

Lower Visceral Fat Area in Patients with Type 2 Diabetic Peripheral Neuropathy

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Objective: There is preliminary evidence that visceral fat area (VFA) was associated with the presence of type 2 diabetic peripheral neuropathy (DPN) in the Korean population; however, no studies have reported the association in Chinese population. The purpose of this study was to explore the possible correlation of VFA with DPN in such a population.

Methods: A total of 2498 hospitalized patients with type 2 diabetes mellitus (T2DM) undergone VFA measurement, and were divided into DPN group (n=900) and non-DPN group (n=1594). The association of VFA with the presence of DPN was evaluated by correlation and multiple logistic regression analyses, generalized additive model with a smooth curve fitting, and receiver operating characteristic (ROC) curve analysis.

Results: The VFA was significantly lower in the DPN group than in the non-DPN group ($P < 0.001$). VFA was significantly and positively associated with sural nerve conduction velocity (SNCV) and amplitude potential (SNAP) and negatively associated with the presence of DPN (all $P < 0.001$); there was no significant difference in the curve fitting ($P = 0.344$). Multivariate logistic regression analysis showed that the risk of presence of DPN decreased progressively across the VFA quartiles (P for trend < 0.001) and was significantly lower in patients in the highest VFA quartile than in those in the lowest quartile (OR: 0.382, 95% CI 0.151–0.968, $P < 0.001$) after multivariate adjustment. The ROC analysis revealed that the best cut-off value of VFA for predicting the presence of DPN was 50.5cm² (sensitivity 84.40%; specificity 34.00%).

Conclusion: These results suggest that lower VFA level may be associated with increased risk of the presence of DPN in T2DM patients.

Keywords: visceral fat area, diabetic peripheral neuropathy, sural nerve conduction velocity, sural nerve amplitude potential, Chinese population

Introduction

Diabetic peripheral neuropathy (DPN) is one of the most common chronic diabetic complications characterized by demyelination and axonal degeneration, leading to reduction in quality of life, disability, enormous health care costs, and even death.^{1,2} DPN may develop at the earliest stage of diabetes, and often progresses asymptotically, without special and effective therapeutic strategies. Despite evidence that DPN may involve glucolipid metabolism disorders, insulin resistance (IR), inflammation, oxidative stress, and vascular dysfunction,¹ its pathogenesis is still not fully understood. Therefore, the identification of a novel modifiable risk factor for DPN in patients with type 2 diabetes mellitus (T2DM) is critical to facilitate early interventions aimed at improving such adverse health outcome and its economic consequences.

Obesity, especially abdominal obesity, has been proven to be a potential risk factor for the development of diabetic macro- and microvascular complications, including DPN,²⁻⁷ but the mechanisms underlying the associations are

multifactorial and still unclear. It has been well established that visceral adipose tissue (VAT) can overproduce several bioactive pro-inflammatory cytokines and adipocytokines that lead to IR, metabolic disorders, chronic inflammation, oxidative stress, endothelial dysfunction, and atherosclerotic vascular damage, subsequently resulting in nerve ischemia and direct axonal injury.^{5,8–11} Obesity is usually measured using several indicators such as body mass index (BMI), waist circumference (WC), waist-to-hip ratio, and body fat mass, however, these indicators are unable to accurately distinguish between VAT and subcutaneous adipose tissue.¹² At present, although magnetic resonance imaging (MRI) and computed tomography (CT) are the gold standard to directly measure VAT, these techniques are not feasible because of consuming time, expense, and radioactivity.¹² Recently, visceral fat area (VFA), measured by the bioelectrical impedance analysis (BIA), has been recognized as a noninvasive, relatively accurate, and low-cost method of quantifying VAT.¹² Studies have demonstrated that VFA level may be strongly associated with IR, inflammation, oxidative stress, metabolic syndrome (MetS), hyperlipidemia, diabetes and its vascular complications including hypertension, cardiovascular disease, diabetic retinopathy (DR), albuminuria, and cardiovascular autonomic dysfunction (one of the main types of diabetic neuropathy),^{2,4,12–14} all of which play pivotal roles in the pathogenesis of DPN,¹ suggesting indirectly that VFA also appears to play a crucial role in the development of DPN. There is preliminary *in vivo* evidence that subjects with DPN had higher VFA levels than those without DPN, and VFA level was associated with the presence of DPN in a small sample of young and middle-aged Korean individuals with T2DM,⁷ however, no studies, as yet, have evaluated the association of VFA level with DPN in Chinese population, and the pathological mechanism underlying the relationship has not been fully understood.

Given diabetes comprises several subtypes (clusters) with distinct heterogeneous features, and different clusters have significantly different patient characteristics and risk of diabetic complications including DPN,^{15,16} the purpose of the present study was to evaluate the association of VFA level with DPN in a Chinese population of T2DM patients aged 18–80 years old, and explores its possible mechanisms.

Materials and Methods

Study Population

This was a cross-sectional study designed to analyze the association between VFA level and DPN. A total of 2804 T2DM inpatients aged from 18 to 80 years in the Endocrinology Department at the Affiliated Hospital of Southwest Medical University between September 2017 and December 2021, who joined the National Metabolic Management Center (MMC) that provide standardised management for metabolic diseases and led by Ruijin Hospital, Shanghai, and received a standardized questionnaire, anthropometric examination, physical examination, laboratory tests, and evaluation of diabetes-related complications. T2DM was diagnosed based on the 1999 World Health Organization criteria.¹⁷ Subjects were excluded if they had any of the following criteria: 1) type 1 diabetes, acute complications of diabetes, including diabetic ketoacidosis, hyperglycemic hyperosmolar state, hyperosmolar coma and hypoglycemia; 2) endocrine diseases other than diabetes mellitus, such as thyroid disease, parathyroid disease, adrenal diseases, pituitary diseases; 3) presence of non-diabetes-related neuropathy such as chronic inflammatory demyelinating polyneuropathy, cervical and lumbar diseases, and severe cerebrovascular disease; 4) severe renal and liver failure, liver cirrhosis, gall bladder and biliary tract diseases, hematological diseases; 5) connective tissue, inflammatory and active infectious disease, autoimmune diseases; 6) history of malignancies; 7) history of mental illness; 8) pregnancy and lactation; 9) use of immunosuppressive agents, antioxidants, antibiotics, analgesics, systemic corticosteroids, multivitamins or vitamin B12 supplements, weight-loss drugs; 10) history of bariatric surgery; 11) missing or incomplete demographic or clinical characteristic data. After applying the exclusion criteria, 2494 participants were eligible and included in the present study (Figure 1).

