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Original Article

High Serum Leptin Level is Associated with Peripheral Artery Disease in Geriatric Individuals

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SUMMARY

Background: Leptin contributes to the pathogenesis of atherosclerosis, endothelial dysfunction, and thrombosis. Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis and is expected to prevail among geriatric individuals. The present study aimed to determine whether serum leptin level is associated with PAD in a geriatric group.

Methods: Blood samples were obtained from 60 participants in the study who were >65 years of age. Ankle-brachial index (ABI) values were measured using the automated oscillometric method. PAD was considered to be present if the left or right ABI values were less than 0.90, and these participants were included in the low ABI group. Serum leptin levels were measured using a commercial enzyme immunoassay kit.

Results: Of these geriatric participants, ten (16.7%) were in the low ABI group. Compared with the elderly participants in the normal ABI group, those in the low ABI group were current smokers ($p = 0.048$) and had higher serum C-reactive protein (CRP, $p = 0.018$) and leptin levels ($p = 0.005$). Multivariate logistic regression analysis of the factors significantly associated with PAD demonstrated that leptin (odds ratio: 1.078, 95% confidence interval: 1.021−1.138, $p = 0.006$) was an independent predictor of PAD. Female ($p = 0.001$), body mass index ($p = 0.008$), and a logarithmically transformed CRP (log-CRP, $p = 0.035$) were found to be associated with serum log-leptin levels among geriatric participants after multivariate forward stepwise linear regression analysis.

Conclusion: High serum leptin level is a risk marker for PAD in geriatric individuals.

1. Introduction

Peripheral artery disease (PAD), which frequently occurs in the elderly, is a condition in which arteries connecting to the extremities become narrow or occult owing to an accumulation of fatty tissue.[1] One of the known risk factors of PAD is aging.[2] Within a population above 60 years of age, the overall incidence of PAD is approximately 20%.[3] PAD also results in elevated risk of other cardiovascular diseases, such as heart attack and ischemic stroke, even in asymptomatic individuals.[4] Ankle-brachial index (ABI) is an important tool for noninvasive detection of this disease.[5] An abnormal ABI, lower than 0.9, is an indicator of PAD and can be used to assess the severity of PAD.[6]

There is evidence that an increase in plasma leptin level is associated with unfavorable outcomes in coronary artery disease and heart failure.[7,8] Leptin induced detrimental responses including vascular inflammation, vasodilatation dysfunction, and arterial stiffness in peripheral tissues have been reported in previous studies.[9,10] However, the relationship between PAD and high serum leptin level in geriatric individuals is unclear. Therefore, in the present study, we aimed to determine the relationship between serum leptin level and PAD in geriatric individuals.

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2. Methods

2.1. Participants

In total, 60 participants aged >65 years were enrolled in this cross-sectional study conducted between January and December 2012 in a medical center in Hualien, Taiwan. Blood pressure (BP) of each patient was measured in the morning by trained staff using standard mercury sphygmomanometers with appropriate cuff sizes after the patient was seated for at least 10 min. Systolic and diastolic BP measurements were recorded thrice at 5-min intervals and were averaged for analysis. The patients were regarded as having hypertension if they had systolic BP $\geq$ 140 mmHg, diastolic BP $\geq$ 90 mmHg, or received any anti-hypertensive medication in the past 2 weeks. The patients were diagnosed with diabetes mellitus if their fasting plasma glucose level was $\geq$126 mg/dl or if they were administered oral hypoglycemic medication or insulin.[11] The Protection of the Human Subjects Institutional Review Board of the Tzu-Chi University and Hospital approved this study. All of the patients provided informed consent prior to participating in this study. Patients were excluded if they had acute infection, acute myocardial infarction, or pulmonary edema, took protease-activated receptor-1 antagonists or Warfarin at the time of blood sampling, or declined to provide informed consent.

