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ORIGINAL RESEARCH

Lower Visceral Fat is Related to Diabetic Peripheral Neuropathy

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Objective: Visceral fat area (VFA) levels have been found to exhibit a strong association with various conditions such as insulin resistance (IR), inflammation, oxidative stress, metabolic syndrome (MetS), hyperlipidemia, diabetes, and its vascular complications. These complications include hypertension, cardiovascular disease, diabetic retinopathy (DR), albuminuria, and cardiovascular autonomic dysfunction, which is considered one of the main types of diabetic neuropathy. This study aimed to investigate the correlation between visceral fat and peripheral neuropathy in patients with type 2 diabetes (T2DM).

Methods: A retrospective analysis of clinical data of patients diagnosed with type 2 diabetes admitted to our hospital was conducted. After excluding 28 cases, a total of 488 patients were included, divided into the group with peripheral neuropathy (207 cases) and the control group without peripheral neuropathy (281 cases). The correlation between VFA and the presence of DPN was assessed using correlation and multiple logistic regression analyses.

Results: In terms of general information, the group with peripheral neuropathy had lower BMI but longer duration of diabetes compared to the control group. Regarding biochemical indicators, VFA were lower in the group with peripheral neuropathy, while FPG and HbA1c levels were higher (all $P<0.05$). Spearman correlation analysis showed a negative correlation between VFA, and the presence of peripheral neuropathy in patients with type 2 diabetes ($P<0.05$). Logistic regression analysis indicated that VFA, duration of diabetes, and HbA1c level were influencing factors for the occurrence of peripheral neuropathy in patients with type 2 diabetes ($P<0.05$).

Conclusion: This study revealed a correlation between visceral fat and peripheral neuropathy in patients with type 2 diabetes, highlighting the importance of monitoring visceral fat in such patients. In addition to lower levels of VFA, factors such as duration of diabetes and glycated hemoglobin (HbA1c) level were also associated with peripheral neuropathy in patients with T2DM.

Keywords: type 2 diabetes, visceral fat, peripheral neuropathy, correlation, metabolic complications

Introduction

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder, with its prevalence steadily increasing worldwide.[1,2] In addition to directly affecting glucose metabolism, T2DM is closely associated with many severe complications, including cardiovascular diseases, nephropathy, retinopathy, and peripheral neuropathy. These complications not only impact the quality of life for patients but also increase healthcare costs and pose a serious threat to their lives.

Diabetic peripheral neuropathy (DPN) is one of the common chronic complications in patients with diabetes, which may lead to foot ulcers and amputations. This is one of the significant reasons for disability and death in diabetic patients, substantially elevating the costs of diabetes treatment. Therefore, early screening and necessary measures are crucial for the prevention and treatment of DPN. Recent studies have indicated that even in the absence of obvious obesity, patients with T2DM may have excessive visceral fat.[3,4] The excessive accumulation of visceral fat is closely associated with metabolic abnormalities such as obesity, hyperglycemia, and hyperlipidemia. Visceral fat plays a crucial role in the onset and progression of T2DM because it can release various adipocytokines, such as tumor necrosis factor-alpha (TNF-α)

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and interleukin-6 (IL-6), triggering inflammatory responses and insulin resistance, exacerbating the pathological process of diabetes. Furthermore, excessive accumulation of visceral fat may increase the risk of atherosclerotic cardiovascular diseases in patients with T2DM through pathways such as low-grade inflammation and oxidative stress, and is also believed to be closely related to diabetic nephropathy.[5] Although it is tentatively speculated that excessive accumulation of visceral fat may be associated with the occurrence of DPN in patients with T2DM, the relationship between visceral fat and diabetic complications is not fully elucidated, and relevant research is relatively limited.

Additionally, it is well-known that prolonged exposure to the metabolic derangements associated with chronic hyperglycemia is a well-established risk factor for the development of DPN. Over time, sustained high blood glucose levels can lead to oxidative stress, inflammation, and microvascular damage, all of which contribute to the progressive deterioration of peripheral nerve function and structure. Poor glycemic control, as reflected by elevated hemoglobin A1c (HbA1c) levels, has been consistently linked to an increased risk and severity of DPN. Persistent hyperglycemia can trigger a cascade of pathological processes, including the formation of advanced glycation end-products (AGEs), oxidative stress, and impaired nerve perfusion, all of which can ultimately result in peripheral nerve damage.

