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Serum leptin is associated with metabolic syndrome in obese and nonobese Korean populations☆

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Abstract

Leptin is mainly secreted from adipose tissue and is known to be associated with cardiovascular diseases. However, there are not many studies on the association between serum leptin and metabolic syndrome. The objective of this study was to determine the association between serum leptin and metabolic syndrome among the Korean adult population. The study population consisted of 3,272 Koreans (men: 1,915, women: 1,357) 30 to 84 years of age who had visited the Health Examination Center. Leptin levels were divided into quintiles and metabolic syndrome was defined by NCEP ATP III. The serum leptin levels increased as the number of components present for metabolic syndrome increased. Controlling for age, smoking, exercise, and LDL cholesterol, subjects with high leptin levels were more likely to have an elevated risk of metabolic syndrome than those with lower levels in both men and women. Subjects in the highest leptin quintile were found to have a higher risk of having metabolic syndrome than those in the lowest quintile (OR = 11.51 for men; OR = 4.65 for women). After further adjustment of the BMI, the risk of metabolic syndrome still increased slightly for men but not for women in increasing leptin categories. This association of leptin levels and metabolic syndrome did not change after stratification into obese and nonobese weight status. Serum leptin is associated with metabolic syndrome in Korean populations independent of body mass index. Thus, the reduction of circulating leptin may confer cardiovascular and metabolic protective effects regardless of weight status.

1. Introduction

Metabolic syndrome is characterized by obesity, hypertension, low levels of high-density lipoprotein cholesterol, and elevated insulin levels. All these factors contribute to the development of heart disease [1,2]. The prevalence of obesity and metabolic syndrome has seen a marked increase in the past decade. This represents a serious cardiovascular health hazard with significant morbidity and mortality. Several previous studies showed that metabolic syndrome is associated with increased risk for cardiovascular disease and diabetes [3-5].

The gene product for the obese gene is Leptin [6]. Leptin is a protein hormone produced by adipocytes that reflects the body's fat content [7]. Leptin signaling may play an important role in regulating body weight by controlling the size of adipose tissue mass [8]. Insulin resistance is known to occur with the manifestation of decreased leptin [9]. Leptin agonist has recently been reported to reduce not only weight but also blood glucose levels in obese animals and increase insulin sensitivity. Among factors affecting the serum leptin concentration, the amount of adipose tissues and body mass index (BMI) were known to be closely related with the serum leptin concentration [10]. Leptin is a crucial factor for metabolic syndrome that is characterized by obesity, insulin resistance, hypertension, and dyslipidemia. Recent studies have suggested that the adipocyte-derived hormone leptin may have an important role in obesity, metabolic syndrome, and cardiovascular disease with a link to all three.

Previous studies have shown an association between leptin and metabolic syndrome but most studies conducted thus far have been based upon Caucasian populations

Conflicts of Interest: none.

Institutional Approval: The Institutional Review Board at the Yonsei University College of Medicine approved the study design and all participants provided written informed consent.

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[11,12]. There have been a few studies on Asian populations, but those studies had various limitations such as small sample size and the sample population being very specific such as children only [13] or obese people only. The aim of this study was to examine the correlation between serum leptin levels and the prevalence of the metabolic syndrome in a large homogenous sample from the Korean population.

2. Subjects and methods

2.1. Study participants

The study population consisted of 9,995 subjects, who participated in the Korean Metabolic Syndrome Research Initiative and had routine health examinations at the Health Promotion Center at University Hospitals from January to June, 2007. The population for the current study was restricted to participants who were all examined based on 1) anthropometric data, 2) biochemical data, and 3) a lifestyle questionnaire on such things as smoking status and exercise at the time of their visit (n = 3,487). These individuals had there serum leptin measured. The analysis excluded subjects who had missing information for the components of metabolic syndrome such as waist circumference (WC), triglycerides, HDL cholesterol, or blood pressure and those who had a history of cardiovascular disease, stroke, or any type of cancer (n = 215). Therefore, we analyzed the data for a total of 3,272 subjects (1,915 men, 1,357 women). The Institutional Review Board at the Yonsei University College of Medicine approved the study design and all participants provided written informed consent.

