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Exercıse And Hormones Related To Appetıte Regulatıon

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ABSTRACT

Background: Obesity is spreading all around the world rapidly, especially in developed and developing countries, due to physical inactivity related to technological developments and increase in the consumption on energy rich food. Discovery of the new stimulants that affect various parts of the hypothalamus and produced from some peripheral tissues, and understanding of their functions better increase our knowledge of energy homeostasis. **Objective**: Especially, the discovery of obese gene (16kDa, ob) product released from adipose tissue, discovery of leptin known as satiety hormone, the discovery of ghrelin known as hunger hormone, and the discovery of obestatin, which is the product of the same gene with ghrelin and thought to resist the effects of ghrelin on food intake started a new era about the opinions on obesity. **Results:** Exercise is a non-pharmacological method used by itself or along with food-intake limitation in obesity treatment and body weight control. This review will attempt to update the knowledge of ghrelin, leptin and obestatin on the body weight regulation and the effect of exercise training on ghrelin, leptin and obestatin concentration. In conclusion, **Conclusion:** findings of the current studies on acute and chronic exercise conducted on human subjects that examined the effect of exercise on ghrelin, leptin and obestatin contradict with each other. Some of these differences may have resulted from differences between intensity, duration, and type of the exercise, or the features of the subjects, different research designs such as time of food intake. For this reason, many more studies using various subject groups and different methods are required in the subject field.

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INTRODUCTION

Obesity is spreading all around the world rapidly, especially in developed and developing countries, due to physical inactivity related to technological developments and increase in the consumption on energy rich food [2].

Discovery of the new stimulants that affect various parts of the hypothalamus and produced from some peripheral tissues, and understanding of their functions better increase our knowledge of energy homeostasis.The brain regulates energy homeostasisin accordance with the stimulants received from adipose tissues and gastrointestinal tract.Various centres in the hypothalamus, brainstem, and limbic systems are affected via these stimulants, and the neuropeptide release is regulated, and the food intake-energy expenditure balance is adjusted. Dysfunctions of this important homeostatic mechanism cause obesity and obesity-related complications. Especially, the discovery of obese gene (16kDa, ob) product released from adipose tissue, discovery of leptin known as satiety hormone, the discovery of ghrelin known as hunger hormone, and the discovery of obestatin, which is the product of the same gene with ghrelin and thought to resist the effects of ghrelin on food intake started a new era about the opinions on obesity [46,115,116]. All these results and new information attracted researchers' attention to the regulation of energy homeostasis, and the number of studies in this field has increased.

Exercise is a non-pharmacological method used by itself or along with food-intake limitation in obesity treatment and body weight control [68,26].During exercise, a negative energy balance occurs depending on the intensity and duration of the exercise, and this negative energy balance affects appetite and food-intake at a great extent [83].The most important hormones that can explain the effect of exercise on appetite and food

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intake are, ghrelin, leptin, and obestatin. Therefore, understanding the effects of exercise and food-intake limitation on appetite, food-intake and on these hormones is very important in terms of obesity aetiology, and its potential treatment. Concordantly, the purpose of the present review is to reveal the effects of exercise on ghrelin, leptin, and obestatin hormones in the light of current information.

Ghrelin, Leptin, Obestatin and ObesityRelationships:

Ghrelin and Obesity:

Ghrelin, is a 28-aminoacid hormone which strongly affects the release of growth hormone endogenously, and plays role in the regulation of energy balance and food intake [3]. It is released primarily by ghrelin cells,like X/A cells that exist in the oxyntic glands of the stomach to blood circulation but it is also released from many other parts of the body in smaller amounts [30]. Ghrelin exists in circulation in two forms: acyl, and des-acyl. Acyl ghrelin is thought to be more effective on appetite. Ghrelin shows its effects by stimulating arcuatenucleusneurons that co-express the Neuropeptide-Y (NPY) and Agulated Related Peptid (AgRP) orexigenic peptides [57].

Ghrelin was first discovered as anendogenousligant for receptor that causes growth hormone release (BHS-R), and later studies have revealed that it strongly stimulates the food intake and body weight [46]. Because of these effects, later studies have focused on the effects of ghrelin on energyhomeostasis.

In the experiments conducted on animal and human subjects, centrally or peripherally injection of ghrelin, continuously or with repetitive periods caused increase in weight, by causing increase in food intake, and decrease in energy expenditure [70,4,110]. Blocking of endogenous ghrelin stimulation via various methods caused decrease in food-intake, and gaining weight [94,69,7,5].Ghrelin's effects in increasingthe body weight is not accomplished, by only via increasing appetite. Besides this, it also contributes to increase in body weight by decreasing energy expenditure and use of fats and increasing the use ofcarbohydrates [109].

