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Association of brachial-ankle pulse wave velocity with subclinical diabetic peripheral neuropathy in patients with type 2 diabetes mellitus

Yue Wang[1†], Ping Liu[2,3†], Chang Shang[1], Yahui Wang[2,3], Mengfei Yuan[1], Guozhen Zhao[4], Luying Sun[1,2,3*]

[1]Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital, Beijing, China, [2]Fangshan District Traditional Chinese Medicine Hospital, Beijing, China, [3]Integrated Chinese and Western Medicine Metabolic Disease Research Center, Fangshan District Traditional Chinese Medicine Hospital, Beijing, China, and [4]Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, China

Keywords
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***Correspondence**
Luying Sun
Tel.: 18600173188
Fax: +861089324693
E-mail address:
luyingsun@outlook.com

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ABSTRACT

Aim: Subclinical diabetic peripheral neuropathy (sDPN) in patients with type 2 diabetes mellitus is insidious, but has been complicated with neurological damage. The aim of this study was to investigate the association between brachial-ankle pulse wave velocity (baPWV) and sDPN in patients with type 2 diabetes mellitus, and to provide reference for clinical prevention and treatment of sDPN.

Materials and Methods: From November 2021 to May 2024, a total of 711 type 2 diabetes mellitus patients without symptoms and signs of peripheral nerve damage were recruited. According to whether the nerve conduction velocity (NCV) was abnormal or not, they were divided into the sDPN group and the non-diabetic peripheral neuropathy (non-DPN) group. Logistic regression model, restricted cubic spline (RCS) analysis and subgroup analysis were used to evaluate the correlation between baPWV and sDPN.

Results: A total of 204 (28.69%) of the 711 participants were diagnosed with sDPN. Both amplitude and conduction velocity were negatively correlated with baPWV. In the fully adjusted model, elevated baPWV levels were significantly associated with an increased sDPN risk, with odds ratio (OR) = 1.084, 95% confidence interval (CI): (1.023, 1.148), $P = 0.006$. RCS showed a linear association between baPWV and sDPN. Subgroup analysis further confirmed that the positive association between baPWV and sDPN was consistent and robust across groups.

Conclusions: Our study indicates a pronounced link between higher baPWV and increased risk of sDPN among type 2 diabetes mellitus patients without symptoms and signs of peripheral nerve damage. These findings underscore the importance of baPWV for early identification of sDPN.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications and major disabling factors in patients with type 2 diabetes mellitus. The pathogenesis of DPN has not yet been clarified, and it is mostly thought to be related to hyperglycemia, insufficient neurotrophic support, oxidative stress induced by impaired insulin signal transduction, mitochondrial dysfunction, and inflammation[1]. Clinically, patients with type 2 diabetes mellitus are often treated for limb numbness and pain; however, studies have shown that about 50% of DPN patients have functional or structural changes in the nervous system without signs and symptoms[2]. It can be detected by electrophysiological examination, which is clinically called subclinical diabetic peripheral neuropathy (sDPN)[3]. According to the toronto diabetic neuropathy expert group[4], sDPN is defined as the presence of abnormal nerve conduction

†These authors are co-first authors of this work.

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tests without neuropathic symptoms or signs. Based on Dyck's research[5], sDPN is classified as an early stage (stage 1a) of DPN, typically characterized by a relatively mild condition. This lesion may be latent or developing, not yet resulting in typical clinical symptoms, but indicative of nerve damage. If it is not identified in time and preventive foot care is not implemented, diabetic patients have the risk of diabetic foot ulcers or even amputation. Therefore, early recognition and treatment of DPN is crucial.

At present, the clinical diagnosis of DPN is mostly based on the clinical symptoms and signs of patients. The high cost of nerve conduction examination instruments and the strict technical requirements of operators limit their application in the clinical diagnosis of DPN. However, when patients are in the early stage of DPN, specifically in sDPN, the application of the above criteria may lead to underdiagnosis, which can subsequently affect early intervention and treatment. Previous studies have shown that arterial stiffness is closely related to DPN[6]. Arterial stiffness results from structural and functional changes in the arterial wall. The artery becomes stiff with age and the occurrence of various diseases. Its cushioning function is impaired, leading to increased pressure and blood flow pulsatility, which in turn damages vascular nerves[7].