The study protocol was approved by the Human Research Ethics Committee of the Affiliated Hospital of Southwest Medical University and followed the Declaration of Helsinki. The patients provided their written informed consent to participate in this study.

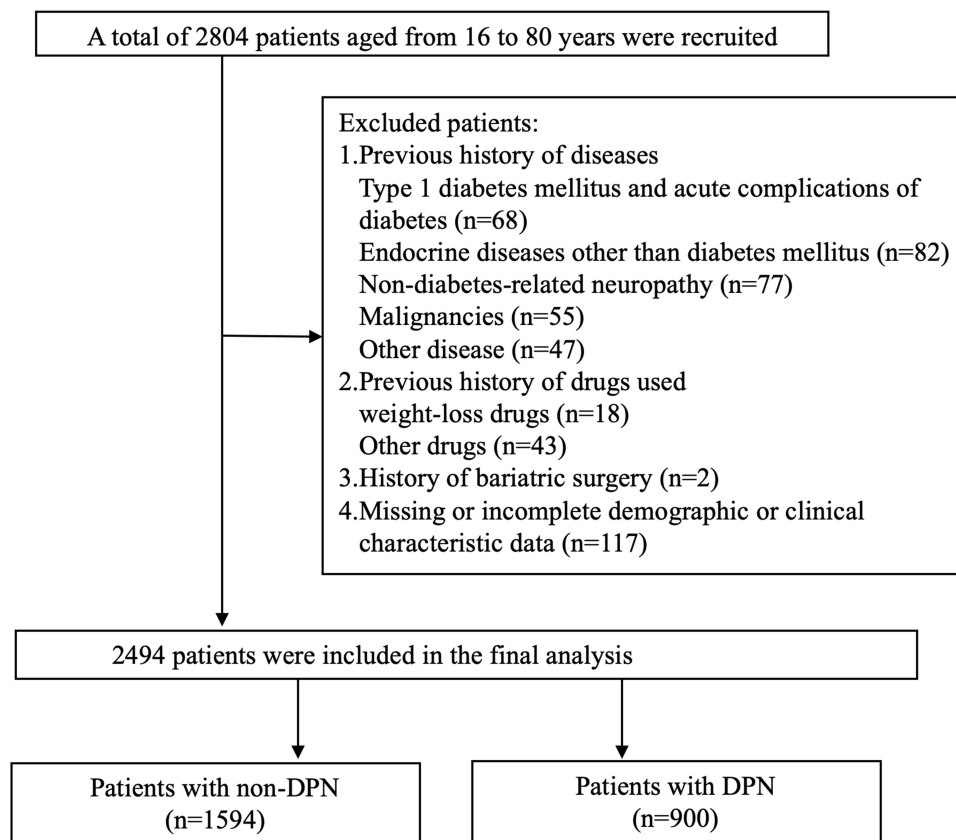


Figure 1 Flow chart of the selection of study participants.

Clinical and Biochemical Measurements

Professionally trained researchers collected data on all participants' demography, lifestyle (smoking, fresh vegetable and fruit intake, soy consumption, fish intake), medical history (hypertension, stroke, coronary heart disease (CHD), diabetic foot ulceration (DFU), peripheral arterial disease (PAD), DR, diabetic nephropathy (DN), and other diseases), and medication status (hypoglycemic drugs, antihypertensive drugs, antihyperlipidemic drugs, antiplatelet drugs). The weight and height of the participants were measured before breakfast in a single light garment without shoes. BMI as a measure of general obesity was calculated by dividing the weight (kg) by the square of height (m). Systolic and diastolic blood pressures (SBP and DBP) were measured on the right arm using a standard mercury sphygmomanometer, and measurements were taken three times and then averaged.¹⁸

Blood samples were collected in the morning either after an overnight fast or 2 h after a 75 g oral glucose tolerance test (OGTT). Fasting blood glucose (FBG), postprandial 2h blood glucose (2hPBG), glycated hemoglobin A1c (HbA1c), fasting C-peptide (FCP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total bilirubin (TBIL), glutamyl transpeptidase (GGT), serum albumin, creatinine (Cr), uric acid (UA), red blood cell count (RBC), hemoglobin (Hb), and white blood cell count (WBC) were determined according to relevant protocols and guidelines at the registered central laboratory located at the Affiliated Hospital of Southwestern Medical University, which is accredited in line with the international organization for standardization (ISO) 15189 standard for quality management specific to medical laboratories.

TyG was calculated as $\ln(TG [mg/dL] \times FBG [mg/dL]/2)$.¹⁹ The atherogenic index of plasma (AIP) was calculated as $\ln(TG/HDL-C)$ and the atherogenic coefficient (AC) was calculated as $(TC-HDL-C)/HDL-C$.²⁰ Instead of insulin, fasting C-peptide was used to evaluate IR according to a modified formula. Insulin resistance index (homeostasis model assessment (HOMA)-insulin resistance): $[HOMA-IR (CP) = 1.5 + FPG (mmol/L) \times CP (ng/mL)/2800]$.²¹

The first urine sample was collected early in the morning for further analysis. Urinary microalbumin and creatinine concentrations were measured by chemiluminescent immunoassay, and urine albumin-to-creatinine ratio (ACR, mg/g Cr) was then calculated. The estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Partnership (CKD-EPI) equation modified by Japanese coefficients.²² Patients were then classified as having DN if they had an eGFR < 60 mL/min/1.73m² and/or an ACR > 30 mg/g.²³

Measurements of VFA

After an overnight fast and urination, VFA was measured using the BIA (DUALSCAN HDS-2000, Omron Healthcare, Kyoto, Japan) according to the manufacturer's protocol.^{24–26} Briefly, the device analyses weak electric currents passing through the body in order to obtain body impedance. In the analyzer, the hospital number, height, weight, age, and sex of each participant were entered. With the “abdominal measurement unit”, we measured the abdominal shape and calculated the cross-sectional area of the abdomen at the umbilicus. The abdominal surface and four limbs were placed on the electrodes to measure abdominal impedance when a mild electric current was generated, which was used to calculate lean tissue area and subcutaneous abdominal fat area (SFA). The VFA was defined as the cross-sectional area minus the sum of the lean tissue area and SFA.