2.2. Clinical and biochemical assessment

Each participant was interviewed using a structured questionnaire to collect demographic characteristics (age, gender, etc.), personal history of cigarette smoking status (never smoked, ex-smoker, current smoker), and information about regular exercise (yes, no). Waist circumference (WC) was measured midway between the lower rib and iliac crest. The participant's weights and heights were measured while wearing light clothing. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2).

2.3. Definition of metabolic syndrome

A diagnosis of metabolic syndrome was defined as a subject presenting at least 3 of the 5 factors for metabolic syndrome described by the Third Adult Treatment Panel (ATP III) of the Korean National Cholesterol Education Program (NCEP) [14]. However, waist circumference cut-offs were modified for Asian populations [15].

The following factors were used to define metabolic syndrome:

(1) Abdominal Obesity: a waist circumference ≥90 cm for men and ≥80 cm for women.
(2) Triglyceride: a triglyceride level ≥150 mg/dL.
(3) Low HDL cholesterol: HDL cholesterol <40 mg/dL for men and <50 mg/dL for women.
(4) High blood pressure: a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥85 mmHg.
(5) Hyperglycemia: fasting plasma glucose levels ≥110 mg/dL.

2.4. Statistical analysis

The odds ratios (ORs) and the 95% confidence intervals (CI) of serum leptin levels for metabolic syndrome were calculated. Serum leptin levels were categorized into quintiles according to the leptin levels (<0.79, 0.79-1.67, 1.68-2.50, 2.51-3.71, ≥3.72 ng/ml for men, and <3.16, 3.16-4.78, 4.79-6.44, 6.45-9.43, ≥9.44 ng/ml for women). Based on the BMI of 25 kg/m^2, differences between serum leptin levels and metabolic syndrome were analyzed in two groups: obese group (BMI ≥ 25 kg/m^2) and nonobese group (BMI < 25 kg/m^2). The data are presented as the mean ± S.D., and the significance of the comparisons was determined using Student's *t*-test. The partial correlation coefficient was used to describe the association between leptin and other continuous variables of interest controlling for the effect of age. A multivariate logistic regression model was used to test the independent association of leptin and metabolic syndrome adjusting for potential confounders such as age, gender, smoking status, LDL cholesterol, and BMI. All analyses were conducted using the SAS version 9.1 software package (SAS Institute Inc, Cary, NC). All statistical tests were two-sided, and statistical significance was accepted for *P*-values <.05.

3. Results

The prevalence of metabolic syndrome for men and women were 17.6% and 12.2%, respectively. Mean subject age was 45.4 years and mean leptin levels were 2.6 ng/ml for men and 6.6 ng/ml for women. The prevalence of metabolic syndrome was 17.6% among men and 12.2% among women. The characteristics of participants stratified by leptin quintiles are shown in Table 1. Subjects in the highest quintile were older, more likely to be obese with higher fasting glucose and triglyceride levels and had lower HDL cholesterol levels than those in the lowest quintile. The prevalence of metabolic syndrome increased with increasing levels of leptin.

In both men and women, leptin levels were highly correlated with BMI and waist circumference. Using the age and gender adjusted Pearson correlation test, serum levels of leptin were found to be inversely correlated with relation to metabolic syndrome, i.e., blood pressure, waist circumference, total cholesterol, triglyceride, LDL cholesterol, and fasting glucose but directly associated with HDL cholesterol ($P < .0001$) (Table 2). The serum leptin levels increased as

Table 1
General characteristics of the study population according to leptin levels

