Ghrelin, Resistin and Leptin Levels in Patients with Metabolic Syndrome

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ABSTRACT

Aim: *This study was designed to compare the fasting ghrelin, leptin and resistin levels between metabolic syndrome (MS) patients with healthy controls.*

Method: *This trial was performed on 21 patients with MS (7 men; mean age, 44±4 years) and 17 healthy controls (8 men; mean age, 43±3 years). Diagnosis of MS was defined based on National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria. Patients meeting at least 3 of the MS criteria, with a body mass index (BMI) ≥30 kg/m² were included in the MS group. Among healthy volunteers, those with a BMI<30 kg/m² were selected as the control group. Plasma ghrelin, serum leptin and resistin concentrations were measured by ELISA method.*

Result: *Ghrelin levels were similar between MS and control groups. There was a negative correlation detected between ghrelin levels with BMI and leptin levels (r=-.54, P=.01 and r=-.56, P=.009, respectively). Resistin levels were found similar between MS with control groups. Leptin levels were significantly higher at the MS group than control group (35±17 ng/ml vs. 14±8 ng/ml, P=.001). Leptin levels had a positive correlation with BMI (r=.56; P=.008).*

Conclusion: *We have demonstrated that leptin levels in MS group were higher than control group. However, ghrelin and resistin levels were similar to control group. In addition, we have showed leptin levels has a positive correlation with BMI and a negative correlation with ghrelin levels.*

Key words: *Metabolic syndrome, obesity, ghrelin, resistin, leptin.*

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Metabolik Sendromlu Hastalarda Grelin, Rezistin ve Leptin Düzeyleri

Amaç: *Bu çalışmada metabolik sendromlu (MS) hastalar ile sağlıklı kontroller arasında açlık ghrelin, leptin ve resistin düzeylerinin karşılaştırılması amaçlanmıştır.*
Metod: *Çalışmaya 21 MS hastası (7 erkek; ortalama yaş, 44±4) ve 17 sağlıklı kontrol (8 erkek; ortalama yaş 43±3) alınmıştır. MS tanısı Ulusal Kolesterol Eğitim Programı (NCEP) Erişkin Tedavi Paneli (ATP) III kriterlerine göre tanımlandı. MS karşılama kriterlerinden en az 3'üne sahip olan ve beden kitle indeksi (BKI) ≥30 kg/m² olan hastalar MS grubuna seçildi. Sağlıklı gönüllüler arasında BKI <30 kg/m² olanlar kontrol grubu olarak seçildi. Plazma ghrelin, leptin ve resistin düzeyleri ELISA yöntemi ile ölçüldü.*
Bulgular: *Ghrelin düzeyleri MS ve kontrol grupları arasında benzerdi. Ghrelin ve Leptin seviyeleri ile BKİ arasında negatif bir ilişki tespit edildi (r=-.54, P=.01 ve r=-.56, p= 0.009, sırasıyla). Resistin düzeyleri kontrol grubu ile MS arasında benzer bulundu. Leptin düzeyleri kontrol grubuna göre MS grubunda (35±17 ng/ml ve 14±8 ng/ml, p= 0.001) anlamlı derecede daha yüksek bulundu. Leptin düzeyleri ile BKİ arasında pozitif korelasyon vardı (r =0.56; p= 0.008). Biz MS grubunda leptin düzeylerinin kontrol grubuna göre daha yüksek olduğunu gösterdik. Ancak, ghrelin ve resistin düzeyleri kontrol grubuna benzerdi.*
Sonuç: *Sonuç olarak biz leptin düzeyleri ile BKİ arasında pozitif bir ilişki olduğunu ve ghrelin seviyeleri ile negatif ilişkili olduğunu gösterdik.*
Anahtar kelimeler: *Metabolik sendrom, obezite, ghrelin, resistin, leptin*

INTRODUCTION

Obesity is a community health problem affecting over one billion adult persons worldwide (1). Obesity is closely related to insulin resistance, hiperinsulinemia, glucose intolerance, dislipidemia, hypertension (HT), premature atherosclerosis and increased risk for coronary artery disease (CAD). The situation that these abnormalities being together are called insulin resistance syndrome or metabolic syndrome (MS) (2). Although there are many considerations to explain the basis of these metabolic abnormalities, the main mechanism of disease has not been determined yet (3).