Many studies have been conducted recently on the regulation of bioactivities oforexigenic factors such as ghrelin, in order to use in the treatment of obesity. Bistable RNA-based compounds that arecreated in vitro and can be related to acyl-ghrelin successfully inhibited the ghrelin mediated GHSR (growth hormone secretagogue receptor) activation on animal subjects [93]. In addition, ghrelin immunoconjugat injection decreased nutrition efficiency and body weight gaining, and also decreased the percentage of body fat among rats [119].

Ghrelin is associated with obesity in two ways: first; its short-term effects on hunger and to stimulate eating (causing more food intake), and second; its long-term effect on the control of energy balance. From these perspectives, using of ghrelin physiology to stimulate long-term and continuous weight loss is a necessity. Sherman *et al*., tested the effect of synthetic oligonucleotide (spiegelmer) that neutralizes the effect of ghrelin by binding to it, on obese rats fattened via diet. Research findings revealed that, fat and body weight, food intake and fat storage decreased on oligonucleotide injected rats compared to the control group.Another research found that GHSR antagonists decreased nutrition among lean and obese rats fattened via diet [4]. Peripherally providing of these antagonists decreases gastric discharge speed, and so protracts the sense of satiety, and this way decreases food intake. Clinical application of these methods doesn't seem likely in a short time. However, it was proved that appetite/energy balance regulation could be controlled with ghrelin in weight loss stimulation; which is pretty promising.

Another possible application field of kinetic effects of ghrelin in based on the finding that gastric discharge is faster among clinical obese patients than normal individuals [38,104].The reason for gastric discharge being faster among obese is that post-prandial ghrelin levels decrease less than normal individuals.This situation among obese contributes to the increase in food intake. Ghrelin antagonists may be used to delay gastric discharge among obese. This way, individuals will feel satiety for longer and so will consume less food.

Ghrelin reducers to be produced in the future won't have a major effect on the loss of body-weight as the basic ghrelin level is already low among obese individuals. However, ghrelin increase caused by the adaptive physiological mechanism to re-gain the lost weight, can be prevented with ghrelin blocker agents, and so the maintenance of the lost weight will be easier [22]. In addition, studies conducted on animal subjects have revealed that, after body weight loss, not only the ghrelin level in the circulation, but also the ghrelin receptor expression in the hypothalamus increase [101]. Besides, orexigenic activity sensitivity of ghrelin also increases [81]. All these findings suggest that anti-ghrelinpharmacotherapeutics may help maintaining body weight.

Obestatin and Obesity:

In addition to ghrelin, another different peptide is coded from the same gene, called obestatin. This peptide was defined by Zhang *et al*., in 2005, and it is a 23 amino acid hormone produced by the same gene with ghrelin.After this hormone was defined, many studies have been carried on its distribution, biological activity, energy balance, growth hormone release, and its effects on increase of body weight on rats [54,74,24]. Acute intraperitoneal and intracerebroventricular obestatin addition suppresses food intake, and daily obestatin addition supresses body weight increase and induces the delay of gastric emptying rate [118]. These findings

suggest that ghrelin and obestatin have opposite effects on food intake and body weight regulation. Discovery of obestatin provides new exciting prospectuses for the management of obesity.

If the relation between these two hormones is simple and close as seen in the beginning, duplex drugs that can activate the decrease of body weight will be produced eventually [36]. Ghrelin antagonists (to decrease food intake and fat storage) and obestatin agonists (for its anorexigenic and decreasing body weight effects) can be used together. Drugs with these features will have strong anti-orexigenic effects.

It was observed that obestatin had effects on gastrointestinal discharge, glucosehomeostasis, cell proliferation, hormone release, sense of thirst, sleep, memory, anxiety, water intake, body weight and energy expenditure [74,55,36]. In addition, plasma obestatin concentration is regulated by hunger and re-alimentation, high-carbohydrate food, weight loss, and obesity [35,90]. Obestatin, and ghrelin are produced by the same gene.However, obestatin suppresses food intake, inhibits jejunal contractions and antagonizes the effects of ghrelin when both peptides are given at the same time [106].For this reason, it is claimed that ghrelin-obestatin balance should be adjusted very carefully in the regulation of energy homeostasis and body weight control. Despite the findings of this research, discussions on obestatin are still ongoing.

