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Original Article

Serum leptin level positively correlates with metabolic syndrome among elderly Taiwanese

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Abstract

Objective: Leptin is an adipocyte-derived hormone and has shown positive correlation with obesity and metabolic syndrome (MetS) in many studies. However, there are few studies investigating this relation in elderly people. Therefore, we aimed to investigate the correlation between the fasting serum leptin level and MetS among older Taiwanese. **Materials and Methods:** The fasting serum leptin level was obtained from 62 Taiwanese participants over 65 years old and was measured using a commercially available enzyme immunoassay kit. MetS and its components were defined using diagnostic criteria from the International Diabetes Federation. **Results:** Thirty elderly participants (48.4%) had MetS. The serum leptin level was positively correlated with MetS ($P < 0.001$). Multivariate logistic regression analysis of the factors significantly associated with MetS showed that logarithmically transformed leptin (log-leptin, each increase 0.1 ng/mL log-leptin, odds ratio: 1.276, 95% confidence interval: 1.015–1.603, $P = 0.037$) was still an independent predictor of MetS in elderly persons. Univariable linear analysis showed that body weight ($r = 0280$, $P = 0.028$), body mass index ($r = 0.417$, $P = 0.001$), waist circumference ($r = 0.419$, $P = 0.001$), blood urea nitrogen ($r = 0255$, $P = 0.046$), log-insulin ($r = 0436$, $P < 0.001$), and logarithmically transformed homeostasis model assessment of insulin resistance ($r = 0359$, $P = 0.004$) positively correlated with fasting serum log-leptin levels. Multivariate forward stepwise linear regression analysis of the factors significantly associated with fasting serum log-leptin levels revealed that waist circumference (adjusted $R^2 = 0.083$, $P = 0.002$), statin use (adjusted $R^2 = 0.058$, $P = 0.016$), and female gender (adjusted $R^2 = 0.041$, $P = 0.034$) were independent predictors of fasting serum log-leptin levels among elderly participants. **Conclusion:** In elderly Taiwanese, the serum leptin level was positively correlated with MetS. Waist circumference, statin use, and female gender were independent predictors of the fasting serum leptin level in elderly participants.

Keywords: *Elderly, Leptin, Metabolic syndrome*

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Introduction

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, consisting of obesity, insulin resistance, dyslipidemia, and hypertension, leading to an increased risk of cardiovascular disease (CVD) and renal events [1,2]. The prevalence of MetS is increasing worldwide, especially among the elderly [2]. The presence of MetS is related to the development of CVD and functional disability in the elderly population, and it is important to recognize it and treat its individual components [3].

Leptin is an adipocyte-secreted hormone with pleiotropic effects in the physiology and pathophysiology of energy homeostasis, endocrinology, and metabolism [4]. Recent research suggests that leptin may be an important factor linking obesity, MetS, and CVD [5]. Previous studies have shown that the serum leptin level is associated with MetS independent of body mass index (BMI) and could be a main factor in explaining the increased risk for CVD with increased levels of leptin [6,7]. However, few studies have examined the correlation between serum leptin levels and MetS in elderly people. The aim of our study was to investigate the relationship between the fasting serum leptin level and MetS in elderly Taiwanese.

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Materials and methods

Participants

This study was approved by the Protection of Human Subjects Institutional Review Board of Tzu Chi University and Hospital (IRB099-97). All participants provided their informed consent before participating in this study. Study participants were recruited in the Cardiovascular Outpatient Department at Buddhist Tzu Chi General Hospital, Hualien, Taiwan, between January and December 2012. A total of 81 participants >65 years old were enrolled in this study. Participants were excluded if there was no measurement of the serum leptin level (n = 17) or they had an acute infection (n = 1) or acute pulmonary edema (n = 1) at the time of blood sampling. Finally, a total of 62 participants older than 65 years of age were enrolled in this study. Trained staff used standard mercury sphygmomanometers with appropriate cuff sizes to measure the blood pressure (BP) of all participants in the right arm after they had rested for at least 10 min in the morning. The systolic BP (SBP) and diastolic BP (DBP) were measured three times at 5-min intervals and were averaged for analysis. Hypertension among the patients enrolled in this study was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg or having received any antihypertensive medication in the past 2 weeks.

