

## Effect of 12 week aerobic exercise on the obestatin level in obese women

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### Abstract

#### Introduction:

Obestatin, an anti-hunger peptide, plays an important role in energy balance and body weight. The Aim of this study was to assess the effect of a 12 week aerobic exercise program on the obestatin level in obese women.

#### Materials and Methods:

Twenty obese volunteer women (age  $35 \pm 6.81$ y, body mass index  $35.8 \pm 3.67$  Kg/m<sup>2</sup>, fat percent  $43.98 \pm 4.02\%$  and waist-hip ratio  $1.03 \pm 0.05$  (means $\pm$ SD) were randomly divided into two equal groups, experience (n=10) and control (n=10). Aerobic training program was performed three sessions per week during 12 weeks using treadmill (start with 60-65% heart rate max/15-20 min, final with 80-85% heart rate max/ 45-50 min). Body composition, glucose, insulin and obestatin level were measured in the two groups before and after the intervention. Insulin resistance index (HOMA-IR) was measured by calculating the relevant equation. For inter- group comparison, paired t-test and for between group comparison independent-t test were used (significance level  $P < 0.05$ ).

#### Result:

The results showed that after a 12-week treatment of aerobic exercises, weight, fat percentage, WHR, and BMI in the experimental group were significantly decreased ( $P < 0.05$ ). It was also revealed that insulin and insulin resistance in the experimental group was significant. The important point was that the glucose level and obestatin did not show any significant changes ( $P < 0.05$ ).

#### Conclusion:

The result showed that 12 week aerobic exercise did not change the plasma obestatin levels significantly; however, body composition and insulin resistance were significantly reduced. It seems that obestatin has no effect on weight loss.

**Keywords:** Aerobic Exercises, Obesity, Women, Insulin Resistance

### Introduction

Obesity is the biggest challenge of the present century posed to the public health; in most countries, healthcare has to deal with issues and complications arising from the increasing incidence of obesity (1). The prevention and treatment of obesity are multifaceted problems that are not

merely restricted to factors such as genetics, hormone levels, overindulgence in food or a sedentary lifestyle (2). Energy balance is regulated by a complex mechanism consisting of central and peripheral factors. Ghrelin and obestatin peptides are two recognized environmental factors that appear to play a major role in regulating

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food intake and body weight (3). Obestatin is mainly secreted from the gastric fundus cells and is discharged into the blood stream (4). The discovery of obestatin goes back to the discovery of ghrelin. Ghrelin contains 28 amino acids with an N-octanol group; the ghrelin gene has shown to be able to produce other active molecules such as obestatin. Although both peptides are formed by the same precursor pre-pro-peptide, most studies reveal they have contradictory physiological roles (5). Compared to ghrelin, obestatin reduces the absorption of food, prevents gastric draining and genome contractile activity and affects weight loss (4 and 6).

Obesity and weight gain result in reduced levels of plasma ghrelin and obestatin. In a study conducted by Beasley et al., overweight people with a BMI of 25-30 and obese people with a BMI above 30 had a lower level of obestatin compared to people with a normal weight (7). In their study on three groups of women, i.e. those with a normal weight, obese women and women suffering from anorexia nervosa, Zamrazilova et al. showed that, compared to women of normal weight, fasting plasma obestatin levels are significantly higher in women with anorexia nervosa and significantly lower in obese women. A similar pattern was observed for their ghrelin level. Furthermore ghrelin to obestatin ratio was significantly higher in women with anorexia nervosa compared to women of normal weight and obese women (8). Overall, it seems that obestatin plays a key role in regulating energy balance and controlling body weight. Ghrelin/obestatin balance could also play a key role in the mechanism of obesity (9).