Assessment and Diagnostic Criteria of DPN

All T2DM patients were asked whether they had neurologic symptoms including numbness, pain (prickling or stabbing, shooting, burning or aching pain), and paresthesia (abnormal cold or heat sensation, allodynia and hyperalgesia) in the toes, feet, legs or upper-limb, and undergone achilles tendon reflexes examination on both sides in the knee standing position (as being either presence or weakening or loss). Then, the bilateral sural nerve conduction velocity (SNCV) and amplitude potential (SNAP) of all patients were measured using the NC-stat DPN Check device (HDN-1000, Omron Healthcare, Kyoto, Japan) according to the test manual by clinical laboratory technicians. Age and height stratified SNAP and SNCV thresholds were used. A reduced SNCV and/ or SNAP in at least one leg were considered as nerve conduction abnormality.^{27–30} DPN was identified as both at least a neurologic symptom/sign and an abnormality of nerve conduction.^{1,27,30–36} SNCV and SNAP were plotted on a reference chart to identify the stage of DPN. All participants were categorized into four different groups (normal, mild, moderate, and severe neuropathy) according to the reference chart.^{30,37}

Other Classifications and Definitions

Hypertension was defined as individuals with self-reported treated hypertension or with an average of 2 blood pressure measurements of at least 140/90 mm Hg using an automated digital device.³⁸ CHD was defined as a positive history of myocardial infarction, bypass operation, a diagnostic finding in angiography or positive exercise test.³⁹ Stroke was considered present if diagnosed according to previous medical records or if a pathological finding by CT and MRI of the brain.⁴⁰ Ankle-brachial index (ABI) measurements were measured by a continuous-wave Doppler ultrasound probe (Vista AVS, Summit Co.). Patients were diagnosed as having PAD if an ABI value <0.9 on either limb.²³ DFU was defined as a full-thickness wound (penetrates dermal tissues) below the ankle in a person with diabetes caused by peripheral neuropathy or ischaemia or both, and consequent trauma to the foot.⁴¹ A Canon CR-2 Digital Retinal Camera was performed to obtain two-field fundus photography of patient's eyes (Canon Inc., Kanagawa, Japan). The presence of DR was assessed by high-quality fundus photographs and an ophthalmologist.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 20.0 (SPSS, Chicago, IL), R statistical software packages (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc, Boston, MA). Data were tested using the Kolmogorov–Smirnov test for normal distribution and Levene's homogeneity of variance test for homogeneity of variance. Continuous variables were represented as mean ± standard deviation (SD), and categorical variables were shown as number (percentages).

Clinical and biochemical characteristics of T2DM patients with and without DPN were compared using the Student's *t*-test (for normally distributed continuous variables), Mann–Whitney *U*-test (for non-normally distributed continuous variables), or χ^2 test (for categorical variables). Clinical characteristics associated with DPN among four VFA quartiles groups were assessed using one-way analysis of variance (ANOVA) (continuous variables with normally distribution and homogeneity of variance), or Kruskal–Wallis test (covariates with nonparametric distribution and/or variance uneven).

The correlations between VFA and other variables were performed by Spearman correlation analysis firstly and then further determined by partial correlation analysis after adjusting for age, sex, BMI, and duration of diabetes. VFA quartiles were classified as follows: Q1 (≤ 54 cm²), Q2 (55–79 cm²), Q3 (80–107 cm²), and Q4 (≥ 108 cm²). To explore the relationship between VFA and the risk of presence of DPN, multivariate logistic regression analysis was performed using the presence of DPN as the dependent variable. Model 1 was unadjusted; Model 2 was adjusted for age, sex, BMI, and diabetic duration; Model 3 was additionally adjusted for glucolipid metabolism parameters based on Model 2; Model 4 was further adjusted for inflammation, oxidative stress, and vascular parameters based on Model 3; Model 5 was further adjusted for medication status, smoking, fresh vegetable and fruit intake, soy consumption, and fish intake based on Model 4. Odds ratios (OR) and 95% confidence intervals (CI) were determined using Q1 as the reference group. To identify the non-linear relationship between VFA and the risk of DPN, we use the generalized additive model (GAM) and smooth curve fitting (penalized spline method). Also, two-piecewise linear regression model was used to further explore the nonlinearity. Finally, the receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off point of VFA for the diagnosis of DPN.

All statistical tests were considered statistically significant at two-sided $P < 0.05$.

Results

Clinical and Biochemical Characteristics of the Study Populations

A total of 2494 T2DM patients were included in this study; around 36.09% of patients had DPN. The clinical and biochemical characteristics of the patients are shown in [Table 1](#). There were no statistically significant differences in sex ratios, BMI, TG, TC, LDL-C, TyG index, AIP, GGT, serum Cr, UA, eGFR, and prevalence of CHD and stroke between DPN and non-DPN group. Compared with those in the non-DPN group, patients with DPN had significantly younger age, longer diabetic duration, higher SBP, DBP, PP, FBG, 2hPBG, HbA1c, HDL-C, WBC, urine ACR, prevalence of DFU, PAD, DN, and DR, less user of metformin, DPP-4 inhibitors, ACEI/ARB, alcium antagonist, fresh fruit intake, soy consumption, fish intake, more user of insulin, and lower VFA, BMI, FCP, HOMA-IR, RBC, Hb, TBIL, serum albumin, SNCV, SNAP, and prevalence of hypertension ($P < 0.01$ or $P < 0.05$; [Table 1](#) and [Figure 2](#)). The prevalence of DPN across VFA quartiles was 51.90%, 34.85%, 30.03%, and 27.16%, respectively (P for trend < 0.01). There was significant reductions in the proportion of unilateral or bilateral nerve conduction abnormality, mild or moderate-to-severe DPN, and a marked increase in levels of SNCV and SNAP in T2DM patients with a higher VFA quartile compared to those with a lower VFA quartile (all $P < 0.01$, [Supplementary Table 1](#)).

Relationship Between VFA and Risk Factors Associated with DPN in Study Participants

VFA levels were positively correlated with SNCV, SNAP, age, BMI, duration of diabetes, SBP, DBP, PP, TG, TyG index, AIP, AC, FCP, HOMA-IR, Hb, RBC, WBC, TBIL, GGT, serum albumin, UA, Cr, prevalence of hypertension and CHD, use of antihypertensive and antihyperlipidemic drugs, fresh vegetable and fish intake, and negatively correlated with gender, HbA1c, HDL-C, eGFR, and prevalence of DPN and DR ($P < 0.01$ or $P < 0.05$; [Table 2](#)). After adjusting for age, gender, BMI, and diabetes duration, the correlations between VFA and SNCV, SNAP, HbA1c, AIP, AC, TyG index, HOMA-IR, FCP, UA, and prevalence of hypertension, DPN, DR, and use of antihypertensive and antihyperlipidemic drugs, fresh vegetable intake remained statistically significant ($P < 0.01$ or $P < 0.05$).