Obestatin and leptin concentrations were found to be higher among obese children than normal children, while their ghrelin concentrationswere significantly lower.[38] High obestatin levels and low ghrelin concentration among obese children are probably an adaptation reaction to increase in body weight.Because, ghrelin stimulates weight gain, while obestatin antagonizes of this effect of ghrelin.The effects of weight loss on obestatin and ghrelin are opposite among obese adults and children.Reinehr *et al*., 2008) reported that ghrelin concentration didn't change, but obestatin levels increased after weight loss among children who participated in a 1-year weight reduction program including diet and exercise.

Leptin and Obesity:

A complex physiological system including afferent stimulants and efferent effectors is effective in energy expenditure balance. After its discovery by Zheng and his team, many studies have been conducted on leptin which is a 167 amino acid hormonal protein produced by obesity gene, and it is mainly released by adipose tissues, and provides brain with information about fat storages [117]. Besides, leptin inhibits nutrition via hypothalamic receptors and decreases body weight by increasing thermogenesis. Serum leptin concentration is related with the size of adipose tissues, and it decreases after weight loss, and increases after weight gain [77,39].

Leptin is primarily released by adipose tissues, but it was shown that, it was also secreted by gastric fundus, skeletal muscles, liver, placenta, heart, human ovaries, humanmammary glands, and gastric epithelium [34,20,12,95].

Deficiency or resistance of leptin hormone that plays an important role in the regulation of nutrition and energy balance results in obesity, diabetes, and infertility among humans. The basic effects of leptin in many systems such as anti-obesity, reproductive, hematopoiesis, angiogenesis, blood pressure, growth, bone volume, lymphoid organ homoeostasis, and T lymphocyte systems have been extensively showed [105].

Theoretically, leptin hormone that decreases appetite and increases energy expenditure is expected to be less among obese individuals. However, researches on the subject matter don't confirm this. Leptin levels are significantly higher among obese individuals than the normal individuals. This is believed to be caused by an insensitivity developed against leptin in hypothalamic receptors among obese individuals [91]. A positive correlation between leptin levels and body-mass index (BMI) was observed among obese female and male individuals. However, no such correlation exists among normal weight individuals [63].

Obesity among humans is not only caused by leptin deficiency. Another reason for the ineffectuality of leptin among obese is the resistance to it. What is important in resistance syndrome is effector levels. Higher level of leptin is required in order to overcome leptin resistance, and so, more leptin is released from fatty tissues, and more leptin release causes increase in the fatty tissues that produce it. The typical reason of leptin resistance syndrome is the dysfunction of leptin receptors or post-receptors. In order to be effective, leptin needs to pass the blood-brain barriers (BBB) and as this transport is dependent on the saturated carriers, and any carrier dysfunction may cause leptin resistance. Any dysfunction in transportmechanism to the BBB also play a role in resistance to leptin in circulation or peripherials, but doesn't change the effect of leptin in central nervous system (CNS).

Data obtained up to now show that leptin resistance is caused by the carriers in BBB and/or impairment of receptor levels in CNS. Data obtained from human and animal subjects reveal that the basic reason for obesity is impairments in the transport of leptin in serum through BBB [9]. Leptin transport through BBBs was observed to have increased or totally disappeared among obese Zucker rats, obese Koletsky rats, LEW rats fattened via diet, and rats with maturation obesity[11].

In maturation obesity model, intravenous administrated leptin carried among obese rats (blood leptin 30 ng/ml), was only 1/3 of the leptin of among normal rats (blood leptin 10 ng/ml). As can be observed, despite serum leptin level was 3 times higher among obese rats, leptin transport was 3 times lower than normal rats.

This finding suggests that BBB transport disorder is almost 100% responsible for leptin resistance. Similarly, data obtained from human subjects showed that transport system disorders are much more important than dis-functioning of leptin receptors in CNS [10].

Ghrelin, Leptin and Obestatin Responses to Exercise:

The effects of exercise on food intake have been studied for a long time. However, with the discovery of new hormones, the number of these studies has increased by the idea that the effects of exercise on food intake can be explained with these hormones. This section discusses the relations between acute and chronic exercise with ghrelin, leptin, obestatin and food intake in the light of information provided by the current researches conducted recently.

Ghrelin and Exercise:

The Effect of Acute Exercise on Ghrelin:

Many studies on acute exercise start with the hypothesis that exercise decreases ghrelin concentration. The first reason for this is that blood distribution changes during exercise. During exercise, splanchnic circulation reduces and blood flow directs to active muscles. Because ghrelin is released primarily from stomach, and blood flow to stomach is reduced during exercise, it is assumed that ghrelin concentration is decreased with exercise. The second reason is that, growth hormone release increases during exercise, and this is supposed to decrease ghrelin release. However, many studies have found that exercise caused increase in growth hormone (GRH)but no changes were observed in ghrelin levels.