Findings of few studies conducted on this subject suggest the likelihood of physical exercise affecting obestatin levels. Ghanbari, Niaki et al. examined the effect of 6 weeks of jogging on total obestatin levels of the intestine and the fundus. Results of their study demonstrated the significant reduction of obestatin levels in the small intestine and fundus of rats that

had exercised, and the lack of a significant change in their total plasma obestatin levels. The reduction in obestatin levels was associated with a significant increase in liver glycogen and plasma growth hormone and no changes in adenosine triphosphate levels in the small intestine and fundus. Researchers believe that the increased plasma growth hormone and glycogen content of the liver may inhibit the synthesis and secretion of obestatin in the small intestine and fundus. It thus seems that increased levels of the growth hormone inhibit obestatin production in the small intestine and fundus via a negative feedback (10). On their study on obese rats, Wang et al. evaluated the effect of 8 weeks of treadmill exercise with an incline of 5 degrees and at a speed of 20 m/min for 5 days a week and 40 minutes a session on the plasma obestatin levels of the rats. By the end of the study, the plasma obestatin levels remained unchanged and hypothalamic obestatin levels reduced; plasma and hypothalamic ghrelin levels were also measured, revealing a similar pattern of change. Therefore, it cannot be easily suggested that these two peptides have reverse effects. To assess the role of ghrelin and obestatin in the mechanism of obesity, Zou et al. conducted a study on obese children with a mean age of  $10.3 \pm 2.1$  years and a BMI of  $25.48 \pm 3.18$  kg/m<sup>2</sup>. Findings indicated that weight loss due to a restricted calorie intake (1300-1600 calories per day) along with a 3-hour daily aerobic exercise in the form of basketball, table-tennis and swimming for the duration of one month, significantly increased ghrelin and obestatin levels as well as ghrelin to obestatin ratio. Before weight loss, however, obestatin and ghrelin levels were lower in obese children compared to children with a normal weight. According to these findings, it appears that ghrelin/obestatin balance plays a key role in the mechanism of obesity. Moreover, reduced ghrelin and obestatin levels in obese children is considered part of the

negative feedback inhibiting appetite and controlling body weight and is not the cause of obesity (12). Furthermore, evidence suggests that obestatin levels reduce in conditions of insulin-resistance (13).

Given the limited scope of findings, the important role of obestatin as an anti-appetite peptide involved in maintaining energy balance so as to prevent weight gain is still a mystery. Obestatin levels are most likely affected by exercise, causing a change in appetite and weight. Given the short time since its discovery as a peptide, few studies have investigated the effect of exercise on obestatin levels. Studies on human subjects examining the effect of aerobic exercise on obestatin levels have also been rare; in particular, no studies aiming obese women have been conducted on this topic to this date. Accordingly, the present study aimed to examine the effect of 12 weeks of aerobic exercise on serum obestatin levels in obese women.

### Materials and Methods

This quasi-experimental fundamental study with pretest-posttest and control group was conducted in 2012 in Isfahan. At the beginning of the research, there was a public call for obese women participants; after the initial screenings, 45 of them with a BMI above 30 were selected. Inclusion criteria were: absence of cardiovascular, respiratory, kidney or metabolic diseases as well as not being on any particular diets (low calorie, low fat or high protein). Participants with a history of exercise, diseases and smoking and also those trying to lose weight were excluded from the study. Prior to the beginning of the exercise program, all participants submitted their written consent. A total of 20 volunteers qualified, who were then randomly divided into an experimental group (10 women) and a control group (10 women).

Study variables were measured, including age, height (using a SECA stadiometer made in Germany with the accuracy of 1mm), weight, fat percentage, BMI, waist to hip ratio (using InBody model 3 by BIOSPACE made in Korea), serum glucose levels (by means of a glucose measuring kit using an enzymatic staining method made by Pars Azmoon Co. with a sensitivity of 1 mg/dl), serum insulin levels (using a Sandijii ELISA kit by Mercodia made in Uppsala Sweden with a sensitivity of 1 milliunit/liter), insulin resistance (using the Homeostasis model assessment formula based on insulin and glucose levels) and serum obestatin levels (using a special kit by Glory Co. made in the USA based on the ELISA method and used according to the manufacturer's guide).

