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ORIGINAL RESEARCH

J-Shaped Relationship Between Visceral Fat Area and Large-Nerve Fiber Dysfunction Estimated by Vibration Perception Threshold in Type 2 Diabetes: A Cross-Sectional Study

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Introduction: Although obesity has been implicated in the development of diabetic peripheral neuropathy (DPN), the relationship remains controversial. This study aimed to clarify the association between visceral fat area (VFA) and large nerve fiber dysfunction, as estimated by vibration perception threshold (VPT), in young and middle-aged Chinese patients with type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study enrolled 501 adults aged 18–65 years with T2DM between March 2020 and August 2024. Visceral fat area was assessed using bioelectrical impedance analysis, and large nerve fiber dysfunction was evaluated via vibration perception threshold measurement. Multivariable logistic regression, generalized additive models, smooth curve fitting, and two-piecewise regression analyses were employed to explore the relationship between VFA and VPT.

Results: Among the participants, 27.5% exhibited abnormal VPT. After adjustment for potential confounders, a nonlinear J-shaped association between VFA and VPT was observed. Two-piecewise logistic regression revealed a turning point at 133.9 cm² with a significant threshold effect (P for log-likelihood ratio test = 0.020). Below this threshold, VFA showed no significant association with abnormal VPT (OR = 1.00; 95% CI, 0.90–1.11; P = 0.978). However, above this threshold, each 10 cm² increase in VFA was associated with a 22% higher risk of abnormal VPT (OR = 1.22; 95% CI, 1.07–1.40; P = 0.003). Subgroup analyses and interaction tests were not significant (all $P > 0.05$).

Conclusion: In young and middle-aged patients with T2DM, the relationship between visceral fat accumulation and large nerve fiber dysfunction exhibits a J-shaped curve. Notably, VFA exceeding the defined threshold of 133.9 cm² significantly increased the risk of impaired nerve function as measured by VPT.

Keywords: diabetic peripheral neuropathy, vibration perception threshold, visceral fat area, type 2 diabetes mellitus

Introduction

Diabetic peripheral neuropathy (DPN) is the most prevalent complication of diabetes, affecting up to 50% of diabetic patients.[1–3] It may result in the development of foot ulcers and amputations, which have been identified as significant contributors to disability and mortality among individuals with diabetes. Consequently, the costs associated with diabetes treatment may increase.[3,4] Therefore, early screening and appropriate prophylactic measures are essential.[5,6] Due to the lack of definitive and effective therapies for DPN, identifying its risk factors is critical to optimize treatment strategies and delay the onset and progression of the disease.[7,8]

Previous studies have identified obesity as a risk factor for DPN.[7,9–13] However, conflicting results have been reported regarding the relationship between obesity and DPN.[14–16] These studies used body mass index (BMI), waist circumference, and weight as measures of obesity, but these indicators provide limited insight into body composition and metabolic

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health. Patients with Type 2 Diabetes Mellitus (T2DM) may have excessive visceral fat accumulation even in the absence of significant obesity.[17,18] Recently, visceral fat area (VFA), measured by bioelectrical impedance analysis (BIA), has emerged as a more convenient and non-invasive method of assessing abdominal obesity.[19,20]

The vibration perception threshold (VPT), assessed using a biothesiometer, is a rapid, non-invasive, and quantitative method that reflects large nerve fiber dysfunction and predicts the risk of foot ulceration, amputation, and mortality.[21] This method is frequently utilized in clinical and primary care settings.[22,23]

To our knowledge, limited research has examined the association between VFA and DPN in patients with T2DM.[24–26] Additionally, no data are currently available for young and middle-aged people in China. Therefore, this cross-sectional study was conducted to investigate the relationship between VFA and VPT, a marker of DPN, in young and middle-aged Chinese adults with type 2 diabetes. We aimed to explore the presence of non-linear associations between VFA and VPT, as well as potential threshold effects.

