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# Effects of a Weight-Reduction Program with Orlistat on Serum Leptin Levels in Obese Women: A 12-Week, Randomized, Placebo-Controlled Study

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## ABSTRACT

***Background:*** Leptin, which has been identified as an antiobesity hormone, regulates body weight by controlling food intake and energy expenditure via the hypothalamic-pituitary-gonadal axis. It appears that leptin may be an important factor in obesity management. Orlistat, a pancreatic lipase inhibitor, could reduce fat absorption and promote weight loss due to leptin metabolism.

***Objective:*** The purpose of this study was to investigate the effects of orlistat therapy on serum leptin levels.

***Methods:*** Obese women (body mass index [BMI], 30 kg/m$^2$) aged 18 to 50 years were randomly assigned to receive 12 weeks of oral treatment with diet-orlistat (120 mg TID) (DO group) or diet-placebo (DP group). During the treatment period, patients were asked to eat a balanced diet of ~1200 to 1600 kcal/d. Body composition was determined by bioelectrical impedance. Serum leptin levels were measured using radioimmunoassay at baseline and at study end.

***Results:*** A total of 24 patients entered the study; 14 patients (mean [SE] BMI, 37.7 [1.1] kg/m$^2$) received orlistat and 10 patients (mean [SE] BMI, 39.4 [1.3] kg/m$^2$) received placebo. Compared with baseline, mean percentages of loss of body weight and fat mass after 12 weeks of treatment were significant in the DO group (9.1% and 14.8%, respectively; both $P = 0.001$) and in the DP group (9.5% and 17.6%; both $P = 0.005$). The between-group differences were not statistically significant. Mean (SE) serum leptin levels also decreased significantly after treatment in the DO group (16.2 [1.2] vs 9.0 [1.0] ng/mL; $P = 0.001$) and in the DP group (19.3 [2.1] vs 9.7 [1.4] ng/mL; $P = 0.005$). The between-group difference was not statistically significant.

***Conclusions:*** In this study of obese women, orlistat treatment was associated with a similar decrease in body weight, fat mass, and serum leptin levels

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as placebo over a 12-week period. In this regard, short-term orlistat therapy may not provide an additional effect on serum leptin levels, and reduction in leptin levels were closely related to the decrease in fat mass. (*Curr Ther Res Clin Exp.* 2004;65:127–137) 

***Key words:*** leptin, obesity, orlistat, pharmacotherapy.

## INTRODUCTION

*Obesity* refers to a condition of an abnormal accumulation of body fat mass (body mass index [BMI], >30 kg/m$^2$), and is often associated with serious medical conditions, including impaired glucose tolerance, insulin resistance, increased blood pressure, altered lipid levels, and other chronic conditions.[1,2] Although the etiology of obesity is complicated and not well understood, obesity is likely due to an increase in energy excess that results from caloric intake that exceeds energy expenditure.[3]

Leptin has been identified as an antiobesity hormone that functions as an afferent signal in a negative feedback system that regulates body weight by controlling food metabolism and energy expenditure by the hypothalamic-pituitary-gonadal axis.[4–6] Considering the regulatory role of leptin in the control of food metabolism, body mass, and energy expenditure, it appears that leptin may play an important role in obesity management. Thus, it is important to understand the factors that affect leptin metabolism.

Leptin levels are closely related to percentage of body fat; markedly higher serum leptin levels have been found in obese individuals compared with nonobese individuals.[7,8] In contrast, leptin levels are severely reduced in underweight individuals compared with normal-weight individuals.[9,10] Increases and decreases in leptin levels have been reported following hypercaloric[11] and hypocaloric diets.[12] The relationship between physical activity and leptin levels also has been assessed in many studies.[13–15] In these studies, leptin levels were not affected by acute exercise,[13,14] but the levels decreased after long-term exercise training as a result of reduced body fat mass.[14,15]

In addition to pharmacotherapy, calorie-restricted diet and increased physical activity are the current protocols used to achieve weight loss. Orlistat (tetrahydrolipstatin), a widely used antiobesity drug, could reduce the absorption of dietary fat from the intestinal lumen by inhibiting pancreatic lipase enzyme activity, and may lower serum cholesterol and triglyceride levels.[16] It is logical to expect that orlistat also may have an effect on serum leptin levels. The impact of body weight loss induced by orlistat on serum leptin levels in obese patients has not been extensively studied, according to a MEDLINE search (key terms, *orlistat, leptin,* and *weight loss*; years, 1974–2004). In addition, orlistat also may promote weight loss due to leptin metabolism.

