The effect of orlistat and weight loss diet on plasma ghrelin and obestatin

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INTRODUCTION

Obesity is a main health-care problem of the new century that is associated with coronary heart disease and cerebrovascular disease. The World Health Organization reported that more than 1 billion adults were overweight, and at least 300 million of them were obese.[1] Most importantly, obesity is associated with an increased risk of developing diabetes, hypertension, osteoarthritis, coronary artery disease, and cancer.[2-5] Calorie restriction and regular physical activity are still the mainstay of treatment in obesity; nevertheless, these methods solely generally do not provide successful outcomes.[6,7] Therefore, pharmacological treatment options are often used in weight reduction programs in addition to dietary restriction and lifestyle adjustment. Pharmacologic treatment options include orlistat, lorcaserin, combination phentermine-topiramate, phentermine, benzphetamine, phendimetrazine, diethylpropion, and liraglutide. In our country, only orlistat is approved by the ministry of health for the pharmacologic treatment of obesity. Orlistat is an inhibitor of the gastrointestinal lipase that decreases the absorption of fat by 30%, and it has a long-term safety

Objective: The objective of this study was to evaluate the effect of weight loss with hypocaloric diet and orlistat treatment in addition to hypocaloric diet on gut-derived hormones ghrelin and obestatin. Materials and Methods: A total of 52, euglycemic and euthyroid, obese female patients were involved in the study. The patients were assigned to two groups: Group 1 (n = 26) received hypocaloric diet alone and Group 2 (n = 26) received orlistat in addition to hypocaloric diet for 12 weeks. Anthropometric measurements, serum lipid, insulin levels, and obestatin and ghrelin values were assessed at the beginning of the study and after 12 weeks of therapy. Results: Baseline clinical characteristics and laboratory parameters including serum ghrelin and obestatin concentrations and ghrelin/obestatin ratio were similar between the two groups. After 12 weeks, mean change in BMI, fat mass, and fat-free mass (FFM) were −1.97 ± 1.56 kg/m² (P = 0.003), −2.63% ± 2.11% (P = 0.003), and −1.06 ± 0.82 kg (P = 0.003), respectively, in Group 1. In Group 2, mean change in BMI was −2.11 ± 1.24 kg/m² (P = 0.001), fat mass was −3.09% ± 2.28% (P = 0.002), and FFM was −1.26 ± 0.54 kg (P = 0.001). However, fasting glucose, lipid, and insulin levels did not change in Group 1. Furthermore, except serum high-density lipoprotein cholesterol and triglyceride levels, no significant change was observed in Group 2. Although serum ghrelin and obestatin concentrations increased significantly in both groups (Group 1: pGhrelin: 0.047, pobestatin: 0.001 and Group 2: pGhrelin: 0.028, pobestatin: 0.006), ghrelin/obestatin ratio did not change significantly. When the changes in anthropometric assessments and laboratory parameters were compared, no significant difference was observed between the two groups. Furthermore, no correlation was observed between ghrelin or obestatin and any other hormonal and metabolic parameters. Conclusions: Weight loss with diet and diet plus orlistat is both associated with increased ghrelin and obestatin concentrations.

Key words: Obesity, obestatin/ghrelin ratio, orlistat


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Gut-derived hormones ghrelin and obestatin have been described as an important physiologic regulator of appetite and energy homeostasis recently. Ghrelin is an endogenous ligand for the growth hormone (GH) secretagogue receptor, and it regulates energy homeostasis and appetite and consequently increases body weight. Whereas exogenous ghrelin administration stimulated appetite and food intake, recent studies reported decreased ghrelin levels in obese patients and serum ghrelin levels are negatively correlated with body mass index (BMI) both in obese and lean participants. Obestatin is encoded by the same gene with ghrelin and down-regulates the effects of ghrelin on food intake. Obestatin treatment of rats suppressed food intake, inhibited jejunal contraction, and decreased body weight gain. However, recent studies were unable to confirm the role of obestatin on food intake, body weight, or GH secretion in humans. The data about the effect of orlistat treatment on ghrelin levels are limited. However, to the best of our knowledge, there is no study concerning the effect of orlistat – the only approved pharmacologic treatment of obesity in our country – on both ghrelin and obestatin levels and ghrelin/obestatin ratio in obese patients. Therefore, the aim of our study was to assess the effect of weight loss with orlistat and hypocaloric diet on gut-derived hormones ghrelin and obestatin and ghrelin/obestatin ratio.