Methods

Study Design and Participants

We performed a cross-sectional observational study. A total of 501 consecutive inpatients with T2DM aged from 18 to 65 years were enrolled from March 2020 to August 2024 at the Department of Endocrinology, Ruijin Hospital Lu Wan Branch, Shanghai Jiaotong University School of Medicine. T2DM was diagnosed according to the 2020 American Diabetes Association (ADA) criteria.[27] All patients underwent measurements of VFA and VPT. The exclusion criteria included: type 1 diabetes or specific types of diabetes, acute complications of diabetes, non-diabetic origin peripheral nerve defects, unstable cardiopulmonary conditions, severe liver disease, renal failure, malignant tumor, pregnancy or lactating women, rheumatic disease, and missing data for VFA or VPT.

The study protocol was approved by the Ethics Committee of Ruijin Hospital Lu Wan Branch, Shanghai Jiao Tong University School of Medicine, following the Helsinki Declaration. All participants gave their informed written consent.

Clinical and Biochemical Analysis

All participants completed structured interviews by trained research staff, including sex, age, duration of diabetes mellitus, smoking status (never, former, or current), alcohol consumption (never or current), and medical history. BMI was calculated as body weight (kg)/height (m^2). Waist circumference measurements were obtained at the midpoint of the lower rib margin and iliac crest, while hip circumference was measured at the widest part of the hip. The waist-to-hip ratio was then calculated by dividing waist circumference by hip circumference. SBP and DBP were measured after a 5-minute rest period using an electronic sphygmomanometer.

Blood samples were collected from the subjects following an overnight fasting period of at least eight hours. Fasting blood glucose (FBG), 2-hour postprandial blood glucose (2hPBG), glycated hemoglobin A1c (HbA1c), fasting C-peptide (FCP), 2-hour postprandial C-peptide (2hCP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and liver and renal function tests were measured using standard methods.

Measurements of VFA

Participants fasted (no food or alcohol) for 8 hours, abstained from water for 2 hours, emptied their bladders, and avoided physical exercise for at least 8 hours before measurements.[28] They were positioned supine for the examination. The abdominal cross-sectional area was measured at the level of the umbilicus. After placing electrode clips and electrodes on the exposed hands, feet, and abdomen, the abdominal VFA and SFA were measured while participants held their breath after a quiet exhalation. Visceral obesity was defined as VFA $\geq$ 100 cm^2, according to the Japan Society for the Study of Obesity guidelines.[29] VFA and subcutaneous fat area (SFA) were measured by the bioelectrical impedance analysis (BIA) method using the DUALSCAN HDS-2000 (OMRON Healthcare Co., Kyoto, Japan).

VPT Measurements

All VPT assessments were conducted by the same trained technicians using a neurothesiometer (Sensiometer A200, Laxons Technology Co., Ltd., Beijing, China) following standardized protocols to ensure technician consistency and minimize variability. Periodic quality control procedures were also implemented throughout the study to maintain measurement consistency. The stimulus was administered to the great toe with the probe positioned vertically on the pulp of the toe on each side, and patients were asked to indicate when they first perceived the vibration sensation. The stimulus intensity was increased gradually from zero to the threshold voltage at which the subject could first perceive vibration. To ensure the subject's adherence to the protocol and comprehension of the testing procedure, a trial utilizing a "null stimulus" was conducted before the commencement of testing. The entire testing procedure was performed with the subject's eyes closed, and both feet were tested three times. The VPT for each foot was calculated as the mean of three measurements in volts, with a range of 0 to 50 V. A VPT value ≥ 15 V in at least one foot showed high sensitivity and specificity for diagnosing DPN in a Chinese population[30] and other ethnic groups.[31] Participants were classified into two groups based on their VPT value: a normal group with a VPT below 15 V for both feet and an abnormal group with a VPT of 15 V or higher in at least one foot.

Statistical Analysis

Continuous variables with normal distributions (assessed by Kolmogorov–Smirnov tests and Q-Q plots) were expressed as mean ± standard deviation, while non-normally distributed variables were expressed as median (interquartile range). Categorical variables were expressed as frequencies (percentages). A comparison of continuous variables between groups was conducted using Student's *t*-test or the Mann–Whitney *U*-test, based on distribution normality. The chi-square test was used for categorical variables.