In the present study, 2 groups of women were examined before and after 12 weeks of weight loss induced by caloric restriction and pharmacotherapy

with orlistat or placebo to investigate the effects of the antiobesity drug on serum leptin levels.

## PATIENTS AND METHODS

Obese women (BMI, >30 kg/m$^2$) aged 18 to 50 years who sought therapy for obesity at the Department of Endocrinology and Metabolic Disease, University of Firat Hospital (Elazig, Turkey) were eligible for the study. Patients who had a history of serious concomitant disease or who currently had such a condition were not eligible for the study. Patients with cortisol, thyroid, or insulin hormonal dysfunction and those taking any medications known to affect body composition also were excluded from the study. Pregnant, possibly pregnant, or breastfeeding women were excluded from the study.

The study protocol was approved by the local ethics committee, and informed written consent was obtained from each patient at the start of the study.

Before the study, each participant underwent medical screening to rule out abnormalities, including medical history, physical examination, hormonal analyses (cortisol, thyroid, insulin), and cardiovascular risk assessment, which included electrocardiography.

After screening, patients were randomly assigned to receive oral treatment with diet-orlistat* 120-mg capsules TID (DO group), the dosage that has been shown to be the most effective,[17] or identical-appearing diet-placebo capsules TID (DP group) for 12 weeks. All patients were encouraged to consume a nutritionally balanced, mildly hypocaloric diet (~1200–1600 kcal/d) during the 12-week study period. The prescribed diet contained ~30% of calories from fat, ~50% from carbohydrate, and ~20% from protein. The patients received dietary advice from a qualified dietitian. Dietary control was based on self-reports of the patients once or twice a week.

During the 12-week study period, each patient was admitted to the hospital for body composition assessment once or twice a week. Body weight and height were measured to the nearest 0.1 kg and 0.5 cm, respectively. Body composition was assessed using leg-to-leg bioelectric impedance (Tanita Body Fat Analyser TBF-300 M, Tanita, Tokyo, Japan). Measurement of body composition was standardized. On the mornings of the study visits, the patients were asked about their menstrual status and about their liquid and food intake that morning. The validity of bioelectric impedance in the measurement of body composition in obese patients has been questioned[18]; however, its usefulness in assessing changes in body composition has been documented.[19]

Blood samples were drawn at study entry and after 12 weeks of therapy. After an overnight fast, a venous blood sample was obtained between 8:00 AM and 9:00 AM, always at approximately the same time in the morning to avoid

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reductions in serum leptin levels over time.[20] The samples were separated by centrifugation (4500 rpm for 10 minutes at 4°C) and stored at –20°C and analyzed within 4 months of study entry. Serum leptin levels were measured in duplicate in the same run using a commercial radioimmunoassay kit (Human Leptin RIA DSL-23100, Diagnostic Systems Laboratories, Inc., Webster, Texas).

### Statistical Analysis

Within-group comparisons of data at baseline and study end were assessed using the Wilcoxon signed-rank test. The Mann-Whitney *U* test was used to assess between-group data. The relationship between change in serum leptin levels and fat mass loss was assessed by Pearson product moment correlation. $P \leq 0.05$ was considered statistically significant. The Statistical Package for Social Sciences software version 9.0 (SPSS Inc., Chicago, Illinois) was used for statistical analysis.

## RESULTS

A total of 24 patients entered the study. Fourteen patients (mean [SE] age, 38.7 [2.9] years [range, 18–50 years]; mean [SE] BMI, 37.7 [1.1] kg/m$^2$) were assigned to the DO group and 10 patients (mean [SE] age, 40.6 [1.8] years [range, 31–47 years]; mean [SE] BMI, 39.4 [1.3] kg/m$^2$) were assigned to the DP group (**Table**).

