Original Article

Exploring the link between leptin levels and metabolic syndrome in elderly Indian patients: Implications for family medicine and primary care practices

Arjun Kumar Singhal[1], Gaurav Singh[2], Shravan Kumar Singh[3], Busi Karunanand[1], Gagan Gunjan[4], Sonu K. Agrawal[5]

[1]Department of Biochemistry, Faculty of Medicine and Health Sciences, SGT, Gurugram, Haryana, India, [2]Department of Microbiology, ESIC Medical College and Hospital, Patna, Bihar, India, [3]Department of Medical Health and Family Welfare, Plibhit, Uttar Pradesh, India, [4]Department of General Medicine, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India, [5]Consultant Microbiologist, Vimta Labs. Limited, New Delhi, India

Abstract

Background: The metabolic syndrome (MetS), according to the Adult Treatment Panel III of the National Cholesterol Education Programme, is a collection of metabolic abnormalities that includes one, two, or all three of the following traits: obesity in the abdomen, dyslipidemia, hypertension, fasting blood sugar, or insulin resistance. This study's aim was to assess the relationship between fasting serum leptin and MetS in elderly adults with T2DM in the Northern Indian population. **Material and Methods:** The following information was collected from all the participants: (1) anthropometric data, (2) biochemical data, and (3) a lifestyle questionnaire on sociodemographic data, dietary practices, smoking, and alcohol intake to identify their risk factors for diabetes mellitus, CVD, and hypertension. **Results:** A total of 36 older participants (56.30%) had a history of hypertension, while 29 elderly participants (44.61%) had diabetes mellitus. A total of 32 elderly participants (49.2%) had MetS, and this group had higher serum leptin (P 0.003), body weight (P = 0.019), BMI (P 0.001), waist circumference (P 0.001), CRP (P = 0.021), insulin (P = 0.001), and HOMA-IR (P = 0.003) values as well as higher percentages of females (P = 0.001), and those with type 2 diabetes mellitus (P = 0.002) and hypertension (P = 0.039) than those in the non-MetS group. **Conclusion:** In older persons with T2DM, our study discovered a favorable correlation between serum leptin and MetS. It can act as a standalone indicator of MetS, offering a way to spot populations at risk for associated consequences and enabling early intervention.

Keywords: Elderly, leptin, metabolic syndrome

Background

The metabolic syndrome (MetS), as defined by the Adult Treatment Panel III of the National Cholesterol Education Programme, comprises various metabolic abnormalities, encompassing obesity in the abdomen, dyslipidemia, hypertension, fasting blood sugar, or insulin resistance.[1] Notably, obesity, insulin resistance, dyslipidemia, and hypertension collectively contribute to MetS, heightening the risk of cardiovascular disease (CVD) and renal events.[2] The prevalence of MetS has surged globally due to urbanization, overeating, obesity, and sedentary lifestyles.[3] This syndrome poses a significant health threat, serving as a combination of risk factors for type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (CVD), leading to a twofold increase in CVD risk and a fivefold increase in T2DM risk.[4,5] Furthermore, individuals with both T2DM and MetS

Address for correspondence: Dr. Arjun Kumar Singha, Department of Biochemistry, Faculty of Medicine and Health Sciences, SGT, Gurugram, Haryana, India.
E-mail: singhal2075@yahoo.co.in

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exhibit a heightened susceptibility to CVD compared to those with T2DM alone.[5] Recognizing the association between MetS and adverse health outcomes, early detection and intervention are crucial to mitigate the prevalence of diseases linked to MetS.[6]

Recent research suggests that the development of metabolic syndrome (MetS) may be linked to the dysregulation of adipokines produced by adipose tissue.[7] One such adipokine, leptin, primarily released by white adipocytes, plays a role in normal physiological processes such as hunger suppression, increased energy expenditure, regulation of glucose uptake, and improved insulin sensitivity.[8] In individuals with obesity, elevated levels of leptin in the bloodstream are observed, often associated with their increased adipose mass.[9] Interestingly, serum leptin levels exhibit a positive correlation with body fat and show a strong association with both obesity and insulin resistance, both of which elevate the risk of type 2 diabetes (T2DM).[8-11]

The potential of serum leptin to identify individuals at risk for MetS-related complications provides an avenue for early intervention. Although the correlation between leptin and T2DM has received more attention in studies, the link between leptin and MetS is equally significant, albeit less explored.[6]

This study aims to evaluate the relationship between fasting serum leptin levels and MetS in elderly adults with T2DM in the Northern Indian population.