We used multivariate logistic regression models to evaluate the independent association between VFA and VPT. The results are presented as odds ratios (ORs) and corresponding 95% confidence intervals (CIs). The crude model was unadjusted. Model 1 was adjusted for age and gender. Model 2 was additionally adjusted for the duration of diabetes and HbA1c. Model 3 was adjusted for all the variables in Model 2, plus BMI, smoking status, alcohol consumption, FBG, FCP, and HDL-C. These possible confounders were selected based on their clinical significance, existing scientific literature, or a variation exceeding 10% in effect estimates.[32] The Variance Inflation Factor (VIF) method was used to assess multicollinearity, with a variance inflation factor of five or higher indicating multicollinearity.

To assess the potential nonlinear association between VFA and VPT, we applied generalized additive models (GAM) with smooth curve fitting. The threshold level was determined using trial-and-error methods, whereby turning points were selected according to a pre-defined interval. Subsequently, the point yielding maximum model likelihood was chosen. A log-likelihood ratio test was conducted to compare the one-line linear regression model with the two-piecewise logistic regression model. We used the bootstrap resampling method to calculate the 95% CI for the turning point, as described in the previous analysis.[33] Subgroup analyses were conducted to assess the robustness of the outcomes and examine interactions. $P < 0.05$ (two-sided) was considered statistically significant. All analyses were performed using SPSS software (Version 25.0), EmpowerStats, and the statistical package R (Version 4.2.0).

Results

Clinical Characteristics of Participants

A total of 501 patients with T2DM were enrolled in the study, including 311 males and 190 females. The clinical and biochemical characteristics are presented in Table 1, classified by vibration perception thresholds. Among the participants, 363 (72.5%) demonstrated normal VPT, while 138 (27.5%) presented with abnormal VPT. Patients with abnormal VPT were significantly older and had a longer duration of diabetes compared to those with normal VPT (both $p < 0.001$). Significant intergroup differences were observed in BMI, diastolic blood pressure, history of stroke, ALT levels, smoking status, and alcohol consumption ($P < 0.01$ or $P < 0.05$). FCP levels were significantly lower in participants with abnormal VPT ($P < 0.01$). However, no significant differences were found between the groups in terms of gender, waist circumference, waist-to-hip ratio, VFA, FBG, 2hPBG, HbA1c, TG, TC, LDL-C, HDL-C, serum Cr, and UA.

Table 1 Comparison of Characteristics Between Participants with Normal and Abnormal Vibration Perception Thresholds