**MATERIALS AND METHODS**

The study was a single-center, prospective, case–control study. A total of 88 sedentary obese women who were admitted to the Outpatient Endocrinology Clinic, for the treatment of obesity, were assessed for eligibility, and the flow of the study was described in Figure 1. The eligible individuals were between 18 and 60 years of age with a BMI >35 kg/m². All the eligible individual were evaluated by serum thyroid-stimulating hormone, fT3, fT4, and morning serum cortisol after 1 mg overnight dexamethasone administration and 2 h oral glucose tolerance test with 75 g of glucose in fasting state. Patients with thyroid dysfunction or abnormal glucose metabolism or serum cortisol values >1.8 mg/dl after overnight dexamethasone suppression were excluded from the study. Furthermore, patients who had a history of cardiovascular or renal diseases and gastrointestinal disorders or who had been taking any medication known to affect body weight were excluded from the study. Finally, a total of 52 patients were enrolled in the study. The Local Ethics Committee of Tepecik Research and Training Hospital approved the study protocol, and the procedures followed were in accordance with the Declaration of Helsinki 1975, as revised in 2000. Informed written consents were obtained from all participants at the beginning of the study. The patients were assigned to two groups: Group 1 (n = 26) received hypocaloric diet alone and Group 2 (n = 26) received orlistat (Thincal and Kocak) 120 mg, 3 times per day in addition to hypocaloric diet for 12 weeks. The percentages of carbohydrate, fat, and proteins were 50%, 25%, and 25%, respectively. The daily regular calorie intake was adjusted as 24 calories/kg of ideal body weight. Ideal body weight was calculated by method of Devine. All the patients were followed up for 12 weeks.

All the participants underwent a thorough physical examination and laboratory assessment. Anthropometric measurements were performed at the beginning and at the end of the study. Anthropometric measurements included measurement of body weight, height, and evaluation of body composition. Measurements of body weight and height were measured using an electronic scale with a resolution of 1 kg and 0.5 cm, respectively. Body composition was evaluated by applying leg-to-leg bioelectrical impedance (Tanita Body Fat Analyzer, TBF 300 M, Tanita, Tokyo, Japan). Assessments of body composition were standardized and performed on the morning of the study visits. The participants were questioned about their menstrual status and their fluid and food consumption, at that morning. Throughout a study period, all assessments were completed with the same material by the same investigator. The accuracy of bioelectrical impedance in the assessment of body composition in obese cases has already been reported.

The blood samples were drawn – at the beginning of the study and after 12 weeks of therapy. Venous fasting blood samples were collected from an antecubital vein in 8 ml evacuated tubes without anticoagulant (Vacuette, Greiner Bio-One, Austria). Blood in the plain tubes was allowed to clot for 30 min and was centrifuged at 3000 rpm for 10 min at room temperature. After centrifugation, the serum samples were aliquoted, frozen, and stored at –80°C for ghrelin and obestatin analysis. Repeated freezing and thawing process
was avoided. Serum total cholesterol, triglyceride (TG), high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL) cholesterol levels were measured in an autoanalyzer with the manufacturer’s commercially available kits (Cobas 8000, Roche Diagnostics, Mannheim, Germany). Insulin levels were measured with chemiluminescence immunometric assay in UniCel DXI 800 analyzer (Beckman Coulter Inc., Fullerton, CA, USA). Serum ghrelin (Phoenix Pharmaceuticals, Inc., CA, USA) and obestatin (Alpco Diagnostics, NH, USA) levels were determined by ELISA method according to manufacturer’s instructions. The intra- and inter-assay coefficients of variations were below 10%.