The Effect of Short Term Acute Exercise on Ghrelin:

The findings of the studies on the effect of acute short-term exercise on ghrelin are very contradictory. Most of the studies have showed that ghrelin levels don't changewithexercise, while there are some other studies that reported increaseor decrease in ghrelin levels [14,21].

Juramai *et al*., [40] who conducted a research on 9 elite oarsmen with a 30-min. exercise under and over anaerobic threshold, reported that they observed increase in GRH, but there were definitely no changes in total ghrelin concentration.Pomerant *et al*., stated in their research that medium-intensity 30 min. exercise didn't effect ghrelin in none of the pubertal periods, among boys of various pubertal development. Schmidit *et al*., stated that GRH increased and ghrelin levels didn't change, during various intensities of exercise on different days, after 40 min. exercise done on the 50% of maximal oxygen capacity (Max.VO_2), and after 20 min. of exercise done on the 70% and 90% of Max.VO_2. Similarly, 6 well-trained athletes did treadmill runs on 60% of Max.$VO_2$for 10 minutes, 75% for 10 minutes, and 90% for 5 minutes, and 100% of Max.$VO_2$for 2 minutes; and their GRH and Insulin like growth factor (IGF-1) concentrations increased, but their ghrelin hormone level didn't change [48]. Sartorio *et al*., [88] reported that growth hormone levels increased but ghrelin levels didn't change among males who did two 30-min. cycling exercises at 80% of Max.VO_2.These studies showed that total ghrelin doesn't affect GRH release during exercise.

Erdmann *et al*., [26] studied the effects of cycling exercise of various durations and intensities (1^{st}group: under anaerobic threshold 30, 60 and 120 minutes; 2^{nd} group: a little over anaerobic threshold 30 mins.), on a group (4 female, 10 male) on ghrelin; and they reported that only 30 minute exercise under anaerobic threshold (60 rpm., 50 Watt) increased ghrelin.Juramai *et al*., [40] reported that ghrelin is 24.4% higher than the basal level after 6000m (average: 19min, 52 sec) rowing exercise among 9 elite oarsmen.

There are also some studies that reported a decrease in ghrelin.Stokes *et al*., [96] who conducted a research on 7 males reported that they observed increase in GRH, but decrease in serum ghrelin after 30sec sprint exercise done at cycling ergometer.As far as it is known, the only research reporting decrease in ghrelin after exercise is this one conducted by Stokes *et al*.,

The Effect of Long Term Acute Exercise on Ghrelin:

Like short-term acute exercise, the effect of long-term acute exercise on ghrelin is contentious.Burns *et al*., who conducted a research on 18 healthy male and female participants reported that there were no significant differences between exercise and control groups in terms of total plasma ghrelin levels during and 2 hours after 1-hour treadmill exercise done at 73.5% of Max. VO_2.Martin *et al*., [66] examined the effects of 60min cycling exercise done at 65% of heart beat rate (Max.HBR) on ghrelin, sense of hunger, and food intake with 12 subjects. According to the findings of this research, medium intensity acute exercise decreased sense of hunger temporarily, and this temporary decrease provided short-term negative energy balance. However, this temporary effect on appetite couldn't be explained with change in ghrelin levels. Christ *et al*., [19] reported that ghrelin levels increased at a significant level after 3 hours long-term exercise done at 50% of Max.VO_2 in cycling ergometer. Sartorio *et al*., stated that 60-90 min continuous exercise done by female and male athletes at 80% of Max. VO_2 caused increase of growth hormone after exercise among both female and male athletes, but ghrelin

hormone increased only among male athletes. This finding suggests that ghrelin release during exercise is different between males and females.

The Effect of Resistant Exercise on Ghrelin:

There have been a number of researches that studied the ghrelin and GRH reaction during resistance exercises.

Saqhebjoo *et al*.,[86] reported that acylated ghrelin level was increased after single session of circuit resistance exercise with 80% 1RM in both fasting and high carbohydrate meal compared to the control group but the levels of insulin, cortisol, and growth hormones did not have any significant change. As a conclusion, they reported that it seems that the increased plasma acylated ghrelin during exercise is due to the decrease of muscle and liver energy stores which provides conditions for increased energy intake and positive energy balance.

Kramer *et al*.,52 who conducted a research on 9 males reported that eccentric and concentric exercises done on different days(10 RM %80, 12 reps, 4 sets, 90 secrest) increased glucose and insulin levels, but didn't change ghrelin levels. Takono *et al*., conducted another research on 11 untrained males and found that short-term and low intensity exercises increased GRH and IGF-1, but didn't effect ghrelin. Chanbari and Niaki reported that ghrelin level was decreased with GRH increase after acute circular resistance exercise (1-RM %60, 10 exercise, 3 sets), and 24 hours after the exercise, ghrelin increased when GRH turned back to normal levels.