Participants took part in 12 weeks of aerobic exercise on a treadmill, 3 sessions per week. Each session began with 60-65% of the maximum heart rate after a 10-minute warm-up by brisk walking, stretching and jogging. The first session contained 15-20 minutes of jogging and reaching 60-75% of the maximum heart rate and maintaining it for 25-30 minutes. The third week's exercise started with reaching 75-80% of the maximum heart rate and maintaining it for 35-40 minutes – a pattern that continued until the sixth week. The seventh week's exercise started with reaching 80-85% of the maximum heart rate and maintaining it for 45-50 minutes –continuing until the twelfth week. Every session ended with 10 minutes of slow cooling down through stretching. In order to control exercise intensity, a Polar stethoscope was used along with the equation for determining maximum heart rate based on age and the Karvonen formula (Maximum Heart Rate = 220 - Age). The control group was only monitored by a diet questionnaire.

Dietary intake data were obtained using 24-hour dietary recalls to determine the approximate amount of nutrients received. Participants were asked to list every food and drink they had consumed over the last 24 hours. This questionnaire was filled out by all participants on three non-consecutive occasions once a month over a 12-week period. The questionnaire used was the 24-hour Dietary Intake Assessment by the Department of Clinical Nutrition and Dietetics of Shahid Beheshti University of Medical Sciences.

Blood samples were collected twice; first, 24 hours before starting the first session of the exercises (pretest), and second, 24 hours after the last session of the exercises had ended (end of the twelfth week); at 8 o'clock in the morning following an overnight of fasting and resting, blood was collected in the amount of 10 ml from the anterior vein of the participants' left arm while in a seated position. Samples taken were then poured into sterile tubes and incubated at room temperature for 10 minutes. Their blood serum was then separated from the blood clot by centrifuging at 3000 rpm for 10 minutes and was kept frozen at  $-70^{\circ}\text{C}$  till the measuring stage.

In the posttest stage, once sample collection was completed, all blood samples were removed from the freezer and planned tests were performed on them with regard to the relevant protocols. In both blood-sampling sessions, participants had fasted for a minimum of 12 hours overnight. Moreover, members of the experimental group were asked not to take part in any form of exercise or take long walks in the 24 hours following the end of the last exercise session. All phases of the blood sampling procedure were carried out by a laboratory technician at the Sport and

Exercise Physiology Laboratory of the university.

In both groups, descriptive statistics were used to examine participants' characteristics, including age, height, weight, BMI, fat percentage, waist to hip ratio and serum glucose, insulin, and obestatin levels. After ensuring the normal distribution of the data using the Kolmogorov-Smirnov test, a dependent t-test was used to make internal comparisons between group members and an independent t-test to compare the two groups with one another. SPSS-19 software was used for analysis of the data and the significance level for computational purposes was decided to be equal to or lower than 0.05.

### Results

Table 1 shows the rate of changes to the various variables within the groups. Results showed a significant reduction in weight, BMI and fat percentage of both groups as a result of performing aerobic exercises ( $P < 0.05$ ). Results of the comparison made between the two groups are shown in table 2. Significant changes were observed in both groups' insulin level and insulin resistance (for the control group, pretest, 1.38 and posttest, 1.23; for the experimental group, pretest 3.76, and posttest, 2.57); however, no significant changes were observed in their obestatin and plasma glucose levels after 12 weeks of aerobic exercise (for the control group, pretest, 0.4 and posttest, 0.42; for the experimental group, pretest, 0.46 and posttest, 0.54) ( $P < 0.05$ ) (table 2). Figure 1 shows the mean rate of changes in obestatin levels of the obese women in both the experimental and the control group before and after the 12-week aerobic exercise program.

Table 1: Changes to the study variables from the pretest to the posttest stage in the control and the experimental group (within groups) (mean  $\pm$  standard deviation)

