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Original Research

Serum Leptin Level is Positively Correlated with Aortic Stiffness in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: The global number of people living with diabetes mellitus (DM) continues to grow. Obesity, smoking, hypercholesterolemia, and hypertension are independently correlated with the risk of cardiovascular disease (CVD) in diabetic patients regardless of differences in race or ethnicity. We aimed to investigate the relationship between serum leptin levels and aortic stiffness in patients with type 2 DM to identify cardiovascular risk at the early stage. **Methods**: A total of 128 diabetic patients were enrolled after screening for eligibility at a medical center in Eastern Taiwan. Aortic stiffness was defined as having a carotid-femoral pulse wave velocity (cfPWV) of >10 m/s using applanation tonometry. Fasting serum levels of leptin and other associated biomarkers were determined by enzyme immunoassay or biochemical analyses. **Results**: Forty-six diabetic patients with a cfPWV of >10 m/s were included in the aortic stiffness group. Compared with the control group (n = 82), our aortic stiffness group was significantly older ($p = 0.019$) and had higher body fat mass ($p = 0.002$), systolic blood pressure (SBP) ($p < 0.001$), serum triglyceride ($p = 0.02$), and serum leptin ($p < 0.001$). Aortic stiffness was also associated with insulin resistance ($p = 0.026$) and poorer blood sugar control (higher fasting glucose ($p = 0.044$) and glycated hemoglobin (HbA1c) ($p = 0.049$)). In the multivariable linear regression analyses examining the correlations between aortic stiffness and clinical variables, we found that age ($\beta = 0.291$; $p < 0.001$), SBP ($\beta = 0.176$; $p = 0.033$), logarithmically transformed urinary albumin-creatinine ratio ($\beta = 0.256$; $p = 0.002$), and serum leptin levels ($\beta = 0.244$; $p = 0.002$) were independently associated with cfPWV values. The analyses showed that only leptin was correlated with a higher probability of aortic stiffness (odds ratio: 1.055, 95% confidence interval: 1.005–1.107, $p = 0.031$). **Conclusions**: The results suggested that serum leptin is positively associated with aortic stiffness in patients with type 2 DM.

Keywords: aortic stiffness; type 2 diabetes mellitus; insulin resistance; leptin; obesity; carotid-femoral pulse wave velocity

1. Introduction

The estimated global number of people living with diabetes mellitus (DM) increased by over 400 million in the past 40 years (from 1980 to 2021), with the greatest relative increase expected to occur in middle-income countries [1,2]. Besides nonmodifiable factors such as genetic predisposition, previous gestational DM, and aging, several factors, including obesity, diet, physical activity, and smoking, could be modified to alleviate the disease course. For example, obesity can lead not only to increased circulating volume-related right and left ventricular hypertrophy but also leptin resistance, insulin resistance, and/or inflammation-mediated vascular and myocardial injury [3–5]. In a cross-sectional survey of American adults, a body mass index (BMI) of 40 or greater was associated with the development of DM (odds ratio (OR): 7.37, 95% confidence interval (CI): 6.39–8.50), elevated blood pressure (OR: 6.39, 95% CI: 5.67–7.16), and elevated cholesterol levels (OR: 1.88, 95% CI: 1.67–2.13) compared with normal BMI [6]. In diabetic patients of different races or ethnicities, obesity, smoking, hypercholesterolemia, and hypertension were all proven to be independent risk factors of cardiovascular disease (CVD), which accounts for 44% and 52% of deaths in type 1 and 2 DM, respectively [7,8]. However, the initial presentations of CVD in the diabetic population could be subtle. The most common CVD is peripheral arterial disease (16.2%), followed by heart failure (14.1%) and stable angina [9]. These findings suggest that early recognition of CVD is crucial, and pulse wave velocity (PWV) is considered a golden standard measurement of aortic stiffness—subclinical but significant alterations of aortic vascular function which can predict the future cardiovascular dysfunction [10–13].