Variables	Normal VPT (n=363)	Abnormal VPT (n=138)	*P* value
Age (years)	52.7 ± 10.5	59.2 ± 6.1	<0.001
Male, n (%)	224 (61.7%)	87 (63.0%)	0.783
Diabetic duration (months)	62.0 (5.5–160.5)	135.0 (60.2–219.8)	<0.001
Body mass index (kg/m^2)	26.3 ± 3.9	25.3 ± 3.4	0.009
Waist circumference (cm)	93.0 ± 10.2	92.0 ± 9.8	0.317
WHR	0.9 ± 0.1	1.0 ± 0.1	0.150
VFA (cm^2)	114.1 ± 43.9	114.0 ± 48.0	0.986
SFA (cm^2)	193.2 ± 71.4	180.2 ± 64.5	0.042
Diastolic blood pressure (mmHg)	76.0 ± 10.4	72.9 ± 11.1	0.004
Systolic blood pressure(mmHg)	125.7 ± 18.1	126.1 ± 18.3	0.837
Fast blood glucose (mmol/L)	7.6 ± 2.7	7.1 ± 2.1	0.109
2h postprandial blood glucose (mmol/L)	11.9 ± 4.1	11.5 ± 3.5	0.405
Fasting C-Peptide (ng/mL)	7.0 (5.9–8.6)	6.8 (5.4–8.2)	0.001
2h postprandial C-Peptide (ng/mL)	11.3 (9.1–14.1)	11.6 (8.8–13.6)	0.023
HbA1c (%)	8.9 ± 2.1	9.1 ± 2.0	0.368
ALT (U/L)	25.0 (16.0–38.0)	20.0 (13.0–29.0)	<0.001
AST (U/L)	21.0 (16.0–27.0)	19.0 (16.0–23.0)	0.080
Serum creatinine (umol/L)	65.9 ± 17.0	65.4 ± 19.5	0.756
Uric acid (umol/L)	359.5 ± 96.5	340.9 ± 91.1	0.051
Triglycerides (mmol/L)	1.7 (1.2–2.5)	1.6 (1.1–2.3)	0.168
Total Cholesterol (mmol/L)	5.1 ± 1.4	5.0 ± 1.4	0.501
HDL-C (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	0.678
LDL-C (mmol/L)	3.3 ± 0.9	3.2 ± 1.0	0.517
Hypertension, n (%)	171 (47.1%)	78 (56.5%)	0.060
Hyperlipidemia, n (%)	133 (36.6%)	51 (37.0%)	0.948
Hyperuricemia, n (%)	52 (14.3%)	25 (18.1%)	0.293
Coronary Heart Disease, n (%)	33 (9.1%)	18 (13.0%)	0.191
Stroke, n (%)	3 (0.8%)	8 (5.8%)	<0.001
Smoking status, n (%)			0.003
Never smoker	222 (61.2%)	74 (53.6%)	
Ex-smoker	9 (2.5%)	13 (9.4%)	
Current smoker	132 (36.4%)	51 (37.0%)	
Alcohol consumption, n (%)	37 (10.2%)	23 (16.7%)	0.046

Abbreviations: WHR, waist-to-hip ratio; VFA, visceral fat area; SFA, subcutaneous fat area; HbA1c, glycosylated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Relationship Between VFA and VPT

Table 2 presents the results of multivariate logistic regression models to assess the independent impact of VFA on VPT. In the crude model, VFA showed no significant association with VPT (OR=1.00, 95% CI: 0.96–1.04, P=0.986). In model 3, each 10 cm² increment in VFA corresponded to an 8% higher risk of DPN (OR=1.08, 95% CI: 0.99–1.18, P=0.073), though this increase did not reach statistical significance.

Subsequently, the continuous variable VFA was categorized into tertiles and then reapplied to the model. Compared to those in the second tertile of VFA, the risk of large-nerve fiber dysfunction was significantly higher for participants in the first and third tertiles, with ORs of 1.18 (95% CI: 0.66–2.12, P=0.577) and 1.49 (95% CI: 0.77–2.86, P=0.236), respectively. These findings suggest a potential nonlinear association between VFA and VPT, although neither association reached statistical significance.

Table 2 Relationship Between Visceral Fat Area and Vibration Perception Threshold in Multivariable Regression Analysis

Variables	Crude Model		Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
VFA, per 10 cm^2	1.00 (0.96, 1.04)	0.986	1.03 (0.98, 1.08)	0.246	1.03 (0.99, 1.08)	0.178	1.08 (0.99, 1.18)	0.073
VFA, tertile, cm^2								
T1: <92.5	1.44 (0.89, 2.35)	0.140	1.30 (0.78, 2.16)	0.317	1.18 (0.70, 1.98)	0.533	1.18 (0.66, 2.12)	0.577
T2: 92.5–130.0	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
T3: >130	1.32 (0.81, 2.16)	0.263	1.61 (0.95, 2.72)	0.076	1.54 (0.90, 2.64)	0.114	1.49 (0.77, 2.86)	0.236
P for trend		0.271		0.076		0.115		0.220

Notes: Crude model: No variables are adjusted. Model 1: Adjusted gender and age. Model 2: Adjusted all the variables in model 1, plus diabetic duration, and HbA1c. Model 3: Adjusted all the variables in model 2, plus Body mass index, smoking status, alcohol consumption, fast blood glucose, fasting C-Peptide, HDL Cholesterol.
Abbreviations: VFA, visceral fat area; CI, Confidence interval; Ref, Reference.

