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Original Article

Association of hyperleptinemia with peripheral arterial disease in hypertensive patients

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Abstract

Objective: Hypertension is a risk factor for peripheral artery disease (PAD). Serum leptin plays an important role in promoting endothelial dysfunction. The aim of this study is to investigate whether the leptin level is associated with PAD in hypertensive patients. **Materials and Methods:** Ninety-eight hypertensive patients were enrolled in this study. Ankle-brachial index (ABI) values were measured using an automated oscillometric device. Patients with an ABI value <0.9 were considered the low ABI group. C-reactive protein (CRP) was measured using standard enzymatic automated methods. Serum levels of human leptin were determined using a commercially available enzyme immunoassay. **Results:** Eighteen (18.4%) hypertensive patients were included in the low ABI group. Hypertensive patients in the low ABI group had higher serum creatinine ($P < 0.001$), CRP ($P = 0.003$), and leptin ($P < 0.001$) levels, higher prevalence of diabetes ($P = 0.036$), and current smoking ($P = 0.034$) than patients in the normal ABI group. Univariate linear regression analyses revealed that body weight ($P = 0.014$), waist circumference ($P = 0.010$), body mass index ($P = 0.002$), and logarithmically transformed CRP (log-CRP, $P = 0.001$) were positively correlated with serum log-leptin levels in hypertensive patients. Multivariate stepwise linear regression analysis showed that log-leptin ($\beta = 0.439$, adjusted R^2 change = 0.224, $P < 0.001$) was also an associated factor of PAD in hypertensive patients. **Conclusion:** A higher log-leptin value is an independent predictor of PAD in hypertensive patients.

Keywords: *Ankle-brachial index, Hypertension, Leptin, Peripheral arterial disease*

Introduction

Leptin, one of the adipokines mainly produced by white adipose tissue, is a 16 kDa nonglycosylated protein [1]. Before 1994, adipose tissue was thought to be only an energy storage tissue, but in recent decades, it has become known as an active regulator of physiological processes [2]. Leptin regulates a variety of processes, including vascular function, inflammation, and immunity [3]. In the cardiovascular system, leptin exerts atherogenic, thrombotic, and angiogenic reactions; thus, hyperleptinemia contributes to endothelial dysfunction especially in hypertensive obese patients [4]. Furthermore, leptin has been linked closely to cardiovascular disease including atherosclerosis, myocardial infarction, and stroke [5].

Peripheral arterial disease (PAD) is a systemic atherosclerotic disease, and it is estimated that >200 million people have it worldwide [6]. The symptoms of PAD range from none to severe, and symptomatic PAD is associated with decreased quality of life and reduced functional capacity [6]. Previous studies focused primarily on intermittent claudication as a marker for PAD, but now, a more objective and inexpensive tool, the ankle-brachial index (ABI), is used because of its high sensitivity and specificity [7].

An evaluation of adipokine markers secreted by adipose tissue showed lower levels of adiponectin and higher levels of leptin in PAD patients than in controls [8]. Leptin levels were higher in patients with uncontrolled hypertension (HTN) than those with controlled HTN [9]. Furthermore, hyperleptinemia was a predictor for arterial stiffness in HTN patients [10] and a critical factor in insulin resistance [4]. However, we could find no research on leptin and PAD in HTN patients, so the aim of this study is to examine the relationship between serum leptin levels and PAD in HTN patients.

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Materials and methods

Patients

From January to December 2012, 98 HTN patients were enrolled at a medical center in Hualien, Taiwan. The blood pressure (BP) of each patient was measured after sitting for at least 10 min in the morning by trained staff using standard mercury sphygmomanometers with appropriate cuff sizes. Systolic BP (SBP) and diastolic BP (DBP) were taken three times at 5-min intervals and averaged for analysis. Patients were regarded as having HTN if they had SBP ≥ 140 mmHg, DBP ≥90 mmHg, or had received any anti-HTN medication in the past 2 weeks. Patients were diagnosed with diabetes mellitus (DM) if their fasting plasma glucose level was ≥126 mg/dL or they had used oral hypoglycemic medications or insulin [11]. The Protection of Human Subjects Institutional Review Board of Tzu Chi University and Hospital had approved this study. All patients provided informed consent before participating in this study (IRB099-97). Patients were excluded from the study if they had an acute infection, acute myocardial infarction, or pulmonary edema; used protease-activated receptor-1 antagonists or warfarin at the time of blood sampling; or declined to provide informed consent.