Encoded by the obese (ob) gene, leptin is a 16-kDa cytokine that is mostly expressed in adipocytes, released into circulation and correlated with whole-body adipose tissue mass. Leptin mainly serves as a long-term system to control feeding behaviors and energy expenditure [14,15]. Generally speaking, elevated circulating leptin lev-

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els are positively associated with hypertension, atherosclerosis, myocardial infarction, cerebrovascular accidents, inflammation, and angiogenesis in obese individuals, albeit some paradoxical observations and controversies remain [16]. Although leptin exerts protective effects on cardiomyocytes against apoptosis induced by hydrogen peroxides or ischemia-reperfusion injury [17,18], unfavorable consequences, including enhanced atherosclerosis, are evident via mechanisms such as endothelial dysfunction, monocyte recruitment into intimal layers, macrophages-to-foam-cell transformation, vascular smooth muscle cell proliferation, and proatherogenic cytokine secretion [19]. In the present study, we aimed to determine the relationship between serum leptin levels and aortic stiffness in type 2 DM patients.

2. Materials and Methods

2.1 Study Design and Participants

Patients with type 2 DM who regularly visited the endocrinology and metabolism clinic of an Eastern Taiwan medical center from March 2018 to December 2018 were screened. The exclusion criteria included acute infection, acute coronary syndrome, amputation, heart failure, or malignancy upon enrollment. One-hundred twenty-eight patients were included, and all provided signed informed consents. This study was approved by the Research Ethics Committee, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (IRB106-111-A). All recruited participants were assigned to the aortic stiffness group or control group according to their carotid-femoral PWV measurement specified in the following section.

2.2 Anthropometric Measurements

Standing body height and body weight were measured and rounded up to the nearest 0.5 cm and 0.5 kg, respectively, while the participant wore light clothes without shoes. Waist circumference was taken midway through the abdomen using a tape measure during exhalation. Hip circumference was recorded by wrapping the same tape measure around the widest portion of the buttocks. BMI was calculated as body weight in kilograms divided by the square of body height in meters. Body composition was evaluated by an analyzer equipped with single-frequency (50 kHz) (Biodynamic-450, Biodynamics Corporation, Seattle, WA, USA). All aforementioned measurements were performed by the same research staff.

2.3 Biochemical Investigations

After an overnight or at least 8-h fast, approximately 5 mL of venous blood was drawn from each participant. The sample was processed immediately after 10-min centrifugation at 3000 $\times$ *g* to measure blood urea nitrogen, creatinine, triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), fasting glucose, and glycated hemoglobin (HbA1c) using an autoanalyzer (Siemens Advia 1800; Siemens Healthcare GmbH, Henkestr, Germany). Serum levels of leptin and insulin were determined using a commercially available enzyme immunoassay with a commercial kit (SPI-Bio, Montigny le Bretonneux, France; Labor Diagnostika Nord, Nordhorn, Germany, respectively) [20,21]. Insulin resistance was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR): HOMA-IR = fasting plasma glucose (mg/dL) $\times$ fasting serum insulin (µU/mL)/405. Urinary levels of albumin and creatinine were measured from a randomly voided urine sample, and the urinary albumin-creatinine ratio (UACR, mg/g) was calculated as albumin in mg/dL divided by creatinine in g/dL. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

2.4 Blood Pressure and Pulse Wave Velocity Measurements

The systolic (SBP) and diastolic blood pressure (DBP) of the dominant arm was measured using a standard mercury sphygmomanometer with an appropriately sized cuff after a 10-min seated rest in the morning. The mean SBP and DBP measured three times with a 5-min interval was taken. Carotid-femoral PWV (cfPWV) was measured with a manual sphygmomanometer (SphygmoCor system, AtCor Medical, Sydney, New South Wales, Australia) by detecting the arterial pulse waveform at the participant's common carotid and femoral arteries after resting in the supine position for longer than 10 min in a quiet and temperature-controlled room [22,23]. Simultaneous electrocardiography (ECG) recording provided R references that gated the time delay between the arrival of the pulse wave at the carotid and femoral detection sites. The "distance" was obtained by subtracting the carotid-sternal notch length from the femoral-sternal notch length. An integral software was utilized to process each set of the pulse wave and ECG recordings on a beat-to-beat basis for an average of 10 consecutive cardiac cycles. The cfPWV was calculated as the distance in meters divided by the mean time delay in seconds between the two detection sites (m/s). The built-in quality indices of the software ensured the uniformity of the data. Participants with a cfPWV of $>$10 m/s were defined as having aortic stiffness based on the European Society of Hypertension and the European Society of Cardiology guidelines. Those with a cfPWV of $\leq$10 m/s were included in the control group [10].

