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Original Article

Hyperleptinemia is an Independent Predictor for Carotid-Femoral Pulse Wave Velocity in Elderly People

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SUMMARY

Background: Leptin may participate in the pathogenesis of atherogenesis. The aim of this study was to evaluate the relationship between fasting serum leptin concentration and carotid-femoral pulse wave velocity (cfPWV) in geriatric people.
Methods: Fasting blood samples were obtained from 80 geriatric people. cfPWV measurements were performed using the SphygmoCor system. Serum leptin levels were measured using a commercially available enzyme immunoassay kit. Geriatric adults with cfPWV values of > 10 m/s were classified in the high arterial stiffness group.
Results: Thirty-nine geriatric adults (48.8%) who belonged to the high arterial stiffness group were higher incidence of diabetes mellitus ($p = 0.045$), higher body weight ($p = 0.008$), body mass index ($p < 0.001$), systolic blood pressure ($p = 0.019$), elevated serum blood urea nitrogen ($p = 0.018$), creatinine ($p = 0.045$), intact parathyroid hormone levels ($p = 0.037$), and leptin levels ($p = 0.013$) than their counterparts in the control group. A multivariable logistic regression analysis identified leptin as an independent predictor of arterial stiffness in geriatric adults (odds ratio, 1.028; 95% confidence interval, 1.004–1.054; $p = 0.024$). Multivariable forward stepwise linear regression analysis also showed that serum logarithmically transformed leptin level (log-leptin, $\beta = 0.330$, adjusted R^2 change: 0.092, $p = 0.001$) was positively associated with cfPWV values in geriatric people.
Conclusions: Serum leptin levels positively correlated with cfPWV in elderly adults.

1. Introduction

Increasing aortic stiffness, related to blood pressure pulsatility, is a major risk factor for age-related morbidity and mortality.[1] Pulse wave velocity (PWV) measurement is one of the non-invasive methods currently used to assess vascular stiffness.[2,3] There are different devices and methods in widespread clinical use with reference values for arterial stiffness; however, the carotid-femoral PWV (cfPWV) has been identified as an easy and intuitive measure to assess aortic stiffness.[3,4]

Leptin is a 16-kDa hormone synthesised and secreted by white adipose cells which stimulates vascular inflammation, oxidative stress and vascular smooth muscle hypertrophy, and play a pathophysiological role in the pathogenesis of hypertension, atherosclerosis and coronary heart disease.[5] Besides, chronic hyperleptinemia may lead to abnormal renal sodium retention and vasoconstriction by contributing to the development of endothelial dysfunction through the regulation of blood vessel tonus and imbalance between endothelial nitric oxide synthase expression and intracellular L-arginine.[6] A cross-sectional analysis of data from the Baltimore Longitudinal Study of Aging showed that leptin was significantly associated with cfPWV.[7] The aim of the present study was to determine the relationship between hyperleptinemia and cfPWV among elderly people.

2. Methods

2.1. Participants

Between January and December 2012, 80 elderly volunteers aged 65 years or older from a medical centre in Hualien, eastern Taiwan, were enrolled into this study. Trained staff measured blood pressure (BP) in the morning for all participants and hypertension was defined as systolic BP (SBP) ≥ 140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg or the prescription of antihypertensive medication in the past two weeks. A subject was regarded as diabetic if the fasting plasma glucose was ≥ 126 mg/dl or if he/she was using diabetes medication (oral or insulin).[8] Participants were excluded if they had an acute infection, acute myocardial infarction and pulmonary oedema at the time of blood sampling; if they were using calcium, active vitamin D metabolites, bisphosphonates, teriparatide or

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estrogens medication or if they declined to provide informed consent for the study. This study was approved by the Protection of the Human Subjects Institutional Review Board of Tzu-Chi University and Hospital (IRB099-97).

2.2. Anthropometric analysis

Patient weight was measured with light clothing and without shoes to the nearest 0.5 kg, and height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in square metres.[9,10]

2.3. Biochemical investigations

Fasting blood samples were immediately centrifuged at 3000 *g* for 10 min. Serum levels of blood urea nitrogen (BUN), creatinine, fasting glucose, total cholesterol (TCH), triglycerides (TG), high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), total calcium and phosphorus were measured using an autoanalyser (COBAS Integra 800, Roche Diagnostics, Basel, Switzerland).[9,10] Serum leptin concentrations were determined using a commercially available enzyme immunoassay (EIA) (SPI-BIO, Montigny le Bretonneux, France).[10] Serum intact parathyroid hormone (iPTH) levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) (Diagnostic Systems Laboratories, Webster, Texas, USA).[10] The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation.