Anthropometric analysis

Waist circumference was measured using a tape measure at the point between the lowest ribs and the hip bones with the hands on the hips. Participants' weight was measured in light clothing and without shoes to the nearest 0.5 kg, while height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared [12-15].

Biochemical investigations

Fasting blood samples (approximately 5 mL) were immediately centrifuged at 3000 ×*g* for 10 min. Serum levels of blood urea nitrogen, creatinine (Cre), fasting glucose, total cholesterol, triglycerides (TGs), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total calcium, phosphorus, and C-reactive protein (CRP) were measured using an autoanalyzer (COBAS Integra 800; Roche Diagnostics, Basel, Switzerland) [12-15]. Serum leptin (SPI-Bio, Montigny-le-Bretonneux, France) concentrations and intact parathyroid hormone (iPTH; Diagnostic Systems Laboratories, Webster, TX, USA) were determined using a commercially available enzyme immunoassay and enzyme-linked immunosorbent assay, respectively [12-15].

Ankle-brachial index measurements

Using an oscillometric method, ABI values were measured using an ABI-form device (VaSera VS-1000; Fukuda Denshi Co., Ltd., Tokyo, Japan) that automatically and simultaneously measures BP in both arms and ankles [16]. With the participants lying in the supine position, occlusion and monitoring cuffs were placed tightly around the four extremities, an electrocardiogram was recorded, and heart sounds were measured for at least 10 min. The ABI was calculated as the ratio of the ankle SBP divided by the arm SBP, and the lowest value of the ankle SBP was used for the calculation. We repeatedly measured these parameters in both legs of each participant and expressed the mean values. PAD was diagnosed based on an ABI <0.9 [17]. In this study, left or right side ABI values <0.9 were used to define the low ABI group.

Statistical analysis

Data were tested for normal distribution using the Kolmogorov–Smirnov test. Normally distributed data are expressed as mean ± standard deviation and comparisons between patients were performed using Student's independent *t*-test (two-tailed). Nonnormally distributed data were expressed as medians and interquartile ranges and comparisons between patients were performed using the Mann–Whitney U-test (TG, fasting glucose, iPTH, CRP, and leptin). Data expressed as the number of patients were analyzed by the Chi-square test. The TG, fasting glucose, iPTH, CRP, and leptin levels were not normally distributed and underwent base 10 logarithmic transformations to achieve normality. Clinical variables that correlated with serum logarithmically transformed leptin (log-leptin) levels in HTN patients were evaluated using univariate linear regression analysis. Variables that were significantly associated with log-leptin levels in HTN patients were tested for independence in multivariate forward stepwise regression analysis. Variables that were significantly associated with PAD were tested for independence in multivariate stepwise linear regression analysis (adapted factors: smoking, diabetes, Cre, log-CRP, and log-leptin). The receiver operating curve (ROC) was used to calculate the area under the curve (AUC) to identify the best cutoff value for the log-leptin level in predicting PAD in hypertensive patients. Data were analyzed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

The clinical and laboratory characteristics of the 98 HTN patients are shown in Table 1. Twenty-nine patients (29.6%) had DM and 77 patients (78.6%) had dyslipidemia. Eighteen HTN patients (18.4%) were included in the low ABI group. Patients in the low ABI group had higher serum Cre ($P < 0.001$), CRP ($P = 0.003$), and leptin ($P < 0.001$) levels, higher prevalence of diabetes ($P = 0.036$), and current smoking ($P = 0.034$) than those in the normal ABI group. The drugs used by patients included angiotensin-converting enzyme inhibitors (ACEi; $n = 36$; 36.7%), angiotensin receptor blockers (ARB; $n = 55$; 56.1%), β-blockers ($n = 55$; 56.1%), calcium channel blockers (CCB; $n = 44$; 44.9%), statins ($n = 53$; 54.1%), fibrates ($n = 25$; 25.5%), aspirin ($n = 59$; 60.2%), and clopidogrel ($n = 22$; 22.4%). There were no statistically significant differences based on gender, dyslipidemia, or use of ACEi, ARB, β-blockers, CCB, statins, fibrates, aspirin, or clopidogrel between the two groups. The leptin levels also did not differ statistically based on gender, coexisting diabetes or dyslipidemia, or ACEi, ARB, β-blocker, CCB, statin, fibrate, aspirin, or clopidogrel use [Table 2].