2.5 Statistical Analysis

The Kolmogorov–Smirnov test was used to examine the distribution of continuous variables. Normally distributed variables were expressed as mean $\pm$ standard deviation and further evaluated by Student's independent *t*-test (two-tailed). Variables that were not normally distributed were expressed as medians and interquartile ranges and evaluated by the Mann–Whitney U test or analyzed after

logarithmic transformation. Categorical variables were analyzed by the χ^2 test. Variables that were significantly correlated with aortic stiffness were examined using multivariable logistic regression analysis for independence. The correlation between cfPWV values and clinical variables of diabetic patients was first examined by simple linear regression analysis. Significant variables were further tested for independence in the multivariable forward stepwise regression model. Data analysis was performed in SPSS (Version 19.0., IBM Corp., Armonk, NY, USA). Statistical significance was considered if $p < 0.05$. We further performed a systematic search on Pubmed using free words "leptin" AND "pulse wave velocity" AND "diabetes" without restriction. After reviewing this literature, cohorts providing the Pearson's correlation (r) between serum leptin level and PWV were converted into the Fisher's z scale (z) and further pooled in the random-effect model for following meta-analyses.

3. Results

The demographic characteristics, biochemical data, and medications of 128 patients with type 2 DM are summarized in Table 1. Forty-six diabetic patients with a cfPWV of >10 m/s were included in the aortic stiffness group. Compared with the control group, the patients in the aortic stiffness group had higher serum leptin levels ($p < 0.001$) and were significantly older ($p = 0.019$), more obese (higher waist circumference, $p = 0.019$; BMI, $p = 0.033$; body fat mass, $p = 0.002$), and more hypertensive (SBP, $p < 0.001$; DBP, $p = 0.003$). Aortic stiffness was also associated with severer kidney disease (lower eGFR, $p = 0.001$; higher UACR, $p < 0.001$) and poorer blood sugar control (higher fasting glucose, $p = 0.044$; higher HbA1c, $p = 0.049$; higher HOMA-IR, $p = 0.026$) despite using similar medications to control blood pressure, glucose, and lipid.

The correlations between the severity of aortic stiffness and clinical variables of patients with type 2 DM were then examined in the simple linear regression analysis. We found that age (r = 0.359; $p < 0.001$), waist circumference (r = 0.231; $p = 0.009$), SBP (r = 0.391; $p < 0.001$), DBP (r = 0.226; $p = 0.01$), logarithmically transformed TG (r = 0.250; $p = 0.004$), log-creatinine (r = 0.232; $p = 0.008$), log-UACR (r = 0.367; $p < 0.001$), log-HOMA-IR (r = 0.190; $p = 0.03$), and serum leptin levels (r = 0.401; $p < 0.001$) were positively correlated, whereas eGFR (r = –0.350; $p < 0.001$) was negatively correlated with cfPWV values. In the multivariable linear regression analysis, we found that serum leptin levels ($\beta = 0.244$; adjusted R^2 change, 0.154; $p = 0.002$), age ($\beta = 0.291$; adjusted R^2 change, 0.055; $p < 0.001$), SBP ($\beta = 0.176$; adjusted R^2 change, 0.087; $p = 0.033$), and log-UACR ($\beta = 0.256$; adjusted R^2 change, 0.048; $p = 0.002$) were still independently associated with cfPWV values (Table 2).

Next, we performed multivariable logistic regression analysis to adjust for the aforementioned factors that were associated with aortic stiffness. Only serum leptin levels were correlated with a higher probability of developing aortic stiffness (OR: 1.055, 95% CI: 1.005–1.107, $p = 0.031$) in patients with type 2 DM (Table 3).