2.4. Carotid-femoral pulse wave velocity measurements

Measurements of cfPWV were performed using a pressure tonometer to transcutaneously record the pressure pulse waveform in the underlying artery (SphygmoCor system, AtCor Medical, Australia), as previously described.[9,10] All measurements were performed in the morning with subjects in the supine position after at least 10-min rest in a quiet, temperature-controlled room. The same operator carried out all participants' data measurements. The cfPWV value was calculated using the distance and mean time difference between the two recorded points (carotid-femoral segment). In this study, geriatric adults with cfPWV values > 10 m/s were assigned to the high arterial stiffness group, whereas those with values $\leq$ 10 m/s constituted the control group according to the ESH-ESC 2013 guidelines.[11]

2.5. Statistical analysis

Data were tested for normal distribution using Kolmogorov-Smirnov statistics. Normally distributed variables are expressed as mean $\pm$ standard deviation (SD), and data not normally distributed are expressed as medians and interquartile ranges. Data expressing the number of patients were analysed by the χ^2 test. Variables shown to correlate significantly with arterial stiffness were tested for independence by multivariable logistic regression analysis. Because TG, glucose, iPTH and leptin levels showed non-normal distribution, a logarithm to base 10 was applied to normalise these parameters. Clinical variables that correlated with cfPWV values in geriatric adults were evaluated by simple linear regression analysis and multivariable forward stepwise regression analysis. Data were analysed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

3. Results

Demographic, biochemical and clinical characteristics of the 80 geriatric adults with or without arterial stiffness are shown in Table 1. Thirty-nine geriatric adults (48.8%) were included in the high arterial stiffness group. Geriatric adults who had diabetes had higher prevalence of arterial stiffness than those without diabetes (p = 0.045). Compared with the control group, geriatric adults in the high arterial stiffness group had higher body weight (p = 0.008), BMI (p < 0.001), elevated serum leptin (p = 0.013), SBP (p = 0.019), BUN (p = 0.018), creatinine (p = 0.045), and iPTH (p = 0.037) levels. There were also no significant differences between the two groups in terms of gender, co-existing hypertension and usage of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, calcium channel blocker, statins and fibrate.

The unadjusted and multivariable logistic regression analysis of the factors significantly associated with arterial stiffness with serum leptin levels is presented in Table 2. The unadjusted serum leptin levels with arterial stiffness showed that leptin increased per 1 ng/ml (odds ratio [OR]: 1.030, 95% confidence interval [CI]: 1.008–1.054, p = 0.009) increased the 3% risk of arterial stiffness in geriatric adults. Multivariable logistic regression analysis adjusted for age and gender revealed a 3.5% increase in the risk of arterial stiffness (adjusted OR: 1.035, 95% CI: 1.010–1.061, p = 0.005) (Model 1). After multivariable logistic regression analysis with Model 1 added with diabetes, and hypertension, an increased 3.3% risk of the arterial stiffness (adjusted OR: 1.033, 95% CI: 1.008–1.059, p = 0.008) was observed (Model 2). Multivariable logistic regression analysis using Model 2 with added BUN, creatinine, and eGFR also revealed an increased 2.8% risk of arterial stiffness (adjusted OR: 1.028, 95% CI: 1.004–1.054, p = 0.024). Each of these analyses confirmed that serum leptin level is positively associated with arterial stiffness in geriatric adults.

