.426)	<0.001
Smoking/cases (%)	119 (18.5)*	216 (37.4)***	272 (44.6)**	90.040	<0.001
Alcohol consumption/cases (%)	43 (6.7)*	84 (14.6)***	129 (21.3)**	49.447	<0.001
Hypertension/cases (%)	259 (40.3)*	300 (52.2)	329 (54)**	17.955	<0.001

*Compare T1 with T2, $P < 0.05$; **Compare T1 with T3, $P < 0.05$; ***Compare T2 with T3, $P < 0.05$.BMI, body mass index; DPB, diastolic blood pressure; Group T1, V/S N ≤ 0.472; Group T2, 0.472 < V/S ≤ 0.586; Group T3, V/S > 0.586; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid; WC, waist circumference.

Logistic regression analysis of influencing factors for comorbid CAS in patients with T2DM

The results of the logistic regression analysis of influencing factors for comorbid CAS in patients with T2DM are shown in Table 4. The risk factors that exhibited statistically significant differences in the preceding t-tests included age, disease duration, smoking status, alcohol consumption status, BMI, TG, and V/S ratio, which were incorporated into the binary logistic regression analysis. The V/S ratio (OR = 2.309, $P = 0.026$), age (OR = 1.079, $P = <0.001$), disease duration (OR = 1.002, $P = 0.012$), and smoking status (OR = 1.817, $P < 0.001$) were identified as independent risk factors for comorbid CAS in patients with T2DM.

Discussion

In this study, we found that a higher V/S ratio was an independent risk factor for comorbid CAS in patients with T2DM. This study is one of the few to investigate the correlation between the V/S ratio and CAS in a population with T2DM.

Table 3 Correlations between general patient characteristics and the V/S ratio.

Item	*r*	*P*
WC	0.100	<0.001
BMI	0.012	0.609
TC	0.04	0.091
TG	0.118	<0.001
LDL-C	0.057	0.015

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

CAS predicts the onset of atherosclerotic CVD (ASCVD) and is associated with significant adverse cardiovascular events in patients with T2DM (19, 20). ASCVD has a high prevalence and mortality rate in China (21), with diabetes mellitus being one of the risk factors for its onset. The risk of ASCVD in patients with T2DM is 2–4 times greater than that in other population (22). Thus, it is crucial to identify risk factors for CAS and improve interventions in patients with T2DM to enhance their prognosis.

The VFA is a critical predictor of cardiometabolic risk. In contrast to visceral fat, it has been reported that subcutaneous fat may even be beneficial for metabolic abnormalities (23, 24). Several studies suggest that subcutaneous fat may offer protective benefits, as an increase in subcutaneous leg fat is linked to a lower risk of glucose metabolism disturbances and dyslipidemia, independent of abdominal fat (23). In contrast, while omentectomy-induced VAT removal improves glucose and insulin levels, liposuction-mediated SAT removal does not consistently enhance glucose metabolism or lipid levels (25, 26). Considering the independent effects of VFA and SFA on CVD, studying the relative distribution of body fat is more important than solely focusing on VFA or SFA alone. Recent studies have indicated that the V/S ratio exhibits superior predictive value compared to the VFA. A cross-sectional study indicates that participants with higher SFA/VFA (i.e. the inverse of our trait) ratios exhibit a greater prevalence of higher glucose and lipid metabolism disorders compared to those with lower SFA/VFA, including HDL cholesterol levels, lower fasting glucose levels, and a lower incidence of metabolic syndrome. It indicates that the correlation between the V/S ratio and CVD risk is stronger than that between the VFA and CVD risk (10). Furthermore,

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Table 4 Logistic regression analysis of influencing factors for comorbid CAS in patients with T2DM. A $P < 0.05$ indicated that the difference was statistically significant.

Item	B	SE	Wald χ^2 value	*P*	OR value	95% CI
Age (years)	0.076	0.006	157.686	<0.001	1.079	1.066–1.092
Disease duration (months)	0.002	0.001	6.243	0.012	1.002	1.0–1.003
Smoking	−0.597	0.128	21.760	<0.001	1.817	1.414–2.334
Alcohol consumption	−0.251	0.167	2.266	0.132	1.285	0.927–1.783
Hypertension	−0.229	0.120	3.611	0.057	1.257	0.993–1.592
BMI (kg/m^2)	−0.029	0.017	3.008	0.083	0.972	0.941–1.004
TG (mmol/L)	0.006	0.025	0.051	0.764	1.007	0.96–1.058
V/S	0.837	0.376	4.943	0.026	2.309	1.104–4.828

BMI, body mass index; TG, triglyceride; V/S, visceral fat area/subcutaneous fat area ratio.