Methods

Study population

The research was carried out at a tertiary care center in northern India, involving a total of 65 participants aged between 50 and 75 years. Comprehensive data were gathered from all participants, encompassing (1) anthropometric information, (2) biochemical data, and (3) lifestyle details obtained through a questionnaire addressing sociodemographic aspects, dietary practices, smoking, and alcohol consumption to identify potential risk factors for diabetes mellitus, cardiovascular disease (CVD), and hypertension.

Subjects with missing data for waist circumference (WC), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, or blood pressure—integral components of metabolic syndrome (MetS)—were excluded from the study. Trained staff utilized standard mercury sphygmomanometers and appropriate cuff sizes to measure blood pressure (BP) in the right arm. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were averaged for analysis. Hypertension indicators in study participants included SBP exceeding 140 mmHg, DBP surpassing 90 mmHg, or recent use of antihypertensive medication within the last two weeks.

Participants with acute infections, acute myocardial infarction, heart failure, or malignancies were excluded from the study to ensure the integrity of the data and the reliability of the findings.

Anthropometric analysis

Participants' body weight and height were measured to the nearest 0.5 kg and 0.5 cm, respectively. Waist circumference was measured with a tape from the point between the lowest ribs to the hip bones with hands on the hips. BMI was calculated using the Quetelet formula (weight in kilograms divided by height in square meters).[12,13]

Biochemical parameters

Diagnosis of metabolic syndrome

Blood samples (approximately 5 mL) were collected from fasting patients and promptly centrifuged at 3000*g* for 10 min. Serum levels of blood urea nitrogen (BUN), creatinine (Cr), fasting glucose, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein, and C-reactive protein (CRP) were measured using an autoanalyzer.[12-14] Serum leptin levels were quantified using a commercial enzyme immunoassay.[12-15] Serum insulin levels were detected with an automated analyzer, and insulin resistance was assessed using the homeostasis model assessment (HOMA-IR). HOMA-IR was calculated as follows: HOMA1-IR = fasting plasma glucose (mg/dL) × fasting serum insulin (U/mL)/405.[15]

This study employed the diagnostic criteria of the International Diabetes Federation to define metabolic syndrome (MetS). Participants were classified as having MetS if they exhibited two out of the following four conditions: (1) triglycerides (TG) equal to or greater than 150 mg/dL; (2) high-density lipoprotein (HDL) cholesterol less than 40 mg/dL for men and 50 mg/dL for women; (3) systolic blood pressure (SBP).[16]

Statistical analysis

Normally distributed data were presented as mean ± standard deviation, and comparisons utilized Student's independent *t* test (two-tailed). Nonnormally distributed measures (age, fasting glucose, CRP, insulin, HOMA1-IR, and HOMA2-IR) were reported as medians with interquartile ranges, and the Mann–Whitney *U* test was employed for patient comparisons. The Chi-square test analyzed data presented as patient counts. Logarithmic adjustments were applied for normality in age, fasting glucose, CRP, insulin, HOMA1-IR, and HOMA2-IR. A significance level of $P < 0.05$ was considered statistically significant.

Results

Table 1 presents the demographic, clinical, and biochemical characteristics of the 65 participants. Of the participants, 56.30% had a history of hypertension, and 44.61% had diabetes mellitus. Additionally, 49.2% of the elderly participants had metabolic syndrome (MetS). The MetS group exhibited significantly higher levels of serum leptin ($P = 0.003$), body weight ($P = 0.019$), BMI ($P = 0.001$), waist circumference ($P = 0.001$), CRP ($P = 0.021$), insulin ($P = 0.001$), and HOMA-IR ($P = 0.003$). They also had a higher percentage of females ($P = 0.001$) and individuals with

Table 1: Demographic, clinical, and biochemical characteristics of the elderly diabetic patients with or without metabolic syndrome