	Leptin levels*					
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*-value
Men						
Age, yr	44.7 ± 8.8	44.7 ± 8.6	44.1 ± 8.5	43.4 ± 9.1	43.6 ± 9.2	.1842
Body mass index, kg/m^2	22.5 ± 2.2	23.9 ± 1.9	25.3 ± 2.2	26.6 ± 2.3	28.1 ± 3.0	<.0001
Waist circumference, cm	79.2 ± 6.3	83.7 ± 5.6	87.6 ± 6.0	90.4 ± 7.4	94.5 ± 8.3	<.0001
Systolic blood pressure, mm Hg	118.1 ± 13.3	121.3 ± 12.8	123.2 ± 12.5	126.3 ± 14.4	125.9 ± 12.9	<.0001
Diastolic blood pressure, mm Hg	77.7 ± 11.1	80.4 ± 10.9	82.0 ± 10.4	83.9 ± 11.5	84.1 ± 10.8	<.0001
Total cholesterol, mg/dl	188.7 ± 31.6	196.6 ± 32.7	201.3 ± 34.8	202.1 ± 33.5	209.2 ± 39.0	<.0001
Triglyceride, mg/dl	112.9 ± 63.8	142.8 ± 87.2	165.1 ± 95.4	174.8 ± 89.9	192.2 ± 111.9	<.0001
HDL cholesterol, mg/dl	51.7 ± 13.0	48.1 ± 10.8	47.2 ± 10.4	47.2 ± 10.1	46.5 ± 10.8	<.0001
LDL cholesterol, mg/dl	116.3 ± 29.1	122.9 ± 28.9	125.4 ± 31.3	126.2 ± 29.3	132.0 ± 33.3	<.0001
Fasting plasma glucose, mg/dl	94.1 ± 22.4	95.9 ± 16.1	97.3 ± 13.1	100.3 ± 18.8	102.3 ± 16.9	<.0001
Leptin, ng/ml	0.9 ± 0.1	1.9 ± 0.4	3.1 ± 0.4	4.9 ± 0.7	8.5 ± 2.4	<.0001
Metabolic syndrome, %	4.8	8.2	14.3	24.5	35.7	<.0001
Women						
Age, yr	43.1 ± 9.3	44.1 ± 9.7	43.6 ± 9.4	45.8 ± 9.6	47.9 ± 10.4	<.0001
Body mass index, kg/m^2	20.2 ± 2.4	20.4 ± 2.1	20.5 ± 1.9	21.9 ± 2.2	24.2 ± 2.8	<.0001
Waist circumference, cm	71.2 ± 8.9	69.6 ± 6.7	70.4 ± 6.0	74.2 ± 6.8	79.8 ± 8.3	<.0001
Systolic blood pressure, mm Hg	112.5 ± 12.6	109.6 ± 14.6	110.6 ± 13.6	113.0 ± 13.1	117.6 ± 16.0	<.0001
Diastolic blood pressure, mm Hg	70.0 ± 10.4	69.5 ± 11.9	71.1 ± 10.5	71.8 ± 10.7	73.9 ± 11.9	<.0001
Total cholesterol, mg/dl	174.7 ± 31.1	180.0 ± 32.9	184.6 ± 33.8	189.7 ± 34.0	198.0 ± 35.9	<.0001
Triglyceride, mg/dl	68.1 ± 42.3	75.3 ± 30.1	83.2 ± 47.8	98.2 ± 57.3	121.4 ± 73.1	<.0001
HDL cholesterol, mg/dl	64.0 ± 15.8	61.1 ± 12.9	59.2 ± 13.6	57.0 ± 12.1	54.3 ± 11.9	<.0001
LDL cholesterol, mg/dl	93.9 ± 23.2	100.6 ± 24.2	106.7 ± 27.8	110.2 ± 28.2	118.3 ± 30.1	<.0001
Fasting plasma glucose, mg/dl	88.4 ± 14.8	85.8 ± 10.4	89.6 ± 12.6	91.8 ± 22.5	93.7 ± 15.2	<.0001
Leptin , ng/ml	0.9 ± 0.2	2.0 ± 0.3	3.2 ± 0.4	5.0 ± 0.7	10.6 ± 4.3	<.0001
Metabolic syndrome, %	4.5	4.0	11.8	15.4	25.4	<.0001

Data represent mean ± SD or proportions.