Anthropometric analysis

The body weight of the participants was measured with 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 around the waist from the point between the lowest ribs to the hip bones with the hands on the hips. BMI was calculated using Quetelet's formula as weight in kilograms divided by the height in square meters [8-10].

Biochemical investigations

After 8 h of overnight fasting, blood samples (approximately 5 mL) collected from all patients were immediately centrifuged at 3000 g for 10 min. Serum levels of blood urea nitrogen (BUN), creatinine (Cre), fasting glucose, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and C-reactive protein (CRP) were determined using an autoanalyzer (COBAS Integra 800, Roche Diagnostics, Basel, Switzerland) [8-10]. Serum leptin concentrations were measured using a commercially available enzyme immunoassay kit (SPI-BIO, Montigny-le-Bretonneux, France) [8-10]. The estimated glomerular filtration rate (GFR) was calculated by the chronic kidney disease (CKD) epidemiology collaboration equation.

Metabolic syndrome and its components

The International Diabetes Federation definition was used in this study for the evaluation of MetS prevalence [11]. Participants were considered as having MetS if they had central (abdominal) obesity with a waist circumference ≥90 cm (men) or ≥80 cm (women) (Chinese criteria) and matched two or more of the following criteria: fasting serum glucose of ≥100 mg/dL, TG of ≥150 mg/dL, HDL-C level <40 mg/dL in men or <50 mg/dL in women, or BP of ≥130/85 mmHg. The use of antihypertensive medication was considered as indicative of high BP in this analysis. Type 2 diabetes was determined according to the World Health Organization criteria [12]. Participants were classified as diabetic if their fasting plasma glucose was ≥126 mg/dL or if their 2-h glucose during an oral glucose tolerance test was ≥200 mg/dL or if they used diabetes medication (oral or insulin). Serum insulin levels were measured using the microparticle enzyme immunosorbent assay with an autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA). Insulin resistance was evaluated using a homeostasis model assessment of insulin resistance (HOMA-IR) as follows: HOMA-IR = fasting plasma glucose (mg/dL) × fasting serum insulin (μU/mL)/405 [10,13,14].

Statistical analysis

Based on a cross-sectional study which analyzed the fasting serum leptin level and MetS in elderly Taiwanese using a linear multiple regression model, we anticipated that using 68 elderly participants would detect a similar magnitude of difference with 80% power and a significance level of 0.05 and effect size of 0.15. Allowing for 10% attrition, we intend to recruit a total of 75 participants. Data were coded, entered, and analyzed using the Statistical Package for Social Sciences for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). The distribution pattern of the variables was checked. Normally distributed variables are expressed as mean ± standard deviation and comparisons between patients were performed using Student's independent t-test (two-tailed). Data not normally distributed are expressed as medians and interquartile ranges and comparisons between patients were performed using the Mann–Whitney U-test (fasting glucose, CRP, insulin, HOMA-IR, and leptin). Data expressing the number of patients were analyzed by Chi-square test. Since fasting glucose, CRP, insulin, HOMA-IR, and leptin were not normally distributed, they underwent base 10 logarithmic transformations to achieve normality. Clinical variables that correlated with serum logarithmically transformed leptin (log-leptin) levels in elderly participants were evaluated using univariate linear regression analysis. Variables that were significantly associated with log-leptin levels in elderly participants were tested for independence using multivariate forward stepwise regression analysis. Variables that were significantly associated with MetS in elderly participants were tested for independence by binary logistic regression analysis (adapted factors: female gender, body weight, BMI, log-insulin, log-HOMA-IR, log-CRP, and log-leptin). $P < 0.05$ was considered as statistically significant.