2.2. Anthropometric analysis

Participant weight was measured without shoes, while wearing light clothing 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.[12–14]

2.3. Biochemical investigation

After 8 h overnight fasting, blood (approximately 5 ml) of all participants was sampled at morning and were immediately centrifuged at 3000 $\times$ *g* for 10 min. Serum levels of blood urea nitrogen), creatinine, fasting glucose, total cholesterol (TCH), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total calcium, phosphorus, and C-reactive protein (CRP) were measured using an autoanalyzer (COBAS Integra 800; Roche Diagnostics, Basel, Switzerland).[12–14] Serum leptin (SPI-BIO, Montigny le Bretonneux, France) level and intact parathyroid hormone level (iPTH; Diagnostic Systems Laboratories, Webster, TX, USA) were determined using a commercially available enzyme immunoassay or enzyme-linked immunosorbent assay, respectively.[12,13]

2.4. 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 of the arms and ankles.[14] 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. ABI was calculated as the ratio of ankle SBP to arm SBP, and the lower value of ankle SBP was used for calculation. We repeatedly measured these parameters for both legs and calculated the mean values. PAD was diagnosed on the basis of ABI <0.9.[15] In the present study, the left or right ABI values < 0.9 were used to define the low ABI group.[14]

2.5. Statistical analysis

Data were tested for normal distribution using the Kolmogorov–Smirnov test. Normally distributed data were expressed as a mean $\pm$ standard deviation, and comparisons between the patients were performed using the Student's independent *t*-test (two-tailed). Non-normally distributed data were expressed as medians and interquartile ranges, and comparisons between the patients were performed using the Mann–Whitney *U* test (TG, fasting glucose, CRP, and leptin). Data expressed as the number of patients were analyzed by the chi-square test. Because TG, fasting glucose, CRP, and leptin 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 the elderly participants were evaluated using univariate linear regression analysis. Variables that were significantly associated with log-leptin levels in the elderly participants were tested for independency in the multivariate forward stepwise regression analysis. Receiver operating characteristic (ROC) was used to calculate the area under the curve (AUC) to identify log-leptin and log-CRP levels to predict PAD in the participants. Variables that were significantly associated with PAD were tested for independence using multivariate logistic regression analysis. Data were analyzed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

3. Results

Demographic, clinical, and biochemical characteristics of the 60 geriatric participants are presented in Table 1. Twenty-four of the participants (40.0%) had diabetes mellitus, and 47 (78.3%) had hypertension. Ten geriatric participants (16.7%) were included in the low ABI group. Those in the low ABI group had high frequency of current smoking ($p = 0.048$) and higher serum CRP ($p = 0.018$) and leptin ($p = 0.005$) levels than those in the normal ABI group. There was no statistically significant difference based on gender, co-existing diabetes or hypertension, or the use of ACEi, ARB, β-blockers, CCB, statins, fibrate, Aspirin, or Clopidogrel between the two groups.

The univariable and multivariate linear analysis of the log-leptin levels in the elderly participants are presented in Table 2. The elderly females ($r = 0.428$, $p = 0.001$), BMI ($r = 0.295$, $p = 0.022$), DBP ($r = 0.261$, $p = 0.044$), TCH ($r = 0256$, $p = 0.048$), and log-CRP ($r = 0.313$, $p = 0.015$) positively correlated with, while height ($r = -0.263$, $p = 0.042$) negatively correlated with the serum log-leptin levels in the elderly participants. After a multivariate forward stepwise linear regression analysis of the factors (gender, height, BMI, DBP, TCH, and log-CRP) that were significantly associated with fasting serum log-leptin levels, it was demonstrated that the females ($\beta = 0.384$, $p = 0.001$), BMI ($\beta = 0.302$, $p = 0.008$) and log-CRP ($\beta = 0.241$, $p = 0.035$) were positively associated with serum log-leptin levels among the elderly participants.

Then a ROC curve analysis was applied to estimate the optimal level of log-leptin and log-CRP predicting the PAD of the elderly participants (Fig. 1). The AUC for log-leptin was 0.782 (95% confidence interval (CI): 0.657–0.878, $p = 0.001$), and AUC for log-CRP was 0.739 (95% CI: 0.609–0.844, $p = 0.004$), respectively.

An adjustment of the factors significantly associated with PAD (diabetes mellitus, hypertension, smoking, gender, age, TCH, TG, HDL-C, LDL-C, CRP and leptin) in a multivariate logistic regression analysis demonstrated that each increase of 1 ng/ml in the serum leptin level (odds ratio: 1.0782, 95% CI: 1.021–1.138, $p = 0.006$) and current smoking (odds ratio: 22.460, 95% CI: 1.428–353.336,

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