* Sex-specific quintiles for leptin levels: men (<0.79, 0.79-1.67, 1.68-2.50, 2.51-3.71, ≥3.72), women (<3.16, 3.16-4.78, 4.79-6.44, 6.45-9.43, ≥9.44).

the number of components present for metabolic syndrome increased ($P < .0001$, data not shown).

The correlation between the metabolic syndrome and quintiles of serum leptin levels were calculated independent of age, smoking, exercise, and LDL cholesterol (Table 3). Compared to the lowest quintile of leptin in men, the odds ratio (OR) and 95% confidence intervals (95% CI) for metabolic syndrome were 1.76 (0.97-3.21) in Q2, 3.40 (1.95-5.94) in Q3, 6.76 (3.96-11.53) in Q4, and 11.51 (6.80-19.49) in Q5, respectively. Weaker correlations were observed in women compared to men. Odds ratios for metabolic syndrome increased across increasing quintiles of leptin (Q5 vs. Q1, 4.65 (2.36-9.16)). After further adjustment of the BMI, the odds ratios for metabolic syndrome still increased slightly for men but not women in increasing leptin categories (Table 3). Thus, leptin is a strong indicator of metabolic syndrome and the odds ratios of association were decreased but statistically significant. Thus, leptin is a strong indicator of metabolic syndrome and the adjustment for BMI did not change the correlation of leptin to metabolic

Table 2
The correlation leptin and cardiometabolic risk factors

	Men		Women	
	Age adjusted	Multivariable adjusted[a]	Age adjusted	Multivariable adjusted
Systolic blood pressure	0.1809**	0.0165	0.2015**	0.0351
Diastolic blood pressure	0.1628**	0.0375	0.1417**	0.0114
Waist circumference	0.5490**	0.1764**	0.4987**	0.0916**
Total cholesterol	0.1626**	0.0634*	0.1516**	0.0789*
Triglyceride	0.2555**	0.1038**	0.2059**	0.0736*
HDL cholesterol	−0.1221**	0.0360	−0.1494**	−0.0037
LDL cholesterol	0.1311**	0.0352	0.0856**	0.0934**
Fasting plasma glucose	0.1299**	0.0677*	0.2001**	0.0292

Values are Spearman correlation coefficients for correlations of leptin and cardiometabolic risk factors.

[a] Adjusted for age, smoking status, exercise, and BMI.

* $P < .05$.

** $P < .001$.

Table 3
Odds ratio of metabolic syndrome with leptin levels by sex-specific quintiles

Leptin quintiles[a]	Men				Women			
	Case	Model 1*	Model 2†	Model 3‡	Case	Model 1*	Model 2†	Model 3‡
Quintile 1	18	1.00	1.00	1.00	12	1.0	1.0	1.0
Quintile 2	32	1.76 (0.97-3.20)	1.76 (0.97-3.21)	1.22 (0.66-2.26)	11	0.93 (0.39-2.20)	0.86 (0.36-2.06)	0.72 (0.30-1.74)
Quintile 3	55	3.36 (1.93-5.85)	3.40 (1.95-5.94)	1.96 (1.10-3.50)	32	2.66 (1.30-5.41)	2.27 (1.10-4.68)	1.37 (0.65-2.90)
Quintile 4	94	6.68 (3.93-11.35)	6.76 (3.96-11.53)	2.45 (1.39-4.33)	42	3.61 (1.80-7.21)	3.01 (1.49-6.11)	1.35 (0.64-2.85)
Quintile 5	137	11.70 (6.95-19.71)	11.51 (6.80-19.49)	2.22 (1.22-4.01)	69	5.51 (2.83-10.73)	4.65 (2.36-9.16)	1.35 (0.63-2.90)
P-for trend		.0135	.0120	.0276		.0083	.0111	.1648

[a] Sex-specific quintiles for leptin levels: men (<0.79, 0.79-1.67, 1.68-2.50, 2.51-3.71, ≥3.72), women (<3.16, 3.16-4.78, 4.79-6.44, 6.45-9.43, ≥9.44).
* Model 1: adjusted for age.
† Model 2: adjusted for age, smoking status, exercise, and LDL cholesterol.
‡ Model 3: adjusted for age, smoking status, exercise, LDL cholesterol, and body mass index.

syndrome in men. The relationship between obese and nonobese groups to the association of leptin and metabolic syndrome was determined (Fig. 1). For both groups obese and nonobese, the correlation of increased serum leptin levels to increased risks of metabolic syndrome was similarly observed. However, the correlation was stronger in nonobese participants than obese participants.