Association of VFA Quartiles with DPN Risk in Study Populations

[Table 3](#) revealed the correlation of VFA quartiles with the risk of presence of DPN. The risk of presence of DPN was decreased by 36.1% for each SD increase in VFA in Model 1 (OR=0.639, 95% CI 0.582–0.702, $P < 0.01$), and were

Table 1 Clinical and Biochemical Characteristics of Patients Stratified by Presence of DPN

Variables	Non-DPN (n=1594)	DPN (n=900)	P-value
Male/Female	837/757	480/420	0.692
Age (years)	56.69±10.99	54.32±11.55	<0.001
BMI (kg/m ²)	25.0±3.4	24.1±3.6	<0.001
VFA(cm ²)	88.88±42.72	71.53± 44.40	<0.001
Diabetic duration (years)	7.94±5.99	9.47± 6.79	<0.001
FBG (mmol/L)	9.39±3.23	10.26± 3.54	<0.001
2hPBG (mmol/L)	14.43±4.65	15.55± 5.12	<0.001
HbA1c (%)	9.44±2.49	10.49±2.53	<0.001
FCP (ng/mL)	1.98±1.52	1.60±1.40	<0.001
HOMA-IR	3.55±2.01	3.39±1.82	0.044
TyG index	9.50±0.78	9.55±0.78	0.062
SBP (mmHg)	133.79±19.08	138.17±23.19	<0.001
DBP (mmHg)	78.58±10.79	80.97±11.93	<0.001
PP (mmHg)	55.22±13.53	57.20±15.54	0.009
TC (mmol/L)	4.77±2.22	4.89± 1.61	0.145
TG (mmol/L)	2.45±2.46	2.36± 2.32	0.183
HDL-C (mmol/L)	1.14±0.33	1.18± 0.40	0.026
LDL-C (mmol/L)	2.80±1.02	2.89± 1.17	0.180
WBC (*10 ⁹ /L)	6.80±2.13	7.11±2.43	0.004
RBC (*10 ¹² /L)	4.65±0.59	4.48±0.71	<0.001
Hb (g/L)	139.00±17.61	132.31±22.12	<0.001
TBIL (μmol/L)	13.48±5.82	12.39±7.29	<0.001
GGT (U/L)	43.11±75.22	49.09±156.72	0.075
Serum albumin (g/L)	44.40±4.36	42.68±5.41	<0.001
Serum UA (μmol/L)	350.22±468.46	341.40±183.74	0.645
Urine ACR (mg/g)	124.67±530.92	440.02± 1141.27	<0.001
Serum Cr (μmol/L)	65.14±26.36	75.10±59.98	0.366
eGFR (mL/min/1.73m ²)	98.61±20.24	96.72±28.34	0.218
AC	3.47±2.91	3.44±2.12	0.862
AIP	0.55±0.81	0.49±0.82	0.093
ABI	1.10±0.09	1.09±0.11	0.068
SNCV (m/s)	54.97±4.02	46.32± 5.63	<0.001
SNAP (μV)	15.87±7.23	8.56± 5.71	<0.001
Microvascular complications			
DN (n, %)	440 (27.60%)	408 (45.33%)	<0.001
DR (n, %)	205 (12.86%)	280 (31.11%)	<0.001
Macrovascular complications			
Hypertension (n, %)	612 (38.39%)	284 (31.56%)	0.001
CHD (n, %)	89 (5.58%)	37 (4.11%)	0.106
Stroke (n, %)	81 (5.08%)	39 (4.33%)	0.402
DFU (n, %)	12 (0.75%)	33 (3.67%)	<0.001
PAD (n, %)	36 (2.26%)	41 (4.56%)	0.001
Hypoglycemic drugs			
Metformin (n, %)	843 (52.89%)	419 (46.56%)	0.002
Sulfonylurea (n, %)	443 (27.79%)	251 (27.89%)	0.959
Alpha-glucosidase inhibitor (n, %)	195 (12.23%)	91 (10.11%)	0.110
DPP-4 inhibitors (n, %)	69 (4.33%)	24 (2.67%)	0.035
SGLT-2 inhibitors (n, %)	15 (0.94%)	11 (1.22%)	0.507
Other oral agents (n, %)	304 (19.07%)	148 (16.44%)	0.102
Insulin (n, %)	457 (28.67%)	374 (41.56%)	<0.001

(Continued)

Table 1 (Continued).

Variables	Non-DPN (n=1594)	DPN (n=900)	P-value
Antihypertensive drugs			
ACEI/ARB (n, %)	215 (13.49%)	59 (6.56%)	<0.001
Calcium antagonist (n, %)	239 (14.99%)	90 (10.00%)	<0.001
Others (n, %)	45 (2.82%)	18 (2.00%)	0.208
Antihyperlipidemic drugs (n, %)	89 (5.58%)	36 (4.00%)	0.082
Antiplatelet drugs (n, %)	22 (1.38%)	6 (0.67%)	0.104
Smoking (n, %)	332 (20.83%)	205 (22.78%)	0.116
Fresh vegetable intake			
≥ 600 g/d (n, %)	249 (15.62%)	124 (13.78%)	0.208
<600 g/d (n, %)	1345 (84.38%)	776 (86.22%)	
Fresh fruit intake			
≥ 200 g/d (n, %)	391 (24.53%)	163 (18.11%)	<0.001
<200 g/d (n, %)	1203 (75.47%)	737 (81.89%)	
Soy consumption			
≥ 100 g/d (n, %)	234 (14.68%)	81 (9.00%)	<0.001
<100 g/d (n, %)	1360 (85.32%)	819 (91.00%)	
Fish intake			
≥ two times/week (n, %)	241 (15.12%)	82 (9.11%)	<0.001
≤ one time/week (n, %)	1353 (84.88%)	818 (90.89%)	

Note: Values are presented as number (percentages) or mean ± standard deviation).