The mathematical method for homeostasis model assessment (HOMA-IR): (fasting insulin [μIU/ml] × fasting glucose [mmol/l]/22.5) was used to describe insulin resistance.

Statistical analysis
SPSS 11.0 (SPSS Inc. Chicago, Illinois, USA) software was used for statistical comparisons of data. Data were presented as mean ± standard deviation. The hypocaloric diet group and hypocaloric diet plus orlistat group were compared using Student’s-t-test. The data of basal and follow-up values after 12 weeks of therapy were compared using paired-sample t-tests and Wilcoxon signed-ranks test. Pearson correlation analysis was used to evaluate the relationship between ghrelin, obestatin, ghrelin/obestatin ratio, and various anthropometric and metabolic variables. P < 0.05 was considered as statistically significant.

RESULTS
Baseline clinical characteristics, anthropometric assessments, and laboratory parameters of the two groups are presented in Table 1. There were no significant differences between the two groups with respect to age, body weight, BMI, fat mass, and fat-free mass (FFM). Furthermore, basal glucose, insulin and lipid levels, and HOMA values were similar between the two groups. In addition, serum ghrelin and obestatin concentrations and ghrelin/obestatin ratio were similar between the two groups.

Twelve weeks of treatment resulted in a significant decrease in total body weight, BMI, fat mass, and FFM in both groups. Mean change in BMI, fat mass, and FFM were −1.97 ± 1.56 kg/m² (P = 0.003), −2.63% ± 2.11% (P = 0.003), and −1.06 ± 0.82 kg (P = 0.003), respectively, in Group 1. In Group 2, mean change in BMI was −2.11 ± 1.24 kg/m² (P = 0.001), fat mass was −3.09% ± 2.28% (P = 0.002), and FFM was −1.26 ± 0.54 kg (P = 0.001) (Tables 2 and 3). However, fasting glucose, lipid and insulin levels, and HOMA values did not change significantly after 12 weeks in Group 1 (P > 0.05).

Furthermore, except serum HDL-cholesterol and TG levels, no significant change was observed after 12 weeks of treatment in Group 2. While serum HDL-cholesterol was increased from 40.63 ± 7.28 to 47.82 ± 6.92 mg/dl (pHDL: 0.04), serum TG levels was decreased from 210.43 ± 70.31 to 153.64 ± 44.77 mg/dl (pTG: 0.018) after diet plus orlistat treatment. Although there were significant increases in serum ghrelin and obestatin concentrations, no significant change was observed in ghrelin/obestatin ratio in both groups after 12 weeks of treatment. Serum ghrelin concentration was increased from 285.33 ± 84.26 to 322.27 ± 87.51 pg/ml (P = 0.028) in Group 2 (P = 0.001), and it was increased from 88.69 ± 10.49 pg/ml to 104.97 ± 13.29 in Group 2 (P = 0.006).

When the changes in anthropometric assessments and laboratory parameters were compared, no significant difference was observed between the two groups as shown in Table 3.

We found no correlation between change in BMI and ghrelin (r = −0.136, P = 0.567) or change in BMI and obestatin (r = −0.228, P = 0.335). Furthermore, there was no correlation between ghrelin or obestatin and any other anthropometric, hormonal, and metabolic parameters both at baseline and at the end of the study (P > 0.05).
No complication was observed followed by orlistat intake.

**DISCUSSION**

Our current research revealed that both hypocaloric diet and medical treatment with orlistat plus low-calorie diet increased serum ghrelin and obestatin concentrations in a reasonably short period of 12 weeks.