Results of the simple linear analysis of cfPWV values in geriatric adults are shown in Table 3. Diabetes (r = 0.307; p = 0.001), age (r = 0.253; p = 0.023), BMI (r = 0.263; p = 0.017), SBP (r = 0.389; p < 0.001), DBP (r = 0.237; p = 0.034), BUN (r = 0.250; p = 0.025), creatinine (r = 0.365; p = 0.001), logarithmically transformed iPTH (log-iPTH; r = 0.255; p = 0.023) and log-leptin (r = 0.387; p < 0.001) positively correlated with cfPWV values, while HDL-cholesterol level (r = -0.240; p = 0.032) and eGFR (r = -0.337; p = 0.002) negatively correlated with cfPWV values. Multivariable forward stepwise linear regression analysis of the variables that were significantly associated with cfPWV levels (diabetes, age, BMI, SBP, DBP, HDL-cholesterol, BUN, creatinine, eGFR, log-iPTH and log-leptin) showed that log-leptin (β = 0.330, adjusted R^2 change = 0.092, p = 0.001), SBP (β = 0.236, adjusted R^2 change = 0.141, p = 0.024) and creatinine (β = 0.274, adjusted R^2 change = 0.059, p = 0.008) were independent predictors of cfPWV values in geriatric adults (Table 3).

4. Discussion

We observed that increase in fasting serum leptin levels significantly increased the adjusted risk of cfPWV values and are identified as an independent predictor of arterial stiffness in geriatric adults after adjusting for other confounders.

Arterial stiffness is an age-related process and may be one important pathway linking diabetes to the increased cardiovascular risk.[12] Diabetes may enhance arterial stiffness through pathological changes in the vascular bed such as reduced nitric oxide bioavailability, increased oxidative stress, chronic low-grade inflammation, increased sympathetic tone and changes in the type or struc-

Table 1
Clinical and analytical characteristics of the 80 geriatric adults with or without arterial stiffness.

Characteristic	All participants (n = 80)	Control group (n = 41)	High AS group (n = 39)	p value
Age (years)	72.45 ± 5.43	72.20 ± 5.38	72.72 ± 5.55	0.670
Height (cm)	159.76 ± 7.85	160.37 ± 7.49	159.13 ± 8.26	0.484
Body weight (kg)	65.35 ± 10.46	62.35 ± 9.67	68.50 ± 10.44	0.008*
Body mass index (kg/m^2)	25.60 ± 3.67	24.22 ± 3.22	27.06 ± 3.59	< 0.001*
cfPWV (m/s)	10.11 ± 2.97	7.82 ± 1.16	12.52 ± 2.32	< 0.001*
Systolic blood pressure (mmHg)	130.49 ± 17.69	126.00 ± 14.77	135.21 ± 19.40	0.019*
Diastolic blood pressure (mmHg)	70.46 ± 8.70	69.02 ± 9.33	71.97 ± 7.82	0.130
Total cholesterol (mg/dl)	171.04 ± 34.56	173.41 ± 31.95	168.54 ± 37.37	0.532
Triglyceride (mg/dl)	118.00 (84.00–162.00)	111.00 (87.00–157.50)	129.00 (89.00–169.00)	0.580
HDL-cholesterol (mg/dl)	46.76 ± 12.60	48.93 ± 12.69	44.49 ± 12.26	0.116
LDL-cholesterol (mg/dl)	101.28 ± 29.31	101.20 ± 28.22	101.36 ± 30.78	0.980
Fasting glucose (mg/dl)	111.00 (96.00–143.75)	106.00 (96.50–132.50)	116.00 (96.00–148.00)	0.324
Blood urea nitrogen (mg/dl)	17.45 ± 5.98	15.93 ± 4.08	19.05 ± 7.19	0.018*
Creatinine (mg/dl)	1.17 ± 0.35	1.09 ± 0.28	1.25 ± 0.41	0.045*
eGFR (ml/min)	65.51 ± 20.05	69.05 ± 18.76	61.79 ± 20.91	0.106
Total calcium (mg/dl)	9.12 ± 0.34	9.14 ± 0.31	9.09 ± 0.37	0.500
Phosphorus (mg/dl)	3.44 ± 0.45	3.45 ± 0.46	3.43 ± 0.45	0.880
iPTH (pg/ml)	43.30 (33.68–65.68)	42.40 (32.65–57.70)	51.90 (39.30–78.90)	0.037*
Leptin (ng/ml)	9.47 (3.57–26.13)	6.13 (2.93–16.82)	14.61 (3.94–46.34)	0.013*
Female, n (%)	26 (32.5)	14 (34.1)	12 (30.8)	0.747
Diabetes mellitus, n (%)	36 (45.0)	14 (34.1)	22 (56.4)	0.045*
Hypertension, n (%)	58 (72.5)	26 (63.4)	32 (82.1)	0.062
ACE inhibitor, n (%)	19 (23.7)	7 (17.1)	12 (30.8)	0.150
Angiotensin receptor blocker, n (%)	34 (42.5)	15 (36.6)	19 (48.7)	0.273
β-blocker, n (%)	35 (43.7)	15 (36.6)	20 (51.3)	0.185
Calcium channel blocker, n (%)	29 (36.2)	12 (29.3)	17 (43.6)	0.183
Statin, n (%)	37 (46.2)	23 (56.1)	14 (35.9)	0.070
Fibrate, n (%)	17 (21.2)	10 (24.4)	7 (17.9)	0.481