Abbreviations: DPN, diabetic peripheral neuropathy; BMI, body mass index; VFA, visceral fat area; FBG, fasting blood glucose; 2hPBG, 2h postprandial blood glucose; HbA1c, glycated hemoglobin A1c; FCP, fasting C-peptide; HOMA-IR, homeostasis model assessment of insulin resistance; TyG index, triglyceride-glucose index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; TBIL, total bilirubin; GGT, gamma glutamyltransferase; UA, uric acid; ACR, albumin-to-creatinine ratio; Cr, creatinine; eGFR, estimated glomerular filtration rate; AC, atherogenic coefficient; AIP, atherogenic index of plasma; ABI, ankle-brachial index; SNCV, sural nerve conduction velocity; SNAP, sural nerve amplitude potential; DN, diabetic nephropathy; DR, diabetic retinopathy; CHD, coronary heart disease; DFU, diabetic foot ulceration; PAD, peripheral arterial disease; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium-glucose cotransporter-2; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker.

further reduced when further adjustment for parameters, such as anthropometry, glucolipid metabolism, inflammation, oxidative stress, diabetic vasculopathy, medication status, smoking, fresh vegetable and fruit intake, soy consumption, and fish intake in Model 5 (OR=0.467, 95% CI 0.336–0.649, $P<0.01$). In addition, the risk of presence of DPN was gradually reduced with increasing VFA quartiles in Model 1–5 (all P for trend <0.01), and there was a significantly lower risk of presence of DPN in patients with the highest quartile of VFA levels than those in the lowest quartile after multivariate adjustment (OR=0.341, 95% CI 0.137–0.847, $P<0.01$).

The Analysis of Non-Linear Relationship Between VFA and Risk of DPN

In the present study, we explored the non-linear relationship between VFA and the risk of DPN because VFA was a continuous variable (Figure 3). We used the two-piecewise linear regression model to calculate the inflection point of the VFA to predict the risk of DPN was 104 (Table 4, after adjusting parameters such as anthropometry, glucolipid metabolism, inflammation, oxidative stress, diabetic vasculopathy, medication status, smoking, fresh vegetable and fruit intake, soy consumption, and fish intake). On the left of the inflection point, a negative relationship was established on the DPN and the risk of DPN (OR = 0.980, 95% CI: 0.970–0.989, $P = 0.000$). On the right of the inflection point, the relationship was getting saturated (OR = 0.989, 95% CI: 0.974–1.004, $P = 0.150$). However, compared with the standard

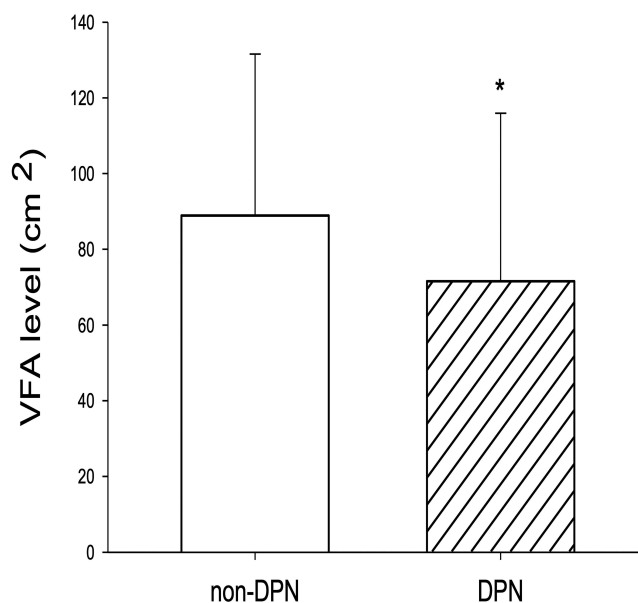


Figure 2 Comparison of VFA levels between non-DPN and DPN groups. *P < 0.01 vs non-DPN group.

linear regression model, the difference is not statistically significant (P for log-likelihood ratio test was 0.344). Thus, the relationship between VFA and the risk of DPN did not conform to the curve relationship, and for each 1cm² increase in VFA, the risk of DPN decreased by 1.8% (95% CI 0.974–0.990, P<0.01).

Table 2 Relationship Between VFA and Risk Factors Associated with DPN in Study Participants

Variables	r	P-value	Adjusted r	Adjusted P-value
Gender	-0.070	<0.001		
Age	0.157	<0.001		
BMI	0.712	<0.001		
Diabetic duration	0.053	0.022		
FBG	0.014	0.490	-0.069	0.362
2hPBG	0.013	0.542	-0.095	0.206
HbA1c	-0.117	<0.001	-0.190	0.011
FCP	0.370	<0.001	0.160	0.033
HOMA-IR	0.321	<0.001	0.111	0.001
TyG index	0.279	<0.001	0.171	<0.001
SBP	0.206	<0.001	0.073	0.334
DBP	0.209	<0.001	0.016	0.832
PP	0.123	<0.001	-0.033	0.320
TC	0.017	0.410	0.056	0.455
TG	0.335	<0.001	0.146	0.051
HDL-C	-0.222	<0.001	-0.011	0.888
LDL-C	-0.023	0.263	-0.061	0.419
WBC	0.085	<0.001	-0.042	0.575
RBC	0.164	<0.001	0.020	0.788
Hb	0.182	<0.001	0.145	0.053
TBIL	0.102	<0.001	0.025	0.742
GGT	0.257	<0.001	0.128	0.088
Serum albumin	0.141	<0.001	0.133	0.075
Serum UA	0.246	<0.001	0.195	0.009

(Continued)

Table 2 (Continued).

Variables	r	P-value	Adjusted r	Adjusted P-value
Urine ACR	0.038	0.082	0.045	0.546
Serum Cr	0.143	<0.001	0.134	0.073
eGFR	-0.149	<0.001	-0.007	0.839
AC	0.211	<0.001	0.065	0.046
AIP	0.343	<0.001	0.176	<0.001
ABI	0.007	0.719	-0.019	0.422
SNCV	0.129	<0.001	0.123	<0.001
SNAP	0.174	<0.001	0.170	<0.001
DPN	-0.201	<0.001	-0.144	<0.001
Hypertension	0.244	<0.001	0.070	0.003
CHD	0.060	0.003	-0.032	0.174
Stroke	0.019	0.352	-0.042	0.072
DFU	-0.027	0.184	0.026	0.259
PAD	0.029	0.152	0.008	0.716
DN	0.036	0.071	-0.020	0.387
DR	-0.060	0.003	-0.049	0.034
Hypoglycemic medication	0.017	0.402	-0.009	0.718
Antihypertensive drugs	0.221	0.000	0.073	0.002
Antihyperlipidemic drugs	0.080	0.000	0.080	0.001
Antiplatelet drugs	0.008	0.690	-0.017	0.489
Smoking	0.040	0.056	0.042	0.080
Fresh vegetable intake	0.060	0.003	0.083	0.001
Fresh fruit intake	0.022	0.283	-0.009	0.695
Soy consumption	0.002	0.915	-0.036	0.136
Fish intake	0.046	0.023	0.025	0.293

