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Original article

# Effects of exercise on ghrelin

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**Abstract**. Ghrelin, a gastric derived acylated peptide, was discovered in 1999 as a mediator of growth hormone secretiation. Since then, ghrelin has been found to significant impacts on many physiological functions of body systems. Ghrelin has a potential on appetite stimulation that influence on regulation of energy metabolism. It is known that exercise has a marked impact on energy homeostasis and consequently many research focused on the interaction between exercise stimulus and ghrelin response. This review provides an overwiew of research relating to the acute and chronic effects of exercise on (total, acyl and desacyl) ghrelin levels and also impact of exercise intensity on ghrelin levels. Although there is uncertainty among the results of previous studies, our review suggests that acute exercise transiently enterferes with the acly and total ghrelin levels. However, chronic exercise may acause increase in ghrelin levels in contrast to acute exercise with related to change of body weight. In adition, inenstiy of exercise may also reveales various results concerning the relationship between exercise and circulation ghreline levels. The discovery of ghrelin has raised our knowledge of food intake regulation, energy homeostasis and metabolic function mechanism. Further studies should be focused betwen the impact of exercise (type, duration and intensity) on circulation ghreline levels. Exercise induced ghrelin levels will likely generate new pharmacological approaches to many metabolic diseases based on inbalance in body energy homeostasis.

**Keywords:** Ghrelin, exercise, total ghrelin, acyl ghrelin, desacyl ghrelin

## Introduction

Ghrelin was discovered in 1999 by Kojima and it consists of 28 amino acids. This peptide is an endogenous ligand linked to growth hormone secretagogue receptor (GHS-R). Ghrelin, discovered as a gastrointestinal hormone capable of stimulating growth hormone (GH) release, was also reported to play a role in regulating energy homeostasis by establishing an endocrine link between the stomach, hypothalamus and pituitary. Ghrelin is an orexigenic peptide, and unlike other gastrointestinal hormones, it actively stimulates eating, triggering increased body weight and fat. Ghrelin achieves its effect on weight gain not only by increasing appetite but also by determining the type of metabolic substrate used. This hormone was reported to reduce energy consumption and use of fats, and increase the use of carbohydrates. The effects of large amount of central and peripheral ghrelins were identified such as stimulation of intestinal motility and secretion of gastric acid, taste sensation and reward seeking behavior, regulation of glucose metabolism, suppression of brown fat thermogenesis, protection against muscle atrophy, modulation of sleep, stress and anxiety. In the light of all this new information, ghrelin has a strong effect on homeostasis and is known to create a positive energy balance, so the response of ghrelin to exercise interventions that create negative energy balance is a matter of curiosity. In this review, the responses of ghrelin to different exercise intensities will be evaluated.

## History of Ghrelin

Ghrelin research has been continuing for more than fourty years. In a study published in 1976, it was discovered as a synthetic peptide analogue with methenephaline opiate and was named 'Growth Hormone Secretory (GHS)' because it causes GH release (1). In 1996, GHS-R1a, a GHS-protein-bound receptor (GPCR), was identified as the receptor for GHS in the pituitary and hypothalamus (2). In 1999, a new peptide was discovered by Kojima due to the GHS-R1a endogenous ligand. Ghrelin consists of 28 amino acids (3) and its molecular weight is 3314 Daltons (4).

