



Leptin is an independent marker of metabolic syndrome in elderly adults with type 2 diabetes

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ABSTRACT

Objective: It is well established that patients with metabolic syndrome (MetS) demonstrate elevated levels of serum leptin. The aim of this study is to identify fasting serum leptin as an independent marker of MetS in geriatric diabetic patients. **Materials and Methods:** Sixty-four patients over 65 years old with type 2 diabetic mellitus (T2DM) were assessed for MetS based on the diagnostic criteria of the International Diabetes Federation. Fasting blood samples including serum leptin concentrations were obtained from the participants. Leptin levels were determined using a commercial enzyme immunoassay. **Results:** Forty-five (70.3%) of the 64 geriatric T2DM patients enrolled in this study were found to have MetS. This group of participants compared with those in the non-MetS group had higher serum levels of leptin ($P = 0.004$), triglycerides ($P = 0.005$), fasting glucose ($P = 0.049$), glycated hemoglobin ($P = 0.016$), white blood cells ($P = 0.003$), C-reactive protein (CRP, $P = 0.028$), insulin ($P < 0.001$), higher homeostatic model assessment insulin resistance values (HOMA1-IR and HOMA2-IR, both $P < 0.001$), a higher body weight ($P = 0.024$), body mass index ($P < 0.001$), body fat mass ($P < 0.001$), waist circumference ($P < 0.001$), systolic blood pressure (BP) ($P < 0.001$), diastolic BP ($P < 0.001$), percentage of women ($P = 0.011$), prevalence of hypertension ($P = 0.042$), and a lower level of serum high-density lipoprotein cholesterol ($P = 0.001$). Univariate linear analysis of the clinical variables associated with the fasting serum leptin level revealed that height ($P = 0.020$) had a negative correlation, while body fat mass ($P < 0.001$) and logarithmically transformed CRP (log-CRP, $P < 0.001$) had positive correlations with serum leptin levels. Multivariate forward step-wise linear regression analysis of the variables significantly associated with fasting serum leptin levels showed that body fat mass ($P < 0.001$) and log-CRP ($P = 0.001$) were independent predictors of these values. **Conclusion:** Serum leptin is positively correlated with MetS. It serves as an independent marker of MetS in elderly patients with T2DM.

KEYWORDS: Elderly, Leptin, Metabolic syndrome, Type 2 diabetes mellitus

INTRODUCTION

Metabolic syndrome (MetS) is a growing health-care concern worldwide as a consequence of urbanization, overnutrition, obesity, and sedentary lifestyles [1]. It is a composite of risk factors for atherosclerotic cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) [2], specifically with a 2-fold increase in the risk of CVD and 5-fold increase in the risk of T2DM [3]. Moreover, it has been shown that patients with both T2DM and MetS tend to have a higher risk of CVD than those with T2DM alone [4]. As such, early diagnosis and subsequent intervention may be helpful in reducing the incidence of MetS-related diseases [5].

It has been suggested that dysregulation of adipokines produced by adipose tissue may contribute to the development of MetS [6].

Leptin, a type of adipokine that is primarily secreted by white adipocytes, plays a part in normal physiologic functions which include reducing appetite, increasing energy expenditure, regulating glucose utilization, and improving insulin sensitivity [7]. Obese persons exhibit high circulating levels of leptin, which appears to be in correspondence with their adipose mass [8]. Indeed, serum leptin levels were found to have a positive correlation with body fat [9] and were highly associated with obesity and insulin resistance [10] which increases the risk of T2DM [7].

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An independent marker of MetS such as serum leptin could provide a means to identify populations at risk for related complications and allows early intervention. Although the correlation between leptin and T2DM has been widely researched, only a few studies have focused on its relationship with MetS [5]. The objective of this study was to evaluate the association between fasting serum leptin and MetS in elderly adults with T2DM.