Values for continuous variables are shown as mean ± standard deviation 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 are presented as number (%) and analysis after analysis by the chi-square test.
AS, arterial stiffness; cfPWV, carotid–femoral pulse wave velocity; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone; ACE, angiotensin-converting enzyme.
* $p < 0.05$ was considered statistically significant.

Table 2
Odds ratio for arterial stiffness by multivariable logistic regression analysis of serum leptin levels among the 80 geriatric adults.

Leptin (ng/ml)	Unadjusted		Model 1		Model 2		Model 3	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Per 1 ng/ml leptin increase	1.030 (1.008–1.054)	0.009*	1.035 (1.010–1.061)	0.005*	1.033 (1.008–1.059)	0.008*	1.028 (1.004–1.054)	0.024*

Model 1 is adjusted for age and gentle. Model 2 is adjusted for the Model 1 variables and for diabetes and hypertension. Model 3 is adjusted for the Model 2 variables and for blood urea nitrogen, creatinine, estimated glomerular filtration rate, and intact parathyroid hormone.
* $p < 0.05$ by multivariable logistic regression analysis.
OR, odds ratio; CI, confidence interval.

ture of elastin and/or collagen in the arterial wall.[13] A recent cohort study of 4,279 older adults demonstrated cfPWV values of 95.8 cm/s was stiffer on average for those with diabetes compared to those with normal glucose in a large, older population.[14] Our study showed that geriatric adults who had diabetes had higher cfPWV values than those without diabetes.

Ageing leads to a multitude of changes in the cardiovascular system, including increased arterial stiffness. Degeneration of elastin fibres, deposition of stiffer collagen and dysfunction of endothelium are considered as a primary cause of age-related arterial stiffening.[15] Greater arterial stiffness results in an earlier return of the reflected pulse wave, adding to the forward wave and consequently increasing SBP and widening the pulse pressure.[16] In our study, SBP and DBP positively correlated with cfPWV values in the geriatric adults. Prior studies have established the role of SBP and PWV as a predictor for cardiovascular events.[17] We have also shown that SBP is an independent predictor of cfPWV values after adjusting by multivariable analysis.

Obesity is a significant independent predictor of cardiovascular risk and mortality.[18] One meta-analysis suggests that weight loss may reduce cfPWV values.[19] In our study, body weight and BMI were higher in arterial stiffness group. Moreover, cfPWV value was positively associated with BMI, which indicates that obesity affects the vascular compliance. HDL-cholesterol is a well-established anti-risk factor for cardiovascular events. Our results showed that HDL-cholesterol negatively correlated with cfPWV values. Corroborating our finding, one large study including 15,302 Chinese healthy participants demonstrated that HDL-cholesterol is inversely and independently associated with cfPWV values.[20] The association is potentially related to the anti-inflammatory effect of HDL-cholesterol.[22] In prospective investigation of the vasculature in Uppsala seniors (PIVUS) study, serum parathyroid hormone (PTH) was associated with an increased risk of nonfatal atherosclerotic disease on elderly patients who were 70 years old.[21] Moreover, primary hyperparathyroidism is associated with increased arterial stiffness,

Table 3
Correlation between carotid-femoral pulse wave velocity levels and clinical variables among the 80 geriatric adults.