Against this background, this study aimed to explore the correlation between visceral fat and peripheral neuropathy in patients with type 2 diabetes, by retrospectively analyzing the clinical data of consecutive patients with type 2 diabetes admitted to our hospital to evaluate the relationship between the two. Other potential confounding factors, such as BMI, duration of diabetes, and glycemic control, were also taken into consideration. This study takes a comprehensive and innovative approach to exploring the relationship between visceral fat and peripheral neuropathy in patients with type 2 diabetes. Unlike previous research, it not only examines the direct correlation between these two factors, but also considers the potential confounding effects of diabetes duration and glycemic control. This multi-faceted analysis allows for a deeper understanding of the complex interplay between metabolic disturbances, disease progression, and the development of diabetic complications. By unveiling these intricate mechanisms, the findings from this study have the potential to inform more effective prevention and management strategies for peripheral neuropathy in the type 2 diabetes population.

Materials and Methods

Study Design and Population

This was a cross-sectional study. A retrospective analysis was conducted, including consecutive patients diagnosed with type 2 diabetes mellitus (T2DM) admitted to our hospital from December 2020 to December 2022 as study subjects. After thorough screening based on inclusion and exclusion criteria, a total of 488 cases were included. General information and biochemical indicators of all study subjects were collected. The study subjects were divided into two groups based on the presence of peripheral neuropathy, with 207 cases in the group with peripheral neuropathy (DPN+ group) and 281 cases in the group without peripheral neuropathy (DPN-group). Statistical methods were employed to assess the correlation between visceral fat and diabetic peripheral neuropathy, considering other potential confounding factors.

Ethics approval and consent to participate

This study was approved by the ethics committee of Hospital of Chengdu University of Traditional Chinese Medicine. Informed consent was obtained from all study participants. All protocols were carried out in accordance with the Declaration of Helsinki.

Inclusion Criteria

Inclusion Criteria: Participants must meet the diagnostic criteria for T2DM proposed by the American Diabetes Association. The diagnosis of DPN in this study was established through clinical assessment methods, such as the Michigan Diabetic Neuropathy Score, Toronto Clinical Neuropathy Score (TCNS), Neuropathy Symptom Score, or Neuropathy Disability Score. Additionally, electrophysiological testing, including nerve conduction studies, quantitative sensory testing (QST), or intraepidermal nerve fiber density (IENFD) analysis, may have been utilized to provide further

support for the diagnosis of DPN. The presence of DPN was confirmed during both the screening and baseline visits based on a TCNS score of 6 or higher.[6] Participants should be aged 18 or above, with no gender restrictions.

Exclusion Criteria: Exclusion criteria included patients with type 1 diabetes, gestational diabetes mellitus (GDM), or special types of diabetes. Patients with non-diabetes-related neuropathies, such as vertebral lesions, ischemic neuropathies, or neuropathic damages caused by other factors, were excluded. Patients with severe renal or hepatic dysfunction, heart diseases, or malignant tumors were also excluded. Women who were pregnant or lactating were not included in the study.

Methods

Using the electromyography instrument from Natus Manufacturing Limited (Model: DantecTMKEYPOINT 9033A07R), with participants lying supine in a quiet and temperature-controlled laboratory while awake. Each participant underwent testing of the median nerve, peroneal nerve, tibial nerve, and sural nerve, with surface electrodes recording sensory and motor nerve conduction velocities. Based on these results, all patients were grouped accordingly. Clinical data from all patients, including general information and biochemical indicators, were collected. Biochemical indicators were obtained through laboratory examinations. Initially, both groups of patients fasted for more than 8 hours, and the next morning, 15 mL of fasting venous blood was collected for testing. Biochemical indicators were analyzed using an automatic biochemical analyzer, with HbA1c measured using high-performance liquid chromatography. In addition, the visceral fat area (VFA) was measured using a human body composition analyzer.