## Biochemical Structure and Secretion of Ghrelin

The ghrelin system consists of three main components: ghrelin, ghrelin-O-acyltransferase (GOAT) and GHSR (Growth Hormone Secratogog Receptor) (5). It was discovered that the first region where ghrelin is produced in the body is the oxyntic glands located in the fundus region of the stomach and where X / A-like cells originate from plasma ghrelin (6). About 65% of circulating ghrelin is produced in the stomach. The stomach is the field with highest production and other fields include the duodenum, jejunum and lung (7). Ghrelin production decreases from the duodenum to the colon (6). In addition, many tissues such as Sertoli cells (8), pancreas (9), intestine, hypothalamus (10), kidney (especially glomerulus) (11), placenta (12), and interstitial Leydig cells have mRNA for ghrelin. In the hypothalamus, ghrelin is released from a number of neurons between the lateral, arcuate, ventromedial, dorsomedial, and paraventricular hypothalamic nuclei (13). GHS-Rs were found to be present in 94% of Neuropeptide Y / Aguti Related Peptide (NPY / AgRP) neurons and 8% of POMC (Proopiomelanocortin) neurons (14). Ghrelin is available in two forms in circulation: acyl ghrelin (AG) and des-acyl ghrelin (DG) (15). Ghrelin is first synthesized by prohormone convertase 1/3 as a prohormone in Golgi, trans-Golgi network or secretory granules (3). The ghrelin precursor (preproghrelin) consists of 117 amino acids and is exposed to acylation in the cytoplasm before it is released. Ghrelin is acylated by adding n-octanoyl to the serine in the third position of ghrelin (3. This unique post-translational modification is catalyzed by the GOAT enzyme in the endoplasmic reticulum of ghrelin cells and the peptide occurs before treatment with prohormone convertase 1/3, is stored and secreted (16). This acylation is necessary so that the ghrelin can bind to GHS-R and show its effect on food intake. The half-life of ghrelin is about 30 minutes (17) because it is destroyed by plasma esterase and converted into desacyl ghrelin (7). The third component, GHS-R, was described by Howard et al. (2). GHS-R mRNA has two forms, type 1a and 1b (18). Both receptors are intensely located in the brain and peripheral organs. It is known that ghrelin exerts its effect on GHS-R1a (3). It is regarded as inactive as des-acyl ghrelin cannot connect to GHS- R1a. However, recent studies revealed that desacyl ghrelin mediates its biological functions independently of GHSR (19).

## Ghrelin's Mechanism of Action

One of the important regions in ensuring energy balance is the hypothalamus. In the arcuate nucleus (ARC) located in the hypothalamus, there are 2 different cell groups, namely orexigenic and anorexigenic. The orexigenic region of neurons secretes agouti-related peptide (AgRP) and neuropeptide Y (NPY), while the anorexigenic region consists of neurons secreting cocaine and amphetamine regulated transcript (CART) and proopiomelanocortin (POMC). Although ARC has a significant influence on the control of food intake of ghrelin, the application of ghrelin to other hypothalamic regions, including the paraventricular nucleus (PVH) and the lateral hypothalamus also promotes a positive energy balance (20). It is considered to show its effects in 3 ways:

1. Ghrelin is synthesized in the stomach, released into the bloodstream and crosses the blood-brain barrier, then reaches the hypothalamus, arcuate nucleus and other parts of the brain.
2. Peripherally synthesized ghrelin stimulates the vagal afferent nerve endings and reaches the hypothalamus through the vagal-connected nucleus solitarius (21).

3. Ghrelin locally synthesized in the hypothalamus directly stimulates NPY / AGRP and other cells in the arcuate nucleus (22).

## Physiological Effects of Ghrelin

Ghrelin is an oxygenic peptide and, unlike other gastrointestinal hormones, acutely stimulates eating, triggering increased body weight and fat (23). Ghrelin provides its effect on weight gain not only by increasing appetite but also by determining the type of metabolic substrate used. It was reported to decrease energy expenditure and the use of fats, while increasing the use of carbohydrates (24). However, besides this, the effects of a large number of central and peripheral ghrelin were described, such as (20, 25) stimulation of intestinal motility and secretion of gastric acid, taste sensation and reward seeking behavior, regulation of glucose metabolism, suppression of brown fat thermogenesis, protection against muscle atrophy, modulation and sleep modulation of stress and anxiety, and modulation of stress and anxiety.