It has recently been thought that some new regulatory peptides might be playing a key role on the pathogenesis of MS (4). One of these peptides is ghrelin hormone having a number of metabolic and cardiovascular (CV) effects (5). Ghrelin being an endogenous ligand for the secretory receptor of growth hormone is a peptide hormone secreted by stomach and small bowel (6). Low ghrelin level in blood is related to the components of MS such as obesity, insulin resistance and blood pressure (7). Ghrelin has a direct effect on energy consumption metabolism and increases food intake beside other metabolic properties (8,9). The previous studies have showed that intact ghrelin signals are quite important in occurrence of diet induced obesity. The ghrelin level in obese persons is higher than that of lean individuals and also a negative relationship has been detected between ghrelin level and body mass index (BMI) (8). Leptin is also a peptide hormone like ghrelin and there is a negative interaction on appetite between leptin and ghrelin (10). Leptin is mainly secreted by adipose tissue and has anorexigenic functions (11). A positive correlation between BMI and leptin has been demonstrated in the previous studies (12). Recently published studies have showed that leptin secretion has a significant effect on central regulation as much as ghrelin (13). Ghrelin is down regulated by insulin and leptin in human obesity. Therefore, leptin and ghrelin have a key role on development of MS and diabetes mellitus (DM) while genetic, environmental and hormonal factors are affecting the process (10). Resistin is a new adipocytokin and mainly secreted by adipose tissue and peripheral mononuclear blood cells in human (14-16). It has been claimed that this molecule is related to metabolic signals, inflammation, and atherosclerosis. Its expression is up regulated by proinflammatory cytokines. There are some studies referring to the role of this molecule in obesity, insulin resistance and increase in blood glucose level (14).

The aim of this study is to investigate the levels of ghrelin, resistin and leptin in patients with MS, and to show the association with the parameters of MS.

Table 1. Baseline Characteristics and Study Parameters in Metabolic Syndrome and Control Groups

	Metabolic Syndrome n:21	Control n:17	p value
Age (years)	44±4.0	43±3.0	0.12
Gender (male/female)	7/14	8/9	0.39
Waist circumference (cm)	113±12	85±9.0	0.001
Body mass index (kg/m²)	36±5.0	25±2.0	0.001
Blood pressures (mmHg)			
Systolic	142±16	118±6.0	0.001
Diastolic	95±11	83±12	0.003
Fasting blood glucose (mg/dL)	102±13	95±10	0.08
Total Cholesterol (mg/dL)	186±36	183±24	0.77
HDL Cholesterol (mg/dL)	43±8.0	47±7.0	0.07
LDL Cholesterol (mg/dL)	114±29	117±25	0.74
Triglyceride (mg/dL)	161±82	86±38	0.001
Study Parameters			
Ghrelin (fmol/mL)	127±46	158±78	0.16
Resistin (ng/mL)	0.99±0.41	1.16±0.48	0.26
Leptin (ng/mL)	35±17	14±8.0	0.001

MATERIALS AND METHODS

Study Population

A total of 38 individuals were enrolled in the study after getting consent, including 21 patients with MS (group I, 7 men; mean age, 44±4 years) and 17 healthy controls (group II, 8 men; mean age, 43±3 years). Approval was obtained from the local ethical committee.