A team of professionally trained researchers meticulously collected data on various aspects of the participants, including demographic information, lifestyle factors, medical history, diabetic foot ulceration (DFU), and medication status.

To assess the participants' physical characteristics, their weight and height were measured before breakfast, with participants wearing a single light garment and no shoes. Body mass index (BMI), a measure of general obesity, was calculated by dividing the weight in kilograms by the square of height in meters. Systolic and diastolic blood pressures (SBP and DBP) were measured on the right arm using a standard mercury sphygmomanometer, with three measurements taken and averaged.

Blood samples were collected in the morning, either after an overnight fast or 2 hours after a 75-gram oral glucose tolerance test (OGTT). Various parameters were analyzed from these blood samples, including fasting blood glucose (FBG), postprandial 2-hour 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). These measurements were performed according to relevant protocols and guidelines at a registered central laboratory accredited in accordance with the ISO 15189 standard for quality management specific to medical laboratories.

The measurement of visceral fat area (VFA) was performed after an overnight fast and urination using a bioelectrical impedance analysis (BIA) device called DUALSCAN HDS-2000 (Omron Healthcare, Kyoto, Japan), following the manufacturer's instructions. This device employs weak electric currents passed through the body to obtain body impedance measurements. The participants' hospital number, height, weight, age, and sex were entered into the analyzer. The "abdominal measurement unit" was used to assess the abdominal shape and calculate the cross-sectional area of the abdomen at the umbilicus. By placing the abdominal surface and four limbs on the electrodes, abdominal impedance was measured when a mild electric current was generated, allowing for the calculation of lean tissue area and subcutaneous abdominal fat area (SFA). VFA was defined as the cross-sectional area minus the sum of the lean tissue area and SFA.

Statistical Analysis

Data were organized and analyzed using SPSS version 26.0. Spearman correlation coefficient was used to analyze the correlation between VFA, and the presence of peripheral neuropathy in patients with type 2 diabetes mellitus. Logistic regression analysis was used to identify factors influencing the occurrence of peripheral neuropathy in patients with type 2 diabetes mellitus. Additionally, Spearman correlation coefficient and logistic regression analysis were used to explore the correlation between visceral fat and peripheral neuropathy in patients with type 2 diabetes mellitus. Continuous data were expressed as (±s) and

compared between groups using *t*-tests; categorical data were expressed as [n (%)] and compared using chi-square tests, with $P < 0.05$ indicating statistical significance.

Results

General Information

In terms of general information, the BMI of the DPN+ (24.48 ± 2.11) was lower than that of the DPN- group (26.09 ± 2.36), while the duration of diabetes mellitus (100.56 ± 49.32) was higher in the DPN+group compared to the DPN- group (86.20 ± 52.33), with statistical significance ($P < 0.05$). There were no significant differences in other indicators ($P > 0.05$). See Table 1.

Correlation

Spearman correlation analysis showed a negative correlation between Visceral Fat Area (VFA) in type 2 diabetes patients with peripheral neuropathy ($P < 0.05$). See Table 2.

Impact Factors

Logistic regression analysis indicated that Visceral Fat Area (VFA), duration of diabetes, and levels of HbA1c were all significant factors influencing the occurrence of peripheral neuropathy in type 2 diabetes patients ($P < 0.05$). See Table 3.