## Effects of Ghrelin on Appetite

In a study, it was discovered that ghrelin acts to regulate food intake, body weight, fatty and glucose metabolism in the brain (26). In humans, a preprandial increase and postprandial decrease occur in plasma ghrelin levels, indicating that the peptide plays a physiological role at the start of the meal and plays a role in determining the amount and quality of the food ingested (27). It also provides stimulation of intestinal motility and secretion of gastric acid (28). In addition to its potential paracrine effects, ghrelin was found to play a role in energy homeostasis by presenting an endocrine connection between the stomach, hypothalamus and pituitary (26, 29). Ghrelin determines a reduction in energy consumption and then promotes the storage of fatty acids in adipocytes (27). Thus, ghrelin causes a positive energy balance in the human body, increased fat gain, as well as an increase in calorie storage, which is seen as an adaptable mechanism for calorie restriction (27).

## Effect of Ghrelin on Glucose Metabolism

Although the highest expression of ghrelin occurs in the stomach, ghrelin-producing cells are also found in pancreatic islets, where it may play a developmental role as well as alter insulin and glucagon secretion (7). It was shown that glucose and insulin play important roles in the suppression of postprandial ghrelin (30). Ghrelin levels are negatively correlated with body mass index (BMI) and insulin resistance (31, 32). In addition, acyl ghrelin (AG) was shown to inhibit glucose-induced insulin secretion (GSIS) in cell lines and animal models (30, 33). In the literature, it was reported that the administration of AG suppresses insulin secretion, induces peripheral insulin resistance and impairs glucose tolerance in humans (34, 35). As a result, ghrelin causes hyperglycemia and reduces gluconeogenesis and glycogen production by suppressing insulin.

## Ghrelin's Effect on the Cardiovascular System

There is also a strong relationship between ghrelin and the cardiovascular system. Ghrelin receptors are found throughout the heart and veins and are linked to many molecular pathways, including regulation of intracellular calcium concentration, inhibition of proapoptotic triggers, and protection against oxidative damage. Ghrelin has cardioprotective effects, including increasing endothelial and vascular function, preventing atherosclerosis, and lowering blood pressure (36). After myocardial infarction, exogenous ghrelin administration preserves heart function, reduces the incidence of fatal arrhythmias, alleviates apoptosis and ventricular remodeling, resulting in improvements in heart failure. It improves cachexia in patients with end-stage congestive heart failure and displayed clinical benefits for pulmonary hypertension (37).

## Ghrelin's Anti-Inflammatory Effect

Ghrelin exerts an anti-inflammatory effect by directly suppressing the production of pro-inflammatory cytokines in monocytes and T cells (38). Ghrelin increases

autophagy, strengthens stem cell function, relieves inflammation and fibrosis, decreases ROS production, and improves mitochondrial and endoplasmic reticulum functions, thereby preserving cellular homeostasis (39).

**Ghrelin's Effect on Hormones**

One of the first effects learned about ghrelin is its relationship with Growth Hormone (GH). Ghrelin stimulates GH release in two different ways:

1. Growth hormone-releasing hormone (GHRH) enters the pituitary through the growth hormone-releasing hormone receptor (GHRH-R) and increases GH release by increasing the intracellular camp level.
2. Growth hormone secretagogue (GHS) or GH penetrate into the pituitary via the growth hormone-releasing receptor (GHS-R) located in the pituitary membrane and as a result of phospholipase C activation, it increases GH release by increasing intracellular Ca2 + ion concentration (40).

In addition, ghrelin level significantly affects neuro-endocrinological parameters. While ghrelin increases the release of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and corticosteroids; increasing CRH decreases ghrelin release (41). In addition, it does not alter luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH) levels, but increases prolactin (PRL) levels (42). In addition, ghrelin, which regulates energy homeostasis, suppresses insulin (5). Ghrelin and GH regulate insulin-like growth factor-1 (IGF-1) synthesis, and this GH / IGF-1 axis is an endocrine axis involved in energy and sleep homeostasis and plays an important role in somatic and brain growth (43).