Table 3 OR and 95% CI of the Risk of DPN According to VFA Quartiles

VFA	DPN				
	Model 1	Model 2	Model 3	Model 4	Model 5
	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)
Per SD increase	0.639 (0.582–0.702)	0.596 (0.509–0.698)	0.572 (0.457–0.716)	0.477 (0.340–0.671)	0.467 (0.336–0.649)
Quartiles of VFA					
Q1 (≤ 54 cm ²)	1	1	1	1	1
Q2 (55–79 cm ²)	0.352 (0.276–0.449)	0.424 (0.313–0.574)	0.376 (0.242–0.586)	0.576 (0.310–1.072)	0.562 (0.305–1.037)
Q3 (80–107 cm ²)	0.401 (0.318–0.506)	0.501 (0.355–0.708)	0.444 (0.270–0.729)	0.480 (0.227–1.014)	0.452 (0.217–0.941)
Q4 (≥ 108 cm ²)	0.346 (0.273–0.437)	0.399 (0.261–0.608)	0.387 (0.212–0.707)	0.382 (0.151–0.968)	0.341 (0.137–0.847)
P for trend	<0.001	<0.001	<0.001	0.001	<0.001
Q4 versus. Q1, Q2, Q3	<0.001	<0.001	<0.001	0.020	0.039

Notes: Data are expressed as OR (95% CI) +P value, unless stated otherwise. Model 1 unadjusted; Model 2 adjusted for age, gender, BMI and diabetic duration; Model 3 adjusted for factors listed in Model 2 plus SBP, DBP, FBG, 2hPBG, FCP, HbA1c, TC, TG, HDL-C, LDL-C, HOMA-IR, TyG; Model 4 adjusted for factors listed in Model 3 plus HB, RBC, WBC, TBIL, GGT, serum albumin, UA, CHD, Stroke, DFU, PAD, DN, DR, AIP, AC; Model 5 adjusted for factors listed in Model 4 plus medication status (hypoglycemic medication, antihypertensive drugs, antihyperlipidemic drugs, and antiplatelet drugs), smoking, fresh vegetable intake, fresh fruit intake, soy consumption, and fish intake.

Abbreviations: OR, odds ratio; CI, confidence interval.

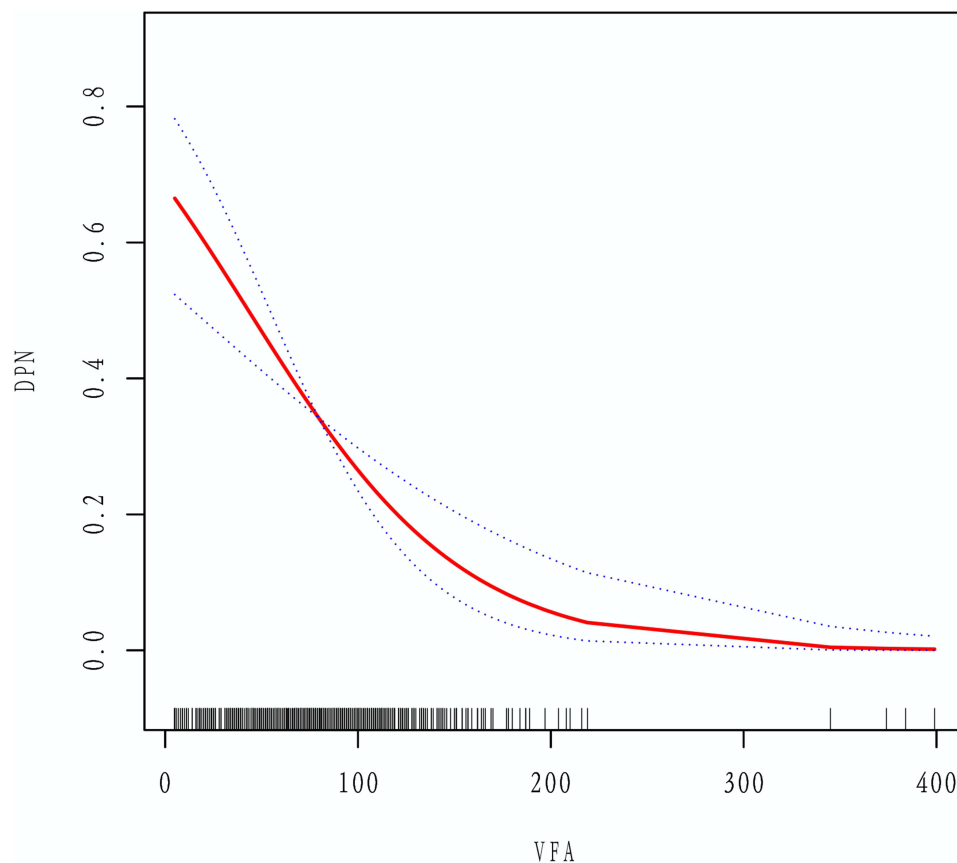


Figure 3 Multivariate adjusted smoothing spline plots of the Risk of DPN hospitalized patients with T2DM. We adjusted parameters such as anthropometry, glucolipid metabolism, inflammation, oxidative stress, and diabetic vasculopathy in Model 5 of Table 3. The solid red line represents the best-fit line, and the dotted blue lines are 95% confidence intervals.

Predictive Value of VFA in Screening for the Presence of DPN in T2DM Patients

To further explore the predictive value of VFA for DPN, the ROC curve analysis was performed. The results showed that the optimal cut-off value for VFA to predict the presence of DPN was 50.5cm² (AUC=0.621, 95% CI, 0.597–0.644; Youden index=0.184; sensitivity, 84.40%; specificity, 34.00%) (Figure 4).

Discussion

To our knowledge, this is the first study to explore the relationship between VFA and the risk of presence of DPN in Chinese population. We found that VFA levels were significantly lower in T2DM patients with DPN compared with those with higher VFA quartile had a significant increase in SNCV and SNAP. Moreover, VFA level was positively correlated with SNCV and SNAP; there was no significant difference in the curve fitting. Additionally, VFA level was an

Table 4 The Result of Two-Piecewise Linear Regression Model

	OR (95% CI)	P value
Fitting model by standard linear regression	0.982(0.974–0.990)	<0.001
Fitting model by two-piecewise linear regression		
Inflection point of VFA (cm ²)	104	–
< 104	0.980(0.970–0.989)	<0.001
≥ 104	0.989(0.974–1.004)	0.150
P for log likelihood ratio test	–	0.344

Notes: We adjusted parameters such as anthropometry, glucolipid metabolism, inflammation, oxidative stress, diabetic vasculopathy, medication status, smoking, fresh vegetable intake, fresh fruit intake, soy consumption, and fish intake.