Table 1 Comparison of General Information Between the Two Groups of Participants

	DPN+	DPN-	t/chi-square	P
Number of Cases	207	281	–	–
Gender (male)	130	162	–	–
Age (years)	45–64	45–64	–	–
	50.56±8.24	51.33±8.13	1.028	0.304
BMI (kg/m^2)	24.48±2.11	26.09±2.36	7.787	<0.001
Duration of DM (month)	100.56±49.32	86.20±52.33	3.07	0.002
SBP (mmHg)	122.96±11.32	121.61±12.13	1.25	0.212
DBP (mmHg)	83.71±10.96	82.22±11.73	1.426	0.155
Smoking	49	67	1.567	0.245
Drinking	45	61	0.782	0.982
Hypoglycemic drugs				
SGLT-2 inhibitors (n)	15	11	9.738	0.527
Sulfonylurea (n)	45	34	8.374	0.939
DPP-4 inhibitors (n)	78	67	3.209	0.031
Alpha-glucosidase inhibitor (n)	102	91	1.283	0.111
Other oral agents (n)	200	148	1.389	0.103
Insulin (n)	178	100	4.902	<0.001
Metformin (n)	166	152	7.882	0.003
SNCV (m/s)	54.67±4.12	46.62± 5.33	2.013	<0.001
FPG (mmol/L)	10.74±3.88	9.01±2.65	6.55	<0.001
HbA1c (%)	10.88±2.73	8.83±2.47	8.663	<0.001
TC (mmol/L)	4.71±1.02	4.72±1.13	0.101	0.92
TG (mmol/L)	1.83±0.84	1.79±0.92	0.492	0.623
LDL-C (mmol/L)	2.73±0.96	2.71±0.88	0.293	0.811
HDL-C (mmol/L)	1.14±0.38	1.15±0.44	0.263	0.793
VFA (cm^2)	77.23±28.65	93.08±29.65	5.92	<0.001

Table 2 Correlation of VFA with Peripheral Neuropathy in Diabetes Patients

	r	P
VFA	−0.187	<0.001
BMI	0.672	<0.001
FBG	0.016	0.477
HbA1c	0.125	<0.001

Table 3 Logistic Regression Analysis of Factors Associated with Adverse Prognosis in Patients

	β	SE	Waldχ^2	P	OR	95% *CI*
VFA	−0.012	0.002	26.869	<0.001	0.984	0.978, 0.994
Duration of DM	0.008	0.001	19.561	<0.001	1.004	1.002, 1.008
HbA1c	0.211	0.034	3.984	<0.001	1.208	1.117, 1.396

Discussion

Visceral fat content is closely associated with insulin resistance in tissues such as the liver and muscles, and is also a significant factor contributing to cardiovascular events in type 2 diabetes mellitus (T2DM) patients. Diabetic peripheral neuropathy (DPN) is a common complication among diabetic patients and is closely related to atherosclerosis and lipid metabolism disorders, which may increase the risk of diabetic foot and amputation, severely impacting the quality of life of patients. Accumulation of visceral fat is closely associated with various metabolic diseases such as hyperglycemia and thyroid hormone abnormalities, and is also one of the important factors influencing the occurrence of peripheral neuropathy.[7,8] Studies on obese populations have suggested that T2DM and waist circumference are high-risk factors for the development of neuropathy, while other research indicates that abdominal fat is associated with low-grade inflammation, insulin resistance, and lipid metabolism abnormalities.[9,10] Prolonged increase in visceral fat may lead to chronic inflammation and promote the development of chronic metabolic diseases, while also potentially damaging endothelial function.[11,12]

This study aimed to explore the correlation between visceral fat and peripheral neuropathy in type 2 diabetes mellitus patients. Through investigation of visceral fat levels and DPN, as well as collection of other clinical data, some important conclusions were drawn. Firstly, clinical results showed that in general data, the BMI of the presence group was lower than that of the control group, while the duration of diabetes was higher than that of the control group; in terms of biochemical indicators, VFA were lower than those of the control group, while FPG and HbA1c levels were higher than those of the control group; all of which were statistically significant ($P < 0.05$), consistent with previous research findings. Dysregulation of glucose metabolism leads to oxidative stress and inflammatory responses in endothelial cells, promoting endothelial cell apoptosis, resulting in damage to vascular and nerve endothelium, thereby leading to peripheral neuropathy. In clinical practice, special attention should be paid to diabetic patients with long-term diabetes duration, poor glycemic control, and the occurrence of related complications, in order to promptly detect and treat them. Additionally, some studies have found that an increase in visceral fat area may lead to abnormalities in multiple metabolic indicators such as transaminases, blood uric acid, and blood lipids, consistent with our research results.[13,14] Furthermore, visceral adipose tissue may increase peripheral vascular resistance by activating the renin-angiotensin-aldosterone system, leading to elevated blood pressure. However, this phenomenon was not observed in our study, which may be related to the limitations of this study. Moreover, this study also found a negative correlation between visceral fat and DPN. Excessive accumulation of visceral fat is closely related to inflammatory responses and insulin resistance, which may be one of the mechanisms leading to DPN, emphasizing the important role of visceral fat in T2DM complications. Secondly, we found that factors such as age, duration of diabetes, and blood glucose control status were also associated with the occurrence of DPN. This