**3.10.GHRELINE AND EXERCISE**

Exercise has been used as an affective tool to provide affective stimuli on energy metabolic system functions and enhange levels of energy regulatory hormones (44). Ghrelin has unique functions in achieving energy homeostasis, including its ability to report current peripheral nutritional status and to compensate for energy (20). The hypothalamus, which provides energy homeostasis, combines neuronal, hormonal and nutrient energy state signals by regulating energy intake and energy consumption. Disruption of the signaling in the hypothalamus causes irregular food intake and weight gain (45). Exercise is recommended as a therapeutic weight management strategy. Exercise increases energy expenditure and contributes to negative energy balance with an increase in energy intake (46). This negative energy balance changes depending on the intensity and duration of the exercise, and significantly affects the appetite, eating behavior and food intake (47).

In recent years, important research was done on the relationship between exercise, appetite regulation and energy homeostasis. In this review, the aim is to examine the effects of exercises with different intensities and durations on total, acyl and desacyl ghrelin.

**Ghrelin In Acute Exercise**

Most of the acute exercise studies began with the assumption that exercise will suppress ghrelin. There are 2 reasons for this:

1. The concentration of ghrelin in circulation will decrease with exercise as the blood flow is directed to working muscles during exercise and the blood flow to the stomach decreases during exercise.
2. GH level increases during exercise and as a result, ghrelin release will decrease.

Some studies suggest that acute exercise temporarily suppresses feelings of hunger during and shortly after exercise, called 'exercise-induced anorexia' (48, 49), although the effects of exercise on ghrelin are contradictory to each o ther.

**3.10.1.1.Total Ghrelin (TG)**

It was shown in many studies that total ghrelin decreases during aerobic exercise (50, 51). Among

studies about resistance exercise, there are studies stating that ghrelin decreases significantly (52, 53). It was reported that total ghrelin concentration did not change in 9 elite rowers, although GH increased after 30 minutes of exercising below and above the anaerobic threshold (54).

**Acyl Ghrelin (Ag)**

In an aerobic exercise study, a significant decrease in AG level was observed after 3 hours of medium-high intensity exercise (60 min) (55). In addition, this result was supported by many studies that followed (48, 56, 57). In a medium-high intensity long-term treadmill exercise (90 minutes), it was reported that there was no change in AG levels after 24 hours of exercise (56). Exercise was reported to temporarily increase plasma ghrelin and endurance capacity. Exercise-induced increases in plasma ghrelin were positively correlated with endurance capacity, and the duration of wasting was reported to be decreased in GHSR-null mice compared to normal mice (57). It was reported that serum ghrelin is lower than pre-exercise and control values with the increase in GH after 30 seconds of sprint exercise on a bicycle ergometer (58). A study reported that ghrelin secretion suppressed during swimming, but there was no change in ghrelin level afterwards (57, 60). In a study conducted by researchers, participants were divided into 3 groups as control, vigorous running and cycling. They showed that the ghrelin level decreased in the cycling and vigorous running groups compared to the control group in measurements immediately after exercise (57). In another study, aerobic exercise and resistance exercise were compared, and it was reported that the effect of resistance exercise was less on AG concentrations (48). In another study comparing aerobic exercise, resistance exercise and combined exercise, it was reported that ghrelin level showed less change in the resistance exercise group (61). In a study conducted by Hagobian et al. in 2010, although it was reported that exercise had less positive effect on ghrelin in women compared to men, a study conducted by the same team in 2013 reported that there was no difference between the two for medium-high intensity exercise (62).

**Desacyl Ghrelin (Dg)**

There are studies reporting that AG decreases in acute exercise but DG level does not change (63). It is not clear whether the temporary impairments of AG in circulation are related to exercise (64). However, studies investigating the effects of exercise on DG are relatively few and limited.