4. Discussion

Our study demonstrates that serum leptin is associated with metabolic syndrome in the adult Korean population. Subjects with high leptin levels had a higher prevalence of metabolic risk factors than those with lower levels. Leptin was found to be correlated with several components from the cluster of cardiovascular risk factors and increased with the increased risk of metabolic syndrome. Moreover, the correlation between serum leptin levels and metabolic syndrome in the two groups, obese and nonobese participants, were observed to be similar. The serum leptin concentration was found to be positively correlated to metabolic syndrome in both groups.

Leptin is a hormone which is produced in adipose tissue and regulates food intake and body weight. Some studies have shown that serum leptin concentration increases with increased levels of body fat particularly with increases of subcutaneous fat [16-18]. Previous studies have shown that plasma leptin and its mRNA in adipose tissue reflects body fat content. A high-fat diet gave rise to increasing circulating leptin [19] while food restriction was associated with a decrease in leptin mRNA expression and leptin levels in mice [8]. A number of studies were done pertaining to the association between leptin, obesity and cardiovascular diseases in animal models. The studies involving humans had only a small study population. Leptin is a risk marker for myocardial infarction and hemorrhagic stroke in the population-based cohort [20,21]. Subjects with higher levels of leptin had a higher incidence of stroke than those with lower levels of leptin [22]. According to the prospective study WOSCOPS cohort on the association between leptin and cardiovascular diseases, leptin was an independent, predictive factor for the incidence of coronary artery disease during a 5-year follow-up [23].

A few population-based studies have shown an association between leptin levels and other cardiovascular risk factors. Previous studies showed the serum leptin concentration to be associated with the amount of body fat, BMI and fasting insulin concentration. In this study, the serum leptin concentration was highly correlated with BMI [r = 0.5466, $P < .0001$] and other risk factors of CVD such as waist circumference [r = 0.4913, $P < .0001$] and triglyceride [r = 0.2105, $P < .0001$]. In previous studies, there was an inconsistent and significant relation between leptin and serum lipids. Some studies have reported no correlation between leptin and serum lipid parameters [24,25]. Other studies have showed a significant positive correlation between leptin and HDL cholesterol [24,26,27] or between leptin and triglycerides [28]. Among biochemical markers in

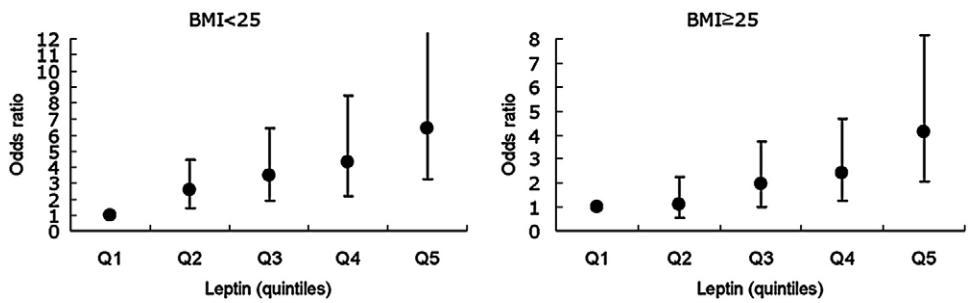

Fig. 1. Odds ratio of metabolic syndrome with increasing leptin levels stratified by body mass index.

particular, triglyceride is stored in adipose tissues as the main form of energy; therefore, it was supposed to have a correlation with leptin [29-31].

So far, there have been several population studies on the association between leptin and metabolic syndrome. However, most studies showed the association between leptin and each component for metabolic syndrome instead of a cluster of metabolic syndrome components. Very few studies have determined the correlation between leptin and metabolic syndrome especially among adult Korean populations.