Narumi *et al.* reported that the V/S ratio outperformed the VFA or SFA alone as a predictor of aortic calcification (13). Katsuyama *et al.* reported that the V/S ratio was significantly and positively associated with brachial-ankle pulse wave velocity (26). In the existing studies that focused on the relationship between the V/S ratio or VFA and the onset of atherosclerosis, atherosclerotic plaques were not detected directly by ultrasonography. Notably, this study diagnosed comorbid CAS directly by ultrasound examination of the carotid arteries, yielding more reliable results. This study found similar results in the T2DM population, confirming the close relationship between V/S and CAS in the T2DM population. V/S is a risk factor for CAS and is expected to be an early warning factor for CAS.

Visceral fat, an essential functional organ, plays a pivotal role in the development and progression of atherosclerosis. Visceral adipose tissue secretes many bioactive proinflammatory adipokines, such as leptin, adiponectin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-8. These proinflammatory adipokines are involved in multiple pathogenetic phases of atherosclerosis. They can also promote endothelial dysfunction and monocyte recruitment and adhesion in the early stages (27, 28). In addition, adipokines such as leptin and plasminogen activator inhibitor-1 (PAI-1) produced by visceral adipose tissue play critical regulatory roles in insulin resistance and in promoting atherosclerosis development and progression (29, 30, 31). The levels of leptin secreted by SAT are 2–3 times higher than VAT (32). Compared with SAT, VAT secretes more adiponectin, interleukin-6, interleukin-8, plasminogen activator inhibitor-1, and angiotensin (33). In this study, even after accounting for confounding factors, the V/S ratio remained an independent risk factor for comorbid CAS in patients with T2DM. In patients with T2DM, the risk of CVD increases significantly with an increasing V/S ratio, whereas VFA, SFA, or BMI alone are not strongly associated with the onset or recurrence of CVD (14). Therefore, to reduce the incidence and recurrence of CVD in patients with T2DM, it is necessary to control their blood glucose, reduce their BMI, quit smoking and drinking, strengthen the management of body fat distribution, and actively control the V/S ratio.

Here, we found that the group with T2DM and comorbid CAS was older and had greater systolic blood pressure, a longer disease duration, and a greater V/S ratio than the group without comorbid CAS. The patients with a higher V/S ratio showed a significantly greater proportion with a comorbid history of hypertension. The V/S ratio positively correlates with TG levels, waist circumference, and LDL-C levels, aligning with previous findings linking it to cardiovascular risk factors. Consistent with previous findings from the Framingham Heart Study, higher V/S ratios were significantly associated with cardiovascular risk factors, including blood pressure and dyslipidemia, independent of BMI (11). Higher V/S ratios are associated with an increased incidence of metabolic syndromes and elevated total cholesterol levels. The tendency of energy to be stored in visceral or subcutaneous adipose tissue is related to the onset of metabolic disorders independent of general obesity and absolute visceral fat mass (10, 11, 12, 13). BMI is commonly used to indicate general obesity; however, it fails to differentiate between fat and nonfat masses. This leads to particularly muscular individuals being misclassified as overweight and individuals with high visceral fat but low subcutaneous fat being misclassified as thin (8, 9). In this study, we found no difference in BMI between the groups with and without comorbid CAS, and the V/S ratio was a better predictor than BMI of the incidence rate of comorbid CAS in patients with T2DM. In clinical practice, the risk of comorbid CAS in patients with T2DM can be better assessed by directly measuring VFA and SFA to determine the relative distribution of body fat.

This study has certain limitations. For example, the cross-sectional study design prevented us from clearly understanding the causal relationship between the V/S ratio and the incidence of CAS. Future studies should be conducted prospectively to validate the generalizability of our findings, determine the impact of the V/S ratio on CAS, and evaluate CVD incidence. In addition, this study included only the T2DM population and did not evaluate members of the general population. Thus, the generalizability of the findings needs to be further validated in future studies.

In conclusion, this study confirms and highlights the importance of the V/S ratio as an independent risk

factor for comorbid CAS in patients with T2DM. These findings provide a new perspective on the clinical intervention and prevention of comorbid CAS in patients with T2DM. To mitigate the risk of CVD in patients with T2DM, it is necessary to enhance the management of traditional cardiovascular risk factors, strengthen routine examinations and analyses of patient body fat, and actively control the V/S ratio, leading to further improvements in the quality of life of patients.

Declaration of interest

The authors declare that no conflict of interest could be perceived as prejudicing the impartiality of the study reported.

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Author contribution statement

BG, YW and DH collected the samples. DH, XG and BG performed the statistical analysis. DH and XG helped interpret the results. All authors drafted, read, and approved the final manuscript.

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