The Effect of Long-Term Chronic Exercise on Ghrelin:

Exercise is an essential part of weight control and it is used along with food limitation.Studies conducted on obese and healthy individuals reported that ghrelin levels increase with weight loss after exercise and food limitation.

Yuki *et al*., conducted a research on 25 obese children (17 male, 8 female) with a 3-month weight-loss program including diet and exercise (aerobic and resistance exercises), and reported that body weight and body fat percentage decreased, GRH and IGF-I didn't change, and serum ghrelin increased after the program. Sontoso *et al*., conducted a 6-month weight-loss program on 35 hyperlipidemic women, and reported that body weight decreased and ghrelin increased at 21.2% after the program. Zahorska *et al*., [114] conducted a 3-month weight-loss program (diet+exercise) on obese women and reported a 8.7kg weight loss, decrease in body-mass index (BMI) and body fat percentage, and increase in ghrelin. Maestu *et al*., [62] reported significant decrease in body weight, BMI, and body fat percentage among 14 body builders (7 competition, 7 control) who increased training volume and decreased food intake in order to decrease body fat percentage 13 weeks before participating in the national championship. In addition, they reported increases in plasma ghrelin 5 weeks (20.4%), and 3 days (6%) before the competition. Additionally, body weight, body fat percentage, and sense of satiety decreased, and serum total ghrelin level increased among non-obese sedentary women after a 3-month diet and exercise program. These findings show that ghrelin is a metabolic stimulant that plays a key role in the system that shows that there is an energy deficit, and it is effective in meeting the possible energy deficit in this system. Contrary to the above findings, Benso *et al*., reported a significant decrease in body weight, but no change in leptin and ghrelin among 9 elite mountaineers after a 7-week climb on Mount Everest. Nonetheless, after high altitude climbing, GRH, and IGF-1, and Insulin like growth factor binding protein (IGFBP-3) increased.

In most of recent studies on adults and children have shown that weight loss increases the ghrelin amount in circulation.Despite the mechanism,whether weight loss increases ghrelin amount in circulation is not known thoroughly, it is assumed that positive energy balance is stimulated due to 3 mechanisms. First; fat use decreases independent from GRH, and carbohydrate use increases. Second; is the anabolic effect caused by the increase in GRH and IGF-1 production. And third is the stimulation of long-term food intake via possibly neuropeptide-Y (NPY) . Nitsche *et al*., reported that BMI decreased after 10-day calorie limitation and exercise among obese children and adolescents, ghrelin increased with respiratory quotient (RQ); and these two are interrelated. This shows that ghrelin is a sensitive indicator of change in substrate oxidation. As RQ levels increase, fats use decreases, and carbohydrate use increases. In other words, as body weight decreases, ghrelin levels increase, and carbohydrate use increases in order to preserve fat storages. In addition, ghrelin activates NPY/AgRP neurones in arcuatenucleus, and stimulates food intake. Ghrelin increase among obese individuals after weight loss is possibly caused by a physiological protection mechanism activating in order to gain the lost weight (with negative energy balance) back with positive energy balance.

The Effect of Exercise on Acyl and Des-acyl Ghrelin:

Intense exercises suppress appetite, but it was found that this suppression is not related to the suppression of total ghrelin concentration. Many researches on ghrelin examined only total ghrelin as there were only total ghrelin kits on the market then. The measurements of acyl ghrelin (AC) that is named as active ghrelin because it can connect to GHSR-1 biologically, and des-acyl ghrelin (DG) named as inactive because it cannot connect to GHSR-1, the effect of exercise on different forms of ghrelin have been being studied only recently.

Therefore, most of the researches conducted on exercise have examined how exercise affected total ghrelin. There have been only a few studies that examined the effects of exercise on acyl and des-acyl ghrelin [45,67,8,98,66]. Acylation of ghrelin is necessary for appetite regulation.Acylated ghrelin (AG) and appetite increased after 1-hour aerobic exercise on 5 sequential days among total ghrelin didn't change among normal weight and obese adolescents [61].On the contrary, Broom *et al*., who conducted a research on 9 healthy males between the ages of 19-25 found that 60 min. exercise at 72% of Max.VO_2suppressed AG and hunger.Similarly, Tiryaki-Sonmez *et al*., [98] reported that 60 min. exercise at 50% of Max.VO2 suppressed acylated ghrelin but didn't change des-acylated ghrelin. The difference between these findings suggest that exercise have different effects on ghrelin among adults and adolescents.