Leptin values increased with an increase in the number of metabolic abnormalities [32]. This study demonstrated the correlation of leptin with each of the risk factor components of metabolic syndrome. Leptin levels increased with increasing numbers of components for metabolic syndrome. After adjusting for confounding variables, leptin was found to be an independent indicator of metabolic syndrome. This is in accordance with some earlier studies. According to a recent study with a Finnish population, leptin was a strong indicator of metabolic syndrome and the association between leptin and metabolic syndrome still remained significant after adjustment for BMI [32]. The levels of leptin reflect by and large the amount of adipose tissue which is associated with metabolic syndrome, but the exact role of BMI as a surrogate marker of subcutaneous fat between leptin and metabolic syndrome remains yet unknown. BMI is responsible for the production of leptin, but it is not fully understood whether BMI acts as a mediator or confounder in the relationship between leptin and metabolic syndrome. Therefore in addition, we have adjusted for BMI to clarify what the exact role of BMI in the relationship of leptin to metabolic syndrome is even though it lies in the causal pathway. Our results have shown that leptin acts as a confounder in the relationship between BMI and metabolic syndrome as elevated levels of leptin causes an increase in risk for metabolic syndrome. After adjustment of BMI, the association of leptin and metabolic syndrome was attenuated but still remained significant. That is, serum leptin is associated with metabolic syndrome independent of body mass index.

In addition, participants with increased weight are widely known to have increased levels of leptin; however, there are few studies about metabolic syndrome stratified by BMI. After controlling for sex, the present study analyzed the correlation between leptin levels and metabolic syndrome without segregating the study population into men and women due to a small number of obese women. We found that higher serum leptin levels in the Korean population were not dependent on obesity. After adjusting for BMI, some studies showed the association between leptin and metabolic syndrome but did not analyze the association between the positive correlation of leptin and metabolic syndrome and the weight status of the participants whether they were obese or nonobese [32]. This study shows that the positive correlation of serum leptin and metabolic syndrome is independent of weight status after stratification according to BMI. There was a positive correlation between increased leptin and increased risk of metabolic syndrome for both obese and non obese adult Korean participants from the study population.

We also show that leptin levels were more strongly correlated to risk of metabolic syndrome in men compared to women after controlling for confounding variables. This is similar to the finding in a previous study [33]. Kennedy et al reported that hyperleptinemia was correlated with insulin resistance and waist/hip ratios in men whereas no correlation was determined in women [33]. Our results have shown that the association remained significant among men, but not women. This may be explained by two reasons. A recent review had shown that men were found to have more visceral and hepatic adipose tissue, whereas women had more peripheral or subcutaneous adipose tissue [34] which may be the reason why men have a higher risk for metabolic syndrome than compared to women. In particular, Korean women who have significantly lower BMI than western populations are very thin having a relatively lower amount of visceral fat. Another explanation may be that there is a higher prevalence of metabolic syndrome among men rather than among women explaining the stronger association of leptin with metabolic syndrome in men compared to women.

The etiology of metabolic syndrome and its various pathogenic mechanisms are incompletely defined and under intense investigations. Leptin possibly as a circulating Biomarker for percent fat mass or an independent correlate of insulin resistance or as a Biomarker of some as-yet-unknown activity of adipose tissue may yield important information with respect to risk of vascular disease [23]. Patel et al (2007) reported that leptin may be an important link in the pathogenesis of hypertension and heart disease induced by obesity and the metabolic syndrome [35].

This study has some limitations. Due to its cross-sectional design, this study cannot determine the direction of causality for the relationship between leptin and metabolic syndrome. The present study was performed with a larger sample size than that of other studies, and like these previous studies, in a Korean population.

In conclusion, these results demonstrate that serum leptin is associated with metabolic syndrome independent of body mass index. These results could be a main factor in explaining the increased risk for cardiovascular diseases with increased levels of leptin. A large-scale prospective study is needed regarding participants with different levels of BMI for better understanding of specific examination of physiological and pathological functions of leptin.

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