Variables	Carotid–femoral pulse wave velocity (m/s)				
	Simple linear regression		Multivariable linear regression		
	r	p value	Beta	Adjusted R^2 change	p value
Female	- 0.079	0.489	-	-	-
Diabetes mellitus	0.307	0.001*	-	-	-
Hypertension	0.150	0.184	-	-	-
Age (years)	0.253	0.023*	-	-	-
Height (cm)	- 0.044	0.698	-	-	-
Body weight (kg)	0.207	0.065	-	-	-
Body mass index (kg/m^2)	0.263	0.017*	-	-	-
Systolic blood pressure (mmHg)	0.389	< 0.001*	0.236	0.141	0.024*
Diastolic blood pressure (mmHg)	0.237	0.034*	-	-	-
Total cholesterol (mg/dl)	- 0.019	0.864	-	-	-
Log-triglyceride (mg/dl)	0.040	0.722	-	-	-
HDL-cholesterol (mg/dl)	- 0.240	0.032*	-	-	-
LDL-cholesterol (mg/dl)	0.079	0.488	-	-	-
Log-glucose (mg/dl)	0.043	0.706	-	-	-
BUN (mg/dl)	0.250	0.025*	-	-	-
Creatinine (mg/dl)	0.365	0.001*	0.274	0.059	0.008*
eGFR (ml/min)	- 0.337	0.002*	-	-	-
Total calcium (mg/dl)	0.003	0.981	-	-	-
Phosphorus (mg/dl)	- 0.091	0.420	-	-	-
Log-iPTH(pg/ml)	0.255	0.023*	-	-	-
Log-leptin (ng/ml)	0.387	< 0.001*	0.330	0.092	0.001*

Data of triglyceride, glucose, iPTH, and leptin showed skewed distribution and therefore were log-transformed before analysis.
Analysis of data was done using the simple linear regression analyses or multivariable stepwise linear regression analysis (adapted factors were diabetes, age, body mass index, systolic blood pressure, diastolic blood pressure, HDL-C, BUN, creatinine, eGFR, log-iPTH and log-leptin).
HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone.
* $p < 0.05$ was considered statistically significant.

which improves after parathyroidectomy.[22] In our study, elevated iPTH levels revealed a significant association with high arterial stiffness and was positively associated with cfPWV values in geriatric adults.

Serum leptin concentration increased in both obese and CKD patients and also proved to be a risk factor for CKD.[23] In this study, serum BUN levels and creatinine levels were higher in arterial stiffness group compared with control group. Our study revealed that creatinine and BUN levels positively correlated with cfPWV values, while eGFR showed a negative correlation. Furthermore, creatinine level was significantly associated with cfPWV values by multivariable logistic regression analysis. These findings are consistent with those of a longitudinal study that showed that leptin concentration was inversely associated with changes of eGFR over time in females.[24]

Functional leptin receptors are present on endothelial cells and may influence atherogenesis.[25] In addition, since leptin is a hypoxia-inducible hormone, it is noted to be most induced under hypoxia of human coronary arterial smooth muscle cells under the pathway of angiotensin II and reactive oxygen species expression, which mediate the induction of leptin expression and then causes artherogenesis through increased transcriptional activity in arterial smooth muscle cells.[26] In fact, hyperleptinaemia is inversely associated with vasodilatation in resistance arteries and also associated with arterial stiffness and hypertension.[26] Accordingly, our study showed that serum leptin levels were identified as independent predictors of arterial stiffness in geriatric adults. After multivariable logistic regression analysis, log-leptin level was significantly associated with cfPWV values among the geriatric adults.

There are some limitations of the current study that should be mentioned. First, this was an observational, cross-sectional relationship, single-centre study with a small sample of elderly participants. Second, participants in this study were not differentiated in race, limiting the conclusions of our findings to other ethnicities. Third, we did not collect data of medication use, except anti-hypertensive and anti-lipid drugs, since use of other medications could have potentially affected the leptin levels or cfPWV values. Further long-term prospective studies are needed to follow-up on the trend between serum leptin and arterial stiffness with increase in age in geriatric adults.