suggests that factors other than visceral fat may also play a role in the pathogenesis of DPN. Particularly, the duration of diabetes and the status of blood glucose control may be important factors influencing the occurrence of DPN. A study conducted by Oh et al found that middle-aged patients with T2DM and DPN had higher levels of VFA compared to those without DPN.[15] The study also revealed that an increase in VFA was associated with a 2.6% higher likelihood of DPN. However, Tayama et al conducted a different study involving 90 Japanese patients with T2DM and demonstrated a positive correlation between levels of preperitoneal fat, as determined by ultrasonography (an indicator of visceral fat deposition), and motor or sensory nerve conduction velocity.[16] The findings of the present study contradict the results reported by Oh et al. There are several possible explanations for these discrepancies, including differences in the study population, sample size, racial origins, methods used to determine VFA, diagnostic criteria for DPN, and adjustment for confounding factors. It is important to consider these variations when interpreting and comparing the results of different studies.

Some researchers have suggested that visceral adipose tissue may be involved in regulating lipid metabolism, inflammation, and cell apoptosis through the production of a large number of adipocytokines. In addition to serving as an energy reservoir, adipose tissue also acts as an endocrine organ synthesizing various biologically active factors collectively known as adipocytokines, including adiponectin, leptin, and resistin, among others.[15,16] Adiponectin is a plasma protein specifically synthesized by mature adipocytes and possesses anti-inflammatory and antioxidant properties. Resistin is a novel adipocytokine, and studies have shown that its serum levels are significantly positively correlated with visceral fat content. Resistin may induce neuronal axon growth through activation of the extracellular signal-regulated kinase-dependent pathway, exerting a protective effect on nerves. Additionally, resistin plays an important role in cellular anti-hypoxia and anti-apoptosis processes. Reduced secretion of resistin may weaken its anti-apoptotic effect, thereby promoting the occurrence of peripheral neuropathy in diabetic patients.[17,18] Therefore, it is speculated that the association between visceral fat area and abnormal nerve conduction velocity in type 2 diabetes mellitus patients may be related to the reduced secretion of adipocytokines such as adiponectin and resistin from visceral adipose tissue, but the specific mechanism needs further investigation. Furthermore, previous studies have shown that an increase in body mass index (BMI) is independently associated with the occurrence of neuropathy in type 2 diabetes mellitus patients, although this conclusion remains controversial.[19,20] In recent years, increasing evidence suggests that the development of adverse metabolism cannot be predicted solely based on BMI, which is consistent with the results of this study.[21]

The primary finding of this study that presented an unexpected inverse relationship between visceral fat and the presence of DPN was quite counterintuitive. Typically, visceral obesity is considered a significant risk factor for the development of various diabetic complications, including peripheral nerve damage. The conventional understanding is that excess visceral adiposity leads to adverse metabolic and inflammatory effects, which in turn increase the susceptibility to diabetic complications like neuropathy. However, the results of this study directly contradicted this established notion. Surprisingly, the data showed that patients who were confirmed to have DPN actually had significantly lower volumes of visceral fat compared to those without neuropathy. This inverse correlation between visceral fat content and the presence of DPN was the exact opposite of what the researchers had hypothesized at the start of the study. We propose two potential mechanisms that warrant further investigation:

1. Reduced Visceral Fat Due to Neuropathy Symptoms: Patients with more severe and advanced neuropathy may experience reduced appetite, impaired nutrient absorption, and other metabolic effects that could lead to a gradual decrease in their visceral fat accumulation over time. The neuropathy-related symptoms may thus be the driving factor behind the lower visceral fat seen in these individuals.
2. Potential Protective Effect of Lower Visceral Fat: Alternatively, it is possible that certain metabolic or inflammatory factors associated with lower visceral fat burden may confer some protective effect against the development or progression of diabetic peripheral nerve damage. This could help explain the inverse relationship observed between visceral adiposity and the presence of DPN.