Variable	Group	Pretest	Posttest	Paired T	Significance Level
Weight (kg)	Control	86.8 $\pm$ 6.21	86.32 $\pm$ 5.73	1.475	0.17
	Experimental	94.11 $\pm$ 5.35	90.59 $\pm$ 5.64	4.53	0.001*
Fat Percentage	Control	42.2 $\pm$ 2.53	41.9 $\pm$ 2.43	1.571	0.15
	Experimental	44.87 $\pm$ 4.39	43.29 $\pm$ 4.53	3.53	0.006*
BMI (kg/m <sup>2</sup> )	Control	33.02 $\pm$ 0.98	33.04 $\pm$ 1.30	-0.16	0.87
	Experimental	37.21 $\pm$ 3.73	35.6 $\pm$ 3.64	3.48	0.007*
Waist to Hip Ratio	Control	1.01 $\pm$ 0.03	1.00 $\pm$ 0.02	0.93	0.37
	Experimental	1.04 $\pm$ 0.06	1.03 $\pm$ 0.05	4.14	0.002*
Glucose (mg/dl)	Control	6.74 $\pm$ 1.77	5.9 $\pm$ 1.00	1.72	0.11
	Experimental	15.82 $\pm$ 4.03	11.77 $\pm$ 2.85	2.99	0.01*
Insulin (mIU/L)	Control	6.74 $\pm$ 1.77	5.9 $\pm$ 1.00	1.72	0.11
	Experimental	15.82 $\pm$ 4.03	11.77 $\pm$ 2.85	2.99	0.01*
Obestatin (ng/ml)	Control	0.40 $\pm$ 0.09	0.42 $\pm$ 0.12	-0.557	0.59
	Experimental	0.46 $\pm$ 0.17	0.54 $\pm$ 0.21	-1.01	0.33
Insulin Resistance	Control	1.38 $\pm$ 0.27	1.23 $\pm$ 0.19	1.64	0.13
	Experimental	3.76 $\pm$ 1.79	2.57 $\pm$ 0.59	2.50	0.03*

\* Significance Level  $\alpha < 0.05$ 

Table 2: Results of the independent t-test in the control and the experimental groups

Variable	Mean difference	Independent t	Significance Level
Weight (kg)	3.04	3.61	0.004*
Fat Percentage	1.32	2.76	0.013*
BMI (kg/m <sup>2</sup> )	1.63	3.40	0.006*
Waist to Hip Ratio	0.01	2.39	0.028*
Glucose (mg/dl)	4.9	1.71	0.115
Insulin (mIU/L)	3.21	2.23	0.04*
Obestatin (ng/ml)	-0.06	-0.69	0.49
Insulin Resistance	1.04	2.15	0.057*

\* Significance Level  $\alpha < 0.05$ 

## Discussion

Results of the present study showed that 12 weeks of aerobic exercise had caused a significant reduction in weight, fat percentage, BMI, waist to hip ratio, insulin levels and insulin resistance; however, changes in glucose and obestatin levels were insignificant.

Exercise and weight loss work in parallel through separate but interrelated mechanisms to improve metabolic and cardiovascular risk factors (14). An aerobics course is expected to reduce weight, BMI, fat percentage and waist to hip ratio, which is confirmed by results of the present study. Although mechanisms of spending energy in the exercise of sports and controlling the appetite are effective for weight loss, their method of operation is still unclear. Various horm-

ones playing key roles in regulating the appetite and body weight have been identified (15), but mechanisms through which obestatin can help regulate food absorption are still unknown. Nevertheless, the appetite suppressing effects of obestatin after an intracerebroventricular injection are indicative of a certain activity taking place in the central nervous system (6).

Some studies have shown that ghrelin and obestatin play key roles in controlling energy balance and weight (16-18). It appears that these peptides perform reverse activities in food intake, weight gain and adipocytes. Studies have demonstrated the sensitivity of ghrelin to conditions of negative energy and its significant role in short-term and long-term energy balance and glucose homeostasis. Vicennati et al.

observed that, compared to women of normal weight, obese women had higher levels of obestatin, lower levels of ghrelin and a lower ghrelin to obestatin ratio. They also observed that there is an inverse correlation between ghrelin to obestatin ratio and BMI or abdominal lipid distribution. Overall, the reduced ghrelin to obestatin ratio in obese women supports the hypothesis that the imbalance of ghrelin and obestatin might be involved in the pathophysiological of obesity (19).

Figure 1: Comparison of mean obestatin variations (ng/ml) in obese women of the control and the experimental group before and after a 12-week aerobic exercise program.

In a study conducted by Haiger et al., the mean obestatin level in extremely obese adults et al. was 131 pg/ml (20); in a study conducted by Guo et al. on obese Chinese adults, this number was 50 pg/ml (17); and, in the present study, it was 430 pg/ml. Given that in the two studies cited, measurements were carried out using a commercial type kit, the disparity in results can be attributed to the variation in age, ethnicity and degree of obesity.