4. Discussion

In this study, we found that type 2 DM patients with aortic stiffness tended to be older; more obese; and have higher blood pressures, poorer blood sugar control, and significant kidney disease compared to those without. Among these well-known confounding factors, serum leptin levels were proven to be independently correlated with aortic stiffness. With a 1 ng/mL increment in serum leptin levels, the risk of aortic stiffness in patients with type 2 DM would increase by 5.5%.

Biologically, leptin contributes to maintaining metabolic homeostasis via modulating insulin secretion, hepatic glucose generation, and lipid metabolism [24–28]. Leptin increases in response to adequate fat storage to further diminish the drive to feed and to enable energy expenditure via various neuroendocrine and autonomic pathways. When individuals experience calorie restriction or stable weight reduction, the falling leptin concentration promotes behavioral adaptations to increase the desire to eat and decrease energy utilization and stores [29,30]. In our study, the aortic stiffness group had higher serum leptin levels and was more obese than the control group. A previous study found a correlation between leptin and unfavorable cardiovascular outcomes [31]. Obesity-induced perivascular adipose tissue dysfunction was also found to participate in the dysregulation of vascular tone or vascular smooth muscle cell proliferation [32,33]. Nevertheless, the coexistence of obesity and hyperleptinemia cannot be simply coined as "leptin resistance". The concentration of leptin does not ensure the activation of leptin receptors and downstream pathways, or "responsiveness"; thus, it cannot be used to directly examine the molecular mechanism underlying leptin resistance in humans. Given the lack of clinically available and quantifiable biomarkers (behavioral or metabolic) to evaluate leptin responsiveness, the more important issue would be to identify patients who may benefit from leptin therapy [34].

The direct adverse effects of leptin on the heart can be contributed to metabolic effects (reduced glucose oxidation, increased fatty acid oxidation) with a subsequent decrease in cardiac efficiency [35,36], hypertrophic effect (partial through a p38 MAPK-dependent signaling pathway) [37,38], and inflammatory effect (through regulating Tolllike receptor expression and inmate immunity activation) [39]. Leptin also has direct effects on the vasculature, including atherosclerotic effects [18,40], endothelial dysfunction resulting from the long-term effect of leptin on NO synthesis and disturbed bioavailability [41], and thrombosis induction (through platelet aggregation via cGMPinhibited 3′,5′-cyclic phosphodiesterase 3a and thrombus formation)

Table 1. Clinical variables of the 128 diabetic patients with or without aortic stiffness.