**Ghrelin in Chronic Exercise**

The effect of acute exercise on ghrelin is questionable, but the ghrelin level returns within 30-60 minutes after exercise (56, 57). However, in studies where chronic exercise was performed by the participants, ghrelin level increased due to a decrease in fat and weight loss (65). However, it has been shown that lowering oxidative stress stimulates ghreline secretion (66). It is also known that exercise training has significant impact on improvement of oxidative acpaity and rudcue oxidative stress levels (67). The mechanism by which weight loss increases circulating ghrelin is not yet fully known, but it is thought that positive energy balance is stimulated by 3 mechanisms:

1. Decrease in fat use and increase in carbohydrate use regardless of GH.
2. Anabolic effect caused by the increase of GH and IGF-1 production.
3. Stimulation of long-term food intake via neuropeptide Y (NPY).

**Total Ghrelin**

In a study of women with normal weight, a 20% increase in total ghrelin was found after 12 weeks of aerobic exercise and diet. In addition, 4% weight loss was reported (68). As a result of 12 weeks of exercise and diet intervention, there was no change in plasma ghrelin level in participants without significant weight loss (<1.5 kg), and ghrelin levels but it was found to be doubled in individuals with significant weight loss (> 1.5 kg) (69). It was reported that body weight decreased

and total ghrelin increased 21.2% after a 6-month program including diet and exercise in 35 hyperlipidemic women (70) after 12 months' aerobic exercise in post menaposal overweight women (71). Exercise trainin protocol has important effects on acylated ghrelin levels without dependent on weight and fat mass loss (72). In contrast, a significant increase in ghreline coc-nentraion following weight loss and changes in energy availability has been reported (73). Ghreline responses to change in body weight and acute exercise could transiently reduce circulating acylated ghrelin levels without affecting unacylated ghrelin (74). They pointed to the difficulty of determining whether the ghrelin change is due to exercise or weight loss. In another study, a diet and exercise program was applied to monozygotic twins. A high-calorie diet of 84000 kcal was administered to 12 pairs of monozygotic twins for a period of 100 days. An exercise program was applied to 7 pairs of twins for a period of 93 days to create an energy deficit of 53000 kcal. Researchers reported a non-significant decrease in ghrelin level in the high-calorie group and a non-significant increase in the exercise group (75). According to this study, no relationship was found between weight change and ghrelin level. In a study comparing the genders, 60-90 minutes of continuous exercise was applied to 80% of the maximum $VO_2$ and it was found that GH increased in women and men after exercise, but ghrelin levels increased only in male athletes (76).

**Acyl Ghrelin**

In a study, obese-male participants were divided into 3 groups as control, resistance, and aerobic exercise. Exercises were done 3 days a week for 12 weeks. While weight was stable in the control and resistance exercise groups, a weight loss of 2 kg was reported in the aerobic exercise group. On the other hand, it was observed that AG levels did not change in all 3 groups and accordingly, the researchers reported that the changes in ghrelin could occur secondary to changes in body weight (77).

**Desacyl Ghrelin**

In a study on desacyl ghrelin, 552 male participants were given military training exercises for 6 months and an overall increase in DG was found. This increase was seen in those with the greatest reduction in waist circumference and those with 2-5% weight loss (78). In addition, an increase in 30.4% of TG and 31% of DG without change in AG accompained with a decrease in body weight, body mass index and body fat percentage were reported after 12 weeks of resistance and aerobic exercise performed in obese children. Furthermore, it was suggested that there is a strong relationship between the decrease in body weight and fat mass and the increase in DG after exercise (79). The exercise performed in normal weight and obese subjects showed a disconnection between exercise and levels of AG and its influence on food intake (80)

Taken together, the disconnect between acylated ghrelin and perceived hunger and fullness in the present study suggests factors other than acylated ghrelin influence the effect of exercise and feeding on appetite in NW and Ob individuals.

**Ghrelin in Low-Intensity Exercise**

Exercises were applied at 30% energy consumption for 2-4 days in 2 different groups with and without dietary intervention. In both groups, only the amount of AG in women increased; it remained stable in males (81). In a study conducted with 11 sedentary men, it was reported that short-term-low-intensity resistance exercises did not affect ghrelin although they increased GH (82). In another study, participants ran at 50% of maximum $VO_2$ and it was determined that plasma ghrelin levels did not change compared to the previous measurement (83). In another study in the literature, participants were exercised on the treadmill at a brisk walking speed (33.8% - 55.5% of maximum $VO_2$) for 60 minutes, although it was previously determined that the amount of AG decreased in acute paced exercise, it was reported that the level of AG did not change in this study (56).