Ghrelin and obestatin (ghrelin-associated peptide) both are developed from the identical peptide precursor (preproghrelin). Ghrelin, a 28-amino acid peptide produced mainly by the stomach, was initially determined as the natural ligand of the GH Secretagogue Receptor type 1a (GHS-R1a). In addition to stimulating GH secretion, ghrelin stimulates prolactin and ACTH release, increases gastric motility and gastric acid secretion, and promotes pancreatic peptide synthesis.[23] After the elucidation of orexigenic behavior of ghrelin in rodents, it was speculated that raised levels of ghrelin could contribute to obesity in humans. Unexpectedly, it was reported that human fasting serum ghrelin levels were lower in obese patients with respect to lean participants.[24-27] This may be explained by the downregulation of ghrelin with a result of energy excess in obese patients.

Obestatin is purified from the rat stomach and binds to the orphan G protein-coupled receptor 39 that is expressed in the brain. Following peripheral administration of obestatin, significant decrease in food ingestion and body weight was observed in rodents.[17] This raises the possibility that obestatin might be involved in the regulation of energy balance and body weight. However, the data about obestatin levels in obesity are conflicting. While some studies report increased levels,[17] some reported decreased levels.[18]

Guo et al. demonstrated increased ghrelin/obestatin ratio in obesity, but Vicennati and Zamrazilova found the decreased ratio.[14,16,17] The difference in results might be explained by the difference in the study population. The study of Guo et al. included both male and female participants; however, the study of Vicennati et al. and Zamrazilova et al. included only female participants. Furthermore, the mean baseline BMI in Guo’s study was 30.1 ± 1.9 kg/m² and in Vicennati’s study was 35.3 ± 4.19 kg/m². Since the obese group still had higher ghrelin to obestatin ratio even after adjustment for

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**Table 2: Baseline and 12th week anthropometric assessments and laboratory parameters of both groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n=26) (diet)</th>
<th>Group 2 (n=26) (diet + orlistat)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>104.48±9.76</td>
<td>104.19±9.76</td>
<td>0.001*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>40.16±2.44</td>
<td>40.51±2.44</td>
<td>0.003*</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>43.08±3.71</td>
<td>42.91±3.21</td>
<td>0.003*</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>44.96±4.56</td>
<td>46.83±3.71</td>
<td>0.001*</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>59.57±7.97</td>
<td>62.22±8.41</td>
<td>0.001*</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>92.51±12.05</td>
<td>96.83±9.98</td>
<td>0.106</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>214.33±50.28</td>
<td>219.61±54.40</td>
<td>0.069</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>131.60±47.16</td>
<td>141.24±29.11</td>
<td>0.368</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>42.97±10.78</td>
<td>40.63±7.28</td>
<td>0.686</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>194.25±104.71</td>
<td>210.43±70.31</td>
<td>0.088</td>
</tr>
<tr>
<td>Insulin</td>
<td>83.14±16.32</td>
<td>88.69±10.49</td>
<td>0.001*</td>
</tr>
<tr>
<td>BMI</td>
<td>2.05±1.43</td>
<td>2.13±0.58</td>
<td>0.105</td>
</tr>
<tr>
<td>Obestatin (pg/ml)</td>
<td>3.42±1.43</td>
<td>3.72±1.23</td>
<td>0.295</td>
</tr>
<tr>
<td>Ghrelin/obestatin ratio</td>
<td>285.33±84.26</td>
<td>322.27±87.51</td>
<td>0.047*</td>
</tr>
<tr>
<td>FFM</td>
<td>197.34±35.54</td>
<td>153.64±44.77</td>
<td>0.018*</td>
</tr>
<tr>
<td>FFM</td>
<td>62.22±8.41</td>
<td>104.97±13.29</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

Paired sample t-test for each group. *P<0.05. BMI=Body mass index; FFM=Fat-free mass; FBG=Fasting blood glucose; TG=Triglyceride; LDL-C=Low-density lipoprotein cholesterol; HDL-C=High-density lipoprotein cholesterol; HOMA-IR=Homeostasis model assessment of insulin resistance

