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Original Article

Low prevalence of obesity in Behçet's disease is associated with high obestatin level

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Abstract

Objective: Chronic inflammatory diseases are associated with altered body composition. Ghrelin has anti-inflammatory effects, and its level is altered in obesity and inflammatory diseases. The aim of the study was to evaluate the prevalence of obesity and ghrelin and obestatin levels in patients with Behçet's disease (BD).

Material and Methods: One hundred and forty-three (143) patients with BD and 112 healthy controls (HC) were enrolled. Participants were subdivided according to the body mass index (BMI) as lean (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥30 kg/m^2). In addition to the routine evaluations (fasting blood glucose, lipid profile, and kidney and liver function tests), serum acylated-ghrelin (AG), unacylated-ghrelin (UAG), total ghrelin (TG) and obestatin levels were analyzed. Student's t-test and chi-square test were used for statistical analysis.

Results: The prevalence of obesity was relatively lower in the BD group than in the HC group (12.6% vs. 20.5%, p=0.089). Serum ghrelin levels were similar in the BD and HC groups (p>0.05 for all) although the obestatin level was higher in the BD group compared to the HC group (p<0.001). Serum UAG, TG and obestatin levels were lower in obese BD patients (n=18) than non-obese BD patients (p=0.027, p=0.014 and p=0.001, respectively).

Conclusion: The obestatin level was high and the prevalence of obesity was low in the BD group. Moreover, obese BD patients had low obestatin levels. These results suggest that obestatin may protect BD patients from obesity.

Keywords: Behçet's disease, obesity, ghrelin, obestatin

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Introduction

Obesity is a major public health threat since it is a well-established risk factor for the development of cardiovascular and metabolic diseases, such as diabetes, hyperlipidemia and insulin resistance, in the general population (1). Ghrelin, a gastric mucosa-derived peptide, is demonstrated to have various metabolic functions including regulation of energy balance, control of appetite, stimulation of gastric acid secretion, and regulation of gastrointestinal motility (2, 3). The administration of ghrelin increases food intake and body weight along with a reduction in fat utilization (2). Negative correlations between circulating ghrelin levels and body mass index (BMI) are found in humans (3, 4). On the other hand, the ghrelin level is reported to be high in patients with anorexia nervosa (5) and subjects with diet-induced weight loss (4). Obestatin is a peptide hormone derived from preproghrelin. It also has a role in regulating food intake and energy expenditures (6). In addition to energy homeostasis, some evidence suggests that ghrelin has direct anti-inflammatory effects (7, 8). Therefore, the ghrelin level has been evaluated in a variety of inflammatory diseases with contradictory results (9-11).

Behçet's disease (BD) is a chronic relapsing inflammatory disease characterized by mucocutaneous lesions, and it can affect ocular, neurological, and gastrointestinal systems (12, 13). BD has been described by a Turkish dermatologist as a triple symptom complex, i.e., oral aphthosis, genital ulcer, and uveitis. BD has a greater incidence and prevalence in the regions along the ancient Silk Road. Although the etiology of BD is not fully known, immune abnormality is thought to be associated with the development and maintenance of BD (12, 13). The prevalence of obesity in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) is reported to be higher (14-19). In RA and SLE, the potential association of obesity with the progression of the diseases has been researched (17-19). However, there is an obvious gap in the literature reporting body composition in BD. In contrast to RA and SLE, the knowledge about body composition and the levels of ghrelin and obestatin in BD is limited (20, 21).

Therefore, the aims of the present study were to evaluate the prevalence of obesity and the levels of ghrelin and obestatin in BD.

Table 1. Demographic characteristics and serum ghrelin and obestatin levels

	BD (n=143)	HC (n=112)	p
Age (years)	37.7±10.9	40.1±13.9	0.139
Sex (female ratio, %)	57.3	57.1	0.974
BMI (kg/m$^{2)}$	25.3±4.8	26.3±5.5	0.108
Diabetes mellitus (n)	8 (5.6%)	9 (8.1%)	0.459
ESR (mm/h)	16.4±8.7	12.1±4.2	<0.001
CRP (mg/dL)	5.9±6.2	3.2±1.7	<0.001
Uric acid (mg/dL)	4.2±1.1	4.5±1.8	0.102
LDL cholesterol (mg/dL)	124.7±21.5	131.2±43.7	0.121
Triglyceride (mg/dL)	136.4±54.2	128.7±62.4	0.294
Acylated ghrelin (pg/mL)	22.6±19.2	24.1±13.6	0.587
Unacylated ghrelin (pg/mL)	100.1±84.3	97.3±58.9	0.801
Total ghrelin (pg/mL)	194.3±167.1	181.8±104.2	0.593
Obestatin (pg/mL)	252.5±86.1	174.1±51.1	<0.001