MATERIALS AND METHODS

Patients

This was a prospective, cross-sectional study conducted at a medical center in Hualien, Taiwan, from November 2014 to March 2015. Sixty-four patients with T2DM over 65 years old were enrolled in the study. T2DM was determined according to the World Health Organization criteria [11]. The study was approved by the Protection of Human Subjects Institutional Review Board of Tzu Chi University and Hospital and is consistent with the Declaration of Helsinki (IRB103-136-A). All patients provided informed consent before participating in this study. Blood pressure (BP) was measured by trained staff in the morning using standard mercury sphygmomanometers with appropriate cuff sizes after the patient had been sitting down for at least 10 min. Systolic BP (SBP) and diastolic BP (DBP) were taken 3 times at 5-min intervals and were averaged for analysis. Patients were diagnosed as having hypertension if their SBP ≥ 140 mmHg, and/or DBP ≥ 90 mmHg, or if they had received any antihypertensive medication in the past 2 weeks. Patients were excluded from the study if they had an acute infection, acute myocardial infarction, heart failure, or malignancy at the time of blood sampling, or if they refused to provide informed consent for the study.

Anthropometric analysis

Body weight was measured to the nearest 0.5 kg with the participant in light clothing without shoes, and body height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of the height in meters. A single-frequency (50-kHz) bioimpedance analyzer (Biodynamic-450, Biodynamics Corporation, Seattle, WA, USA) was applied by an experienced operator, according to a standardized, tetrapolar, whole body (hand-foot) technique, and a specific formula offered by the manufacturer was used to calculate and analyze the body fat mass. Waist circumference was measured using a measuring tape around the waist from the point between the lowest ribs and the hip bones with the participants' hands on the hips. All measurements were carried out by the same operator [12-15].

Biochemical investigations

Fasting blood samples of approximately 5 mL were obtained from each participant. About 0.5 mL of it was used to calculate white blood cell counts (Sysmex SP-1000i, Sysmex American, Mundelein, IL, USA) and the remainder was immediately centrifuged at 3000 $\times g$ for 10 min. Serum levels of albumin, fasting glucose, glycated hemoglobin (HbA1c), total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and C-reactive protein (CRP) were measured using an auto-analyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany) [12-15]. Serum leptin (SPL-BIO, Montigny le Bretonneux, France) concentrations were determined using a

commercial enzyme immunoassay [12-15]. Serum insulin levels were measured using a commercial enzyme-linked immunosorbent assay (Labor Diagnostika Nord, Nordhorn, Germany) [16]. Insulin resistance was evaluated using a homeostasis model assessment of insulin resistance (HOMA-IR) as follows: $HOMA1-IR = \text{fasting plasma glucose (mg/dL)} \times \text{fasting serum insulin } (\mu\text{U/mL})/405$ [16]; HOMA2-IR is a computer model which better reflects human physiology and is recalibrated to modern insulin assays (the HOMA2-IR model is available from www.OCDem.ox.ac.uk) [17].

Metabolic syndrome and its components

In this study, the definition of MetS was based on the diagnostic criteria of the International Diabetes Federation [18]. Participants were defined as having MetS if they had central obesity (defined as waist circumference >90 cm for men and >80 cm for women from the Chinese ethnic group) and any two of the following four factors: (1) TG ≥ 150 mg/dL; (2) HDL-C <40 mg/dL for men and <50 mg/dL for women; (3) SBP ≥ 130 mmHg or DBP ≥ 85 mmHg, or treatment of previously diagnosed hypertension; (4) fasting serum glucose ≥ 100 mg/dL or a previous diagnosis of T2DM).