**Table.** Demographic and clinical characteristics of study patients at baseline and after 12 weeks of treatment with diet-orlistat 120 mg TID (DO group) or diet-placebo (DP group) (N = 24).* (Values are expressed as mean [SE].)

| | DO Group (n = 14) | | | DP Group (n = 10) | | |
|---|---|---|---|---|---|---|
| Characteristic | Baseline | Week 12 | % Change | Baseline | Week 12 | % Change |
| Age, y | 38.7 (2.9) | – | – | 40.6 (1.8) | – | – |
| Body weight, kg | 92.0 (3.2) | 83.5 (2.7)† | −9.1 | 93.8 (4.0) | 84.8 (3.3)‡ | −9.5 |
| Height, cm | 156.0 (1.5) | – | – | 154.3 (1.0) | – | – |
| BMI, kg/m$^2$ | 37.7 (1.1) | 34.3 (0.9)† | −9.1 | 39.4 (1.3) | 35.5 (1.0)† | −9.6 |
| Fat mass, kg | 40.3 (2.1) | 34.4 (1.9)† | −14.8 | 42.6 (2.7) | 34.8 (1.7)‡ | −17.6 |
| Serum leptin level, ng/mL | 16.2 (1.2) | 9.0 (1.0)† | −44.4 | 19.3 (2.1) | 9.7 (1.4)‡ | −49.2 |

BMI = body mass index.
*No significant between-group differences were found.
†$P$ = 0.001 versus baseline.
‡$P$ = 0.005 versus baseline.

After 12 weeks of treatment, mean percentages of body weight loss in the DO and DP groups, respectively, were 9.1% (from 92.0 [3.2] kg to 83.5 [2.7] kg; $P = 0.001$) and 9.5% (from 93.8 [4.0] kg to 84.8 [3.3] kg; $P = 0.005$) (Table). The between-group differences were not statistically significant. Furthermore, fat mass decreased significantly in both groups: 14.8% (from 40.3 [2.1] kg to 34.4 [1.9] kg; $P = 0.001$) in the DO group and 17.6% (from 42.6 [2.7] kg to 34.8 [1.7] kg; $P = 0.005$) in the DP group. The between-group differences were not statistically significant.

After 12 weeks of treatment, serum leptin levels decreased markedly compared with baseline levels in all patients in both groups (Table and **Figure 1**). Mean (SE) leptin levels decreased from 16.2 (1.2) ng/mL (baseline) to 9.0 (1.0) ng/mL (12 weeks) in the DO group (44.4%; $P = 0.001$) and from 19.3 (2.1) ng/mL to 9.7 (1.4) ng/mL in the DP group (49.2%; $P = 0.005$) (Table). The decreases in serum leptin levels were not significantly different between the 2 groups. A significant correlation was found between decrease in serum leptin level and fat mass loss after the 12-week study period in the DO group ($R = 0.632$; $P = 0.01$) (**Figure 2**). However, no significant correlation was found in the placebo group.

In the DO group, serum leptin levels per kilogram of fat mass (ng/mL·kg FM) significantly decreased after weight loss (0.4053 [0.02] vs 0.2624 [0.02] ng/mL·kg FM; $P = 0.001$), with a mean posttreatment value 41.6% lower than that at baseline. In the DP group, the decrease was 38.1% (0.4753 [0.06] vs 0.2819 [0.04] ng/mL·kg FM; $P = 0.005$) (**Figure 3**). The between-group difference was not statistically significant.

## DISCUSSION

Leptin affects body weight regulation and endocrine parameters via central and peripheral actions.[4] Understanding leptin functions and the factors affecting leptin metabolism are important issues in obesity treatment and prevention. Many investigations[8–15] have examined serum leptin levels in response to body weight loss induced by diet and/or exercise. However, few studies have looked at the relationship between serum leptin levels and pharmacotherapy-induced weight loss. Orlistat, a widely used drug, reduces the absorption of dietary fat in the intestine by inhibiting lipase enzyme activity, and may lower serum cholesterol and triglyceride levels.[16,21] Therefore, orlistat may be expected to affect serum leptin levels.