Two-Piecewise Logistic Regression Analysis According to Smooth Curve Fitting

We identified a J-shaped relationship between VFA and VPT using a generalized additive model with smooth curve fitting after adjusting for confounding factors in Model 3 (P for log-likelihood ratio test = 0.020; Table 3, Figure 1). Further analysis with a two-piecewise logistic regression model revealed a turning point at 133.9 cm^2. When VFA was below 133.9 cm^2, no significant association with VPT was observed (OR = 1.00; 95% CI, 0.90–1.11; P = 0.978). However, when VFA exceeded 133.9 cm^2, each 10 cm^2 increase in VFA was associated with a 22% higher risk of abnormal VPT (OR = 1.22; 95% CI, 1.07–1.40; P = 0.003; Table 3).

Stratification and Interaction Analyses

Stratified and interaction analyses showed no significant effect modification of the association between VFA and VPT by age, sex, HbA1c, or diabetes duration (all *P* for interaction > 0.05, Supplemental Table 1).

Discussion

To our knowledge, this is the first study to describe a J-shaped relationship between VFA and VPT in young and middle-aged T2DM patients in China. We revealed a turning point of 133.9 cm^2 using threshold effect analysis. We found that VFA exceeding 133.9 cm^2 significantly increased the incidence of large-nerve fiber dysfunction. Below this threshold, there was little to no increase in the risk of large-nerve fiber dysfunction associated with VFA. As a cross-sectional study, causality cannot be inferred. However, these findings suggest a potential link between elevated visceral fat area and diabetic peripheral neuropathy risk, implying that visceral fat area measurement may help identify individuals at higher risk of large nerve fiber dysfunction in this population.

Table 3 Threshold Effect Analysis of Visceral Fat Area and Vibration Perception Threshold Using Two-Piecewise Regression Model

Models	Per 10 cm^2 Increase	
	Adjusted OR (95% CI)	*P* value
Fitting model by standard logistic regression	1.08 (0,99, 1.18)	0.073
Fitting model by two-piecewise logistic regression		
Turning point of VFA (cm^2)	133.9 (119.6, 148.4)	
< 133.9 cm^2	1.00 (0.90, 1.11)	0.978
≥ 133.9 cm^2	1.22 (1.07, 1.40)	0.003
P for log-likelihood ratio test		0.020

Notes: Adjusted for gender, age, diabetic duration, HbA1c, Body mass index, smoking status, alcohol consumption, fast blood glucose, fasting C-Peptide, HDL Cholesterol.
Abbreviations: OR, odds ratio; CI, confidence interval.