Statistical analysis

Statistical data were tested for normal distribution using Kolmogorov-Smirnov test. Normally distributed data were expressed as mean \pm standard deviation, and comparisons between patients were performed using Student's independent *t*-test (two tailed). Data that were not normally distributed were expressed as medians and interquartile ranges, and comparisons between patients were performed using Mann-Whitney U-test (age, fasting glucose, CRP, insulin, HOMA1-IR, and HOMA2-IR). Data expressed as the number of patients were analyzed by Chi-square test. Since age, fasting glucose, CRP, insulin, HOMA1-IR, and HOMA2-IR were not normally distributed, base 10 logarithmic transformations were made to achieve normality. Clinical variables that correlated with serum leptin levels in geriatric T2DM patients were evaluated using univariate linear regression analysis. Variables that were significantly associated with leptin levels in these patients were tested for independence in multivariate forward step-wise regression analysis. The significance of differences in leptin levels between groups (number of MetS criteria) was analyzed by one-way analysis of variance. Data were analyzed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Demographic, clinical, and biochemical characteristics of the 64 geriatric T2DM patients are presented in Table 1. A total of 36 participants (56.3%) had a medical history of hypertension and 45 (70.3%) had MetS. This group with MetS had higher levels of serum leptin ($P = 0.004$), TG ($P = 0.005$), fasting glucose ($P = 0.049$), HbA1c ($P = 0.016$), white blood cells ($P = 0.003$), CRP ($P = 0.028$), insulin ($P < 0.001$), higher HOMA1-IR ($P < 0.001$) and HOMA2-IR ($P < 0.001$) values, a higher body weight ($P = 0.024$), BMI ($P < 0.001$), body fat mass ($P < 0.001$), waist circumference ($P < 0.001$), SBP ($P < 0.001$), DBP ($P < 0.001$), percentage of women ($P = 0.011$), prevalence of hypertension ($P = 0.042$), and a lower level of serum HDL-C ($P = 0.001$) than those in the non-MetS group.

Clinical characteristics and serum leptin values for these patients are presented in Table 2. The leptin level was statistically significantly higher in women with DM ($P < 0.001$) and patients with hypertension ($P = 0.042$). No statistically significant differences in leptin levels were found as a result of the use of statins, fibrates, or antidiabetic drugs.

Univariate linear analysis of the clinical variables associated with fasting serum leptin levels in these patients is presented in Table 3. Height ($r = -0.290$; $P = 0.020$) was negatively correlated, while body fat mass ($r = 0.597$; $P < 0.001$) and the logarithmically transformed CRP (log-CRP, $r = 0.536$; $P < 0.001$) were positively correlated with serum leptin levels.

Multivariate forward step-wise linear regression analysis of the variables significantly associated with fasting serum leptin levels revealed that body fat mass (adjusted R^2 change = 0.346; $P < 0.001$) and log-CRP (adjusted R^2 change = 0.106; $P = 0.001$) were independent predictors of these values in these patients [Table 4].

Fasting serum leptin levels are presented according to the different numbers of diagnostic criteria for MetS in Figure 1. A statistically significant difference between the number of MetS criteria and serum leptin levels in geriatric T2DM patients ($P = 0.027$) was established.

DISCUSSION

In this study, the serum leptin level was found to have positive correlations with MetS and its components in elderly

adults with T2DM. Participants with elevated levels of fasting serum leptin have more metabolic risk factors than those with lower leptin levels [5]. Moreover, serum leptin levels increased with the number of MetS criteria in our participants. This result is in coherence with similar research conducted in different populations in those with different characteristics worldwide [7].

The global prevalence of MetS ranges from 4% to as high as 84%, depending on the defining criteria and parameters such as the gender, age, and ethnicity of the population [19]. Ford *et al.* noted that the prevalence of MetS increases with the age in researched populations, with rates of 6.7% in participants 20–29 years old, 43.5% in those 60–69 years old, and 42.0% in those over 70 years old [20]. In our study, the prevalence of MetS in patients over 65 years old with T2DM was 70.3%. Participants with MetS had a significantly larger waist circumference, higher TG, higher fasting glucose level, higher prevalence of hypertension, and lower serum HDL-C level than those without MetS.

Participants in our study who had MetS had higher levels of fasting serum leptins, white blood cells, CRP, insulin, and HOMA-IR values than those in the non-MetS group. Studies have proposed that hypertrophic adipocytes in obese human are subjected to hypoxia leading to cell death and macrophage infiltration [21], causing an overproduction of pro-inflammatory adipokines such as leptin, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and CRP [22]. These adipokines play crucial roles in mediating physiologic processes involving inflammatory responses, energy metabolism, insulin sensitivity,

Table 1: Clinical variable of the 64 elderly diabetic patients with or without metabolic syndrome