Results

Demographic, clinical, and biochemical characteristics of the 62 elderly participants are presented in Tables 1 and 2. A total of 27 elderly participants (43.5%) had diabetes mellitus and 49 (79.0%) had a medical history of hypertension. Thirty elderly participants (48.4%) had MetS, and this group of participants had higher serum leptin ($P < 0.001$), body weight ($P = 0.013$), BMI ($P < 0.001$), waist circumference ($P < 0.001$), BUN ($P = 0.016$), CRP ($P = 0.020$), insulin ($P = 0.036$) and HOMA-IR ($P = 0.004$) values and higher percentages of females ($P = 0.002$), and those

Table 1: Clinical variables of 62 elderly participants with and without metabolic syndrome

Items	All participants (*n*=62)	No metabolic syndrome (*n*=32)	Metabolic syndrome (*n*=30)	*P*
Age (years)	73.32±5.28	73.66±5.76	72.97±4.78	0.611
Height (cm)	159.60±7.73	161.28±6.63	157.80±8.50	0.076
Body weight (kg)	64.10±10.37	60.97±8.06	67.43±11.60	0.013*
BMI (kg/m^2)	25.17±3.66	23.43±2.79	27.02±3.60	<0.001*
Waist circumference (cm)	91.53±11.07	85.41±8.25	98.07±9.98	<0.001*
Systolic blood pressure (mmHg)	130.81±18.54	127.19±14.18	134.67±21.87	0.113
Diastolic blood pressure (mmHg)	70.84±9.07	70.09±8.74	71.63±9.50	0.509
TCH (mg/dL)	174.60±34.15	173.25±35.08	176.03±33.67	0.751
TG (mg/dL)	134.97±73.11	114.03±77.73	157.30±61.52	0.019*
HDL-C (mg/dL)	48.63±12.80	51.97±14.60	45.07±9.55	0.033*
LDL-C (mg/dL)	103.00±28.41	100.03±28.84	106.17±28.08	0.400
Fasting glucose (mg/dL)	105.50 (93.75-138.50)	95.50 (89.00-106.75)	122.50 (105.75-163.00)	<0.001*
BUN (mg/dL)	17.81±6.04	16.03±4.31	19.70±7.05	0.016*
Creatinine (mg/dL)	1.17±0.36	1.12±0.26	1.22±0.44	0.286
GFR (mL/min)	61.56±18.69	65.55±15.60	57.30±20.93	0.082
C-reactive protein (mg/dL)	0.20 (0.15-0.24)	0.18 (0.14-0.22)	0.21 (0.17-0.27)	0.020*
Insulin (uIU/mL)	9.72 (5.94-17.08)	7.58 (4.90-12.12)	12.50 (8.19-20.33)	0.036*
HOMA-IR	2.92 (1.52-4.69)	2.12 (1.22-3.68)	3.97 (2.65-6.76)	0.004*
Leptin (ng/mL)	10.31 (3.84-26.91)	5.74 (2.67-12.53)	18.57 (7.89-46.90)	<0.001*
Female (%)	21 (33.9)	5 (15.6)	16 (53.3)	0.002*
Hypertension (%)	49 (79.0)	22 (68.8)	27 (90.0)	0.040*
Diabetes (%)	27 (43.5)	8 (25.0)	19 (63.3)	0.002*

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; values presented as *n* (%) were analyzed using Chi-square test. *P<0.05 was considered statistically significant after Student's *t*-test or Mann–Whitney U-test. HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, HOMA-IR: Homeostasis model assessment of insulin resistance, BMI: Body mass index, SD: Standard deviation, BUN: Blood urea nitrogen, TG: Triglycerides, TCH: Total cholesterol, GFR: Glomerular filtration rate

with type 2 diabetes mellitus (P = 0.002) and hypertension (P = 0.040) than those in the non-MetS group. Binary logistic regression analysis of the factors (adapted factors: body weight, BMI, BUN, log-CRP, log-insulin, log-HOMA-IR, female gender, and log-leptin) significantly associated with MetS revealed that log-leptin (each increase 0.1 ng/mL log-leptin, odds ratio: 1.276, 95% confidence interval: 1.015–1.603, P = 0.037) was also an independent factor for MetS among elderly participants (data not shown).

