



Original Article

Positive correlation of serum leptin levels and peripheral arterial stiffness in patients with type 2 diabetes

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ABSTRACT

Objective: Leptin plays a pathophysiologic role in the pathogenesis of aortic dysfunction and peripheral arterial stiffness (PAS). Our aim was to evaluate the risk factors for developing PAS and the association of leptin and PAS in patients with type 2 diabetes mellitus (DM). **Materials and Methods:** Fasting blood samples were obtained for biochemical data and leptin determinations from 105 patients with type 2 DM. In this study, we applied an automatic pulse wave analyzer (VaSera VS-1000) to measure the brachial-ankle pulse wave velocity (baPWV); a baPWV value >14.0 m/s on either side was considered high PAS. **Results:** Seventy-five patients (71.4%) had high PAS and they included a higher percentage of patients with hypertension ($P < 0.001$), older age ($P < 0.001$), and a higher body fat mass ($P = 0.043$), systolic blood pressure ($P < 0.001$), diastolic blood pressure ($P = 0.016$), serum blood urea nitrogen ($P = 0.003$), and leptin level ($P < 0.001$), and lower height ($P = 0.027$) and glomerular filtration rate ($P < 0.001$) compared with type 2 DM patients with low PAS. After adjusting for factors significantly associated with PAS in these patients by multivariate logistic regression analysis, age ($\beta = 0.470$, adjusted R^2 change = 0.279; $P < 0.001$), logarithmically transformed leptin (log-leptin, $\beta = 0.259$, adjusted R^2 change = 0.085; $P = 0.001$), and hypertension ($\beta = 0.197$, adjusted R^2 change = 0.031; $P = 0.011$) were significant independent predictors of PAS in type 2 DM patients. **Conclusion:** The serum leptin level could be a predictor of PAS in type 2 DM patients.

KEYWORDS: Brachial-ankle pulse wave velocity, Leptin, Peripheral arterial stiffness, Type 2 diabetes mellitus

INTRODUCTION

The arterial system undergoes structural and functional changes with age, characterized by endothelial dysfunction, wall thickening, reduced distensibility, and arterial stiffening [1]. Arterial stiffness represents vascular damage and has been identified as an independent risk factor for the development of cardiovascular mortality [2]. Arterial stiffness can be measured by pulse wave velocity (PWV). This method is noninvasive and reproducible and is the simplest way to measure arterial stiffness [3]. Brachial-ankle PWV (baPWV) is one measure arterial stiffness using brachial to ankle arterial wave analyses and has been used to assess peripheral arterial stiffness (PAS) compared with carotid-femoral PWV which is used to assess central arterial stiffness using carotid-to-femoral arterial waves [3,4]. A meta-analysis of 12 cohort studies confirmed that baPWV is an independent predictor for cardiovascular disease onset, and an increase of 1 m/s was associated with a 12% increase in the risk of cardiovascular

events [5]. baPWV is also a useful early marker for the detection of vascular dysfunction in patients with type 2 diabetes mellitus (DM) [6].

Leptin, a 16-kDa adipokine hormone peptide product encoded by the obesity (*ob*) gene, regulates energy balance by inhibiting hunger [7]. Leptin exerts many potentially atherogenic effects such as induction of endothelial dysfunction and stimulation of the inflammatory reaction, oxidative stress, platelet aggregation, and vascular smooth muscle hypertrophy [8]. Circulating leptin is considered a risk factor for coronary heart disease [9], and a predictor of central arterial stiffness in patients with coronary artery disease [10], hypertension [11], and kidney transplantation [12]. Moreover,

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the serum leptin level is also a predictor of PAS in kidney transplantation patients [13]. baPWV was a predictor of all-cause mortality in diabetic patients after nontraumatic lower extremity amputation [14]. The aim of the present study was to determine the risk factors for PAS and the relationship between the serum leptin concentration and PAS in type 2 DM patients.