Diagnosis of MS was defined based on National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria (17). Patients meeting at least 3 of the MS criteria, with a BMI ≥30 kg/m² were included in the MS group (group I). Body mass index was calculated, dividing the patient weight by the square of height in square meters. Among healthy volunteers, those with a BMI<30 kg/m² were included as the control group (group II). Waist circumference was measured with a soft tape on standing individuals midway between the lost rib and the iliac crest. The blood pressure was measured on both arms by the physician after 15 minutes of resting while the patient was in sitting position and the mean value was obtained. Following 12 hours of fasting, venous blood sample was obtained from all patients and fasting blood glucose (FBG) and lipid panel was measured. Exclusion criteria included coronary cardiac disease history, cardiomyopathy, chronic lung disease, DM, antihypertensive drug use, creatinine >2.0 mg/dl, malignancy.

Ghrelin, resistin and leptin measurement

All obtained serum and plasma samples after overnight fasting (12 hours) were collected from antecubital vein. For Ghrelin measurements blood was directly drawn in to a centrifuge tube that contains 500 U of Aprotinin and 1.25mg of EDTA-2Na per 1 mL of blood. All tubes were immediately centrifuged at 1500 x g for 15 minutes at +4°C. Then plasma samples were separated. For Resistin and Leptin measurements blood samples were obtained in to a serum tube that contains no anti-coagulant. All tubes were waited to let blood clot at room temperature for 30 minutes. Clotted blood centrifuged at 3000 x g for 15 minutes at +4°C. Then serum samples were separated. All serum and plasma specimens were stored at a – 80°C for approximately 2 months until all samples were collected and analyzed. Plasma Ghrelin and serum Leptin and Resistin concentrations were measured by ELISA method (Linco Research, Missouri, USA) according to the instructions of the manufacturer.

Statistical analysis

Statistical analysis was performed using designated software (SPSS 13, SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean±SD. Continuous variables between groups were compared 'Student's t test' or 'Mann-Whitney U' test as appropriate. Categorical variables are presented as absolute values and comparisons were tested using chi-square test. Pearson's correlation test was used to demonstrate the correlations

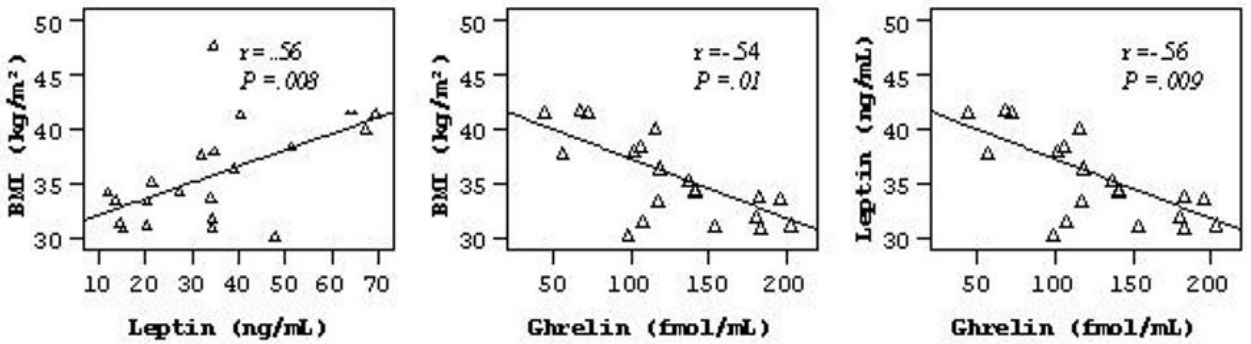

***Figure 1**. Correlations were showed among ghrelin, leptin and BMI.*

between the data exhibiting parametric distribution. A p values <0.05 are considered statistically significant.

RESULTS

Clinical Features

The basic characteristics of groups are presented in Table. There was no difference between the MS and control groups with respect to age and gender. The waist circumference and BMI were significantly higher at the MS group compared to the control group. Systolic and diastolic blood pressure, triglyceride (TG) levels were different between the MS and control group.