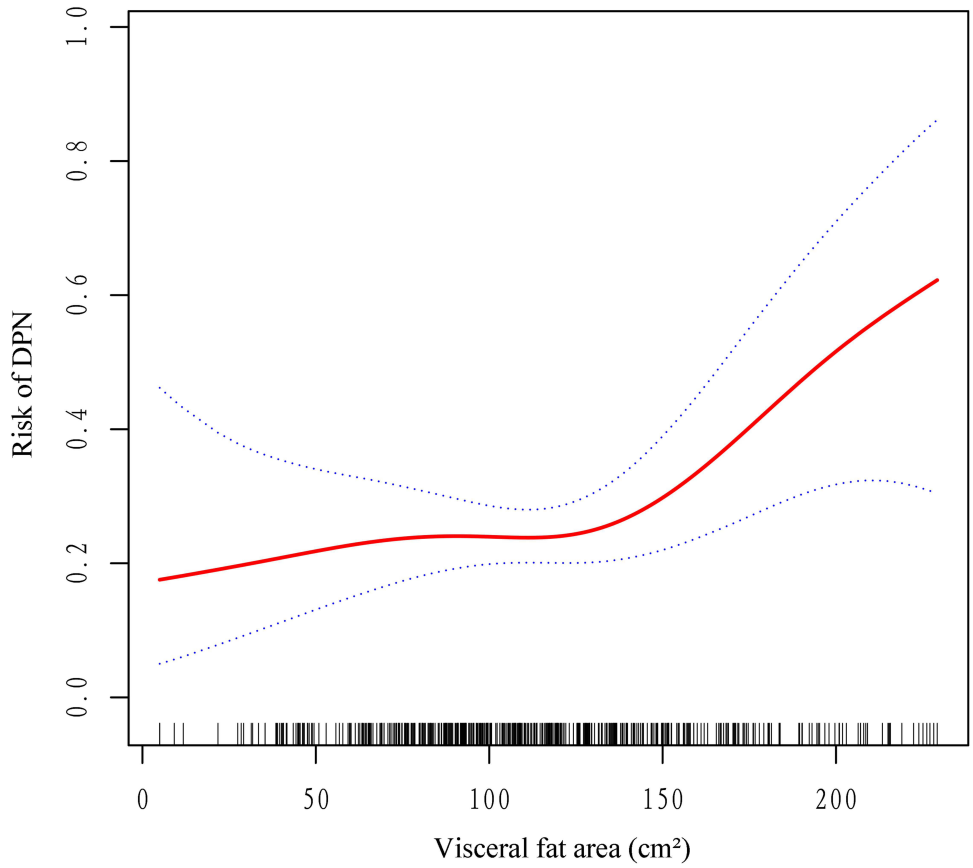

Figure 1 The nonlinear dose-response relationship between VFA and VPT. Adjusted for gender, age, diabetic duration, HbA1c, Body mass index, smoking status, alcohol consumption, fast blood glucose, fasting C-Peptide, HDL Cholesterol. The solid line and dashed line represent the estimated values and their corresponding 95% confidence intervals, respectively.

Growing evidence supports a close association between obesity and DPN. Most studies have established positive correlations between obesity indices and DPN progression.[7,9–13] Cohort studies from Denmark,[11] China,[13] Germany,[12] and the United States[7] have consistently identified this positive association. Nevertheless, some studies have yielded conflicting findings. A cross-sectional analysis of type 2 diabetes patients with well-controlled HbA1c levels revealed that individuals with DPN had a significantly lower BMI compared to those without DPN, suggesting that lower BMI could be a risk factor for DPN[14] Likewise, a nationwide epidemiological survey spanning 24 Chinese provinces demonstrated an inverse relationship between BMI and DPN.[8] Consistent with the previous two studies, we observed patients with DPN exhibited a lower BMI than those without (25.3 ± 3.4 vs 26.3 ± 3.9 kg/m², P = 0.009). However, Zhang et al[15] identified a U-shaped relationship, indicating both low and high BMI were associated with increased DPN risk. In contrast, a meta-analysis failed to find a significant overall association between BMI and DPN.[16] Collectively, these studies measure obesity either centrally using waist circumference or overall using BMI or weight.

Current research indicates that BMI is an imperfect measure of obesity as it cannot distinguish between lean body mass and fat mass, which may compromise its effectiveness in revealing true health impacts.[34] In contrast, visceral fat tissue, strongly linked to metabolic abnormalities, serves as a more accurate indicator of T2DM than BMI.[35] Even in individuals without overt obesity, excessive visceral fat is common among those with T2DM.[17] This phenomenon is particularly prevalent in Asian countries like China, where people often have lower BMI yet remain susceptible to type 2 diabetes.[36] Therefore, directly measuring visceral fat is essential for assessing DPN risk, especially in Asian diabetic patients.

In our study, unadjusted analysis showed no significant difference in VFA between normal and abnormal VPT groups (P = 0.986, Table 1). Notably, SFA was significantly lower in the abnormal VPT group compared to controls (P = 0.042).

This reduction in SFA may reflect more advanced diabetes or poorer metabolic control, conditions commonly observed in patients with DPN. However, this analysis did not adjust for potential confounders, and given that comparisons can be influenced by other factors, the observed difference in SFA should be interpreted with caution. The current study did not explore this relationship further, and further research is needed to clarify the mechanisms underlying changes in subcutaneous fat within this context.