The findings of this study highlight the complex and multifaceted nature of the relationship between visceral fat, metabolic disturbances, and the pathogenesis of diabetic neuropathy. The unexpected inverse correlation challenges the conventional understanding and points to the need for further research to elucidate the underlying mechanisms.

In recent years, studies have gradually regarded inflammation, mitochondrial dysfunction, oxidative stress damage, and impaired energy processing and utilization as potential central mechanisms through which metabolic syndrome affects peripheral nerves. Visceral fat may be involved in the occurrence and development of diabetic peripheral neuropathy through more complex mechanisms, which require further in-depth research in the future.

Limitations of the Research

1. Retrospective Design: The study utilized a retrospective design, which has inherent limitations such as potential bias in data collection and the inability to establish causality. Prospective studies with a larger sample size would provide more robust evidence.
2. Single-Center Study: The research was conducted in a single center, which may limit the generalizability of the findings. The results may not be representative of the entire population of patients with type 2 diabetes and peripheral neuropathy.
3. Selection Bias: The study included patients admitted to a specific hospital, which may introduce selection bias. Patients with more severe or specific conditions may be overrepresented, affecting the generalizability of the results.
4. Lack of Longitudinal Data: The study relied on cross-sectional data, providing a snapshot of the correlation between visceral fat and peripheral neuropathy at a specific point in time. Longitudinal data would be valuable to assess the temporal relationship and evaluate the predictive value of visceral fat for the development and progression of peripheral neuropathy.
5. Confounding Factors: Despite statistical adjustments, there may be unmeasured or residual confounding factors that influence the observed correlation. Factors such as lifestyle, physical activity, dietary habits, and genetic predisposition were not fully accounted for, potentially impacting the association between visceral fat and peripheral neuropathy.

Implications for Diabetes Mellitus Patients

1. Awareness of Visceral Fat: The study highlights the importance of monitoring visceral fat in patients with type 2 diabetes. Patients should be educated about the potential impact of visceral fat on the development and progression of peripheral neuropathy, emphasizing the need for lifestyle modifications and weight management strategies.
2. Comprehensive Diabetes Management: Healthcare providers should consider assessing visceral fat as part of routine care for patients with type 2 diabetes. Incorporating measures to reduce visceral fat, such as physical activity, healthy eating, and weight loss interventions, may help prevent or mitigate the risk of peripheral neuropathy.

Implications for Health Services

1. Screening and Early Detection: The findings underscore the need for early screening and detection of peripheral neuropathy in patients with type 2 diabetes, particularly those with elevated visceral fat. Health services should implement standardized protocols for the assessment of peripheral neuropathy, including regular monitoring of symptoms, clinical examinations, and nerve conduction studies.
2. Multidisciplinary Approach: Given the complex nature of diabetes complications, a multidisciplinary approach involving endocrinologists, neurologists, dieticians, and other healthcare professionals is essential. Collaborative efforts can optimize patient care, enhance education on risk factors, and develop tailored interventions targeting visceral fat reduction and glycemic control.
3. Health Promotion Strategies: Health services should prioritize health promotion strategies that emphasize the importance of maintaining a healthy weight, lifestyle modifications, and regular physical activity to reduce visceral fat and mitigate the risk of peripheral neuropathy in patients with type 2 diabetes.

Conclusion

In summary, this study identified a correlation between VFA and DPN in T2DM patients, highlighting the importance of monitoring visceral fat in such patients. In addition to lower levels of VFA, factors such as diabetes duration and levels of HbA1c are also associated with the occurrence of peripheral neuropathy in T2DM patients. These findings contribute to a deeper understanding of the pathogenesis of T2DM-related complications and provide potential targets for clinical intervention.

Disclosure

The authors report no conflicts of interest in this work.

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