Brachial-ankle pulse wave velocity (baPWV) is a non-invasive method for detecting arterial stiffness, which has the advantages of short time-consuming, simple operation, and moderate cost, making it widely used in clinical practice. Previous studies have predominantly focused on the relationship between DPN and baPWV in clinical diagnosis. Typically, when patients present clinical symptoms, it indicates that the disease has already progressed to a certain extent. Therefore, it is of critical importance to identify the potential risk of neuropathy at an earlier stage. This study investigated the association between arterial stiffness and sDPN based on baPWV in type 2 diabetes mellitus patients without symptoms and signs of peripheral nerve damage, aiming to provide insights for early identification and prevention of DPN.

MATERIALS AND METHODS

Study design and participants

This retrospective study was conducted at the sub-center of the National Metabolic Management Center (MMC) at Fangshan Hospital of Beijing University of Traditional Chinese Medicine, spanning from November 2021 to May 2024. Inclusion criteria included: (a) patients who met the 2023 American Diabetes Association (ADA) diagnostic criteria for type 2 diabetes mellitus; (b) patients without symptoms and signs of peripheral nerve damage. Exclusion criteria included: (a) patients under 18 years old; (b) patients with missing or inaccurate data on baPWV and nerve conduction velocity (NCV). A total of 711 patients were included for analysis. Ethics approval was obtained from the Ethics Committee of Fangshan Hospital of Beijing University of Chinese Medicine (approval number: [FZYLK-2024-039]). Patient confidentiality was maintained, and informed consent was waived by the ethics committee due to the non-collection of personal patient information. All methods were conducted in accordance with relevant guidelines and regulations.

Measurement of baPWV

BaPWV was measured by trained nurses using the plethysmography apparatus (BP-203RPE III, Omron, Japan). Blood pressure cuffs were wrapped on both the arms and ankles. The heartbeat monitor was placed on the left edge of the sternum, and electrocardiogram electrodes were placed on the wrists. BaPWV measurements were taken bilaterally, and the average of these measurements was recorded[8]. High baPWV was defined as the highest quartile of values among the research participants.

Assessment of sDPN

SDPN is diagnosed by NCV. In this study, the NCV was measured using DPNcheck instruments (NEUROMetrix, USA), which were used to detect peroneal nerve conduction by trained doctors from our hospital. The instrument was positioned on the leg, with the large probe placed on the lateral side of the ankle, in the anatomical position of the lateral nerve before the Achilles tendon. The biosensor was placed in the lower calf parallel to the probe. After placing the instrument correctly, press the button to start the measurement for 10–15 s to obtain the result. The average values of amplitude (AMP) and conduction velocity (CV) are calculated based on the bilateral results[9]. If either CV or AMP falls below the threshold, DPNcheck will identify DPN. The thresholds are determined according to the manufacturer's standard data as outlined in the DPNcheck reference manual: AMP threshold = 11.2–0.099 × age (years), CV threshold = 88.5–0.13 × age (years) − 0.20 × height (cm). Any abnormality in either the sural nerve conduction velocity or amplitude in either limb was considered to be sDPN[3].

Covariates

Covariates included age, gender, education level, neck circumference, waist circumference, hip circumference, body mass index (BMI), visceral fat area (VFA), subcutaneous fat area (SFA), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), tobacco smoking, alcohol drinking, duration, medication use, comorbidities, fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), fasting insulin (FINS), fasting C-peptide (FCP), hemoglobin (Hb), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), albumin (ALB), blood urea nitrogen (BUN), serum creatinine (Cr), uric acid (UA), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and urinary albumin/creatinine ratio (UACR). BMI was calculated using the formula: BMI = weight (kg)/height^2 (m^2). In this study, variables with missing values

exceeding 10% were excluded. Missing numerical values were imputed using the mean or median, while missing categorical values were imputed using the mode.

Statistical analyses

Stata 18.0 software was used for difference analysis and regression analysis. Variables conforming to a normal distribution were presented as mean ± SD and analyzed using an independent *t*-test, while variables conforming to a non-normal distribution were presented as medians and interquartile ranges and analyzed using the Mann–Whitney *U* test. Categorical variables were described by frequency and percentage and analyzed using the Chi-square test. Univariate analysis was performed to identify the variables affecting sDPN. Multivariate logistic regression models were used to assess the associations between baPWV and sDPN in type 2 diabetes mellitus patients without symptoms and signs of peripheral nerve damage, with odds ratios (ORs) and 95% confidence intervals (CIs). Model 1 was not adjusted for any potential confounding factors. Model 2 was adjusted for age and gender. Model 3 was further adjusted for duration, tobacco smoking, alcohol drinking, SBP, HR, neck circumference, Hb, FBG, HbA1c, FCP, and insulin treatment. R 4.2.2 software was used to examine the association between AMP, CV, and baPWV using Spearman's correlation analysis, as well as to evaluate the linear relationship between baPWV and sDPN through restricted cubic spline (RCS) analysis. Finally, the following variables were used in subgroup analysis: age, gender, duration, tobacco smoking, alcohol drinking, SBP, HR, neck circumference, Hb, FBG, HbA1c, FCP, and insulin treatment. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the included participants