In this study, a 44.4% decrease in serum leptin level was associated with a 9.1% decrease in body weight and a 14.8% decrease in fat mass over the 12-week orlistat treatment period. The reduction in serum leptin levels at week 12 was ~5-fold greater than the relative reduction in body weight. This result was similar to the finding of Considine et al,[8] who found a decrease of 10% in body weight associated with a 53% reduction in serum leptin level.

During the 12-week treatment period, orlistat therapy resulted in marked reductions in body weight and fat mass compared with baseline values. Sur-

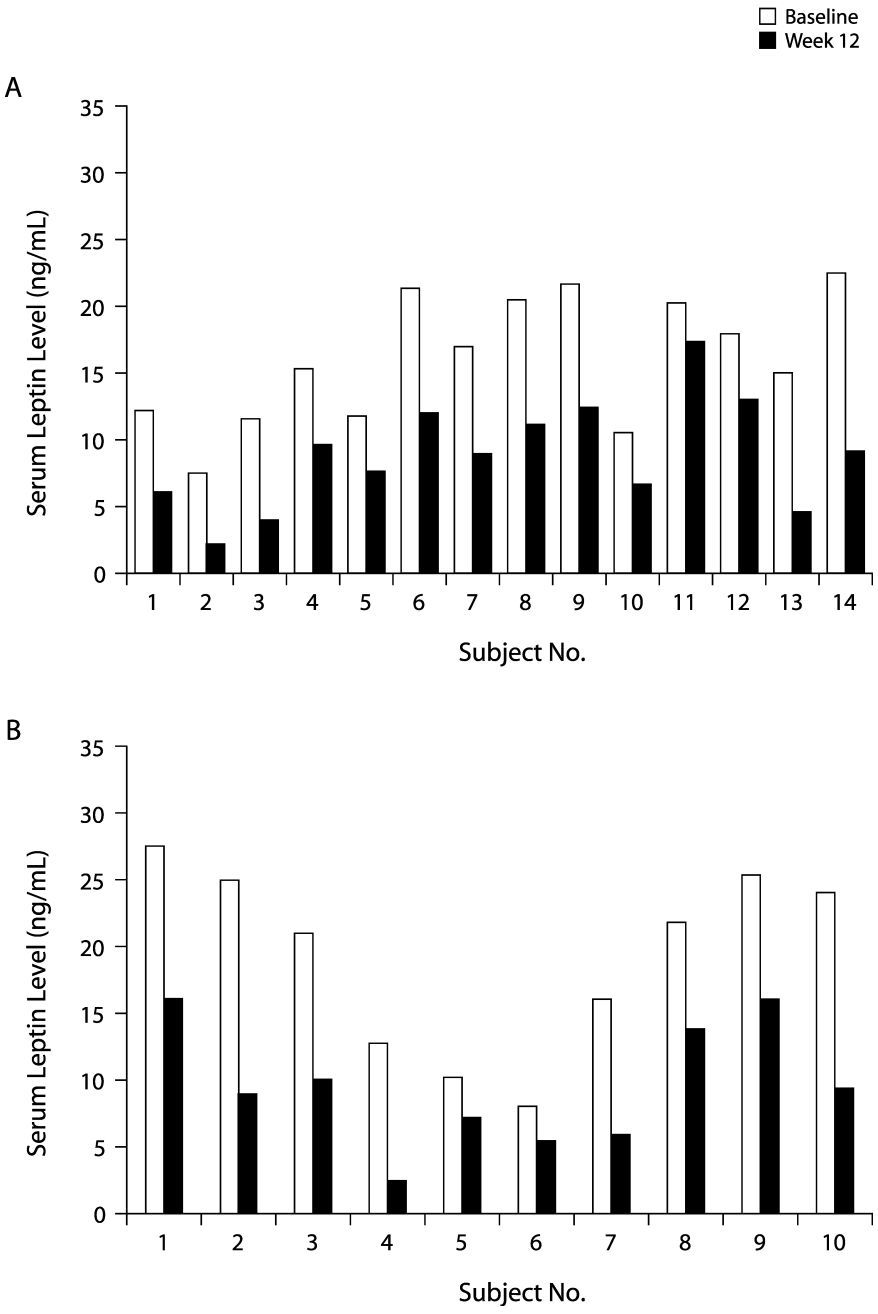


**Figure 1.** Individual serum leptin levels at baseline and after 12 weeks of treatment with (A) orlistat 120 mg TID or (B) placebo.