In conclusion, the previous study, the leptin level was associated with SBP, arterial stiffness, metabolic disorder, coronary artery disease and renal function. The leptin level was also related the arterial stiffness in elderly population after adjusting age, gender, hypertension, renal function and iPTH level in this article.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

1. Kaess BM, Rong J, Larson MG, et al. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA.* 2012;308:875–881.
2. Tomiyama H, Yamashina A. Non-invasive vascular function tests: Their pathophysiological background and clinical application. *Circ J.* 2010; 74:24–33.
3. McEniery CM, Cockcroft JR, Roman MJ, et al. Central blood pressure: Current evidence and clinical importance. *Eur Heart J.* 2014;35:1719–1725.
4. Vlachopoulos C, Xaplanteris P, Aboyans V, et al. The role of vascular biomarkers for primary and secondary prevention. A position paper from

the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis.* 2015;241:507–532.
5. Katsiki N, Mikhailidis DP, Banach M. Leptin, cardiovascular diseases and type 2 diabetes mellitus. *Acta Pharmacol Sin.* 2018;39:1176–1188.
6. Yiannikouris F, Gupte M, Putnam K, et al. Adipokines and blood pressure control. *Curr Opin Nephrol Hypertens.* 2010;19:195–200.
7. Windham BG, Griswold ME, Farasat SM, et al. Influence of leptin, adiponectin, and resistin on the association between abdominal adiposity and arterial stiffness. *Am J Hypertens.* 2010;23:501–507.
8. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med.* 1998;15:539–553.
9. Lee CJ, Wang JH, Chen YC, et al. Serum osteopontin level correlates with carotid-femoral pulse wave velocity in geriatric persons. *Biomed Res Int.* 2014;2014:570698.
10. Tsai JP, Wang JH, Chen ML, et al. Association of serum leptin levels with central arterial stiffness in coronary artery disease patients. *BMC Cardiovasc Disord.* 2016;16:80.
11. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens.* 2013;31:1281–1357.
12. Stehouwer CDA, Henry RMA, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: A pathway to cardiovascular disease. *Diabetologia.* 2008;51:527–539.
13. de Oliveira Alvim R, Santos PCJL, Musso MM, et al. Impact of diabetes mellitus on arterial stiffness in a representative sample of an urban Brazilian population. *Diabetol Metab Syndr.* 2013;5:45.
14. Loehr LR, Meyer ML, Poon AK, et al. Prediabetes and diabetes are associated with arterial stiffness in older adults: The ARIC Study. *Am J Hypertens.* 2016;29:1038–1845.
15. Payne RA, Wilkinson IB, Webb DJ. Arterial stiffness and hypertension. *Hypertension.* 2010;55:9–14.
16. Steppan J, Barodka V, Berkowitz DE, et al. Vascular stiffness and increased pulse pressure in the aging cardiovascular system. *Cardiol Res Pract.* 2011;2011:263585.
17. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: The Framingham Heart Study. *Circulation.* 2010;121:505–511.
18. McGee DL. Body mass index and mortality: A meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol.* 2005;15:87–97.
19. Petersen KS, Blanch N, Keogh JB, et al. Effect of weight loss on pulse wave velocity: Systematic review and meta-analysis. *Arterioscler Thromb Vasc Biol.* 2015;35:243–252.
20. Wang X, Du Y, Fan L, et al. Relationships between HDL-C, hs-CRP, with central arterial stiffness in apparently healthy people undergoing a general health examination. *PLoS One.* 2013;8:e81778.
21. Hagström E, Michaëlsson K, Melhus H, et al. Plasma-parathyroid hormone is associated with subclinical and clinical atherosclerotic disease in 2 community-based cohorts. *Arterioscler Thromb Vasc Biol.* 2014;34:1567–1573.
22. Rosa J, Raska I Jr, Wichterle D, et al. Pulse wave velocity in primary hyperparathyroidism and effect of surgical therapy. *Hypertens Res.* 2011;34:296–300.
23. Pedone C, Roshanravan B, Scarlata S, et al. Longitudinal association between serum leptin concentration and glomerular filtration rate in humans. *PLoS One.* 2015;10:e0117828.
24. Koh KK, Park SM, Quon MJ. Leptin and cardiovascular disease: Response to therapeutic interventions. *Circulation.* 2008;117:3238–3249.
25. Chiu CZ, Wang BW, Shyu KG. Molecular regulation of the expression of leptin by hypoxia in human coronary artery smooth muscle cells. *J Biomed Sci.* 2015;22:5.
26. Gonzalez M, Lind L, Söderberg S. Leptin and endothelial function in the elderly: The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. *Atherosclerosis.* 2013;228:485–490.