The study ultimately included 711 participants, of whom 204 (28.69%) were diagnosed with sDPN. The median age of this population was 59 (51–66) years, and 360 (50.63%) were male. Their baseline characteristics are summarized in Table 1. Overall, gender, duration, tobacco smoking, alcohol drinking, SBP, HR, neck circumference, Hb, UACR, FBG, HbA1c, FCP, and insulin treatment were statistically significant between participants with non-DPN and sDPN. Moreover, baPWV was higher in subjects with sDPN in both male and female (all $P < 0.05$).

BaPWV is associated with elevated risk of sDPN in type 2 diabetes mellitus participants with no signs or symptoms of neuropathy

As shown in Figure 1a,b, both AMP and CV were negatively correlated with baPWV (AMP, $R = -0.252$, $P < 0.001$; CV, $R = -0.153$, $P < 0.001$). Gender, duration, tobacco smoking, alcohol drinking, SBP, HR, neck circumference, Hb, UACR, FBG, HbA1c, FCP and insulin treatment were identified as potential interacting or confounding factors related to sDPN by univariate analysis ($P < 0.05$), as presented in supplemental Table S1. Table 2 lists the relationship between baPWV and sDPN using univariate and multivariate weighted logistic analysis. Three models were constructed: Model 1 (not adjusted for covariates), Model 2 (adjusted for gender and age), Model 3 (adjusted for gender, age, duration, tobacco smoking, alcohol drinking, SBP, HR, neck circumference, Hb, FBG, HbA1c, FCP, and insulin treatment). The OR for sDPN increased with increasing baPWV. In Model 1, the OR was 1.084 (95% CI 1.032, 1.137; $P = 0.001$). After adjustment for confounders, in Model 2, the OR was 1.137 (95% CI 1.075, 1.203; $P < 0.001$). In Model 3, the OR was 1.084 (95% CI 1.023, 1.148; $P = 0.006$). The association between baPWV and sDPN was statistically significant in both males and females, except for females in model 3. Based on whether the age of the patients with type 2 diabetes is over 60 years, they were divided into the elderly group and the non-elderly group. The results showed that, except for the elderly group in model 3, the association between baPWV and sDPN was statistically significant in both elderly and non-elderly patients. Notably, individuals belonging to the highest quartile of baPWV had a 135.5% higher risk of developing sDPN than those in the lowest quartile of baPWV. We further investigated the dose–response association between baPWV and the risk of sDPN using RCS analysis. The findings revealed that baPWV was linearly and positively related to the incidence of sDPN in Figure 2.

Subgroup analysis

Subgroup analysis results are presented in Figure 3 (Table S2). High baPWV and the risk of sDPN did not interact significantly with gender, age, duration, tobacco smoking, alcohol drinking, SBP, HR, neck circumference, Hb, FBG, HbA1c, FCP, and insulin treatment (all interactions $P > 0.05$). This suggests that the association between high baPWV and the risk of sDPN was consistent across all 13 prespecified subgroups.

DISCUSSION

The aim of this study was to investigate the relationship between baPWV and sDPN in type 2 diabetes mellitus patients without symptoms and signs of peripheral nerve damage. The analysis of the relationship between AMP, CV, and baPWV revealed significant correlations, though the associations were relatively weak. A direct and positive association with a linear trend was observed between increased baPWV levels and the risk of sDPN. Additionally, the subgroup analysis confirmed the correlation between baPWV and sDPN. These results indicate that elevated baPWV levels represent a significant risk factor for sDPN, particularly in type 2 diabetes mellitus patients without symptoms and signs of peripheral nerve damage, aiding in early detection and preventive management of DPN in this population.