MATERIALS AND METHODS

Participants

We enrolled 105 patients with type 2 DM from a medical center in Hualien, Taiwan from November 2014 to March 2015. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Protection of the Human Subjects Institutional Review Board of Tzu Chi University and Hospital (IRB103-136-A). Informed written consent was obtained from all participants before their enrolment in this study. The study participants were recruited in the outpatient metabolism and endocrinology clinic at Buddhist Tzu Chi General Hospital, Hualien, Taiwan. Patients were excluded if they had an acute infection, limb amputation, acute myocardial infarction, heart failure, or malignancy at the time of blood sampling, or if they refused to provide informed consent for the study.

Anthropometric analysis

Body weight of the participant was measured in light clothing and without shoes to the nearest 0.5 kg, and body height was measured to the nearest 0.5 cm. Waist circumference was measured using a tape measure around the waist from the point between the lowest ribs and the hip bones with the hands on the hips. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Bioimpedance measurements of fat mass were performed at the bedside according to the standard tetrapolar whole-body (hand-foot) technique, using a single-frequency (50 kHz) analyzer (Biodynamic-450, Biodynamics Corporation, Seattle, USA) [10-13,15,16]. All measurements were carried out by the same operator.

Biochemical investigations

Fasting blood samples (approximately 5 mL) were immediately centrifuged at $3000 \times g$ for 10 min. Serum levels of albumin, blood urea nitrogen (BUN), creatinine (Cre), fasting glucose, glycated hemoglobin, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured using an autoanalyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany) [10-13,15,16]. Serum leptin (SPI-BIO, Montigny le Bretonneux, France) concentrations were determined using a commercially available enzyme immunoassay [10-13,15]. The estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease equation in this study.

Measurements of blood pressure and brachial-ankle pulse wave velocity

After blood sampling, patients rested in the supine position for 10 min. Blood pressure was determined by an automatic upper arm oscillometric device, and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were

checked three times in the right brachial artery. Hypertension was defined as SBP ≥ 140 mmHg, and/or DBP ≥ 90 mmHg, or if the patient had received any antihypertensive medication in the past 2 weeks. Then, four pneumatic cuffs connected to both plethysmographic and oscillometric sensors were wrapped around both upper arms and ankles for the assessment of the baPWV by a volume-plethysmographic apparatus (VaSera VS-1000, Fukuda Denshi Co. Ltd., Tokyo, Japan) [13,16]. To monitor the electrocardiogram and heart sounds, a microphone was placed on the left side of the sternum, and electrocardiogram electrodes were placed on both wrists. Phonocardiography, electrography, and arterial pressure waveforms of the brachial and ankle arteries were measured, and the left-baPWV and right-baPWV were automatically calculated by the analyzer. The baPWV was calculated as the length of an arterial segment between the brachium and ankle divided by the time interval between the wavefront of the brachial waveform and that of the ankle waveform. Based on the recursive partitioning analysis in the Kyushu Prevention Study of Atherosclerosis, a baPWV of 14 m/s was considered a statistically adequate cutoff point for coronary artery events and cerebrovascular events in diabetic populations [17]. Therefore, in the present study, patients were in the high PAS group if their left or right baPWV values were >14.0 m/s [13,16,18].

Statistical analysis

Data were tested for normal distribution using the Kolmogorov–Smirnov test. Data were expressed as means \pm standard deviation (SD) for normally distributed data and comparisons between patients were performed using the Student's independent *t*-test (two-tailed). Data were expressed as medians and interquartile ranges for nonnormally distributed data (TG, fasting glucose, BUN, Cre, and leptin) and comparisons between patients were performed using the Mann–Whitney U-test. Data expressed as the number and percentage of patients were analyzed by the Chi-square test. TG, fasting glucose, BUN, Cre, and leptin were not normally distributed and underwent base 10 logarithmic transformations to achieve normality. Variables that were significantly associated with PAS in type 2 DM patients were tested for independence in multivariate forward stepwise regression analysis (adopted factors: age, hypertension, height, body fat mass, SBP, DBP, log-BUN, GFR, and log-leptin). Data were analyzed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). The $P < 0.05$ was considered statistically significant.