AG is thought to be effective in regulation of food intake and appetite because of its connectivity to GHSR-1. However, current studies show that reverse AG(DG) may also activate unidentified receptors, and stimulate different physiological and metabolic effects [72].A previous research reported that DG stimulated negative energy balance by decreasing food intake and delaying gastric discharge [4].Kim *et al*., [45] reported that body weight, BMI, and body fat percentage decreased while total ghrelin increased at 30.4%, and DG at a 31.9%, and besides AG didn't change among obese children after a 12-week resistance and aerobic exercise program.There is a strong correlation between the decrease in body weight and body fat and increase in plasma DG among obese children after exercise.Consequently, acyl and des-acyl ghrelin levels should be measured separately for a better understanding of different roles of different forms of ghrelin.

In conclusion,findings of many studies on ghrelin levels during exercise conducted on human subjects contradict with each other. Many studies reported that short or long-term acute exercise didn't affect ghrelin levels in circulation, but ghrelin increased after weight loss after long-term chronic exercises. These differences may be resulted from the differences in intensity, duration, and type of the exercise, or the features of subjects or study design. More comprehensive and controlled studies to be conducted in this field may illuminate the roles of ghrelin and ghrelin forms.

Exercise and Obestatin:

There is no correlation between obestatin and ghrelin, despite they are the products of the same gene. The effect of exercise on obestatin has become a matter of interest, and the number ofstudies on the subject matterhasincreased recently. The findings of the limited number of published studies are pretty contradictory. Tiryaki-Sonmez *et al*., who conducted a research on nine overweight women found that 60 min. exercise at 50% of Max.VO_2 didn't change obestatin level. Similarly, Wang *et al*., reported that acute and chronic treadmill exercises didn't change obestatin.Unlike these, Reinehr *et al*., reported that plasma obestatin concentration increased after diet and exercise programs conducted for weight-loss among obese children.The possible reason for these contradictory results is the differences in research methodology. The features of these subjects are totally different, and in order to explain the effect of exercise on plasma obestatin, more studies on each of these groups with different exercise intensities are required.

Exercise and Leptin:

Leptin is known as anti-obesity hormoneas it is thought to suppress food intake and cause negative energy balance and how it would be affected by exercise has been a matter of interest and therefore many acute and chronic exercise studies have been conducted on patients and healthy individuals in order to reveal the possible correlation between leptin and exercise.

Acute Effect of Exercise on Leptin Concentration:

The effect of physical exercise on leptin concentration is a debated issue. Many researchers reported that leptin concentration decreased depending on the duration and calorie burn of the exercise, while some other reported that leptin concentration was not affected at all.

Zoladz *et al*., [118] who conducted a research on 8 healthy males, examined leptin after maximal incremental exercise on a full stomach, and submaximal incremental exercise on an empty stomach. Growth hormone and norepinephrine concentration increased after exercise, but leptin concentration didn't change after both exercises.Weltman *et al*., [108] reported that leptin hormone didn't change during and in recovery (3.5 hours) after 30 min exercises with different calorie burn and intensities (150±11 with 529±45 kcal) among 7 healthy young males.Bouassida *et al*., reported that plasma leptin concentration didn't decrease during 45-second supramaximal exercise done at 120% of peak aerobic strength among physically active 12 females and 5 males.

Torjman *et al*., [99] examined the effect of 60 min. treadmill exercises done at 50% of Max.VO_2 on 6 healthy sedentary males, and reported that insulin and free fatty acid levels decreased during 4-hour recovery, but leptin concentration didn't change.Landt *et al*.,[56] reported an insignificant decrease of 8% in leptin concentration after a 2-hour cycling exercise done by 12 males.

Contrary to the above studies, there are some researches that reported decrease in leptin concentration.Ozen *et al*.,[78] reported that serum leptin concentration decreased at 17% after treadmill exercise done at 50% of Max.VO2, by 7 healthy male.Bouassida *et al*., [15] found that leptin concentration decreased 30, 60, 90 minutes after 20-minute high intensity cycling exercise (80% of peak aerobic strength) among middle-aged male. The same research found that leptin concentration didn't change after low intensity (60% of peak aerobic strength) cycling exercise.Essig *et al*., [27] reported that leptin concentration decreased among trained males after 800 and 1500 kcal treadmill exercises.Elias *et al*., [25] stated that leptin decreased among 18-55 years old males after incremental treadmill tests conducted until exhaustion.These researchers specifically stressed out that decrease in leptin concentration after 48 hours occurred before the decrease in insulin hormone concentration.Olive and Miller [76] measured leptin concentrations of 9 trained male athletes, immediately, 24 and 48 hours after 60 min. (energy expenditure: 882.7±14.4 kcal) submaximal (70% of Max.VO2) and maximal exercise (energy expenditure:197.5±11.8 kcal), and reported that only exercise done at 70% of Max.VO2 decreased leptin concentration at a significant level. The findings of this research suggest that the reaction of leptin to exercise is independent from insulin, and glucose concentration.Kraemer *et al*., stated that 30min. exercise done at 80% of Max. VO_2 is correlated with the decrease in leptin concentration. However, it was understood from the control samples collected from the same subjects that this decrease in leptin was related with circadian rhythm. In this research, leptin concentration was not affected from exercise, but cortisol and growth hormone concentrations increased as a reaction to exercise.