Clinical diagnosis of DPN is based on neuropathic symptoms and signs. However, clinical assessment can be subjective, and its sensitivity and specificity in detecting DPN may vary depending on the patient's self-report and the severity of the

Table 1 | Comparison of baseline data between sDPN group and non-sDPN group

Variables	sDPN (n = 204)	Non-sDPN (n = 507)	P value
Gender (male, %)	125 (61.3)	235 (46.4)	<0.001
Age (years)	57.00 (49.50, 66.00)	59.00 (52.00, 66.00)	0.089
Education level (high school and above, case, %)	90 (44.1)	256 (50.5)	0.124
Disease duration (months)	111.00 (36.00, 178.50)	70.00 (15.00, 137.00)	0.001
Family history (%)	92 (45.1)	226 (44.6)	0.899
Tobacco smoking (%)			
No	125 (61.3)	375 (74.0)	0.001
Occasionally	25 (12.3)	54 (10.7)	
Daily or almost daily	54 (26.5)	78 (15.4)	
Alcohol drinking (%)			
No	109 (53.4)	320 (63.1)	0.045
Occasionally	77 (37.7)	145 (28.6)	
Daily or almost daily	18 (8.8)	78 (15.4)	
Medical history			
Hypertension (%)	129 (63.2)	319 (62.9)	0.937
Hyperlipidemia (%)	125 (61.3)	294 (58.0)	0.420
Hyperuricemia (%)	15 (7.4)	52 (10.3)	0.231
Coronary heart disease (%)	41 (20.1)	114 (22.5)	0.486
Stroke (%)	17 (8.3)	39 (7.7)	0.774
Thyroid (%)	16 (7.8)	57 (11.2)	0.177
Physical examination			
SBP (mmHg)	139.50 (127.00, 154.00)	135.00 (122.00, 149.00)	0.035
DBP (mmHg)	81.46 ± 11.73	80.23 ± 11.32	0.193
HR (bpm)	80.00 (72.00, 88.50)	77.00 (71.00, 85.00)	0.020
BMI (kg/m^2)	26.60 (24.10, 29.55)	26.30 (24.20, 28.80)	0.464
Neck circumference (cm)	38.50 (36.50, 40.50)	38.00 (35.00, 40.00)	0.002
Waist circumference (cm)	94.84 ± 10.12	93.55 ± 9.09	0.100
Hip circumference (cm)	99.25 (95.00, 104.75)	99.00 (95.00, 104.00)	0.962
VFA (cm^2)	111.00 (82.00, 139.00)	108.00 (84.00, 135.00)	0.581
SFA (cm^2)	190.50 (147.50, 232.00)	191.00 (158.00, 239.00)	0.255
Indicators			
Hb (g/L)	146.00 (136.00, 157.00)	143.00 (132.00, 154.00)	0.008
ALT (U/L)	21.00 (15.00, 32.50)	21.00 (15.00, 30.00)	0.380
AST (U/L)	20.00 (16.00, 25.00)	20.00 (16.90, 25.00)	0.838
ALP (U/L)	73.00 (59.50, 87.55)	73.40 (61.00, 88.00)	0.655
GGT (U/L)	25.00 (18.10, 39.00)	25.00 (18.00, 36.00)	0.772
ALB (g/L)	43.60 (40.60, 46.15)	43.60 (41.40, 46.10)	0.354
BUN (mmol/L)	5.45 (4.54, 6.83)	5.44 (4.52, 6.55)	0.458
Cr (μmol/L)	72.50 (60.10, 82.85)	71.00 (61.00, 82.50)	0.686
UA (μmol/L)	323.45 (268.00, 381.50)	330.00 (275.60, 384.00)	0.293
TG (mmol/L)	1.50 (1.02, 2.30)	1.50 (1.03, 2.09)	0.705
TC (mmol/L)	4.66 (3.77, 5.44)	4.60 (3.80, 5.34)	0.490
HDL-c (mmol/L)	1.17 (1.01, 1.38)	1.17 (1.00, 1.35)	0.470
LDL-c (mmol/L)	2.94 (2.29, 3.60)	2.90 (2.19, 3.53)	0.485
UACR (mg/g)	21.31 (10.63, 62.83)	18.50 (9.25, 32.00)	0.005
FPG (mmol/L)	8.71 (6.99, 11.84)	7.97 (6.71, 9.73)	<0.001
HbA1c (%)	7.90 (6.92, 9.60)	7.50 (6.51, 8.48)	<0.001
FINS (uIU/mL)	12.79 (8.56, 20.54)	12.70 (8.52, 18.53)	0.465
FCP (ng/mL)	2.17 (1.23, 3.20)	2.45 (1.65, 3.43)	0.004
baPWV-total (m/s)	16.29 (14.56, 19.14)	15.67 (14.02, 17.69)	0.003
baPWV-female (m/s)	16.87 (15.28, 19.49)	16.08 (14.46, 18.02)	0.031
baPWV-male (m/s)	15.99 (14.52, 18.84)	15.18 (13.73, 17.29)	0.006

Table 1. (*Continued*)