RESULTS

The clinical characteristics and biochemical data of our 105 type 2 DM patients are presented in Table 1. Seventy-five patients (71.4%) were in the high PAS group with a left or right baPWV value >14.0 m/s, and the others were classified as the low PAS group. Compared with the low PAS group, type 2 DM patients in the high PAS group were older age ($P < 0.001$) and had higher body fat mass ($P = 0.043$), SBP ($P < 0.001$), DBP ($P = 0.016$), BUN ($P = 0.003$), and leptin levels ($P < 0.001$), and lower height ($P = 0.027$) and GFR ($P < 0.001$). Comparisons of age and leptin levels in the high and low PAS groups in patients with type 2 DM are presented in Figure 1.

Table 1: Clinical variables of 105 diabetic patients with high and low peripheral arterial stiffness

Characteristics	All patients (n=105)	Low PAS group (n=30)	High PAS group (n=75)	P
Age (years)	60.91±14.11	49.03±13.95	65.67±11.11	<0.001*
Height (cm)	161.16±8.48	164.03±8.09	160.01±8.40	0.027*
Body weight (kg)	71.67±14.32	73.71±16.29	70.85±13.49	0.357
BMI (kg/m ²)	27.42±3.96	27.21±4.80	27.51±3.61	0.732
Body fat mass (%)	33.06±7.10	30.85±7.46	33.95±6.81	0.043*
Waist circumference (cm)	91.44±9.95	88.47±11.81	92.63±8.92	0.053
SBP (mmHg)	142.25±20.53	130.80±16.35	146.83±20.33	<0.001*
DBP (mmHg)	83.02±11.92	78.63±9.87	84.77±12.27	0.016*
Left-baPWV (m/s)	16.31±3.39	12.82±0.74	17.70±3.00	<0.001*
Right-baPWV (m/s)	16.13±3.17	12.64±0.83	17.53±2.63	<0.001*
Albumin (mg/dL)	4.27±0.27	4.34±0.31	4.25±0.25	0.088
Total cholesterol (mg/dL)	161.79±31.27	158.87±33.27	162.96±30.58	0.547
Triglycerides (mg/dL)	114.00 (89.50-162.00)	107.50 (87.50-149.00)	119.00 (90.00-171.00)	0.314
HDL-C (mg/dL)	47.10±13.17	47.30±13.66	47.01±13.06	0.920
LDL-C (mg/dL)	100.24±26.34	101.97±24.20	99.55±27.28	0.673
BUN (mg/dL)	16.00 (12.00-18.00)	13.00 (12.00-16.25)	17.00 (14.00-21.00)	0.003*
Creatinine (mg/dL)	0.80 (0.70-1.00)	0.80 (0.60-0.90)	0.90 (0.70-1.00)	0.119
GFR (mL/min)	89.09±29.06	104.64±33.81	82.88±24.52	<0.001*
Fasting glucose (mg/dL)	139.00 (121.50-172.50)	130.00 (122.50-163.75)	142.00 (121.00-175.00)	0.419
Glycated hemoglobin (%)	7.99±1.78	7.93±1.88	8.02±1.75	0.823
Leptin (ng/mL)	25.06 (20.06-34.89)	21.45 (16.00-25.38)	29.31 (20.79-41.86)	<0.001*

* $P < 0.05$ was considered statistically significant. Values for continuous variables are given as means±SD and were tested by Student's *t*-test; variables not normally distributed are given as medians and interquartile range and were tested by the Mann-Whitney U-test. PAS: Peripheral arterial stiffness, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, baPWV: Brachial-ankle pulse wave velocity, SD: Standard deviation, BMI: Body mass index, GFR: Glomerular filtration rate, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, BUN: Blood urea nitrogen