Abbreviations: OR, odds ratio; CI, confidence interval.

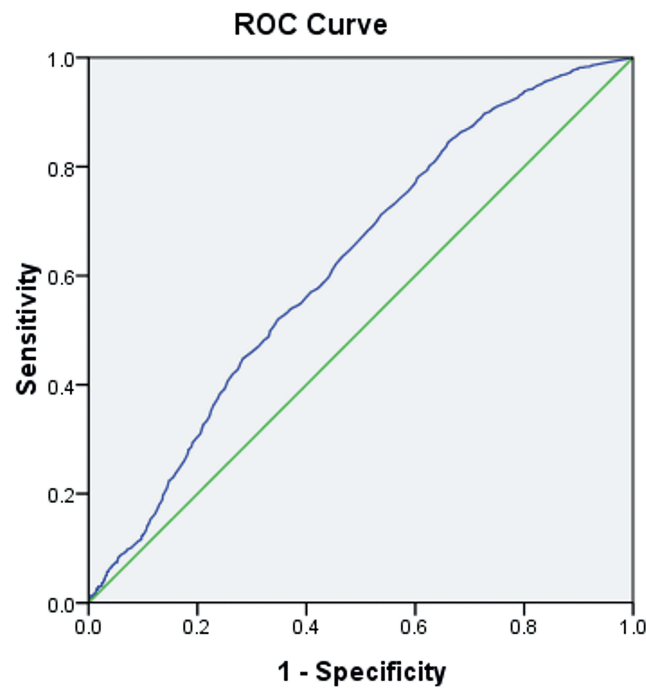


Figure 4 ROC analysis of visceral fat area (VFA) to predict the presence of DPN in T2DM patients. AUC = 0.621; 95% CI, 0.597–0.644; $P < 0.001$; identified VFA cutoff value = 50.5 cm²; Youden index = 0.184; sensitivity: 84.40%; specificity: 34.00%.

independent decisive factor for the presence of DPN after multivariate adjustment. Further, VFA levels with 50.5 cm² could predict the presence of DPN. These findings suggest that lower VFA may be associated with an increased risk of presence of DPN.

Numerous studies have demonstrated that obesity, especially visceral adiposity, plays an important role in the onset and development of DPN.^{6,42} Visceral adiposity, commonly assessed by WC, could contribute to IR, hyperglycaemia, dyslipidemia, hypertension, chronic inflammation and oxidative stress,^{43,44} and has been reported to be associated with damaged nerve conduction velocity and higher DPN risk.⁴⁵ VFA, which can provide relatively accurate estimates of VAT, might also be correlated with DPN. Oh et al showed that VFA level was higher in middle-aged T2DM patients with DPN than those without DPN, and VFA level was associated with a 2.6% increase in likelihood of DPN.⁷ On the contrary, another study of 90 Japanese patients with T2DM conducted by Tayama et al demonstrated that levels of preperitoneal fat determined by ultrasonography, an indicator of visceral fat deposition, were positively correlated with motor or sensory nerve conduction velocity.⁴⁶ The present study's findings were in contrast to the report performed by Oh et al⁷ which can be partially explained by different study population, sample size, racial origins, determination method of VFA, diagnostic criteria of DPN, and adjusted confounding factors. Interestingly, however, the results of our present study were similar to the results obtained in a previous study.⁴⁶ We showed that patients with DPN had significantly lower VFA levels than those without DPN, and VFA level was positively correlated with neurophysiological parameters including SNCV and SNAP. Moreover, VFA level was a significant and independent risk factor for the presence of DPN, and there was a 52.3% decrease in the risk of presence of DPN for each SD increase in VFA after multi-factorial adjustment. In addition, VFA levels with 50.5 cm² could predict the presence of DPN. These findings suggest that an appropriately high level of VFA may have a protective effect on DPN. Further, we demonstrated that there was significant reductions in the proportion of nerve conduction abnormality, mild or moderate-to-severe DPN, and marked increase in SNCV and SNAP in T2DM patients with a higher VFA quartile compared to those with a lower quartile, suggesting that VFA levels may be associated with the presence and severity of DPN, and higher VFA may confer a decreased risk of DPN in a Chinese population of T2DM patients.

Biological mechanisms that explain the relationships between VFA levels and DPN prevalence have not been elucidated, but there are some potential candidates. First, growing evidence suggests that multiple adipocytokines secreted by VAT could exert beneficial effects such as regulating glucose and lipid metabolism, inflammation and oxidative stress, improving insulin resistance and endothelial function, and ameliorating atherosclerosis,⁴³ all of which partially offset the negative effects of obesity. Second, the metabolic protective effects of subcutaneous fat accumulation itself on DPN can be also an important reason.⁴⁵ Third, although diabetic subjects with visceral obesity (high level of VFA) often have dyslipidemia and multiple complications including DN, hypertension, and CHD than those without (low level of VFA), they may pay more attention to their illness, and employ various strategies including tight control of blood glucose, blood pressure, and blood lipids and other risk factors, and change the composition of the diet (eating more fresh vegetable and fruit, and fish), all of which were significantly associated with decreased visceral fat and improvement of overall nutritional status and peripheral nerves function.^{47–50} Fourth, it is a plausible explanation that inadvertent weight loss may occur in individuals with longstanding inadequate diabetes control as consequences of multiple systemic insults or comorbidities.⁵¹ There have been a few studies reporting that in individuals with progressive metabolic deterioration due to lack of diabetes control, obviously elevated resting metabolic rate would lead to ongoing increased energy expenditure, which may have a long-term impact on body weight or body composition regulation that appears as sustained unintentional weight loss.⁵² However, more evidence is required from longitudinal and randomized controlled studies to validate our suspicion.