Items	All participants (n=64)	No metabolic syndrome (n=19)	Metabolic syndrome (n=45)	P
Age (years)	70.50 (67.00-76.00)	68.00 (66.00-80.00)	71.00 (67.00-76.00)	0.762
Height (cm)	159.62±8.66	161.00±7.67	159.03±9.06	0.411
Body weight (kg)	68.13±10.77	63.49±8.65	70.09±11.05	0.024*
BMI (kg/m ²)	26.65±2.94	24.37±1.64	27.61±2.85	<0.001*
Body fat mass (%)	31.87±6.73	26.10±4.49	36.30±6.02	<0.001*
Waist circumference (cm)	90.96±7.52	84.87±5.98	93.53±6.60	<0.001*
SBP (mmHg)	145.03±21.04	129.63±15.47	151.53±19.75	<0.001*
DBP (mmHg)	81.27±11.72	72.53±9.41	84.96±10.65	<0.001*
Albumin (mg/dL)	4.20±0.24	4.15±0.17	4.22±0.27	0.281
Total cholesterol (mg/dL)	156.88±29.91	160.47±29.05	155.36±30.46	0.536
TG (mg/dL)	127.64±62.20	94.42±54.48	141.67±60.40	0.005*
HDL-C (mg/dL)	47.13±12.35	54.58±12.70	43.98±10.87	0.001*
LDL-C (mg/dL)	93.56±25.09	91.68±27.52	94.36±24.28	0.700
Fasting glucose (mg/dL)	131.00 (121.00-174.50)	123.00 (117.00-142.00)	138.00 (125.00-180.50)	0.049*
HbA1c (%)	7.82±1.58	7.10±1.24	8.13±1.62	0.016*
White blood count (×1000/μL)	6.89±1.82	5.88±1.31	7.31±1.85	0.003*
CRP (mg/dL)	0.12 (0.05-0.24)	0.05 (0.05-0.15)	0.15 (0.05-0.29)	0.028*
Insulin (uIU/mL)	7.66 (3.54-13.13)	3.28 (1.99-5.89)	9.00 (5.28-16.89)	<0.001*
HOMA1-IR	2.40 (1.16-4.70)	1.14 (0.75-1.66)	3.45 (1.93-5.94)	<0.001*
HOMA2-IR	1.10 (0.50-1.93)	0.46 (0.41-0.81)	1.25 (0.78-2.36)	<0.001*
Leptin (ng/mL)	27.34±14.10	19.67±13.36	30.58±13.25	0.004*
Female, n (%)	29 (45.3)	4 (21.1)	25 (55.6)	0.011*
Hypertension, n (%)	36 (56.3)	7 (36.8)	29 (64.4)	0.042*

* $P < 0.05$ was considered statistically significant after Student's *t*-test or Mann-Whitney U-test. Values for continuous variables given as mean±SD and are tested by Student's *t*-test; variables not normally distributed given as medians and interquartile range and are tested by Mann-Whitney U-test; values are presented as *n* (%) and analysis was done using Chi-square test. SD: Standard deviation, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, CRP: C-reactive protein, HOMA-IR: Homeostasis model assessment of insulin resistance, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HbA1c: Glycated hemoglobin, TG: Triglyceride

and oxidant stress [1]. Serum levels of CRP increase with the number of MetS components and are associated with a higher BMI, larger waist circumference, higher fasting glucose, and insulin resistance [23]. In individuals with insulin resistance, a larger amount of insulin is secreted by the pancreatic β -cells to overcome the hyperglycemic state. As a result of hyperinsulinemia and insulin resistance, such individuals are more likely to develop T2DM, hypertension, and CVDs [24]. A proposed hypothesis is that hyperinsulinemia and insulin resistance activate the sympathetic nervous system (SNS) [25] and the rennin angiotensin system [26], causing vasoconstriction and sodium reabsorption, which subsequently results in hypertension.

In the present study, we found a positive correlation between hypertension and serum leptin levels in our participants. Besides regulating metabolism and appetite, leptin plays a role in raising BP by activating the SNS and increasing renal adrenergic activity [27], which may explain why obese humans who demonstrate elevated renal sympathetic tone have high levels of serum leptin as well [28]. Our study also noted a higher percentage of female participants with MetS and this was significantly correlated with elevated levels of serum leptin. In general, women have significantly higher serum leptin levels than men [29], although it has been suggested that serum leptin has a stronger correlation with the risk of MetS in men than in women after adjusting for other confounding variables [30]. Possible explanations that may

account for this phenomenon include increased mRNA production by 17β -estradiol and a negative correlation between testosterone and leptin levels [31]. Moreover, postmenopausal women with MetS were found to have elevated leptin levels and this was associated with an increased prevalence of abdominal obesity [32]. The decline in metabolic rate and energy expenditure as a result of menopause and decreased physical activity due to old age may explain this finding [33]. On the other hand, age is also a factor that increases the risks of MetS because of metabolic alterations, leading to accumulation of visceral fat and insulin resistance [34].