**Ghrelin in Medium Intensity Exercise**

There was no change in ghrelin in participants who performed medium intensity bicycle ergometer exercise at 65% of their maximum heart rate for

60 minutes. However, it was also stated that ghrelin level may have been affected since the participants were given a small meal before exercise (84). In another study, it was reported that ghrelin decreased with an increase in GH after acute circular resistance exercise (1 RM 60%, 10 exercises, 3 sets), and ghrelin increased with the return of GH to its normal level 24 hours after exercise (52).

## Ghrelin in High Intensity Exercise

Obese women and men were given aerobic exercise at 75% of the maximum heart rate 5 days a week for 12 weeks, and it was found that the low level of AG was increased after the intervention (84). In a study of running at 74% of maximum $VO_2$ for 60 minutes, a decrease in ghrelin level was observed in the measurements made after 1 hour (85). In nine men, it was reported that eccentric and concentric (10 RM 80%, 12 repetitions, 4 sets, 90 seconds rest) exercise on different days did not alter the ghrelin level (53). In another study, exercises were performed on different days, 40 minutes at 50% of maximum $VO_2$, 20 minutes at 70% of maximum $VO_2$, and 20 minutes at 90% of maximum $VO_2$. It was found that GH increased and ghrelin did not change (86). In 3 studies in which rowing exercises were performed by elite athletes, there was an increase of 7% for AG during 30 minutes of exercise at 79% of maximum $VO_2$, an increase of 24% for AG during 20 minutes of exercise at 81% of maximum $VO_2$, and an increase of 15% for AG in exercise performed for 120 minutes at 67% of maximum heart rate (87). In a study comparing high intensity interval exercise (HIIE) and medium intensity continuous exercise (MICE), MICE (60% of peak $VO_2$,), HIIE (60 sec work at 100% peak oxygen uptake; 240 sec rest at 50% of peak $VO_2$,) it was seen that AG was lower in HIIE for measurements after 30 minutes (88). It has been reported that high intensity exercise induced increased lactate levels may suppress AG secretion and application of sodium bicarbonate increase AG secretion (89). Moderate-to-high intensity exercise acutely suppresses acyl ghrelin concentrations (90). This hormonal change is temporary and coincides with the decrease in hunger typically seen during and immediately after exercise (49, 55). This decrease in ghrelin level was more pronounced after high intensity exercise (60% of peak $VO_2$,) (49, 55) compared to low intensity exercise (50% of peak $VO_2$,) (56, 83) In studies comparing high intensity exercise and acute moderate intensity exercise, it may be more effective to recommend high intensity exercise to suppress AG concentration (91, 92). Exercise intensity was identified as a potential predictor that modulates the AG response to exercise (49, 55). It has also been shown that the short term very high intensity exercise could transiently increase ghrelin levels (93, 94). The long term high intensity may cause increase in circulation ghrelin levels and decreasing leptin levels that results in resistance to fat mass loss (95).

## Conclusions

Since the first introduction of ghrelin in 1999, the interest in ghrelin and its function in many part of clinical medicine is impressive. Ghrelin has great potential in clinical medicine on diagnosis and also treatment of serious metabolic disorders. Ghrelin has increased our understanding with regarding regulatory factors on body energy homeostasis. Ghrelin strengthen and provides new approaches to diseases of impaired energy balance. A close and fundamental relationship between exercise (especially chronic, or high intensity exercise) and apetite regulatory hormones of ghrelin has been shown in many studies. Exercise induced ghrelin production may be use to support treatment of obesity or impairment of glucose metabolism. Future researchs will be elucidate ghrelin actions and physiological functions.

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