Variables	All patients (n = 128)	Control group (n = 82)	Aortic stiffness group (n = 46)	*p*
Age, years	62.27 ± 12.49	60.34 ± 11.82	65.70 ± 13.05	0.019*
Height, cm	162.65 ± 8.13	163.50 ± 8.05	161.12 ± 8.15	0.112
Body weight, kg	71.44 ± 13.08	70.85 ± 13.74	72.51 ± 11.89	0.492
Waist circumference, cm	90.88 ± 9.57	89.40 ± 10.19	93.52 ± 7.78	0.019*
Body mass index, kg/m^2	26.89 ± 3.77	26.36 ± 3.83	27.83 ± 3.51	0.033*
Body fat mass, %	30.45 ± 7.26	28.97 ± 7.09	33.08 ± 6.87	0.002*
cfPWV, m/s	9.53 ± 2.64	7.96 ± 1.27	12.35 ± 2.04	<0.001*
SBP, mmHg	141.77 ± 20.18	136.57 ± 18.25	151.02 ± 20.32	<0.001*
DBP, mmHg	82.77 ± 11.34	80.59 ± 10.63	86.65 ± 11.65	0.003*
Total cholesterol, mg/dL	162.64 ± 31.06	162.39 ± 27.32	163.09 ± 37.13	0.904
Triglyceride, mg/dL	114.50 (85.25–180.02)	109.00 (79.50–149.75)	130.50 (97.75–211.00)	0.020*
HDL-C, mg/dL	46.55 ± 12.38	47.55 ± 11.96	44.78 ± 13.04	0.227
LDL-C, mg/dL	100.38 ± 26.14	101.24 ± 23.05	98.85 ± 31.12	0.621
Fasting glucose, mg/dL	140.00 (121.00–176.75)	130.50 (118.75–166.50)	153.00 (125.50–197.00)	0.044*
Glycated hemoglobin, %	8.02 ± 1.79	7.78 ± 1.68	8.43 ± 1.92	0.049*
Blood urea nitrogen, mg/dL	16.00 (13.00–19.75)	16.00 (12.00–18.00)	18.00 (14.00–22.00)	0.044*
Creatinine, mg/dL	0.90 (0.70–1.00)	0.90 (0.70–1.00)	0.90 (0.80–1.30)	0.076
eGFR, mL/min	86.29 ± 26.94	92.04 ± 25.94	76.05 ± 25.88	0.001*
Total calcium, mg/dL	9.14 ± 0.52	9.16 ± 0.52	9.09 ± 0.53	0.462
Phosphorus, mg/dL	3.59 ± 0.51	3.54 ± 0.52	3.67 ± 0.50	0.167
UACR, mg/g	18.50 (8.28–101.45)	12.35 (7.27–36.28)	36.05 (14.78–347.25)	<0.001*
Insulin, uIU/mL	6.53 (3.17–12.99)	6.03 (3.04–11.27)	8.83 (4.44–16.30)	0.095
HOMA-IR	2.44 (1.23–4.65)	2.15 (1.02–3.63)	2.67 (1.58–5.86)	0.026*
Leptin, ng/mL	22.01 ± 10.79	19.06 ± 8.33	27.27 ± 12.64	<0.001*
Male, n (%)	76 (59.4)	53 (64.6)	23 (50.0)	0.106
Hypertension, n (%)	64 (50.0)	39 (47.6)	25 (54.3)	0.461
Metabolic syndrome, n (%)	87 (68.0)	49 (59.8)	38 (82.6)	0.008*
ACE inhibitor use, n (%)	6 (4.7)	4 (4.9)	2 (4.3)	0.892
ARB use, n (%)	52 (40.6)	29 (35.4)	23 (50.0)	0.106
β-blocker use, n (%)	17 (13.3)	8 (9.8)	9 (19.6)	0.117
CCB use, n (%)	37 (28.9)	21 (25.6)	17 (31.5)	0.991
Statin use, n (%)	62 (48.4)	39 (47.6)	23 (50.0)	0.791
Fibrate use, n (%)	4 (3.1)	2 (2.4)	2 (4.3)	0.551
Metformin use, n (%)	72 (56.3)	46 (56.1)	26 (56.5)	0.963
Sulfonylureas use, n (%)	69 (53.9)	44 (53.7)	25 (54.3)	0.940
DDP-4 inhibitor use, n (%)	76 (59.4)	50 (61.0)	26 (56.5)	0.623
Insulin use, n (%)	33 (25.8)	21 (25.6)	12 (26.1)	0.953

[1] Normally-distributed continuous variables are expressed as mean ± standard deviation and tested by Student's *t*-test; non-normally distributed variables as median (interquartile range) and tested by Mann–Whitney U test; categorical values as number (%) and compared by χ^2 test. *$p < 0.05$ was considered statistically significant.

[2] Abbreviations: cfPWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; HOMA-IR, homeostasis model assessment of insulin resistance; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DDP-4, dipeptidyl peptidase 4.

[42–44]. Altogether, leptin could result in increased arterial stiffness [45,46].

Although several studies have attempted to analyze the relationship between serum leptin and arterial stiffness to provide evidence of leptin as an independent cardiovascular risk factor in different cohorts, inconsistencies, and heterogeneities still exist. In a meta-analysis of observational studies published by D'Elia *et al.* [47], 11 cohorts with a total of 7580 participants of different disease backgrounds were included. Their pooled analysis demonstrated a positive correlation between serum leptin level and PWV value, albeit great heterogeneity existed across these studies. To address this issue specifically in diabetic cohorts, we reviewed the studies of Teoh *et al.* [48] and Khiyami *et al.* [49] and found that log-transformed leptin was not associated with arterial stiffness. Another study published by

Table 2. Correlation between carotid-femoral pulse wave velocity and clinical variables among patients with diabetes.