In this study, univariate linear analysis of the clinical variables revealed that height had a negative correlation, while body fat mass and log-CRP had positive correlations with serum leptin levels. Multivariate forward step-wise linear regression analysis of the variables significantly associated with fasting serum leptin levels showed that body fat mass and log-CRP were independent predictors of those values. Yu *et al.* conducted a research in mainland Chinese population and found not only a strong correlation between body fat mass and leptin, but also suggested that fat mass is a key factor responsible for metabolic abnormalities related to hyperleptinemia [35]. The relationship between CRP and leptin has been studied extensively in both genders [36]. It was proposed that pro-inflammatory adipokines such as TNF- α and IL-6 mediate the production of CRP under the influence of leptin [37] and that a direct CRP-stimulatory activity by leptin independent of adipokines is present [38].

Table 2: Clinical characteristics and fasting serum leptin levels of 64 elderly diabetic patients

Characteristics	n (%)	Leptin (ng/mL)	P
Gender			
Male	35 (54.7)	21.00 \pm 10.01	<0.001*
Female	29 (45.3)	35.00 \pm 14.66	
Hypertension			
No	28 (43.8)	23.29 \pm 13.17	0.042*
Yes	36 (56.2)	30.50 \pm 14.18	
Statin			
No	35 (54.7)	25.45 \pm 12.37	0.242
Yes	29 (45.3)	29.63 \pm 15.87	
Fibrate			
No	61 (95.3)	26.67 \pm 13.38	0.109
Yes	3 (4.7)	41.02 \pm 24.48	
Metformin			
No	29 (45.3)	26.34 \pm 14.29	0.607
Yes	35 (54.7)	28.18 \pm 14.10	
Sulfonylureas			
No	30 (46.9)	28.81 \pm 13.62	0.439
Yes	34 (53.1)	26.05 \pm 14.59	
DDP-4 inhibitor			
No	27 (42.2)	30.37 \pm 14.50	0.143
Yes	37 (57.8)	25.13 \pm 13.57	
Thiazolidinediones			
No	62 (96.9)	27.69 \pm 14.19	0.270
Yes	2 (3.1)	16.46 \pm 0.26	
Insulin			
No	45 (70.3)	27.51 \pm 13.84	0.885
Yes	19 (29.7)	26.95 \pm 15.90	

Data are expressed as medians and interquartile range. * P <0.05 was considered statistically significant after Student's *t*-test. DDP-4: Dipeptidyl peptidase 4

Table 3: Correlation of fasting serum leptin levels and clinical variables by univariable linear regression analyses among the 64 elderly diabetic patients

Items	β	P
Log-age (years)	0.179	0.158
Height (cm)	-0.290	0.020*
Body weight (kg)	-0.053	0.676
BMI (kg/m ²)	0.240	0.056
Body fat mass (%)	0.597	<0.001*
Waist circumference (cm)	0.122	0.338
SBP (mmHg)	0.089	0.483
DBP (mmHg)	0.055	0.663
Albumin (mg/dL)	0.059	0.642
Total cholesterol (mg/dL)	-0.013	0.919
TG (mg/dL)	-0.062	0.628
HDL-C (mg/dL)	0.022	0.861
LDL-C (mg/dL)	0.058	0.646
Log-glucose (mg/dL)	0.143	0.260
HbA1c (%)	0.234	0.062
White blood count ($\times 1000/\mu$ L)	0.236	0.060
Log-CRP (mg/dL)	0.536	<0.001*
Log-insulin (μ IU/mL)	0.229	0.069
Log-HOMA1-IR	0.246	0.050
Log-HOMA2-IR	0.273	0.029*