Our study further emphasizes the clinical relevance of VFA with DPN risk. Using dual bioelectrical impedance analysis, we identified a novel nonlinear association between VFA and VPT. Importantly, we found a VFA threshold of 133.9 cm^2, beyond which the risk of DPN increased markedly. This finding aligns with a Korean study[24] involving 65 patients with T2DM, which reported a 2.6% increased neuropathy risk for each unit increase in VFA. While this early work provided preliminary evidence, its limited sample size may have restricted the detection of more complex dose-response relationships. In contrast, our findings differ from a cross-sectional study conducted in China among hospitalized patients with T2DM aged 18 to 80 years, which identified a linear inverse association between VFA and the risk of developing DPN.[25] In our study, we specifically targeted adults aged 18 to 65 years to minimize confounding effects caused by age-related changes in body composition, such as sarcopenia, which are more prevalent in older populations beyond 65 years.[37] This age range encompasses both young and middle-aged adults, allowing us to capture the relevant physiological variations while maintaining a relatively homogeneous group in terms of age-related body composition. These inconsistent findings may be attributable to several factors, including differences in participant age distribution, DPN diagnostic criteria, and methods for covariate adjustment.

The pathogenesis of DPN remains multifactorial and incompletely elucidated. Clinical observations show intensive glycemic control has limited efficacy in preventing neuropathy in type 2 diabetes compared to type 1 diabetes,[38] suggesting that non-glycemic factors play important roles in T2DM-related DPN pathogenesis. Longitudinal studies have identified components of the metabolic syndrome, including central obesity, dyslipidemia, and hypertension, are independent risk factors for DPN progression, regardless of glycemic status.[6] Visceral fat contributes to DPN through several interconnected mechanisms. Visceral adipose tissue is metabolically active and secretes pro-inflammatory cytokines, adipokines, and free fatty acids (FFAs) that induce chronic low-grade inflammation, oxidative stress, and insulin resistance, all of which contribute to neuronal injury.[39] Elevated FFAs and inflammatory mediators can directly damage dorsal root ganglion neurons, unmyelinated C-fibers, and disrupt the blood–nerve barrier, leading to impaired nerve function and structure.[40] Additionally, visceral adiposity promotes endothelial dysfunction, impairing microvascular blood supply and increasing ischemia and oxidative stress in peripheral nerves.[6] Our study further revealed a J-shaped association between VFA and DPN risk, indicating that exceeding a specific VFA threshold results in marked exacerbation of adipose tissue dysfunction and accelerated neuropathic progression. Below this threshold, compensatory mechanisms may partially mitigate inflammation and metabolic disturbances. Despite these insights, the precise biological pathways underlying this threshold effect remain to be fully elucidated. Future experimental and longitudinal studies are warranted to validate and expand upon these findings.

There were several limitations in our study. First, as this was a cross-sectional study, we could not allow causal inference of the associations between VFA and VPT. Second, an electrophysiologic study was not used to confirm DPN. Nerve conduction studies are sensitive, accurate, and reliable for diagnosing DPN. However, due to their high cost and time investment, they are impractical for routine screening. Third, our study population consisted of younger and middle-aged hospitalized patients from a single center, which may limit the generalizability of the findings to other populations. Fourth, despite adjustment for multiple confounders, there may still be interference from unmeasured or residual confounding factors, such as physical activity, diet, or medications (eg, statins, insulin).

Conclusions

This study identified a J-shaped association between VFA and VPT in young and middle-aged adults with type 2 diabetes in China. The findings highlight visceral adiposity as a modifiable and clinically relevant risk factor for DPN, particularly when VFA exceeds a critical threshold. These findings support the incorporation of VFA measurement into routine metabolic assessments in this population. Future large-scale, multicenter prospective cohort studies are warranted to

clarify potential causal pathways and explore effect modifiers. Additionally, mechanistic investigations are warranted to elucidate the underlying biological pathways mediating the observed nonlinear association.

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Disclosure

The authors declare that they have no conflict of interest.

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