The effect of long and tiring exercises such as marathons on leptin concentration has also attracted the interest of researchers.Leal-Cerro*et al*., [59] studied the possible changes incircadian rhythm of leptin after 42 kilometre marathon run, and reported a slight decrease in leptin after the marathon run. They discussed that the possible reason for the decrease in leptin was related to the use of great energy expenditure during the marathon.Karamouzis *et al*., [43] reported that 12 km exercise increased plasmatic Neuropeptide-Y (NPY) at 81%, and this decreased leptin in relation to energy imbalance.Zaccaria *et al*.,[112] examined the effect of 3 endurance-based sports (half marathon: energy expenditure, 1400 kcal; alpine skiing: energy expenditure, 5000 kcal.ultra marathon, energy expenditure, 7000kcal) on serum leptin levels among 45 male athletes who participated one of these; and reported that serum leptin level decreased at a significant level only after competitions requiring great energy expenditure such as alpine skiing and ultra-marathon.

Very long-term exercises creating adequate energy imbalance can suppress the diurnal rhythm amplitude of leptin.The decrease after extreme exercises such as marathon and ultra marathon can be explained with the suppression of leptin for the re-regulation of impaired nutrition balance (energy deficiency). The most important point in these findings is the close correlation between leptin and energy expenditure.

Consequently, many researches reported that leptin concentration didn't change especially after short-term (<60 min.) and low energy expenditure (<800 kcal.).Eventhough, there are some researches that reported decrease in leptin concentration after exercise, these changes may be related to circadian rhythm and/or diurnal decrease, and hormonal changes due to exercise.

Chronic Effect of Exercise on Leptin Concentration:

Many previous researches examined the effect of exercise on leptin, and reported that short-term trainings (<12 weeks) didn't affect leptin concentration, while long-term training (>12 weeks) decreased or increased leptin level.

Abrenhard *et al*., [1] examined the effect of of 12-month reduced calorie, weight loss and exercise interventions on leptin concentrations among 439 overweight/obese postmenopausal women who participated one of these; and reported that leptin concentrations decreased in all of the intervention groups, but the greatest reduction occurred with diet + exercise. Weight loss and exercise exerted some beneficial effects on chronic diseases via effects on leptin level. Houmard *et al*., [37] reported that leptin concentration didn't change despite the increase in insulin levels among healthy young and old individuals after 60min exercise done at 75% of Max.VO_2 for 7 days.Kraemer *et al*., [43] examined the leptin concentration during recovery and post-maximal exercise in competition season among adolescent female athletes.Leptin levels didn't give any acute reaction to recovery or exercise despite a significant decrease insubcutaneous fat thickness during 7-week competition period.Kraemer *et al*., 44 reported that 9-week exercise program (2days/week 20-30 min step-aerobic, treadmill run, and cycling exercise; 3-4 days a week) increased Max.VO_2 capacity among middle aged obese women, but didn't change fat mass and leptin levels.Kosydar *et al*., [47] reported that 6-week exercise program (3 days a week, at 60-80% of maximal heart beat rate) increased physical capacity but didn't change leptin concentration among coronary artery patient males (age average:55).The same researchers observed increase in leptin concentration among coronary artery patients who didn't do exercise.

Contrary to the above researches, there some studies which reported that leptin is affected by chronic exercise.Lakhdar *et al* [55] reported that six months heavy cycling training decreased leptin concentration (-44.91%).

Gomez-Marino *et al*., [33] reported that 3-week military training decreased leptinemia. This decrease was thought to be resulted from increase in catecholamines and hyperinsulinemia induced by exercise. Unal *et al*., [102] measured leptin concentration among trained young athletes of various sports and sedentary males, and reported that leptin decreased at a significant level after exercise; and decreased fat percentage due to regular exercise suppresses serum leptin level.Papini *et al* reported that 1 year community-based exercise program increased leptin levels.Unal *et al*., [103] conducted another research on professional athletes and sedentary individuals and reported that serum leptin was significantly lower among athletes than sedentary participants, and body fat is the major indicator of leptin level in serum.Martins *et al*., reported that 12-wk supervised exercise program in 22 sedentary overweight/obese individuals decreased fasting and postprandial leptin concentrations.