Variables	sDPN (n = 204)	Non-sDPN (n = 507)	P value
Medication use before admission			
Antihypertensive drugs (%)	118 (57.8)	286 (56.4)	0.727
Oral antidiabetic drugs (%)	155 (76.0)	364 (71.8)	0.256
Insulin treatment (%)	85 (41.7)	148 (29.2)	0.001

The data are summarized as the mean ± SD or median (interquartile range) for continuous variables or as a numerical proportion for categorical variables. ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BUN, blood urea nitrogen; Cr, serum creatinine; DBP, diastolic blood pressure; FCP, fasting C-peptide; FINS, fasting insulin; FPG, fasting plasma glucose; GGT, Gamma-glutamyltransferase; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; HR, heart rate; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; sDPN, subclinical diabetic peripheral neuropathy; SFA, subcutaneous fat area; TC, total cholesterol; TG, triglyceride; UA, serum uric acid; UACR, urinary albumin/creatinine ratio; VFA, visceral fat area.

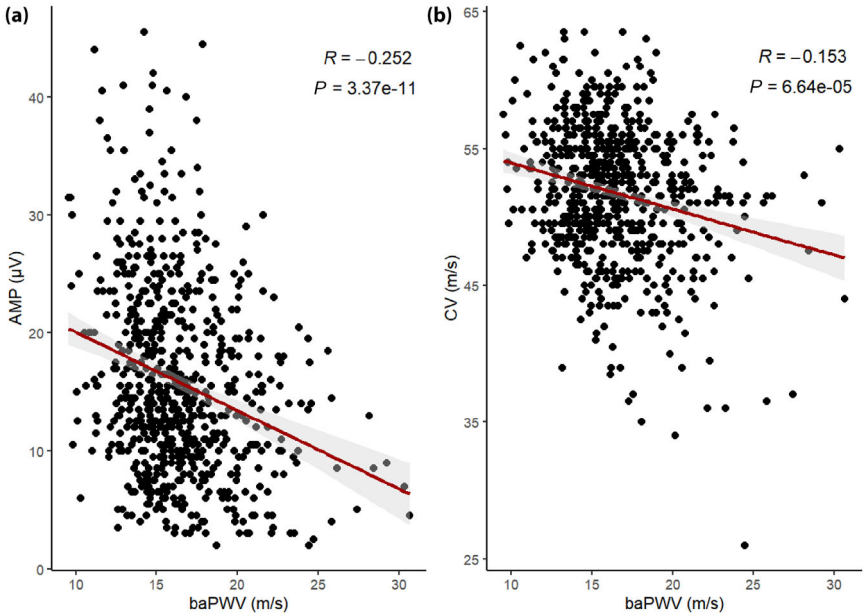

Figure 1 | Spearman's correlation coefficients of AMP, (a) and CV, (b) with baPWV. AMP, amplitude; baPWV, brachial-ankle pulse wave velocity; CV, conduction velocity.

condition[10]. Studies have shown that the progression of neuropathy is a continuous process, ranging from normal nerve function to subclinical neuropathy detectable through nerve conduction studies, and then to clinically evident neuropathy detectable through neurological examination[11, 12]. Therefore, in the early stages of DPN, when no obvious clinical symptoms and signs are present, NCV studies can detect nerve dysfunction. The DPNCheck used in this study can measure the AMP and CV of the sural nerve, which represent the number of axons capable of conducting impulses and the relative degree of myelination in the axons, respectively[13]. Previous research has found that a slight decrease in AMP and CV in early-stage patients can predict the development of DPN[14]. Therefore, identifying risk factors for sDPN, detected by NCV, is crucial for preventing further progression of the disease in diabetic patients and improving their quality of life.

BaPWV is one of the indicators used to assess arterial stiffness and is widely employed in clinical practice. The higher the baPWV, the lower the arterial compliance and stiffness, and its predictive value for cardiovascular disease has been largely confirmed[15]. Increased arterial stiffness can cause significant hemodynamic changes, such as premature return of late systolic reflection waves, elevated central pulse pressure, and increased systolic blood pressure. The decreased elasticity of blood vessels can not effectively buffer the impact of blood flow, which may lead to uneven distribution of blood flow and increase the pressure and the risk of injury of blood vessel walls in certain areas[16].