Variables	Carotid-femoral pulse wave velocity (m/s)				
	Simple linear regression		Multivariable linear regression		
	r	*p*	Beta	ΔR^2	*p*
Female	0.116	0.194	—	—	—
Hypertension	0.163	0.065	—	—	—
Age (years)	0.359	<0.001*	0.291	0.055	<0.001*
Height (cm)	–0.114	0.200	—	—	—
Body weight (kg)	0.064	0.475	—	—	—
Waist circumference (cm)	0.231	0.009*	—	—	—
Body mass index (kg/m^2)	0.168	0.058	—	—	—
Body fat mass (%)	0.250	0.004*	—	—	—
Systolic blood pressure (mmHg)	0.391	<0.001*	0.176	0.087	0.033*
Diastolic blood pressure (mmHg)	0.226	0.010*	—	—	—
Total cholesterol (mg/dL)	–0.032	0.719	—	—	—
Log-Triglyceride (mg/dL)	0.250	0.004*	—	—	—
HDL-C (mg/dL)	–0.120	0.178	—	—	—
LDL-C (mg/dL)	–0.118	0.183	—	—	—
Log-Glucose (mg/dL)	0.123	0.168	—	—	—
Glycated hemoglobin (%)	0.134	0.132	—	—	—
Log-BUN (mg/dL)	0.189	0.033*	—	—	—
Log-Creatinine (mg/dL)	0.232	0.008*	—	—	—
eGFR (mL/min)	–0.350	<0.001*	—	—	—
Log-UACR (mg/g)	0.367	<0.001*	0.256	0.048	0.002*
Total calcium (mg/dL)	–0.063	0.479	—	—	—
Phosphorus (mg/dL)	0.050	0.574	—	—	—
Log-Insulin (uIU/mL)	0.167	0.060	—	—	—
Log-HOMA-IR	0.190	0.030*	—	—	—
Leptin (ng/mL)	0.401	<0.001*	0.244	0.154	0.002*

[1] Values of triglyceride, glucose, BUN, creatinine, UACR, insulin, and HOMA-IR were log-transformed to avoid skewness before analysis.

[2] Analyses were performed using a simple linear regression model or multivariable stepwise linear regression model (adopted factors included age, waist circumference, body fat mass, systolic blood pressure, diastolic blood pressure, log-triglyceride, log-BUN, log-creatinine, eGFR, log-UACR, log-insulin, log-HOMA-IR, and leptin). *$p < 0.05$ was considered statistically significant.

[3] Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; HOMA-IR, homeostasis model assessment of insulin resistance.

Yu *et al*. [50] included patients with obesity and diabetes. After pooling with our own data, we demonstrated a significant and positive correlation between leptin and PWV (r = 0.38, 95% CI: 0.24–0.50, $p < 0.01$) using a random-effect model. The Cochrane Q test was used to evaluate statistical heterogeneity, and a *p*-value of 0.53 for Q indicated unlikely heterogeneity (Fig. 1) [51].

We acknowledge that there are still some limitations in this study. The small size and single-center, cross-sectional design of this study might hamper the generalizability of our findings to the whole population. Although the multivariable regression analysis was performed, age, SBP, albuminuria, and leptin still affected cfPWV. Although we analyzed the major components of metabolic syndrome in the multivariable logistic regression model, only leptin positively correlated with aortic stiffness. Whether the metabolic syndrome exerts a mediator effect between leptin and aortic stiffness in diabetes patients is still unresolved, given its high prevalence in our study participants (68%). Nevertheless, leptin is found to positively correlate with arterial stiffness across patients with different diseases [47]. Therefore, a population-based, longitudinal cohort study might be worthy to establish in order to address the long-term effect of leptin on cardiovascular disease.