Results of a study by Mansoori et al. on the effect of a non-aerobic exercise program on plasma obestatin levels revealed its lack of changes among the study participants; it was thus concluded that obestatin levels are not affected by short-term exercise programs (21).

Wang et al. studied the effect of an 8-week treadmill jogging exercise on plasma and hypothalamic obestatin and ghrelin levels in obese rats. They found that after 8 weeks of exercise, the rats' plasma obestatin levels had remained unchanged while their levels of hypothalamic obestatin had been reduced. Furthermore, simultaneous assessments of plasma and hypothalamic ghrelin levels showed a similar pattern of change to obestatin's. They attributed appetite and weight loss to the reduction in hypothalamic ghrelin levels. In this study, obestatin's function and gene expression were not clearly

identified; however, variations in obestatin and ghrelin levels were similar. It cannot thus be easily surmised that these peptides have reverse effects (11). Results of the present study are in line with results of the discussed study and it appears that obestatin has no effect on weight loss.

In another study, a dietary regimen and physical exercise were used to examine weight loss in over-weight children; results showed that a combination of high-carbohydrate low-fat diet and physical exercise leads to weight loss and subsequently increases obestatin levels while keeping ghrelin levels unchanged. Researchers suggested that increased obestatin levels following weight loss might be the required mechanism for maintaining weight loss (22). In the present study, while a significant reduction was achieved in participants' weight, their plasma obestatin levels remained unchanged after 12 weeks of aerobic exercise. Plasma obestatin level variations might therefore be related to participants' age and nutritional status.

In their study, Saghebjo et al. investigated the effect of 4 weeks of circuit endurance training with 40% and 80% of maximum repeat intensities on plasma ghrelin to obestatin ratio of young women. They claimed that plasma obestatin levels had significantly been reduced in the group exercising 80% of maximum repeat intensity, while in the group exercising 40% of maximum repeat intensity, the change was not significant. Given that ghrelin to obestatin ratio had significantly increased in the group exercising 80% of maximum repeat intensity, researchers concluded that the energy drop following the exercise had caused proghrelin to produce more ghrelin instead of turning into other elements, thus resulting in reduced secretion of obestatin and increased ghrelin to obestatin ratio. This increase might have occurred in order to stimulate food intake and to compensate for lost sources of energy (3). It is possible that plasma obestatin levels have remained

unchanged in the present study due to its low intensity of exercises and their aerobic nature. It has now been well demonstrated that ghrelin and obestatin are encrypted by the same gene –although ghrelin forms a significant portion of this conversion. It is possible that conditions emerging from the exercise might have disturbed the balance and have turned more towards the probable expression of ghrelin (23).

As the main regulator of blood glucose level, lipid synthesis, adipose protein and glycogen, insulin stimulates muscular and liver cells and inhibits the disintegration of glycogen and lipids and the destruction of proteins (24). In a study conducted by Granata et al. on rats fattened through 8 weeks of high-fat diet, obestatin caused a reduction in insulin resistance and increased its secretion from the pancreatic Langerhans islets.

Results of the present study demonstrate that obestatin contributes to the functioning of lipid cells and glucose metabolism; it is thus suggested that it be used for the treatment of insulin resistance (25). The insulin resistance drop observed in the present study has likely caused increased hypothalamic obestatin levels and has kept plasma obestatin levels unchanged. Overall it seems that the type and intensity of exercises and the age of participants

have affected the responses and compatibilities. In addition, the fasting or non-fasting status of participants, their weight and BMI, type of exercise performed and even the timing of post-activity sampling must have affected findings of the study. It is therefore advised that these factors be taken into consideration in future studies. Moreover, since studies demonstrate that high-intensity interval exercise increases fat oxidization and mitochondrial enzymatic activities (26), investigating the effect of interval exercise on variables examined in the present study is encouraged.

### Conclusion

Overall, results of the present study demonstrated that a 12-week aerobic exercise program does not cause a significant change in plasma obestatin levels while it significantly reduces body compounds and insulin resistance. It thus appears that plasma obestatin levels are not associated with changes of weight and insulin resistance.

### Conflict of interest

The authors declare no conflicts of interest.

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