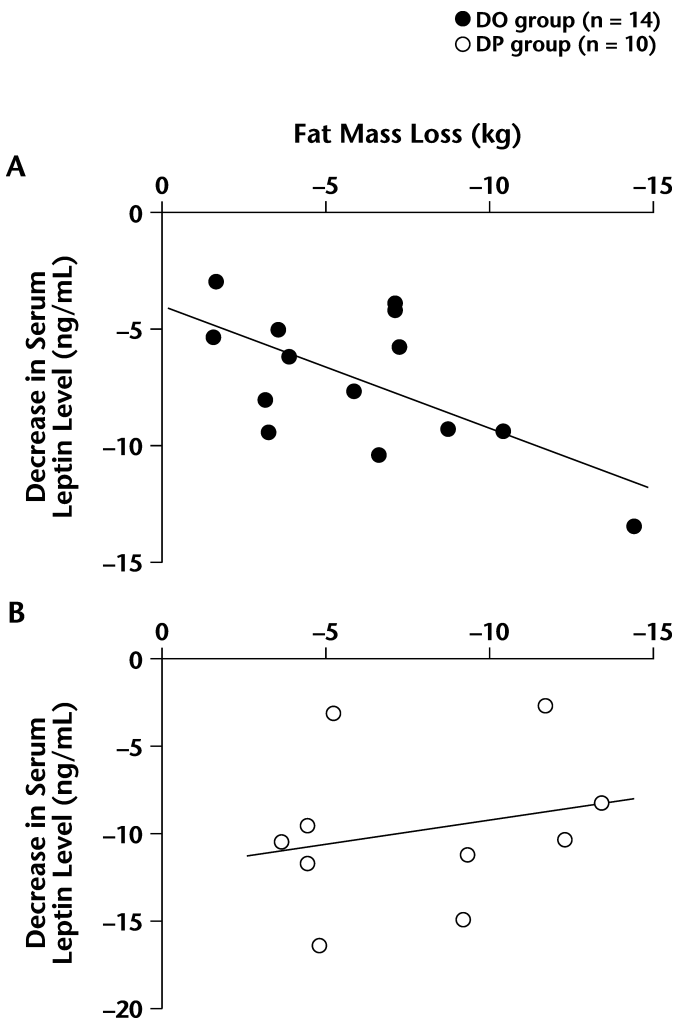


**Figure 2.** Correlation between the decrease in serum leptin level and fat mass loss during the 12 weeks of treatment with (A) diet-orlistat 120 mg TID (DO group; $R = 0.632$; $P = 0.01$) or (B) diet-placebo (DP group; $R = –0.239$; $P = 0.5$).

prisingly, the DO and the DP groups had similar reductions in body mass (9.1% and 9.5%, respectively) and fat mass (14.8% and 17.6%, respectively) after treatment. However, a significant difference might be expected with long-term therapy. Previous studies[17,21] showed that long-term orlistat therapy may facilitate weight loss and weight maintenance compared with placebo. Although serum leptin levels are known to be high in obese patients,[8] decreased efficiency in leptin function is attributed to increased leptin resistance rather than