Ghrelin, resistin and leptin levels

Ghrelin, resistin and leptin levels are presented in Table. Ghrelin levels were similar between MS and control groups. There was a negative correlation between ghrelin levels and BMI in MS group (r= -0.54, p= 0.01). Resistin was also found similar between MS and control groups. Leptin levels were significantly higher in MS group compare to control group (p= 0.001). There was a positive correlation between leptin levels and BMI in MS group (r= 0.56, p= 0.008). There was a negative correlation between ghrelin and leptin levels in MS group (r= -0.56, p= 0.009) (Figure 1). Ghrelin, leptin and resistin were not considerably associated with the other MS parameters such as FBG, HDL cholesterol, TG and blood pressure.

DISCUSSION

In this study, leptin found considerably higher in patients with MS than control group. Also a positive correlation between leptin levels and BMI, a negative correlation between leptin and ghrelin levels has been demonstrated (6,10,12). On the other hand, there was no difference for resistin between the MS and control groups.

Even a small but chronically problem to come into existence between energy intake and consumption may be resulted in obesity. Obesity, DM, CAD and hypertension are closely related to increased mortality (18). High level of leptin is an important marker of MS in obese patients. In some studies, it has been shown that obesity, MS, and cardiovascular risk factors are closely associated with increase in leptine level (19). Leptin is a major hormone having properties such as suppression of food intake and making energy consumption increased, however it can also enhance peripheral insulin sensitivity and pancreatic ß-cell function independent of these features (1). Leptin level in obese and overweight persons have a positive correlation with BMI, however it has a negative correlation with ghrelin (20). It has been noted in the previous studies that high leptin and low ghrelin level are associated with MS, DM and premature atherosclerosis (10). In this study, significant positive correlation between leptin and BMI and a negative correlation between leptin and ghrelin has been determined concordant with the literature (12,20).

Ghrelin is a somatotropic and orexigenic hormone; however it has quite important regulatory functions on energy metabolism (19). Ghrelin increases food intake by performing direct effect on it and decreases energy consumption. However, direct infusion of ghrelin increases blood glucose level, decreases glucose tolerance and restricts releasing of insulin (8). In some

studies, plasma ghrelin level in insulin-resistant obese individuals has been found lower than that of insulin sensitive ones and it has been shown that MS and DM are associated with ghrelin (10,16). Ghrelin level in many obese persons tends to be lower than that of underweight persons (16,21). It has been asserted that this condition might be an adaptive response to make weight decreased in obese persons (22). In this study, ghrelin was similar in patients with MS and healthy cotrols. In literature, a negative correlation between ghrelin level and BMI has been determined in both of obese and normal weight persons (8,20). In this study as well, we have demonstrated a considerable negative correlation between ghrelin and BMI in patients with MS. In previous studies, a negative relation between ghrelin concentration and waist circumference has been detected (22-24). However, in our study, we were unable to detect a considerable negative correlation between ghrelin concentration and waist circumference in MS group.

Resistin is a peptide hormone secreted by adipose tissue and its effects on glucose and insulin metabolism are controversial (1,16). It has been stated that resistin could cause MS and obesity through increasing insulin resistance and metabolic enzyme transcription (14). Although some investigators claimed that resistin was associated with obesity and DM, this result could not been confirmed by the other studies (1). Recently published studies have claimed that inflammatory molecules in endothelial cells up regulate resistin secretion and that resistin may be an important marker for atherosclerosis in human (14,25). The relation between resistin concentration and increased coronary arterial calcification has been shown in a study performed in MS patients (26). Resistin concentration was found increased in a study performed in patients with acute coronary syndrome (14). In this study we have found that resistin levels were similar between MS and control groups. And also, any considerable relevant between parameters of MS and resistin level could not be demonstrated.

We have found that leptin levels in MS group were higher but ghrelin and resistin levels were similar to control group. Leptin had a positive correlation with BMI and a negative correlatin with ghrelin. Also these hormones were not considerably associated with the other MS parameters such as waist circumference, FBG, HDL cholesterol, TG and blood pressure. This study and further researches can be guidance for effective treatment of MS and obesity in the future.

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