BD: Behçet's disease; HC: healthy control; BMI: Body Mass Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LDL: low density lipoprotein

Table 2. Ghrelin and obestatin levels in obese and non-obese subgroups

	BD group			HC group		
	BMI<30 (n=125)	BMI≥30 (n=18)	p	BMI<30 (n=89)	BMI≥30 (n=23)	p
AG (pg/mL)	18.8 (5.6-198.2)	15.9 (4.9-40.2)	0.346	23.6 (2.3-117.1)	20.1 (3.8-36.4)	0.050
UAG (pg/mL)	87.6 (32.1-946.1)	69.2 (32.6-130.1)	0.027	87.7 (10.2-451.5)	82.5 (16.4-136.3)	0.735
TG (pg/mL)	164.3 (41.1-1517.5)	118.3 (88.4-179.4)	0.014	169.7 (20.9-684.5)	148.8 (23.8-286.5)	0.426
Obestatin (pg/mL)	255 (89-602)	198 (98-268)	0.001	172 (71-374)	174 (99-313)	0.383

BD: Behçet's disease; HC: healthy control; BMI: Body Mass Index; AG: acylated ghrelin; UAG: unacylated ghrelin; TG: total ghrelin
Data were presented as median (minimum-maximum).

Material and Methods

Participants

This cross-sectional comparison study included 143 patients with BD. Patients were diagnosed according to the established criteria (22), and they were in the age range of 18-72 years. Age-, sex- and origin-matched (Table 1) 112 healthy subjects were recruited from the staff employed in our hospital and faculty to serve as healthy controls (HC). The protocol of this study was approved by the Institutional Ethics Committee of Fırat University, and all the participants gave informed consent before enrolling in the study.

Detailed histories of all the participants were obtained and printed on research forms. Their systemic and rheumatologic examinations were performed by one rheumatologist (SSK). Glucocorticoid and disease-modifying anti-rheumatic drugs usages were also recorded. The pathergy test was performed in all the patients with BD, and 24-48 hours later, the patients were evaluated in terms of papulopustular lesions.

Anthropometric measure of body compositions

In all the participants, the height and weight were measured to determine the BMI. Participants were subdivided according to the body mass index (BMI) as lean (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥30 kg/m^2) according to the World Health Organization (WHO) guidelines (23).

Determination of disease activities

In the BD group, patients were interpreted as active when they had at least two of the following: genital ulcer, skin lesions, recent eye involvement, recent vascular involvement, recent neurological involvement, active arthritis, positive pathergy test sign in addition to oral ulcer, as well as high erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) levels (10).

Laboratory analysis

Blood samples were drawn from all the participants who had fasted overnight. Subsequently, in addition to the routine laboratory evaluations, the serum samples were stored at -20℃ for further measurements of acylated-ghrelin (AG), unacylated-ghrelin (UAG), total ghrelin (TG), and obestatin levels. Serum AG, UAG, TG, and obestatin levels were analyzed using commercially available enzyme-linked immunosorbent assay (ELISA) kits (AG, UAG, and TG kits were purchased from the Bertin Pharma, Paris, France; obestatin kit was purchased from the Wuhan EIAab Science Co. Ltd.; Wuhan, China) by ELISA method. The minimal detectable levels were 5 and 21.5 pg/mL for ghrelin and obestatin, respectively.