The drugs used included angiotensin-converting enzyme inhibitors (ACEi; n = 14; 22.6%), angiotensin receptor blockers (ARBs; n = 27; 43.5%), β-blockers (n = 32; 51.6%), calcium channel blockers (CCBs; n = 23; 37.1%), statins (n = 29; 46.8%), and fibrates (n = 10; 16.1%). Serum log-leptin levels did not differ statistically by hypertension and use of ACEi, ARB, β-blockers, CCB, or fibrates, but there was a statistically significant difference in gender (P = 0.008) and use of statins (P = 0.012) among elderly participants.

Results of the univariable linear analysis of log-leptin levels in elderly participants are presented in Table 3. Body weight (β = 0280, P = 0.028), BMI (β = 0.417, P = 0.001), waist circumference (β = 0.419, P = 0.001), BUN (β = 0255, P = 0.046), log-insulin (β = 0436, P < 0.001), and log-HOMA-IR (β = 0359, P = 0.004) positively correlated with log-leptin levels in our elderly participants.

Multivariate forward stepwise linear regression analysis of the factors (gender, statin use, body weight, BMI, waist circumference, BUN, log-insulin, and log-HOMA-IR) significantly associated with fasting serum log-leptin levels revealed that waist circumference (adjusted R^2 = 0.083, P = 0.002), statin use (adjusted R^2 = 0.058, P = 0.016), and female gender (adjusted R^2 = 0.041, P = 0.034) were independent predictors of fasting serum log-leptin levels among elderly participants [Table 4].

Discussion

In our study, the serum leptin level was positively correlated with MetS in elderly Taiwanese. People with MetS were mostly female and had higher BMI, serum BUN, and serum CRP levels than those without MetS. Waist circumference, statin use, and female gender were independent predictors of the fasting serum leptin level in the elderly population.

MetS is a cluster of metabolic abnormalities consisting of obesity, insulin resistance, dyslipidemia, and hypertension [1]. In our study of 62 elderly people, BMI, waist circumference, TG, HDL-C, fasting glucose, and proportions of hypertension and diabetes were significantly different between the MetS and no MetS groups. Lin *et al*. reported a prevalence of MetS of 43.23% in men and 51.82% in women in a survey, 2359 Chinese adults 65 years old and over [15]. Our results showed a MetS prevalence of 48.4% in older Taiwanese. The BMI was also positively related to MetS in both genders. Elevation of CRP levels has been linked to the risk of MetS in previous studies [16,17], and we found similar results. Recent studies have revealed the correlation of MetS and the development of CKD and even end-stage renal disease [18,19], but we found no difference in the serum Cre level and GFR between the MetS

Table 2: Clinical characteristics and fasting serum leptin levels of 62 elderly participants

Characteristic	*n* (%)	Log-leptin (ng/mL)	*P*
Gender			
Male	41 (66.1)	0.89±0.55	0.008*
Female	21 (33.9)	1.26±0.42	
Hypertension			
No	13 (21.0)	0.84±0.37	0.192
Yes	49 (79.0)	1.06±0.57	
Diabetes			
No	35 (56.5)	0.99±0.58	0.650
Yes	27 (43.5)	1.05±0.49	
ACE inhibitor use			
No	48 (77.4)	0.99±0.52	0.620
Yes	14 (22.6)	1.08±0.61	
ARB use			
No	35 (56.5)	1.03±0.51	0.836
Yes	27 (43.5)	1.00±0.58	
β-blocker use			
No	30 (48.4)	0.89±0.53	0.088
Yes	32 (51.6)	1.13±0.54	
CCB use			
No	39 (62.9)	0.92±0.59	0.079
Yes	23 (37.1)	1.17±0.42	
Statin use			
No	33 (53.2)	1.17±0.51	0.012*
Yes	29 (46.8)	0.83±0.52	
Fibrate use			
No	52 (83.9)	0.97±0.54	0.124
Yes	10 (16.1)	1.25±0.49	