Univariate and multivariate linear analyses of the clinical variables associated with the serum leptin levels in HTN patients are shown in Table 3. Body weight ($r = 0.247$; $P = 0.014$), waist circumference ($r = 0.259$; $P = 0.010$),

Table 1: Clinical variables of the 98 hypertensive patients in the normal and low ankle brachial index group

Characteristic	All patients (*n*=98)	Normal ABI group (*n*=80)	Low ABI group (*n*=18)	*P*
Age (years)	64.72±9.92	64.39±9.10	66.22±13.18	0.481
Height (cm)	161.38±8.37	161.62±8.34	160.33±8.64	0.559
Body weight (kg)	69.87±13.00	69.61±12.45	71.00±15.55	0.685
Waist circumference (cm)	93.53±11.12	93.20±10.69	95.00±13.12	0.538
BMI (kg/m^2)	26.72±3.81	26.56±3.72	27.39±4.20	0.405
Left ABI	1.07±0.12	1.11±0.07	0.89±0.10	<0.001*
Right ABI	1.05±0.13	1.10±0.08	0.84±0.10	<0.001*
SBP (mmHg)	133.31±16.61	132.45±16.84	137.11±15.39	0.284
DBP (mmHg)	74.80±10.72	74.63±10.51	75.56±11.89	0.741
TCH (mg/dL)	173.88±40.88	171.04±40.67	186.50±40.51	0.148
TG (mg/dL)	128.00 (94.005-170.50)	125.00 (94.00-178.00)	134.50 (101.00-156.75)	0.840
HDL-C (mg/dL)	44.82±12.73	44.29±11.85	47.17±16.27	0.389
LDL-C (mg/dL)	102.11±31.57	100.56±33.35	109.00±21.40	0.308
Fasting glucose (mg/dL)	108.00 (96.00-139.50)	107.50 (96.00-137.00)	114.50 (95.25-173.50)	0.734
Blood urea nitrogen (mg/dL)	17.18±5.80	17.15±5.12	19.50±8.08	0.121
Creatinine (mg/dL)	1.16±0.32	1.11±0.29	1.41±0.37	<0.001*
Total calcium (mg/dL)	9.13±0.38	9.12±0.39	9.14±0.32	0.851
Phosphorus (mg/dL)	3.51±0.52	3.53±0.52	3.43±0.53	0.458
iPTH (pg/mL)	47.70 (32.40-63.05)	47.40 (32.95-61.90)	49.05 (30.23-67.43)	0.854
CRP (mg/dL)	0.21 (0.15-0.27)	0.19 (0.14-0.26)	0.26 (0.21-0.72)	0.003*
Leptin (ng/mL)	13.36 (3.98-44.04)	8.90 (3.56-24.84)	56.58 (31.88-89.82)	<0.001*
Male, *n* (%)	66 (67.3)	55 (68.8)	11 (61.1)	0.532
Diabetes, *n* (%)	29 (29.6)	20 (25.0)	9 (50.0)	0.036*
Dyslipidemia, *n* (%)	77 (78.6)	65 (81.3)	12 (66.7)	0.173
Smoking, *n* (%)	9 (9.2)	5 (6.3)	4 (22.2)	0.034*
ACE inhibitor use, *n* (%)	36 (36.7)	30 (37.5)	6 (33.3)	0.740
ARB use, *n* (%)	55 (56.1)	44 (55.0)	11 (66.1)	0.637
β-blocker use, *n* (%)	55 (56.1)	42 (52.5)	13 (72.2)	0.128
CCB use, *n* (%)	44 (44.9)	38 (47.5)	6 (33.3)	0.275
Statin use, *n* (%)	53 (54.1)	43 (53.8)	10 (55.6)	0.890
Fibrate use, *n* (%)	25 (25.5)	20 (25.0)	5 (27.8)	0.807
Aspirin use, *n* (%)	59 (60.2)	46 (57.5)	13 (72.2)	0.249
Clopidogrel use, *n* (%)	22 (22.4)	20 (25.0)	2 (11.1)	0.202