Statistical analysis

The Statistical Package for the Social Sciences version 16.0 (SPSS Inc.; Chicago, IL, USA) was used for analysis. Normal distributions were tested with the Kolmogorov-Smirnov test with Lilliefors correction. Quantitative data were presented as mean±standard deviation (S.D.). Parametric data were analyzed using the Student's *t*-test. Mann-Whitney U test was performed to compare nonparametric data (obese and non-obese subgroup comparisons) and to compare the skewed data (AG, UAG, TG, and obestatin). Fisher's exact tests or Pearson's χ^2 tests were used to compare categorical variables, and the odds ratio (OR) and the 95% confidence interval (CI) were used for the assessment of risk factors. Correlation analyses were made using the Pearson's product moment test in both the BD and HC groups. A model of multiple regression analysis (standard linear regression analysis) was constructed with BMI as the dependent variable and the age, usage of any medication, and the levels of AG, UAG, TG and obestatin as the independent variables in the BD group. Moreover, it was analyzed whether the same independent variables predicted the presence of obesity by logistic regression analysis. P values less than 0.05 were considered significant.

Results

The demographics and clinical laboratory data of the BD and HC groups are summarized in Table 1. There was no difference in terms of demographics between the study groups. The mean disease duration was 5.3±6.2 years in the BD group. Mean ages were 37.7±10.9

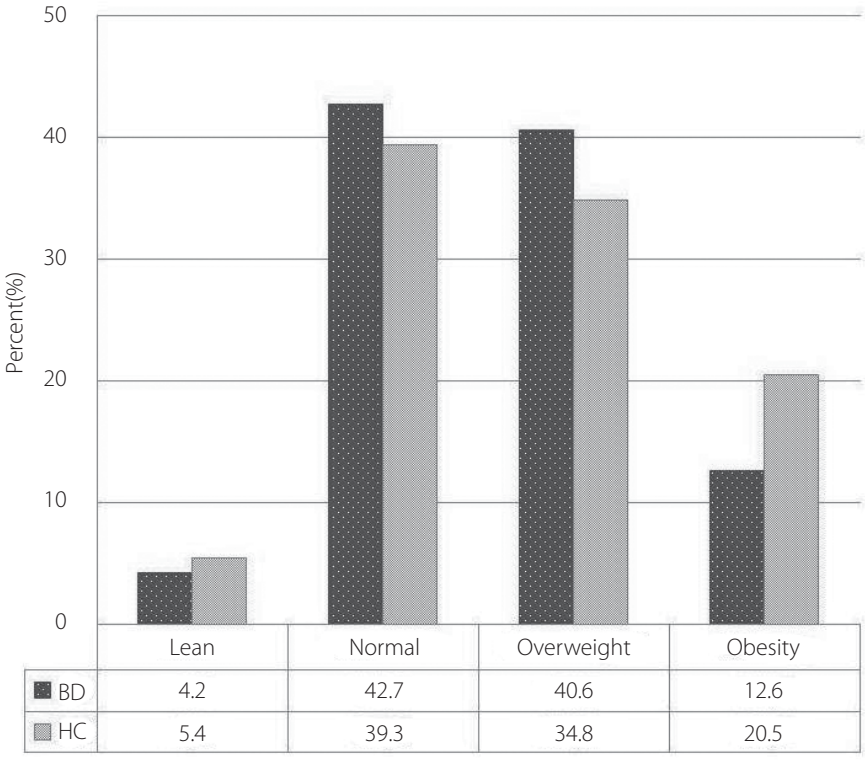

Figure 1. The body compositions in the study groups
BD: Behçet's disease; HC: healthy control

and 40.1±13.9 years in the BD and HC groups (p=0.139). 57.3% (n=82) of BD patients and 57.1% (n=64) of healthy subjects were female (p=0.974).

The prevalence of obesity was 12.6% in the BD group and 20.5% in the HC group (p=0.089, OR: 0.56, 95% CI: 0.28-1.09, Figure 1).

The serum ghrelin levels were similar in the BD and HC groups (Table 1), although the obestatin level was higher in the BD group compared to the HC group (p<0.001). Serum UAG, TG and obestatin levels were lower in the obese BD patients (n=18) than the non-obese BD patients (Table 2) (p=0.027, p=0.014 and p=0.001, respectively). However, they were not significantly different in the obese and non-obese controls (Table 2).