Data for leptin levels showed a skewed distribution and therefore were log-transformed before analysis. Data are expressed as means±SD.
*$P<0.05$ was considered statistically significant after Student's *t*-test.
ARB: Angiotensin receptor blocker, ACE: Angiotensin-converting enzyme, CCB: Calcium channel blocker, SD: Standard deviation

and no MetS groups. Our data showed that the BMI, CRP, and BUN statistically differed between the MetS and no MetS groups. Insulin and its signaling cascade control cell growth and metabolism and have a central role in nutrient homeostasis and organ survival [20]. Impaired insulin signaling and insulin resistance have been associated with the development of many clinical syndromes, most commonly type 2 diabetes mellitus and MetS [20,21]. In a recent study, insulin provided early information for the development of MetS [22]. Utzschneider *et al*. even reported that insulin resistance was the best predictor of MetS [23]. According to our data, the HOMA-IR and insulin level were significantly higher in the MetS group.

The serum leptin level in our study was significantly different in the MetS and no MetS groups. A lot of recent evidence has indicated that leptin may be an important factor linked to MetS [5]. Leptin is a hormone synthesized by adipocytes, which acts directly on the hypothalamus and interferes with body weight and fat deposition by appetite inhibition, stimulation of the metabolic rate, and thermogenesis [4]. Leptin resistance is defined as lack of response to exogenous leptin and an attenuated response to an elevated level of endogenous leptin [24]. Contemporary studies proposed that leptin resistance may promote insulin resistance and cause abnormal accumulation of lipids in the liver and cardiac and skeletal muscle, reducing fatty acid oxidation, consequently leading to obesity and the MetS [5].

In our study, we analyzed the correlation of the serum leptin level with several variables. The insulin level and HOMA-IR were positively correlated with the serum leptin level. Actually, a higher leptin level has already been proven to be associated with both insulin and insulin resistance [25]. Fasting plasma leptin levels can even provide a surrogate measure of insulin action and insulin sensitivity [26]. Recently, a mechanism showing how insulin plays an important role in stimulating leptin secretion and enhancing leptin synthesis was found [27,28]. Elderly women had higher serum leptin levels than men in our study. This correlation has been reported in previous studies. A study in Caucasian adults 35–74 years old reported that women had higher leptin levels than men [29]. A possible explanation may be differences in body composition and sex hormone levels between genders [30]. Waist circumference, a diagnostic criterion of MetS, is an effective surrogate measure for central or visceral adipose tissue and is associated with a higher risk of diabetes, CVD, and mortality [11,31]. In a prospective study, waist circumference had a strong positive association with leptin both in women and men [32]. In a study in random target adults, leptin levels were directly associated with waist circumference [33]. In our study, we noted that waist circumference was positively correlated with the serum leptin level in elderly people and was an independent predictor for the serum leptin level. Leptin is able to promote CRP production from hepatocytes and endothelial cells *in vitro,* and clinical studies showed a direct association between CRP and leptin plasma levels in healthy volunteers and people with obesity and type 2 diabetes mellitus [34]. Ble *et al*. noted a direct association between serum leptin and CRP in 946 community-dwelling older participants in the InCHIANTI study in two cities in the Chianti area, Tuscany, Italy [35]. Although we did not find statistically significant differences between serum leptin and CRP, our results noted a tendency toward a positive association of the serum log-leptin and log-CRP level among older Taiwanese ($P = 0.097$). An association between an increased serum leptin level and GFR decline over time was also noted in the InCHIANTI study [36]. Our results did not show a relationship between the log-leptin level and GFR in the elderly participants studied. Further studies are required to elucidate the relationship between the leptin level and CRP or GFR in older Taiwanese.