*Values of $P<0.05$ were considered statistically significant. Values for continuous variables are shown as mean±SD after analysis by Student's *t*-test; variables not normally distributed are shown as median and interquartile range after analysis by the Mann–Whitney U-test; values presented as *n* (%) are shown after analysis by the Chi-square test. ABI: Ankle brachial index, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, CRP: C-reactive protein, ACE: Angiotensin-converting enzyme, ARB: Angiotensin-receptor blocker, CCB: Calcium-channel blocker, SD: Standard deviation, BMI: Body mass index, TCH: Total cholesterol, iPTH: Intact parathyroid hormone, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TGs: Triglycerides

BMI (r = 0.311; P = 0.002), and log-CRP (r = 0.332; P = 0.001) were positively correlated with the serum log-leptin levels in HTN patients. Multivariate forward stepwise linear regression analysis of the variables significantly associated with the fasting serum log-leptin levels revealed that BMI (β = 0.292; P = 0.002) and log-CRP (β = 0.315; P = 0.001) were independent predictors of log-leptin values for HTN patients.

Multivariable stepwise linear regression analyses of PAD in HTN patients are shown in Table 4. Log-leptin level (β = 0.439; adjusted R^2 change = 0.224; P < 0.001) and Cre (β = 0.302; adjusted R^2 change = 0.083; P = 0.001) were independent predictors of PAD for HTN patients. Plotting of the ROC curve for prediction of PAD revealed that the AUC was 0.874 (95% confidence interval, 0.792–0.933; P < 0.001) and the sensitivity was 88.89% and specificity was 76.25% at a cuff value of 1.40 ng/mL for the serum log-leptin level [Figure 1].

Discussion

In this study, we found that the HTN patients who were in the low ABI group had higher serum Cre, CRP, and leptin levels, were more likely to have diabetes, and be current smokers than those in the normal ABI group. The serum log-leptin level was an independent factor of PAD in HTN patients after multivariate analysis. In this population, BMI and log-CRP were correlated with the serum log-leptin level after multivariate analysis.

One study reported an 8.7% prevalence of PAD in Han Chinese patients with HTN at around 58 years of age [18]. The prevalence of PAD was sharply age related, rising >10% among those 60–70 years old [6]. In our study, the prevalence of PAD was 18.4% in HTN patients at a mean age of 65 years. Inflammation is involved in the development and progression of atherosclerosis and cardiovascular disease [19]. CRP is a special marker of inflammation which is related to

Table 2: Clinical characteristics and serum leptin levels of 98 hypertensive patients

Characteristic	*n* (%)	Leptin (ng/mL)	*P*
Sex			
Male	66 (67.3)	11.11 (3.38-33.77)	0.054
Female	32 (32.7)	22.01 (6.67-45.94)	
Diabetes			
No	69 (70.4)	13.01 (3.97-41.88)	0.439
Yes	29 (29.6)	15.72 (4.11-50.86)	
Dyslipidemia			
No	21 (21.4)	18.85 (3.78-50.03)	0.533
Yes	77 (78.6)	12.62 (3.97-39.67)	
ACE inhibitors			
No	62 (63.2)	13.36 (4.11-35.33)	0.674
Yes	36 (36.8)	15.93 (3.75-46.10)	
ARB			
No	43 (43.9)	13.01 (4.17-46.34)	0.425
Yes	55 (56.1)	13.49 (3.84-32.89)	
β-blockers			
No	43 (43.9)	13.01 (2.91-35.53)	0.286
Yes	55 (56.1)	15.72 (4.78-46.12)	
CCB			
No	54 (55.1)	10.30 (3.58-41.20)	0.349
Yes	44 (44.9)	15.77 (5.77-44.99)	
Statins			
No	45 (45.9)	16.24 (5.59-44.31)	0.329
Yes	53 (54.1)	9.27 (3.63-40.38)	
Fibrates			
No	73 (74.5)	13.49 (4.08-44.31)	0.864
Yes	25 (25.5)	12.62 (3.75-39.95)	
Aspirin			
No	39 (39.8)	16.24 (6.58-33.53)	0.324
Yes	59 (60.2)	12.29 (3.30-48.56)	
Clopidogrel			
No	76 (77.6)	17.03 (4.64-45.26)	0.052
Yes	22 (22.4)	6.54 (3.13-19.71)	