5. Conclusions

Our study suggested that higher serum leptin levels were significantly associated with aortic stiffness that was diagnosed by carotid-femoral pulse wave velocity in type 2 DM patients.

Table 3. Multivariable logistic regression analysis of the factors correlated with aortic stiffness among the 128 diabetic patients.

Variables	Odds ratio	95% confidence interval	*p*
Leptin, 1 ng/mL	1.055	1.005–1.107	0.031*
Age, 1 year	1.035	0.983–1.089	0.194
Body mass index, 1 kg/m^2	1.019	0.811–1.281	1.019
Waist circumference, 1 cm	1.000	0.916–1.093	0.992
Body fat mass, 1%	1.050	0.976–1.130	0.194
Systolic blood pressure, 1 mmHg	1.011	0.977–1.046	0.547
Diastolic blood pressure, 1 mmHg	1.016	0.957–1.078	0.609
Estimated glomerular filtration rate, 1 mL/min	0.986	0.964–1.008	0.217
Urine albumin-to-creatinine ratio, 1 mg/g	1.000	1.000–1.001	0.392
Fasting glucose, 1 mg/dL	1.007	0.994–1.020	0.296
Triglyceride, 1 mg/dL	0.998	0.991–1.005	0.617
Insulin, 1 uIU/mL	0.997	0.845–1.177	0.974
HOMA-IR	1.048	0.712–1.542	0.814

[1] Analysis was performed by using the multivariable logistic regression model with adopting factors that were found with significance in Table 1. *$p < 0.05$ was considered statistically significant.

[2] Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance.

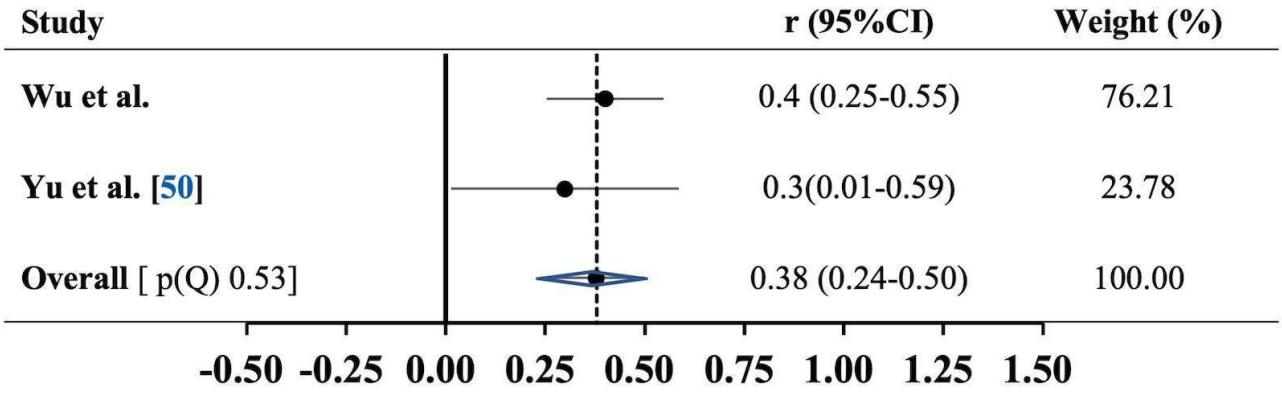

Fig. 1. Association between carotid-femoral pulse wave velocity and serum leptin levels. Results are expressed as correlation (r) and 95% confidence intervals (95% CI). Horizontal lines represent 95% CI. Diamond indicates the overall correlation with its 95% CI. Heterogeneity *p*-value of Cochrane Q test, (*p*(Q)).

Availability of Data and Materials

The dataset that used, analyzed, or generated in this research is available from the corresponding author, BGH., upon reasonable request.

Author Contributions

BGH and DAW designed and performed the research study. DAW provided help and advices. BGH and TJW analyzed the data. TJW wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The Research Ethics Committee, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation had granted the ethical approval of this study (IRB106-111-A). All of the patients provided signed informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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