Items	All participants (*n*=65)	No metabolic syndrome (*n*=18)	Metabolic syndrome (*n*=47)	*P*
Age (years)	62.50 (50–75)	65.00 (55–75)	60.00 (50–70)	0.672
Height (cm)	153.51±6.51	159.00±6.18	152.05±8.01	0.379
Body weight (kg)	69.21±9.67	61.38±6.53	71.17±9.07	0.019*
BMI (kg/m^2)	26.77±1.87	23.89±1.12	27.82±1.79	0.001*
Body fat mass (%)	32.58±5.84	25.09±4.67	37.04±5.69	0.002*
Waist circumference (cm)	89.76±6.97	81.35±6.97	90.79±7.80	0.001*
SBP (mmHg)	144.05±20.05	128.52±14.36	152.67±19.48	<0.001*
DBP (mmHg)	79.25±10.61	71. ± 9.41	83.87±9.85	<0.001*
Total cholesterol (mg/dL)	158.87±29.61	156.28±27.01	155.51±27.32	0.397
TG (mg/dL)	126.52±58.61	93.25±53.45	139.78±59.48	0.004*
HDL (mg/dL)	46.11±10.45	52.48±11.35	44.88±11.77	0.001*
LDL (mg/dL)	91.66±24.08	92.78±28.42	95.63±23.26	0.8
Fasting glucose (mg/dL)	133	122.5	137.5	0.039*
HbA1c (%)	7.67±1.67	7.07±1.35	7.89±1.59	0.018*
CRP (mg/dL)	0.11	0.04	0.17	0.021*
Insulin (μIU/mL)	7.58	3.67	8.98	0.001*
HOMA1-IR	2.39	1.11	3.47	<0.001*
HOMA2-IR	1.12	0.47	1.19	<0.001*
Leptin (ng/mL)	26.89±13.19	18.96±13.46	29.98±14.01	0.003*
Female, *n* (%)	30 (46.1)	5 (27.77)	27 (41.53)	0.017*
Diabetes, *n* (%)	29 (44.61)	5 (27.77)	30 (63.82)	0.002*
Hypertension, *n* (%)	36 (56.3)	7 (36.8)	29 (64.4)	0.039*

*P<0.05 was considered statistically significant. Values for continuous variables given as mean±SD; values are presented as *n* (%) HDL-C: High-density lipoprotein, LDL-C: Low-density lipoprotein, 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

type 2 diabetes mellitus ($P = 0.002$) and hypertension ($P = 0.039$) compared to the non-MetS group. The use of statins, fibrates, or antidiabetic medications did not result in statistically significant variations in leptin levels.

Table 2 summarizes the results of univariate linear analysis for clinical factors influencing fasting serum leptin levels in patients. Height exhibited a negative association ($r = -0.289$; $P = 0.020$), while body fat mass ($r = 0.586$; $P < 0.001$) and logarithmically transformed CRP (log-CRP, $r = 0.518$; $P < 0.002$) showed positive associations with serum leptin levels.

Multivariate forward stepwise linear regression analysis revealed that body fat mass and log-CRP independently predicted fasting serum leptin levels in these patients. The variables significantly associated with fasting serum leptin levels demonstrated an adjusted R2 change of 0.351, and both predictors were statistically significant ($P < 0.001$) [Table 3].

Table 2: Showing elderly diabetes patients' fasting serum leptin levels and clinical parameters were correlated using univariable linear regression models

Items	β	*P*
Log age (years)	0.168	0.147
Height (cm)	−0.289	0.031*
Body weight (kg)	−0.047	0.572
BMI (kg/m^2)	0.239	0.047
Body fat mass (%)	0.586	0.001*
Waist circumference (cm)	0.199	0.377
SBP (mmHg)	0.078	0.476
DBP (mmHg)	0.055	0.611
Total cholesterol (mg/dL)	−0.009	0.781
TG (mg/dL)	−0.059	0.598
HDL (mg/dL)	0.021	0.854
LDL (mg/dL)	0.049	0.548
Log-glucose (mg/dL)	0.153	0.281
HbA1c (%)	0.245	0.059
Log-CRP (mg/dL)	0.518	0.002*
Log-insulin (μIU/mL)	0.219	0.078
Log-HOMA1-IR	0.275	0.041
Log-HOMA2-IR	0.287	0.019*

*P<0.05 was considered statistically significant HDL High-density lipoprotein-cholesterol, LDL: 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

Discussion

In this study of seniors with type 2 diabetes mellitus (T2DM), a positive correlation was observed between serum leptin levels and metabolic syndrome (MetS) and its components. Higher fasting blood leptin concentrations were associated with an increased number of metabolic risk factors.[6] The prevalence of MetS varies globally (4% to 84%) based on defining criteria, gender, age, and ethnicity.[17] Ford *et al.*[18] reported an age-related increase in MetS prevalence, ranging from 6.7% in individuals aged 20 to 29 years to 43.5% in those aged 60 to 69 years and 42.0% in participants aged over 70 years. Subjects with MetS were more likely to have hypertension, larger waist circumference, higher triglycerides, elevated fasting glucose, and lower serum high-density lipoprotein levels.