*Values of $P<0.05$ were considered statistically significant after analysis by the Mann–Whitney U-test. Data are expressed as median and interquartile range after analysis by the Mann–Whitney U-test. ACE: Angiotensin-converting enzyme, ARB: Angiotensin-receptor blocker, CCB: Calcium-channel blocker

Table 3: Correlation between log-leptin levels and clinical variables among the 98 hypertensive patients

Variable	Log-leptin (ng/mL)			
	Univariate		Multivariate	
	r	*P*	β	*P*
Age (years)	−0.050	0.628	-	-
Height (cm)	−0.004	0.972	-	-
Body weight (kg)	0.247	0.014*	-	-
Waist circumference (cm)	0.259	0.010*	-	-
BMI (kg/m^2)	0.311	0.002*	0.292	0.002*
SBP (mmHg)	−0.040	0.697	-	-
DBP (mmHg)	0.138	0.176	-	-
TCH (mg/dL)	0.186	0.066	-	-
Log-TG (mg/dL)	0.172	0.090	-	-
HDL-C (mg/dL)	0.059	0.564	-	-
LDL-C (mg/dL)	0.105	0.306	-	-
Log-glucose (mg/dL)	−0.018	0.858	-	-
Blood urea nitrogen (mg/dL)	0.086	0.399	-	-
Creatinine (mg/dL)	0.140	0.169	-	-
Total calcium (mg/dL)	0.024	0.812	-	-
Phosphorus (mg/dL)	−0.005	0.961	-	-
Log-iPTH (pg/mL)	0.186	0.067	-	-
Log-CRP (mg/dL)	0.332	0.001*	0.315	0.001*

*Values of $P<0.05$ were considered statistically significant. Data for the leptin, triglyceride, glucose, iPTH, and CRP levels showed a skewed distribution and were therefore log-transformed before analysis. Analysis of the data was done using the univariate linear regression analyses or multivariate stepwise linear regression analysis (adopted factors: Body weight, waist circumference, BMI, and CRP). SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, iPTH: Intact parathyroid hormone, CRP: C-reactive protein, BMI: Body mass index, TCH: Total cholesterol, TGs: Triglycerides

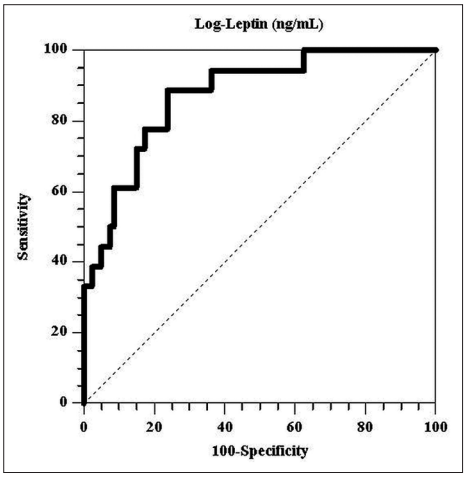

Figure 1: The area under the receiver operating characteristic curve indicates the diagnostic power of the log-leptin level for predicting peripheral artery disease in hypertensive patients. Area under the receiver operating characteristic curve: 0.874, 95% confidence interval, 0.792–0.933, $P < 0.001$. Cuff value of serum log-leptin: 1.40 ng/mL, sensitivity: 88.89%, specificity: 76.25%, respectively