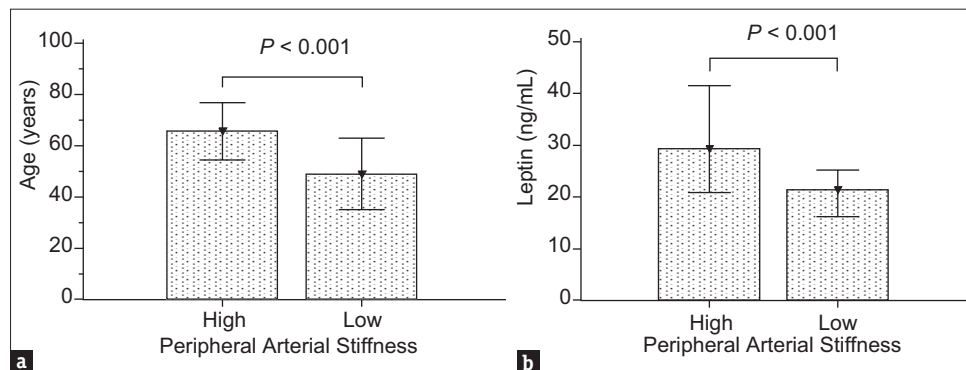


Figure 1: Comparison of (a) age (mean ± standard deviation) and (b) leptin levels (median and interquartile range) in the high and low peripheral arterial stiffness groups in patients with type 2 diabetes mellitus

The data for gender, hypertension, and drugs use are presented in Table 2. Among these patients, 59 had hypertension (56.2%). Type 2 DM patients with hypertension ($P < 0.001$) were prone to develop high PAS. No statistically significant differences in PASs were found in patients using statins, fibrates, or antidiabetic drugs.

Multivariable forward stepwise linear regression analysis was used to delineate the significant variables associated with PAS in type 2 DM patients, and the results are presented in Table 3. We found that age ($\beta = 0.470$, adjusted R^2 change = 0.279; $P < 0.001$), logarithmically transformed leptin (log-leptin, $\beta = 0.259$, adjusted R^2 change = 0.085; $P = 0.001$), and hypertension ($\beta = 0.197$, adjusted R^2 change = 0.031; $P = 0.011$) were independent predictors of PAS in type 2 DM patients.

DISCUSSION

The results of our study showed a high prevalence of PAS in patients with type 2 DM. The fasting serum leptin level, hypertension, and older age were independent predictors of PAS among the type 2 DM patients.

Arterial stiffness is related to atherosclerosis and cardiovascular disease and has been considered a strong independent predictor of coronary events and cardiovascular mortality [2]. Katakami et al. noted the cumulative incidence rates of cardiovascular events (coronary heart disease, cerebrovascular events, peripheral artery disease, and heart failure) were significantly higher in patients with high baPWV values (≥ 1550 cm/s) than those with low baPWV values (< 1550 cm/s), and a multivariate analysis in 1040 type 2 DM patients revealed that baPWV was still an independent predictor for cardiovascular events even after

Table 2: Distribution of diabetic patients with high and low peripheral arterial stiffness in subgroup analysis

Characteristics	Low PAS group (%)	High PAS group (%)	P
Gender			
Male	17 (56.7)	34 (45.3)	0.294
Female	13 (43.3)	41 (54.7)	
Hypertension			
No	22 (73.3)	24 (32.0)	<0.001*
Yes	8 (26.7)	51 (68.0)	
Statins			
No	16 (53.3)	38 (50.7)	0.805
Yes	14 (46.7)	37 (49.3)	
Fibrates			
No	29 (96.7)	71 (94.7)	0.664
Yes	1 (3.3)	4 (5.3)	
Metformin			
No	17 (56.7)	30 (40.0)	0.121
Yes	13 (43.3)	45 (60.0)	
Sulfonylureas			
No	13 (43.3)	36 (48.0)	0.665
Yes	17 (56.7)	39 (52.0)	
DDP-4 inhibitors			
No	9 (30.0)	34 (45.3)	0.149
Yes	21 (70.0)	41 (54.7)	
Thiazolidinediones			
No	30 (100.0)	74 (98.7)	0.525
Yes	0	1 (1.3)	
Insulin			
No	26 (86.7)	54 (72.0)	0.111
Yes	4 (13.3)	21 (28.0)	

* $P < 0.05$ was considered statistically significant. Data are expressed as n (%) of patients. Analysis was done using the Chi-square test. PAS: Peripheral arterial stiffness, DDP-4: Dipeptidyl peptidase 4

Table 3: Multivariable stepwise linear regression analysis of peripheral artery stiffness in 105 diabetic patients

Items	β	Adjusted R^2	Adjusted R^2 change	P
Age (years)	0.470	0.279	0.279	<0.001*
Log-leptin (ng/mL)	0.259	0.364	0.085	0.001*
Hypertension	0.197	0.395	0.031	0.011*