Table 2 | The association between baPWV and sDPN in type 2 diabetes mellitus participants with no signs or symptoms of neuropathy

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
baPWV-total (continuous)	1.084 (1.032, 1.137)	0.001	1.137 (1.075, 1.203)	<0.001	1.084 (1.023, 1.149)	0.006
baPWV-female (continuous)	1.116 (1.033, 1.204)	0.005	1.141 (1.047, 1.244)	0.003	1.077 (0.968, 1.198)	0.171
baPWV-male (continuous)	1.081 (1.013, 1.152)	0.018	1.134 (1.052, 1.222)	0.001	1.143 (1.050, 1.244)	0.002
baPWV-elderly (continuous)	1.096 (1.019, 1.178)	0.014	1.092 (1.014, 1.176)	0.020	1.067 (0.982, 1.160)	0.126
baPWV-non-elderly (continuous)	1.133 (1.051, 1.222)	0.001	1.147 (1.063, 1.239)	<0.001	1.157 (1.050, 1.275)	0.003
Quartiles of baPWV (categorical)						
Q1	Ref		Ref		Ref	
Q2	1.192 (0.734, 1.937)	0.478	1.368 (0.828, 2.258)	0.221	1.265 (0.747, 2.141)	0.382
Q3	1.291 (0.802, 2.079)	0.292	1.754 (1.051, 2.928)	0.032	1.581 (0.915, 2.730)	0.101
Q4	1.955 (1.230, 3.106)	0.005	2.920 (1.716, 4.967)	<0.001	2.355 (1.294, 4.286)	0.005
P for trend		0.005		<0.001		0.004

Model 1: Unadjusted. Model 2: Adjusted for age, gender. Model 3: Adjusted for age, gender, duration, tobacco smoking, alcohol drinking, SBP, HR, neck circumference, Hb, FBG, HbA1c, FCP, and insulin treatment. baPWV, brachial-ankle pulse wave velocity; CI, confidence interval; OR, odds ratio; ref, reference; sDPN, subclinical diabetic peripheral neuropathys.

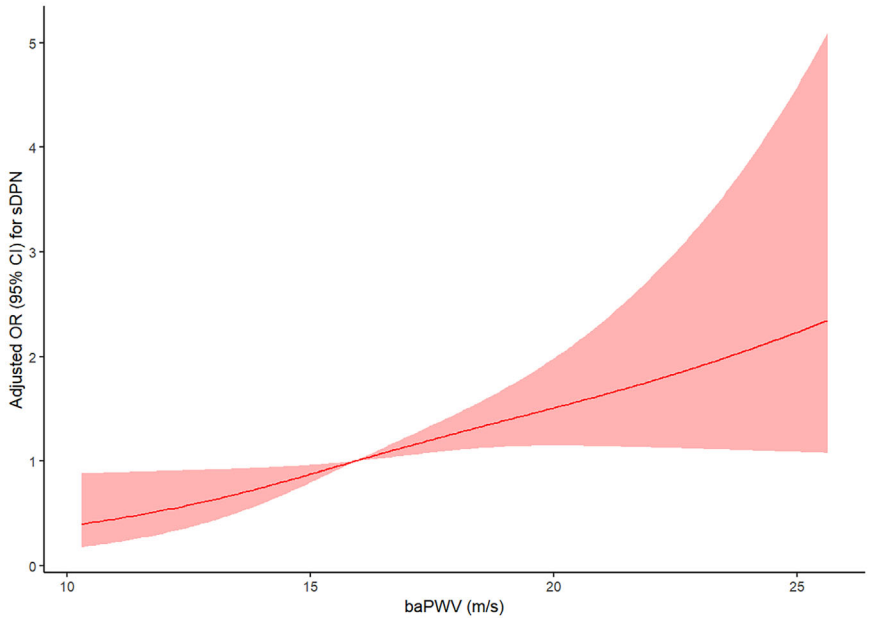

Figure 2 | RCS plot of baPWV and sDPN. baPWV, brachial-ankle pulse wave velocity. OR, odds ratio; RCS, restricted cubic spline; sDPN, subclinical diabetic peripheral neuropathys.

Studies have found a higher risk of arterial stiffness in patients with type 2 diabetes mellitus compared to individuals without type 2 diabetes mellitus. Furthermore, patients with comorbid DPN exhibit an even higher risk of arterial stiffness compared to those with type 2 diabetes mellitus alone[17]. Ha *et al.*[18] found that the max-baPWV were significantly higher in the patients with DPN compare to the patients without DPN. Yokoyama *et al.*[19] found that baPWV was significantly associated with DPN after adjusting for conventional cardiovascular risk factors, suggesting that baPWV is an important independent influencing factor in neuropathy. A recent meta-analysis of 18 studies showed that pulse wave velocity was higher in patients with DPN compared to those without DPN, further confirming the association between baPWV and DPN[6]. In addition, Tentolouris *et al.*[20] found that for every 1 m/s increase in carotid-femoral pulse wave velocity (cfPWV),