Table 3: Gender, hypertension, height, body fat mass, and log-C-reactive protein multivariable stepwise linear regression analysis: Correlation to fasting serum leptin level in senior diabetes individuals

Items	β	Adjusted R^2	Adjusted R^2 change	*P*
Body fat mass (%)	0.451	0.351	0.351	0.001*
Log-CRP (mg/dL)	0.346	0.445	0.104	0.001*

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

Participants with MetS exhibited higher fasting serum leptins, C-reactive protein (CRP), insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) values compared to those without MetS. Studies suggest that hypertrophic adipocytes in obese individuals lead to hypoxia, causing cell death, macrophage infiltration, and increased production of pro-inflammatory adipokines like leptin, tumor necrosis factor (TNF), interleukin-6 (IL-6), and CRP.[19,20] These adipokines play crucial roles in oxidative stress, energy metabolism, inflammatory responses, and insulin sensitivity. Elevated BMI, larger waist circumference, fasting hyperglycemia, and insulin resistance are associated with higher CRP levels as the number of MetS components increases.[21] Hyperinsulinemia in response to insulin resistance may lead to various complications, including type 2 diabetes, hypertension, and cardiovascular diseases.[22] The activation of the sympathetic nervous system and the renin–angiotensin system contributes to vasoconstriction and sodium reabsorption, resulting in hypertension.[23,24]

In this study, a correlation was found between individuals' serum leptin levels and hypertension. Leptin not only regulates metabolism and hunger but also increases blood pressure by activating the sympathetic system and enhancing renal adrenergic activity.[25] This may explain the elevated serum leptin levels in obese individuals with heightened renal sympathetic tone.[26] Female participants, in particular, demonstrated a higher prevalence of metabolic syndrome (MetS), which significantly correlated with elevated blood leptin levels. Although serum leptin has a stronger association with MetS risk in men, women generally exhibit higher leptin levels, possibly influenced by increased mRNA synthesis by 17-estradiol and a negative correlation between testosterone and leptin levels.[27] Postmenopausal women with MetS were found to have elevated leptin levels, linked to a higher frequency of abdominal obesity, possibly attributable to the metabolic rate decline and decreased physical activity associated with aging.[28,29] Age, as a factor, increases the likelihood of MetS due to metabolic changes, leading to visceral fat accumulation and insulin resistance.[30]

In the univariate linear analysis, height showed a negative association with serum leptin levels, while body fat mass and log-CRP had positive correlations. In a multivariate forward stepwise linear regression analysis, body fat mass and log-CRP were identified as independent predictors of fasting serum leptin levels. Abdullah *et al.*[31] found a substantial link between body fat mass and leptin in the mainland Chinese population, indicating that fat mass contributes significantly to the metabolic anomalies associated with hyperleptinemia. Previous research has highlighted the relationship between CRP and leptin, suggesting that leptin influences the production of pro-inflammatory adipokines, such as TNF-α and IL-6, and directly stimulates CRP without the involvement of adipokines.[32-33]

The association between MetS and leptin has gained widespread acceptance, with studies conducted in various populations globally. Circulating leptin levels were found to be associated with an increased risk of MetS in the Framingham Third Generation Cohort. Leptin predicts MetS irrespective of gender, as observed in the adult Taiwanese population. In obesity, individuals may develop leptin resistance, a condition thought to be the primary pathophysiology in obese individuals. This resistance may arise from changes at or near hypothalamic ObRb receptors, signal inhibitors, or issues in leptin trafficking across the blood–brain barrier.[34-35]

In the study of geriatric T2DM patients, no statistically significant variations in leptin levels were observed with the use of statins, fibrates, antidiabetic medications, or insulin. Despite the known stimulation of leptin release by insulin, no statistically significant link was found between insulin usage and serum leptin.

Understanding the link between leptin levels and metabolic syndrome in elderly Indian patients holds significant importance for family medicine and primary care practices. It provides family physicians with valuable insights into potential risk factors for metabolic syndrome, allowing for early identification and targeted interventions. This knowledge can guide personalized care plans tailored to each patient's specific health profile, contributing to more effective and preventive healthcare strategies within the realm of family medicine. Additionally, by recognizing the association between leptin and metabolic syndrome, family physicians can play a pivotal role in promoting lifestyle modifications, managing obesity, and mitigating the risk of related complications in their elderly patients.

Several limitations were present in our study. Firstly, the statistical robustness may be influenced by the relatively small sample size. Secondly, the generalizability of our results to patients from diverse racial or ethnic backgrounds is uncertain. The study participants from northern India may not be representative of the entire Indian population, and further investigation is needed to ascertain the applicability of our findings to other Indian populations.

Conclusion

Our study in older individuals with type 2 diabetes mellitus (T2DM) revealed a positive correlation between serum leptin and metabolic syndrome (MetS). Serum leptin can serve as a standalone indicator for identifying populations at risk of MetS, facilitating early intervention. In older individuals with T2DM,

body fat mass and log-CRP levels independently predicted serum leptin levels. Given the limited data in our country, additional region-specific studies are needed to enhance our understanding.

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Conflicts of interest

There are no conflicts of interest.

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