Data for BUN and leptin levels showed skewed distributions and therefore were log-transformed before analysis. * $P < 0.05$ was considered statistically significant in multivariable stepwise linear regression analysis (adopted factors: Age, hypertension, height, body fat mass, SBP, DBP, log-BUN, GFR, and log-leptin). BUN: Blood urea nitrogen, GFR: Glomerular filtration rate, DBP: Diastolic blood pressure, SBP: Systolic blood pressure

adjusting for conventional cardiovascular risk factors [19]. In a Mendelian randomization analysis, type 2 DM was causally associated with arterial stiffening using the measurement of baPWV in 11,385 participants from a well-defined community study in Shanghai from 2011 to 2013 [20]. Diabetes may enhance arterial stiffness through pathological changes in the vascular bed, such as reduced nitric oxide bioavailability, increased formation of advanced glycation endproducts, and collagen cross-linking in the arterial wall [21]. In this study, 71.4% of type 2 DM patients were in the high PAS group.

Age is an important determinant of PWV and induces structural and functional abnormalities such as arterial wall

hypertrophy and degeneration or disorganization of the medial layer [22]. SBP was significantly associated with baPWV in patients with type 2 diabetes [23]. The frequencies of hypertension, older age, and SBP were significantly higher in type 2 DM patients with higher baPWV values compared with those with lower baPWV values [19]. Recent study showed that each SD increase in fat percentage in the trunk was associated with a 1.03 m/s increase in baPWV [24]. Increased visceral adiposity with normal weight (BMI <25 kg/m² and visceral fat area ≥ 100 cm²) remained independently associated with baPWV levels in multivariate linear regression analysis in type 2 DM patients [25]. Our results found that hypertension, older age, body fat mass, SBP, and DBP were higher in the high PAS group than the low PAS among the type 2 DM patients. After adjustment for a variety of confounders in multivariable forward stepwise linear regression analysis, age and hypertension remained independent predictors of PAS among the type 2 DM patients.

High PWV values are significantly and independently associated with reduced GFR in normal individuals [26]. Arterial stiffness increases circumferential and shear stresses in the arterial lumen and results in endothelial dysfunction and microvascular ischemia leading to kidney injury [27]. Other possible mechanisms include chronic inflammation, oxidative stress, and activation of the renin-angiotensin system which reduce GFR [28]. Sedaghat et al. noted each SD higher PWV was associated with a 7% higher risk of incident chronic renal disease [29]. Our study revealed that the GFR was lower in the high PAS group than the low PAS among the type 2 DM patients.

Leptin has peripheral actions to stimulate vascular inflammation, oxidative stress, and vascular smooth muscle hypertrophy which may exert actions on endothelial function, vascular homeostasis, and atherogenesis [30]. Hyperleptinemia associated inversely with vasodilatation in resistance arteries by endothelial-dependent vasodilatation and endothelial-independent vasodilatation and associated with arterial stiffness and hypertension in a cross-sectional study which included 1016 participants aged 70 years [31]. Furthermore, the serum leptin level is also a predictor for PAS in kidney transplantation patients [13]. Our study also found that the leptin level was higher in the high PAS group than the low PAS among the type 2 DM patients. After multivariate stepwise linear regression analysis, log-leptin remained an independent predictor of PAS among the type 2 DM patients.

There were some limitations in this current study. First, this was an observational, single-center study with a small number of participants with type 2 DM. Second, participants in this study were not differentiated by race, limiting the conclusions of our findings in other ethnicities. Third, although we collected data on antidiabetic and anti-lipid drugs, we did not collect data on medications such as antihypertensives which could have potentially affected serum leptin levels or baPWV values. Another limitation is that the blood pressure was measured with the patient in a supine position, which may have affected the reading. Usually, blood pressure is significantly lower in the sitting than the supine position [32]. Whether a patient's

position affects baPWV values is unclear. Further long-term prospective studies are needed to follow-up on the trend between serum leptin and PAS in type 2 DM patients.

CONCLUSION

The present study revealed a high prevalence of PAS in type 2 DM patients. Hyperleptinemia positively correlated with PAS in type 2 DM patients.

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Conflicts of interest

There are no conflicts of interest.

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