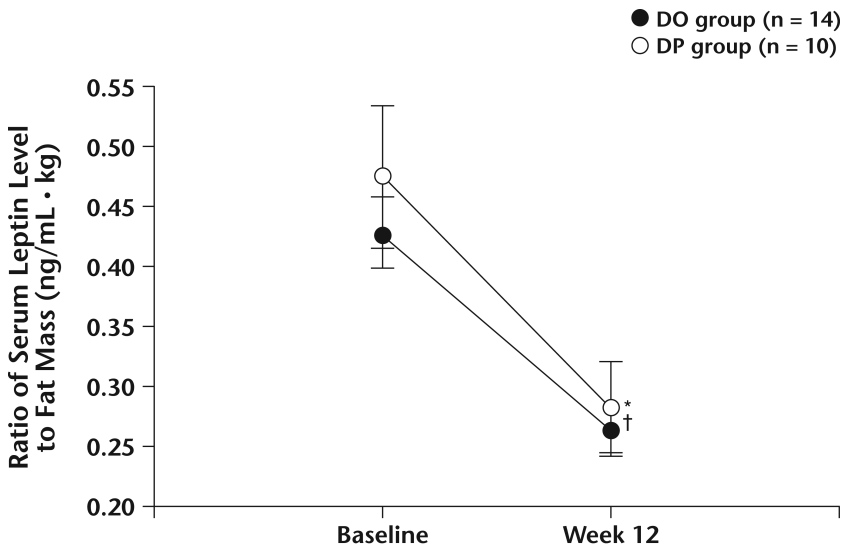


**Figure 3.** Ratio of mean (SE) serum leptin level to fat mass before (baseline) and after 12 weeks of treatment with diet-orlistat 120 mg TID (DO group) or diet-placebo (DP group). *$P$ = 0.001 versus baseline; †$P$ = 0.005 versus baseline.

a deficiency of leptin in obese patients.[22,23] Previous studies[5,24] in rodents have reported an increase in peripheral leptin resistance as a result of consuming a high-fat diet.

Klein et al[25] reported that leptin levels increase faster than body fat. The large-percentage decrease in leptin levels in the present study could represent a normalization of leptin function. Weight loss, in addition to fat mass loss, triggers a decrease in serum leptin level that reflects restoration of leptin sensitivity.[24,25] In accordance with previous studies,[26,27] in the present study, weight loss was associated with a decrease not only in absolute serum leptin levels but also in serum leptin expressed per kilogram of fat mass. This finding contradicted that of Rodrigues et al,[28] who did not find a change in ratio of serum leptin level to fat mass after 2 months of antiobesity therapy that included orlistat. In contrast, a significant decrease in cerebrospinal fluid to serum leptin level ratio has been reported[28] in orlistat-treated patients compared with a centrally acting pharmacologic agent. However, the decrease in ratio of cerebrospinal fluid to serum leptin level during treatment with orlistat, which acts peripherally, was attributed to weight loss rather than the direct effects of the drug.[28]

In the present study, changes in serum leptin levels after weight loss were correlated with changes in body fat mass in the DO group but not in the DP group. There is no clear explanation for these results, but they may be affected by the lower number of patients in the DP group. Another important point that

needs to be clarified is whether posttreatment leptin levels were influenced by the continued state of energy restriction. One study[26] showed that when body weight is stable, leptin levels are determined by the amount of fat mass and by sex. During dynamic weight loss, in addition to fat mass loss, metabolic factors also could have an effect on leptin levels.[29,30] Serum leptin levels do not depend only on the size of adipose tissue mass because fasting decreases leptin levels without marked changes in the body fat mass. The degree of short-term caloric restriction has an effect on acute changes in serum leptin levels that may not be correlated with fat mass loss.[31,32] In the present study, the patients in both study groups were encouraged to consume a diet containing ~1200 to 1600 kcal/d. However, during the study period, the control of the patients' diet was based on self-report. In the present study, to avoid the additional effects of exercise training on serum leptin levels and body composition, we did not give the patients an exercise training program.[14,15]

Further research is required to understand the factors affecting leptin metabolism and its role in the regulation of energy balance, which is a key factor in obesity management.

## CONCLUSIONS

In this study of obese women, orlistat treatment was associated with a similar decrease in body weight, fat mass, and serum leptin levels as placebo over a 12-week period. In this regard, short-term orlistat therapy may not provide an additional effect on serum leptin levels, and reduction in leptin levels were closely related to the decrease in fat mass.

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