For the disease activity in the BD group, 67 (46.1%) patients were active while 76 (53.1%) were inactive. ESR (23.9±22.7 vs. 12.8±10.1 mm/hour, p<0.001), CRP level (21.7±37.2 vs. 4.1±3.4 mg/L, p<0.001) and white blood cell count (8.4±3.2 vs. 7.2±2.6 /μL, p=0.022) were higher in the active BD patients compared to the inactive ones. While there was no significant difference between the active and inactive BD patients in terms of serum UAG (111.5±113.4 vs. 19.8±9.2 pg/mL, p=0.130) and obestatin (255.6±100.6 vs. 249.8±71.4 pg/mL, p=0.631) levels, serum AG (25.7±25.9 vs. 19.8±9.2 pg/mL, p=0.065) and TG (230.7±236.5 vs. 163.6±54.1 pg/mL, p=0.068) levels were relatively higher in the active subgroups than the inactive subgroup. 8 (12.6%), 23 (34.3%) and 11 (16.4%) of the active BD patients and 6 (7.9%), 35 (46.1%) and 7 (9.2%) of the inactive BD patients were lean, overweight and obese, respectively (p=0.120). The mean BMI was not significantly different in the active and inactive BD subgroups (25.3±5.3 vs. 25.3±4.4 kg/m^2, p=0.958). There were no obvious effects from clinical involvements and medications on the ghrelin and obestatin levels as well as on the BMI and body compositions in the BD group.

Prediction of obesity

The BMI was correlated with age (r=0.534, p<0.001) in the HC group. The BMI was correlated with age (r=0.471, p<0.001) and serum obestatin level (r=-0.267, p=0.001) in the BD group. The BMI was not correlated with the levels of the acute phase reactants. Multiple regression analysis also showed that only the age (β=0.438, p<0.001) and serum obestatin level (β=-0.189, p=0.012) were significant predictors of BMI. Similarly, logistic regression analysis also showed that age (p=0.011, OR; 1.12, 95% CI; 1.03-1.23) and serum obestatin levels (p=0.011, OR; 0.98, 95% CI; 0.96-0.99) were predictors of the presence of obesity in BD.

Discussion

The present study demonstrated that the prevalence of obesity was lower in the BD group. In addition, the serum obestatin level was higher in the BD group than in the healthy subjects, while the circulating ghrelin levels were not different.

Behçet's disease is a multisystemic vasculitis of unknown etiology characterized by mucocutaneous, ocular, arthritic, and vascular manifestations, and it has a high prevalence all along the ancient Silk Road, from Asia to the Mediterranean basin (12, 13). Although the etiopathogenesis of BD remains uncertain, immunological abnormalities including innate and adaptive immunity in humoral and cellular immunity settings are supposed to be the cornerstone of the pathogenesis of BD (13, 24). A variety of cytokines such as IL-6, IL-17, IL-18, and IL-21 are increased in BD; moreover, the numerous polymorphisms of the cytokine gene including TNF-α, IL-1, IL-12, IL-23, and IFNγ are also associated with the disease (13, 24).

The close associations of obesity with inflammatory status and increased atherosclerotic complication lead to a great interest in the body composition in chronic inflammatory diseases. The prevalence of overweight and obesity patients is common in RA and SLE (14-19). However, in our study, the prevalence of obesity was not higher in the BD group than in the HC group and general population (25). The causes of obesity are associated with sedentary life style, physical inactivity, and glucocorticoid usages in RA and SLE (17). BD may have a milder disease course than RA and SLE. A low percentage of BD patients require the use of glucocorticoid usage. Physical inactivity is observed in a low percentage of patients, or it continues a short time. Moreover, oral ulcers reduce food intake in BD patients. Therefore, the prevalence of obesity is not increased in BD in contrast to other chronic inflammatory diseases.

The impact of body composition on the severity and activity of chronic inflammatory diseases is also ascertained due to the inflammatory nature of obesity, including increased CRP and TNF-α levels. Obese RA patients have been documented to have higher disease activity and worse quality of life than non-obese ones (17). Obesity has also been reported to be associated with increased inflammatory markers and impaired functional capacity in SLE (18). Conversely, Chaiamnuay et al. (19) demonstrated that obesity is associated with fibromyalgia but not with disease activity indices in SLE. In spite of these controversial results in the lit-

erature, our study documents that obesity is not associated with disease activity and acute phase reactants levels in BD.