Evidence suggests that long-term hyperglycemia and related chronic low-grade inflammation and oxidative stress play important roles in the development of DPN.^{1,53,54} HbA1c as an index of long-term glycemic control has been demonstrated to be a strong independent predictor of DPN in both cross-sectional and prospective epidemiological studies.^{53,55} In the present study, we found that patients with DPN had significantly longer diabetic duration and higher FBG, 2hPBG, and HbA1c compared with those without DPN, suggesting the possible role of poor glycemic control in the development of DPN. Also, we found that FCP was significantly decreased in DPN subjects along with longer diabetic duration, and VFA level was positively correlated with FCP and negatively with HbA1c, demonstrating that weakened or even deterioration of pancreatic islet β cell function induced by long-term hyperglycemia may lead to increased prevalence of DPN, and may at least partially mediate a potential relationship between VFA and DPN. Additionally, we found that diabetic subjects with the lower VFA quartiles have lower level of FCP and higher prevalence of DR and DPN compared with those with higher quartiles, which was similar to the findings of previous studies that diabetes comprises several subtypes (clusters) with distinct heterogeneous features, and cluster 2 (insulin deficient), represent a new form of diabetes previously masked within type 2 diabetes, had the highest risk of DR.^{15,16} Together, these data suggested that insulin deficiency or hyperglycaemia appeared to be important triggers of DPN in diabetic subjects with lower VFA, but more research is still needed to validate these findings. Moreover, our study provided further evidence supporting the potential role of increased inflammatory oxidative response induced by long-term hyperglycemia in the development of DPN, since we showed that patients with DPN had significantly higher levels of WBC (pro-inflammatory marker) and lower levels of RBC, Hb, TBIL, and serum albumin (antioxidative biomarkers) compared with those without DPN. Further, we showed that VFA levels were positively correlated with WBC, Hb, RBC, TBIL, UA, and serum albumin, which are partially inconsistent with previous studies.^{56–61} Together, these lines of evidence, combined with the results of our study, suggested that increased inflammatory response and decreased antioxidant capacity induced by long-term hyperglycemia may be involved in the negative association of VFA levels and DPN, and an appropriately high level of VFA may exert a neuroprotective effect by regulating inflammatory oxidative response. Perhaps the protective effect of VFA is weakened because of the decreased VFA and impairment of VAT function in T2DM patients with DPN; however, the specific mechanism remains to be further investigated.

Considerable evidence suggests that that macro- and microvascular complications associated with atherosclerosis due to endothelial dysfunction are the critical factors in the development of DPN.^{1,53,54,62} Urine ACR as a sensitive marker of DN and strong predictor of future progression of renal dysfunction has been reported to be an important marker of microvascular damage and generalized endothelial dysfunction.⁶³ Our study found that patients with DPN had significantly higher blood pressure, urine ACR, and prevalence of DFU, PAD, DN, and DR compared with those without DPN, supporting the potential role of atherosclerotic vascular lesions in the development of DPN. Moreover, we demonstrated

that VFA levels were positively correlated with atherogenic indices (TyG index, AIP, and AC) and prevalence of hypertension and its components (SBP, DBP), and negatively correlated with prevalence of DR independent of age, gender, BMI, and diabetes duration, in good agreement with previous studies.^{52,64–67} A cross-sectional study conducted by Song et al revealed that AIP was higher in the VFA ≥ 100 cm² group, and VFA level was an independent related factor of AIP in 175 Chinese patients with T2DM.⁶⁷ Another cross-sectional study of 326 participants with MetS in Spain performed by Bullón-Vela et al showed that TyG index increased with VAT tertiles, and could be a reliable indicator of VAT in subjects at high cardiovascular risk diagnosed with MetS.⁶⁶ Data from two population-based cohort studies showed that visceral fat index and VAT were significantly and positively associated with blood pressure and risk of hypertension.^{64,65} Recently, Sasongko et al demonstrated that per SD increases in visceral fat (0.77 [0.67–0.88]) were significantly associated with decreased odds of having any level of DR, and VF was also inversely associated with severity of DR in a cross-sectional study from Jogjakarta Eye Diabetic Study in the Community.⁵² Both our hereby presented findings and the results of previous studies indicate that visceral fat accumulation could lead to atherosclerotic vascular diseases probably through multiple risk factors, and might mediate the relationship of VFA with DPN; however, the mechanism of action needs to be further investigated.

There are still some limitations in our study. First, because this was a cross-sectional and retrospective study, it is difficult to assess the causal relationship between VFA and DPN, which need to be further confirmed by prospective studies. Second, the current “gold standard” for the diagnosis of DPN is nerve conduction study (NCS); however, professional staff and expensive equipment required make the NCS less frequently used and difficult to apply in large studies. Therefore, DPN Check was used to assess sural nerve conduction, which has a sensitivity of 95% and a specificity of 71% when compared to traditional NCS in patients with DPN, with reproducible results.²⁷ Third, our findings may not be generalizable to other populations with different ethnic and severity of disease because the present study was based on Chinese Han inpatients with T2DM at a single center, who generally had more serious illness than diabetic outpatients. Fourth, we only evaluated WBC as inflammation marker, and serum albumin, TBIL, RBC, Hb, GGT, and UA as oxidative stress parameters. The lack of classical inflammatory and oxidative stress markers, such as C-reactive protein, tumor necrosis factor- α , interleukin-6, glutathione, or superoxide dismutase analysis and/or correlation makes it difficult to draw any consistent conclusion regarding the possibility of these indicators as mentioned above to predict and evaluate the relationship of VFA with the presence of DPN. Finally, as we did not measure adipokines such as adiponectin, omentin-1 and vaspin in study subjects that were not analyzed in the final results, which might have influenced the results. Despite these limitations, the current study is not without strengths, including a relatively large sample size, the use of a standardized method at a single center, and adequate adjustment, which can raise the reliability of our findings. More importantly, our study, to our knowledge, provides the first clinical evidence on a potential link between VFA and DPN in Chinese patients with T2DM.

Conclusion

The present study suggest that lower VFA level may be independently associated with increased risk of presence of DPN in hospitalized Chinese patients with T2DM, and lower VFA level might mediate the development and progression of DPN through various mechanisms, such as dysregulation and dysfunction of adipocytokines, intervention of diet composition and medication, insulin deficiency or hyperglycaemia, inflammatory oxidative response and atherosclerotic vascular diseases. Further prospective studies are needed to clarify the associations of VFA with DPN and to elucidate the precise mechanism underlying the association.

Data Sharing Statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding authors.

Ethics Approval and Informed Consent

The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was reviewed and approved by was approved by the Human Research Ethics Committee of the Affiliated Hospital of Southwest Medical University (No. 2018017). The patients provided their written informed consent to participate in this study.

Consent for Publication

All authors gave final approval of the version to be published and agreed to be listed as authors.

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Author Contributions

All the authors contributed significantly to the manuscript. YRW conducted the population study, analyzed and interpreted the data, and drafted the manuscript. PJY significantly revised the draft, interpreted the data, and involved in data analyses. JL, KL, QW, and YX conducted the study, collected the information and participated in data interpretation. ZHZ, QT, YM, and PC involved in the sample test, data management and draft revision. PJY is the PI of project, who designed the study and critically revised the manuscript. All authors read and approved the final manuscript.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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