cardiovascular disease and atherosclerosis, including PAD [20]. Higher CRP levels are positively correlated with PAD [21]. Our study revealed that a higher CRP level was associated with PAD in HTN patients, similar to previous studies. Kidney disease is another independent risk factor of PAD [22,23]. Uremic syndromes and the associated chronic inflammation and oxidative stress in these patients in turn can lead to hypoalbuminemia, which is known to be associated with PAD [24]. In our study, patients with PAD had a higher serum Cre level than those in the normal ABI group. Previous epidemiological studies have confirmed an association between smoking, diabetes, and an increase in prevalence of PAD [6,25]. In one study of DM patients at a mean age of 58 years, 16% of patients were diagnosed with PAD at baseline and 24% developed new PAD during 11 years of follow-up [26]. Another study concluded that diabetes was one of the most important risk factors unquestionably associated with the progression of PAD [27]. Our study revealed significantly more patients with DM and those who were current smokers in the PAD group than the normal ABI group. Leptin plays a pathogenic role in atherosclerosis through several mechanisms [28]. First, it plays a crucial role in inflammatory pathways at the initial

Table 4: Multivariable stepwise linear regression analysis of peripheral artery disease among the 98 hypertensive patients

Items	β	Adjusted R^2	Adjusted R^2 change	*P*
Log-leptin (ng/mL)	0.439	0.224	0.224	<0.001*
Creatinine (mg/dL)	0.302	0.307	0.083	0.001*

Data for the leptin levels showed a skewed distribution and therefore were log-transformed before analysis. *P<0.05 was considered statistically significant in the multivariable stepwise linear regression analysis (adopted factors: Smoking, diabetes, creatinine, log-CRP and log-leptin). CRP: C-reactive protein

phase of atheroma formation, as it increases the secretion of CRP, tumor necrosis factor alpha, interleukin-6, and monocyte chemoattractant protein-1 [29]. Second, leptin induces vessel lumen narrowing by vascular smooth muscle hypertrophy and induces plaque rupture by the production of matrix metalloproteinase 2 [28]. Third, leptin stimulates vascular remodeling by promoting profibrotic cytokines production [30]. Finally, it promotes expression of adhesion molecules such as vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and E-selectin [5]. Gherman and Mironiuc revealed that hyperleptinemia is associated with PAD [8]. Our study also found that serum leptin levels were positively associated with PAD in HTN patients. After adjustment for a variety of confounders in multivariable forward stepwise linear regression analysis, serum Cre and log-leptin levels remained independent predictors of PAD among the HTN patients.

Leptin can regulate energy balance by influencing energy expenditure which is mediated by activation of sympathetic nerves innervating thermogenically active brown adipose tissue [31]. Numerous studies have reported that circulating leptin concentrations are highly correlated with indices of adiposity, such as BMI, percentage of body fat, and total fat mass in humans [32-34]. Our study revealed that body weight, waist circumference, and BMI were positively associated with serum log-leptin levels among HTN patients. CRP is a sensitive marker of inflammation and has direct proinflammatory effects [35]. Molecular studies revealed that leptin could regulate CRP expression levels, both directly by facilitating its hepatic and vascular production and indirectly throughout its action on IL-6 [36,37]. One study found an independent association between leptin and CRP levels in 946 older community-dwelling adults [38]. In our study, CRP was also positively correlated with the serum log-leptin level in HTN patients. After adjustment for other confounding variables in multivariate stepwise linear analysis, BMI and CRP were positively correlated with the serum log-leptin level in HTN patients.

The limitations of this study include its cross-sectional design and that it was conducted at a single center with a limited number of HTN patients. Another limitation was that we did not measure serum leptin levels in healthy controls as a control group, so we could not determine whether serum leptin levels were higher in hypertensive patients than normotensive individuals. Furthermore, women have higher serum leptin levels than men [39]. Our results noted a trend of higher serum leptin levels in female than male HTN patients, but it was not a statistically significant difference (P = 0.054). This may be due to the small sample of HTN participants, different comorbidity conditions, or different drugs used in different study designs. Therefore, the findings of this study need to be confirmed by further longitudinal studies before a cause-and-effect association between serum leptin and PAD can be established in the HTN population.

Conclusion

The leptin level has been postulated to be a strong predictor of PAD in HTN patients. In this study group, BMI and CRP were positively correlated with the serum leptin level.

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Conflicts of interest

There are no conflicts of interest.

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