Ghrelin has various metabolic functions including regulation of energy balance and control of appetite (2, 3). Subsequently, it is documented that ghrelin levels negatively correlated with the BMI and decreased in obese patients (3, 4). Similarly, ghrelin levels have been reported to decrease in inflammatory diseases, including RA, juvenile idiopathic arthritis, SLE, and Takayasu arteritis (9, 10, 26-28). Conversely, it has also been reported that ghrelin levels are increased in RA, and that the level is similar in healthy controls and SLE patients (10, 29). In our study, the levels of AG, UAG, and TG were similar in the BD and HC groups. These variations in the ghrelin levels in different inflammatory diseases may be caused by differences in inflammatory status. On the other hand, the decreased obesity prevalence may be a cause of unaltered ghrelin levels in BD in contrast to other chronic inflammatory diseases. Indeed, obese BD patients had lower UAG and TG levels compared to the non-obese ones, in our study. Or, it may be possible that ghrelin levels decrease in RA and SLE as a consequence of the increased fat mass.

Obesity is a well-established risk factor for atherosclerotic cardiovascular diseases in the general population (1). It has been reported that weight loss ameliorates several metabolic complications associated with atherosclerotic diseases and improves cardiac functions (30, 31). Similarly, decreased ghrelin levels are associated with a variety of metabolic abnormalities and atherosclerotic cardiovascular diseases (32). RA and SLE are associated with an increased prevalence of obesity and decreased ghrelin levels, and they lead to accelerated atherosclerosis. In contrast to the other chronic inflammatory diseases, BD does not lead to accelerated atherosclerosis (33). Therefore, it may be suggested that the decreased prevalence of obesity and unaltered ghrelin levels may also protect the BD patients from accelerated atherosclerosis.

In our study, the obestatin levels were high, in contrast to the ghrelin levels, in BD patients. Obestatin is a 23-amino acid peptide hormone that is derived from the posttranslational cleavage of preproghrelin and released from the stomach (6, 34). In contrast to ghrelin, which has orexigenic properties, obestatin may have anorectic effects (6, 34). Treatment of rats with obestatin suppresses food intake, inhibits jejunal contraction, and decreases weight gain (34-36). Indeed, in our study, while the circulating obestatin level was high in BD, obese BD patients had lower serum obestatin levels compared to the non-obese ones. These results may suggest that high obestatin may protect the BD patients from obesity.

Obestatin exists in plasma, saliva, and semen (reviewed in 37). Moreover, it is detected in various tissues including adipose tissue, gastrointestinal tract, muscle, lung, and liver (37). Obestatin leads to anti-inflammatory and anti-oxidant actions, in addition to metabolic effects (38, 39). It has been reported that obestatin decreases IL-1β, TNF-α, and nuclear factor-κB expressions and the activities of malondialdehyde and myeloperoxidase (38, 39). In hemodialysis patients, Beberashvili et al. (40) have shown that low obestatin levels are predictors of mortality, especially due to cardiovascular diseases. In our study, the obestatin levels are low in the BD patients with obesity, which is related to accelerated atherosclerosis.

We realize that the present preliminary study has some limitations. First, the assessment of obesity was performed using BMI according to the WHO definition in the present study. BMI is widely used in clinical practice, and it is easy to perform whereas the evaluation of body fat may be required for more sophisticated methods. Moreover, the WHO definition is valid in the general population. However, BMI may be inaccurate to adjust body composition, especially in the situation of cachexia since body fat can be different even at the same BMI level in cachexia. It can be a limitation of the study that a more accurate method of detecting the body fat percentage could be used instead of BMI. On the other hand, this study is an observational case-control study. This study design has advantages in addition to the disadvantages. For instance, a longitudinal follow-up could improve our results.

In contrast to ghrelin leading to hyperphagia and obesity, obestatin is known as an anorectic hormone. In BD, the prevalence of obesity was lower than in the general populations, and the serum obestatin levels were higher than in healthy subjects. Moreover, when compared to the non-obese BD patients, serum obestatin levels decreased in obese BD patients. These results suggest that the prevalence of obesity is not increased in BD and that obestatin may protect the BD patients from obesity. However, it has to be tested further in prospective studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Fırat University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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