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**Table 3: Changes in body composition and laboratory parameters in both groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n=26) (diet)</th>
<th>Group 2 (n=26) (diet + orlistat)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔBody weight (kg)</td>
<td>-5.24±2.16</td>
<td>-6.14±1.58</td>
<td>0.301</td>
</tr>
<tr>
<td>ΔBMI (kg/m²)</td>
<td>-1.97±1.56</td>
<td>-2.11±1.24</td>
<td>0.114</td>
</tr>
<tr>
<td>ΔFat mass (%)</td>
<td>-2.63±2.11</td>
<td>-3.09±2.28</td>
<td>0.639</td>
</tr>
<tr>
<td>ΔFat mass (kg)</td>
<td>-4.87±2.79</td>
<td>-6.71±3.83</td>
<td>0.238</td>
</tr>
<tr>
<td>ΔFFM (kg)</td>
<td>-1.06±0.82</td>
<td>-1.26±0.54</td>
<td>0.551</td>
</tr>
<tr>
<td>ΔFBG (mg/dl)</td>
<td>-2.75±6.86</td>
<td>-6.14±10.75</td>
<td>0.410</td>
</tr>
<tr>
<td>ΔTotal cholesterol (mg/dl)</td>
<td>-18.25±27.92</td>
<td>-9.96±16.40</td>
<td>0.384</td>
</tr>
<tr>
<td>ΔLDL-C (mg/dl)</td>
<td>-7.47±24.71</td>
<td>-8.73±17.88</td>
<td>0.594</td>
</tr>
<tr>
<td>ΔHDL-C (mg/dl)</td>
<td>1.98±6.78</td>
<td>7.63±9.28</td>
<td>0.106</td>
</tr>
<tr>
<td>ΔTG (mg/dl)</td>
<td>-53.36±87.71</td>
<td>58.43±62.31</td>
<td>0.115</td>
</tr>
<tr>
<td>ΔInsulin</td>
<td>-4.84±7.90</td>
<td>-5.99±14.07</td>
<td>0.551</td>
</tr>
<tr>
<td>ΔHOMA-IR</td>
<td>-0.91±1.58</td>
<td>-0.89±2.50</td>
<td>0.599</td>
</tr>
<tr>
<td>ΔGhrelin (pg/ml)</td>
<td>144.21±198.17</td>
<td>123.72±149.76</td>
<td>0.697</td>
</tr>
<tr>
<td>ΔObestatin (pg/ml)</td>
<td>14.63±9.84</td>
<td>16.37±14.29</td>
<td>0.660</td>
</tr>
<tr>
<td>ΔGhrelin/obestatin ratio</td>
<td>1.12±2.42</td>
<td>0.72±1.69</td>
<td>0.610</td>
</tr>
</tbody>
</table>

Independent t-test. P<0.05, significant. BMI=Body mass index; FFM=Fat-free mass; FBG=Fasting blood glucose; TG=Triglyceride; LDL-C=Low-density lipoprotein cholesterol; HDL-C=High-density lipoprotein cholesterol; HOMA-IR=Homeostasis model assessment of insulin resistance

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No complication was observed followed by orlistat intake.
gender and age in the study of Guo et al., it is unlikely that
the discrepancy in data resulted from the gender difference.
Hence, larger researches are required to elucidate these
controversial results.

Although obesity was associated with decreased serum
ghrelin levels, after diet-induced weight loss plasma
ghrelin levels were found to be increased.[24] This increase
in ghrelin might be an adaptive response to prevent further
weight loss by upregulating hunger levels and energy
intake.[24,25] In accordance with these findings, in our study,
we found increased ghrelin levels both after diet-induced
weight loss or diet plus orlistat treatment-induced weight
loss. However, weight loss after RYGP was reported
to be associated with decreased serum ghrelin levels.
Patients who underwent gastric by-pass felt less hungry
and consumed fewer meals. Hence, the suppression of
ghrelin was proposed as a potential mechanism by which
this procedure caused weight reduction.[20] In contrast to
these findings, Martins et al. reported increased plasma
ghrelin and obestatin levels, but there is no difference in
ghrelin/obestatin ratio after RYGB.[18]