Data of age, glucose, CRP, insulin, and HOMA1-IR levels show skewed distribution, 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, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HbA1c: Glycated hemoglobin, BMI: Body mass index, TG: Triglyceride

Table 4: Multivariable step-wise linear regression analysis of gender, hypertension, height, body fat mass, and log-C-reactive protein: Correlation to fasting serum leptin level among 64 elderly diabetic patients

Items	β	Adjusted R^2	Adjusted R^2 change	P
Body fat mass (%)	0.460	0.346	0.346	<0.001*
Log-CRP (mg/dL)	0.363	0.452	0.106	0.001*

* $P < 0.05$ was considered statistically significant after multivariable step-wise linear regression analyses. CRP: C-reactive protein

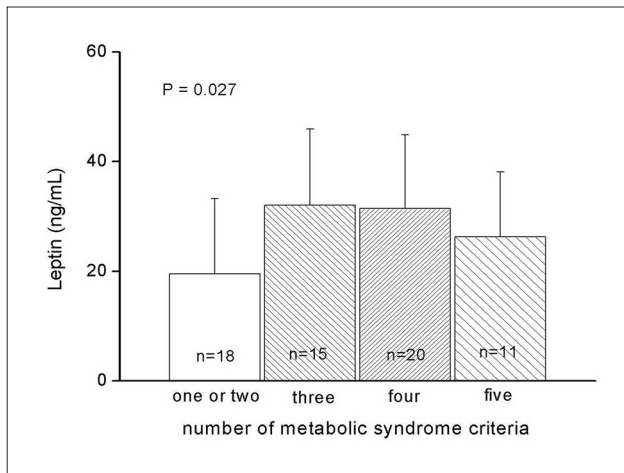


Figure 1: Fasting serum leptin levels according to different numbers of diagnostic criteria for metabolic syndrome in 64 elderly diabetic patients. Data were analyzed by one-way analysis of variance

The relationship between MetS and leptin has become a widely accepted concept in the recent years, and numerous studies have been conducted in different populations worldwide [7]. The Framingham Third Generation Cohort found that circulating levels of leptin were linked with an increased risk of MetS [39]. The same correlation has also been identified in the adult Taiwanese population and leptin is predictive of MetS regardless of gender [5]. Leptin functions in normal human physiology to regulate energy homeostasis by increasing energy expenditure and decreasing food intake. However, despite having high levels of leptin, obese people develop resistance to its effects [8]. Resistance to leptin is proposed to be caused by defects in leptin transport across the blood-brain barrier [8], alterations at or downstream of hypothalamic ObRb receptors, or induction of signal inhibitors [9]. Leptin resistance is hence considered to be the fundamental pathology in obese people [40]. In this study involving geriatric patients with T2DM, no statistically significant differences in leptin levels were found as a result of use of statins, fibrates, or antidiabetic drugs such as metformin, the sulfonylureas, dipeptidyl peptidase-4 inhibitors, thiazolidinediones, and insulin. A study conducted in patients with T2DM in Turkey revealed that thiazolidinediones had no significant effect on serum leptin levels [41]. In addition, although insulin is known to stimulate leptin secretion from adipocytes [42], we did not find a statistically significant correlation between the use of insulin and serum leptin.

Our study had some limitations. First, the nature of cross-sectional studies resulted in difficulties in identifying the direction of causality

between MetS and serum leptin. Second, research participants who gave their consent to participate in this study were supposedly more conscious of their own health, as they came to the hospital for medical treatment, and hence our results might underestimate the actual prevalence of MetS. Third, the sample size of 64 patients from Hualien county may not be representative of the entire Taiwanese population and this result may not apply to patients of different ethnicities. Finally, the duration of DM in our participants was not recorded, which could provide additional information when evaluating the relationship between leptin and MetS.

CONCLUSION

Our study found that serum leptin was positively correlated with MetS in elderly adults with T2DM. It can serve as an independent marker of MetS which could provide a means to identify populations at risk for related complications and allow early intervention. Body fat mass and log-CRP levels were independent predictors of serum leptin levels in elderly adults with T2DM.

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Conflicts of interest

There are no conflicts of interest.

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