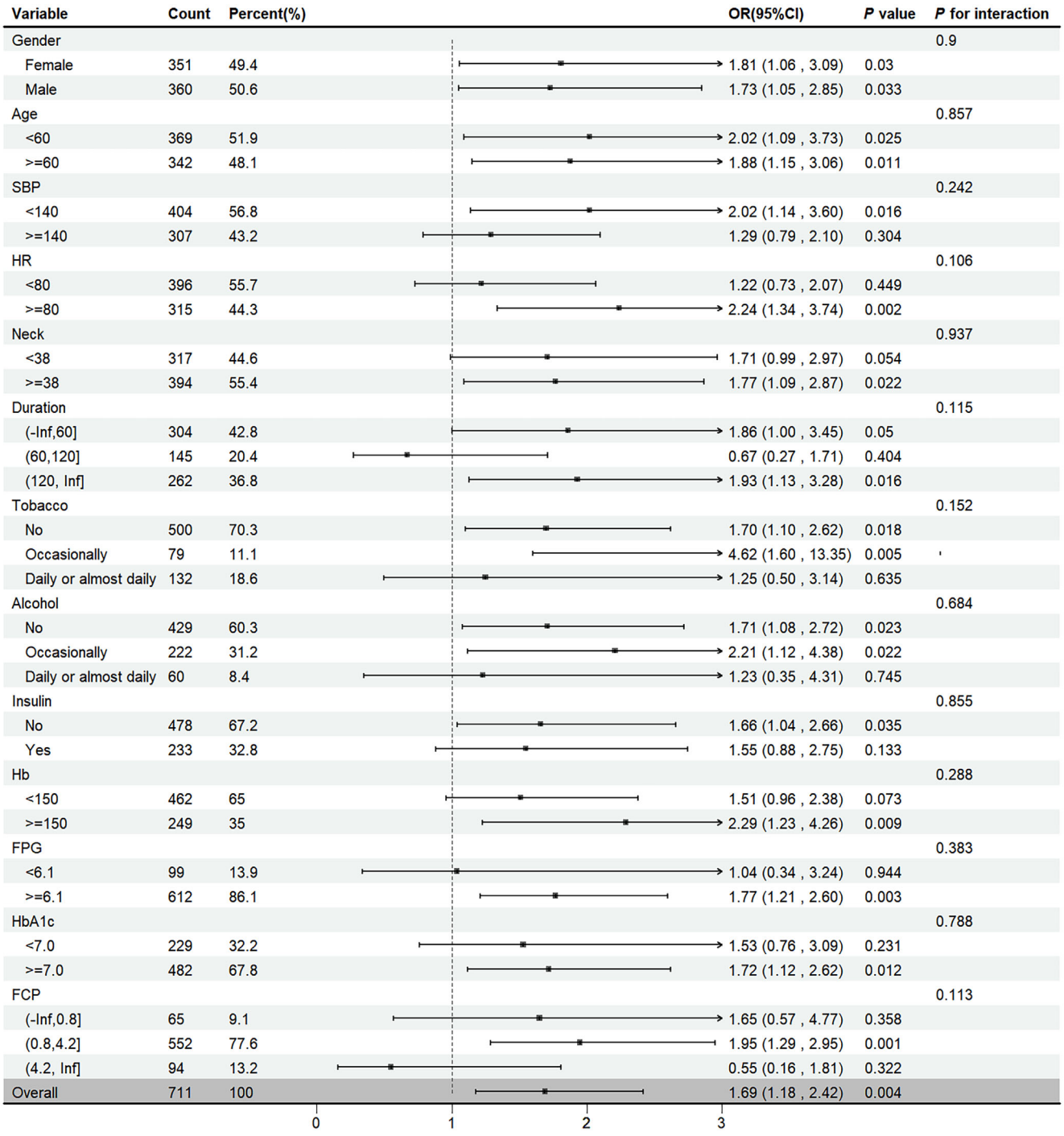

Figure 3 | Subgroup and interaction analyses of the association between baPWV and sDPN. baPWV, brachial-ankle pulse wave velocity; CI, confidence interval; DBP, diastolic blood pressure; FCP, fasting C-peptide; FPG, fasting plasma glucose; Hb, hemoglobin; HbA1c, hemoglobin A1c; HR, heart rate; Inf, infimum; OR, odds ratio; SBP, systolic blood pressure; sDPN, subclinical diabetic peripheral neuropathys.