Many studies have investigated the relationship between statins and the serum leptin level. One study noted that 12-week treatment with pravastatin 40 mg/day does not change the leptin level in healthy volunteers [37]. However, a recent study reported that in patients with coronary heart disease, simvastatin had beneficial effects in reducing leptin levels independent of its lipid-lowering action [38]. Maeda *et al*. suggested that simvastatin suppresses leptin expression in preadipocyte cells (3T3-L1) by activation of the cyclic adenosine monophosphate-protein kinase A pathway induced by protein prenylation inhibition [39]. In our present study, we found that elderly people taking statins had a lower serum leptin level and

Table 3: Correlation of fasting serum log-leptin levels and clinical variables by univariable linear regression analyses among 62 elderly participants

Items	Beta	*P*
Age (years)	0.200	0.119
Height (cm)	−0.161	0.213
Body weight (kg)	0.280	0.028*
BMI (kg/m^2)	0.417	0.001*
Waist circumference (cm)	0.419	0.001*
Systolic blood pressure (mmHg)	0.033	0.801
Diastolic blood pressure (mmHg)	0.162	0.209
TCH (mg/dL)	0.200	0.119
TG (mg/dL)	0.190	0.140
HDL-C (mg/dL)	−0.035	0.790
LDL-C (mg/dL)	0.177	0.170
Log-glucose (mg/dL)	−0.004	0.975
BUN (mg/dL)	0.255	0.046*
Creatinine (mg/dL)	0.030	0.815
GFR (mL/min)	−0.144	0.265
Log-CRP (mg/dL)	0.213	0.097
Log-insulin (uIU/mL)	0.436	<0.001*
Log-HOMA-IR	0.359	0.004*

Data for glucose, CRP, insulin, HOMA-IR, and leptin levels showed skewed distributions and therefore were log-transformed before analysis. *P<0.05 was considered statistically significant after univariable linear analyses. HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, CRP: C-reactive protein, HOMA-IR: Homeostasis model assessment of insulin resistance, BUN: Blood urea nitrogen, BMI: Body mass index, TG: Triglycerides, TCH: Total cholesterol, GFR: Glomerular filtration rate

Table 4: Factors significantly correlated with fasting serum log-leptin levels in multivariable stepwise linear regression analysis among 62 elderly participants

Items	Beta	Adjusted R^2	Adjusted R^2 change	*P*
Waist circumference (cm)	0.346	0.083	0.083	0.002*
Statin use	−0.257	0.141	0.058	0.016*
Female	0.243	0.182	0.041	0.034*

*P<0.05 was considered statistically significant after multivariable stepwise linear regression analyses (adopted factors: Gender, statin use, body weight, waist circumference, BMI, BUN, log-insulin, and log-HOMA-IR). HOMA-IR: Homeostasis model assessment of insulin resistance, BUN: Blood urea nitrogen, BMI: Body mass index

use of statins was an independent factor to predict the serum leptin level. This finding may be explained by studies on the role of statins in the pathway for leptin production.

There were some limitations in our study. First, the study had a cross-sectional design. Therefore, we could not make causal inferences, and a positive correlation between the serum leptin level and MetS cannot be established until further long-term prospective studies are done. Second, the study had a small sample size, which may have affected the statistical significance. Only 62 older participants were enrolled in this study, and the power to predict MetS was only 0.76. Third, our study participants were elderly people from eastern Taiwan, and further assessment is needed to determine whether the results are applicable in other populations.

Conclusion

The serum leptin level was positively correlated with MetS in elderly Taiwanese. Waist circumference, statin use, and female gender were independent predictors of the fasting serum leptin level.

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Conflicts of interest

There are no conflicts of interest.

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