Orlistat is a reversible inhibitor of gastrointestinal lipases
that are extensively used in the pharmacotherapy of morbid
obesity, and it blocks the fat absorption in the intestine,
controls hypertension and dyslipidemia apart from weight
loss, and decreases the risk of development of diabetes
mellitus. It has been reported that orlistat had a favorable
effect on insulin resistance, blood pressure, and TG levels
in addition to weight loss. Previous trials demonstrated
that orlistat reduced total cholesterol, LDL-cholesterol, and
TG levels.[29]

Similar to previous studies, our study revealed that orlistat
treatment with a low-calorie diet regimen caused a significant
decrease in TG and statistically significant increase in
HDL-cholesterol levels in obese women after 12 weeks of
treatment. There are only two studies which investigated
the effect of orlistat therapy on serum ghrelin levels.[19,20]
Ozkan et al. compared serum leptin and ghrelin levels in
obese participants who take orlistat with those receiving
only dietary treatment. They found lower ghrelin levels in
obese participants with respect to controls and reported
that ghrelin levels increased in both obese groups after
12 weeks of therapy, but the increase was similar.[19] In the
other study, orlistat was found to have no effect on ghrelin
levels.[20] In our study, we observed increased ghrelin levels
after 12 weeks of orlistat treatment and similar to the study
of Ozkan et al., we found that the increase was not different
between the diet and orlistat groups.

There are no studies about the effect of orlistat on obestatin
levels or ghrelin/obestatin ratio. Our study is the first
study which evaluated the effect of orlistat on obestatin or
ghrelin/obestatin ratio. We found increased obestatin levels
both after diet-induced or diet plus orlistat therapy-induced
weight loss. However, we observed no significant change
in ghrelin/obestatin ratio in both groups after 12 weeks of
treatment.

Ghrelin/obestatin ratio was negatively correlated with BMI
and indices of abdominal fat distribution, fasting insulin,
and HOMA-IR, but positively correlated with ISI composite
in previous reports.[14] However, Guo et al. found a positive
correlation between ghrelin/obestatin ratio and BMI.[14] In
our study, we did not observe any correlation between
BMI or antropometric data and ghrelin, or obestatin both at
baseline and at the end of the study. This may be related to
that previous studies included distinct ethnic groups of the
younger age range. They showed that decreased obestatin
centations were independently and significantly
associated with impaired glucose regulation and type 2
diabetes.[30] However, in our study, we did not find any
correlation between insulin or HOMA-IR and ghrelin or
obestatin both at baseline and at the end of the study. This
may be explained by that in our study; we excluded patients
with type 2 diabetes.

Our study has a couple of limitations. First, it has a very
small sample size. Second, we measured total ghrelin,
not acylated ghrelin, which is thought to be principal
for ghrelin biologic actions. Nevertheless, in a previous
report, total ghrelin levels correlated well with the acylated
ghrelin.[18,23] Third, ghrelin and obestatin concentrations
merely measured in the fasting state in our study.
However, ghrelin concentrations increase expeditiously
after fasting in normal-weight individuals, but this rise
is postponed in obese animals, suggesting that excess
energy deposit adjusts short-term ghrelin secretion. On
the other hand, a measuring of morning fasting ghrelin
concentrations has been reported as a reliable approach
to characterize ghrelin status even if ghrelin is released
episodically.[31] Furthermore, our study sample included
only female patients and we did not measure fasting
plasma ghrelin and obestatin levels in lean control
volunteers for comparison.

In summary, this is the first study that evaluated the
effect of low-calorie diet and diet plus orlistat in obese
premenopausal women on orexigenic hormone – ghrelin
and anorexigenic hormone – obestatin ratio. Weight loss
with diet and diet plus orlistat is associated with increased
ghrelin and obestatin concentrations.

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Nil.
Conflicts of interest
There are no conflicts of interest.

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