the risk of DPN increased by 17.4%, and multifactorial linear regression analysis showed that elevated neurological function score (NDS) was significantly and independently correlated with cfPWV, which indicated that cfPWV is not only closely associated with the presence of DPN in type 2 diabetes mellitus patients, but also closely associated with the severity of DPN. A

cohort study with a median follow-up of 6.2 years found that elevated arterial stiffness can predict new or progressive DPN[21]. However, in previous studies, the diagnosis of DPN has largely relied on clinical symptoms and signs, without nerve conduction testing. This may result in sDPN patients being overlooked and misclassified as non-DPN, thus missing their potential impact on the progression of DPN. Compared to clinically diagnosed DPN, sDPN patients exhibit significantly higher sural nerve amplitude and conduction velocity in nerve conduction studies, suggesting that the nerve damage in sDPN is milder than in DPN[14]. In this context, our study elucidated the association between baPWV and sDPN in patients with type 2 diabetes mellitus. In the subclinical or early stages of DPN, neurovascular lesions are considered the predominant mechanism compared to metabolic damage, with structural or functional changes in axons thought to be related to the mechanism[22]. Previous studies[23, 24] have found that nerve NCV, as an important indicator for diagnosing and evaluating the severity of DPN, is negatively correlated with baPWV, indicating that baPWV may be an effective risk indicator for DPN even if no clinical symptoms or signs related to peripheral neuropathy have occurred. Our study confirmed this possibility.

Our study found that the association between baPWV and sDPN is robust, especially in non-elderly males. This may be attributed to physiological differences between males and females, such as differences in metabolism, hormone levels, cardiovascular health, and lifestyle factors. For example, arterial stiffness tends to develop earlier and progress more rapidly in males compared to females, and males have higher rates of smoking and alcohol consumption. Additionally, the hormonal changes occurring in females post-menopause may affect arterial elasticity, thereby influencing the relationship between baPWV and sDPN[25, 26]. In contrast, in elderly populations, the relationship between baPWV and sDPN may be influenced by various confounding factors such as comorbid chronic diseases, medication use, physical activity levels, and age-related physiological degeneration, which may weaken or obscure the association. In non-elderly males, the relationship between baPWV and sDPN is more significant, and an elevated baPWV may show a stronger correlation and predictive significance in this group.

However, the mechanism of sDPN related to arterial stiffness remains unclear. Arterial stiffness impairs vascular buffering capacity, leading to increased pressure and blood flow pulsatility. This increased pulsatility may propagate distally, impairing microcirculation[27]. In addition, they may share common physiopathological pathways, such as oxidative stress, chronic inflammation, endothelial dysfunction, formation of advanced glycation end products, and excessive activation of the renin-angiotensin system[28].

This study has several limitations. First, other indicators of arterial stiffness, such as cfPWV, were not collected in this study, despite their high correlation[29]. Second, The NCV in this study did not use electromyography system (EMGS) but instead employed the DPNcheck to measure the sural nerve AMP and CV as research indicators. Although this device has been validated in previous studies as an accurate screening tool and shows significant correlation with the results of EMGS[30, 31]. Third, Our study population consists of patients with type 2 diabetes, and whether the findings can be generalized to individuals with type 1 diabetes remains to be further investigated. Fourth, as a cross-sectional study, the causal link between baPWV and sDPN could not be confirmed. Large prospective cohort studies should be conducted to investigate the causality. Fifth, despite adjustment for potential confounders, including SBP, there may still be residual confounders that may affect the relationship between baPWV and sDPN.

CONCLUSIONS

This cross-sectional study was based on type 2 diabetes mellitus patients without symptoms and signs of peripheral nerve damage, and adjusted for potential confounding factors. The study showed that the increase of baPWV was closely related to the risk of sDPN in type 2 diabetes mellitus patients. Arterial stiffness may be used to identify people with high risk of neuropathy. In the future, accurate sDPN prediction models based on baPWV and effective early intervention programs can be developed to detect and prevent the further development of the disease. In addition, the reduction of arterial stiffness may also be one of the directions for future research on the prevention and treatment of neuropathy, but this requires further causal evidence and support from evidence-based studies.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: The study was approved by the Ethics Committee of Fangshan Hospital of Beijing University of Chinese Medicine (approval number: FZYLK-2024-039).
Informed consent: The requirement for informed consent was waived because the data were gathered from electronic medical records, and the participants' identities were anonymized.
Registry and the registration no. of the study: N/A.
Animal studies: N/A.

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SUPPORTING INFORMATION

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

Table S1 | Univariate analysis of sDPN.

Table S2 | Hierarchical analysis on the relationship of baPWV and sDPN.