As can be seen in above studies, when body fat percentage decreases with regular exercises, serum leptin level also decreased. Okazaki *et al*., [75] found that 12-week aerobic exercise and individual diet program decreased the proportion of leptin concentration to fat mass and BMI among middle age obese and sedentary non-obese women. In addition, this study suggested that decrease in leptin concentration was related with the decrease in body weight.

Acute and Chronic Effect of Resistance Exercise on Leptin Concentration:

Information on the reaction of leptin to short-term resistance exercises is very limited.Unlike medium level long-term run, heavy resistance exercises create different neuronal, metabolic, and endocrine reactions [29].The findings of the limited number of studies on subject matter are quite contradictory.Kanaley *et al*., [42] reported that leptin concentration decreased 24 hours after resistance exercise in diabetic and healthy individuals, while Nindl *et al*.,[71] stated that decrease in leptin occurred 9-13 hours after exercise.A current study examined leptin concentration on a group of trained male participants with low fat percentage and high muscle mass. According to the findings of this research, there is a correlation between BMI and leptin among obese individuals, while this correlation cannot be observed among athletes and control group [32].Nindl*et al*., found that, leptin concentration was lower after 50 set resistance exercise (energy expenditure:855.42±114.38 kcal) than control measures done after 9, 12, and 13 hours later. The decrease in leptin concentration found in this research was not related with decrease in fat mass, and the possible reason for it was thathigh intensity exercise impaired metabolic balance and caused increase in oxygen intake after exercise.Zafeiridis *et al*., (2003) found that GRH and glucose hormone concentration increased and serum leptin levels decreased at a significant level 30 minutes after maximal strength, muscle hypertrophy, and resistance exercise protocols.

Researchers also studied the effect of long-term resistance exercise on leptin.Fatouros *et al*., [28] found that 6-month (3days/week, 10 exercises/3 sets) resistance exercises decreased leptin concentration among 50 inactive male participants. The researchers also stressed that, decrease in leptin concentration occurred along with decrease in BMI and skinfold totals.Ryan *et al*., (2000) examined plasma leptin and insulin changes among obese, postmenopausal women who lost and didn't loose weight after a 16-week resistance exercise program. It was reported in this research that, leptin concentration decreased at 36% in the group, which lost weight. This change in leptin levels is not related to the changes in recovery metabolic rate and/or plasmacatecholamine.Gippini *et al*., [32] found that resistance exercises didn't affect leptin concentration independently from body compositions in body builders and sedentary individuals.

Consequently, the effect of exercise and recovery after exercise on leptin levels couldn't be set out in full. The studies, which found decrease in leptin concentration related this decrease to many possible reasons. It is known that with physical exercise, energy balance changes, fat mass decreases, and hormonal concentrations (catecholamines, insulin, growth hormone, cortisol, testosterone etc.), and metabolites (free fatty acids, lactic acid, triglyceride etc.) change. All these changes can change the reaction of leptin during exercise. Contradictions between the findings of the studiess which examined the reaction of leptin to exercise, may be resulting from many methodological differences such as; the intensity, duration, frequency, and extent of the exercise, nutritional states of the participants, circadian rhythm of leptin, the time and frequency of taking samples. Further studies with more controls are required to understand the effects resistanceexercises on leptin response.

Conclusion:

In conclusion, findings of the current studies on acute and chronic exercise conducted on human subjects that examined the effect of exercise on ghrelin, leptin and obestatin contradict with each other. Some of these differences may have resulted from differences between intensity, duration, and type of the exercise, or the features of the subjects, different research designs such as time of food intake. For this reason, many more studies using various subject groups (active, inactive, obese, non-obese etc.), different methods (duration, intensity, and context of exercise, time of takin blood samples etc.) are required in the subject field.Studies conducted up to now provide these findings; 1) low and medium intensity short-term exercises don't affect hunger, food intake, and ghrelin, while high intensity exercises decrease hunger and food intake, and this

decrease is related especially with acyl ghrelin, 2) chronic exercises along with food intake control contribute to weight-control and weight-loss.

However, weight-loss after weight-loss programs increases sense of hunger and ghrelin via a regulation mechanism and results in the re-gaining of the lost weight. In light of this information, individuals shouldn't stop exercise right after long-term exercise programs, continue exercise programs with a re-arrangement of intensity, duration and extents in order to maintain loss weight, and do exercise regularly as a life style.

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