# 12 Ghrelin Responses to Acute Exercise and Training

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## Introduction

The importance of physical exercise to influence energy balance and body mass is widely recognized [1]. A complex neuroendocrine system is involved in the regulation of energy homeostasis including central and peripheral tissues [2, 3]. Important to this regulatory system is the existence of several appetite hormones, including adipose and gut tissue hormones that communicate the status of body energy stores to the hypothalamus [2]. Energy intake is an integral to energy balance and is regulated via neuronal circuits interacting with gut hormones, key among these being ghrelin and peptide YY [4, 5]. It appears that peptide YY functions as a negative feedback signal and is responsible for inducing satiety and cessation of eating after food intake [5]. In contrast, ghrelin is a hormone well known for its acute orexigenic properties stimulating food consumption [6, 7]. Changes in these circulating appetite hormones influence the physiological drive to eat, weight gain and also reproductive function [4]. Furthermore, ghrelin may also be involved in pubertal development, where rapid growth and development need careful coordination of energy balance and appetite regulatory signals [4]. Finally, circulating ghrelin concentrations may vary dramatically depending on specific body composition, physical activity and physical fitness parameters [2]. This chapter focuses on the available information about the effects of acute exercise and chronic exercise training on the secretion of ghrelin.

Ghrelin, a peptide secreted by distinct endocrine cells of the stomach, was first described as an endogenous ligand for the growth hormone secretagogue receptor [8]. However, ghrelin role in body mass regulation is more prominent than its role in growth hormone secretion [9]. Ghrelin promotes positive energy balance by increasing appetite and food intake [10, 11]. Specifically, the rise in circulating ghrelin concentration before a meal is a physiological signal for hunger and the body's cue for meal initiation [12]. Therefore, the rise in ghrelin levels and hunger occurs independent of food and time of day cues [12]. Meal responses of ghrelin are related to acute caloric intake over a typical day of eating in normal-weight subjects [13]. Furthermore, ghrelin levels have been demonstrated to be negatively correlated with 24-h caloric intake [14], and ghrelin concentrations decrease after caloric intake and increase while fasting [2]. The decrease in ghrelin release is related to the specific amount of calories ingested [15]. Accordingly, ghrelin is responsive to diet- and exercise-induced changes in body mass [16].

In addition to total ghrelin, acylated and desacylated forms of ghrelin have been described

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[17]. The acylated form of ghrelin is thought to be essential for ghrelin biological activity [18], whereas unacylated ghrelin has been suggested to be biologically inactive [19]. Specifically, acylated ghrelin has been reported to be associated with the regulation of growth hormone secretion, cardiac performance, cell proliferation and adipogenesis and affects appetite, food intake and energy balance [8, 20, 21]. There are also some studies suggesting that unacylated ghrelin is related to insulin resistance [22–24]. It has also been demonstrated that total ghrelin and acylated ghrelin are positively correlated [25–27] and both forms of the ghrelin potentially play a role in energy balance [28]. Based on these results, it could be suggested that acylated and desacylated forms of ghrelin change similar to changes in energy balance, and total ghrelin concentration can be used as a biomarker in energy balance studies [4, 29, 30]. Future studies, nonetheless, are needed to better clarify the responses of total ghrelin and its specific forms in various conditions of energy balance.

## Ghrelin During Growth and Maturation in Children

Ghrelin is a hormone that could influence somatic growth [4] and sexual maturation [31]. Specifically, a negative association of circulating ghrelin level with age [4, 31] and pubertal development [32] has been found. It has been hypothesized that ghrelin provides a link between energy homeostasis, body composition and pubertal development through actions on the hypothalamus [33], where ghrelin stimulates the secretion of gonadotropin-releasing hormone, which in turn stimulates the secretion of the gonadotropins required for pubertal onset [16]. It has been found that the initiation of puberty substantially decreases ghrelin concentrations in both sexes [4, 31]. A negative correlation between ghrelin and testosterone has been found in boys entering puberty [32]. In contrast, a recent study demonstrated no effect of testosterone and estradiol on ghrelin decrease during pubertal growth in boys and girls, respectively [4]. It was found that a drop in circulating total ghrelin to its lowest levels occurred during peak pubertal growth [4]. Furthermore, Cheng et al. [4] suggested that adolescent ghrelin concentrations may be more strongly associated with markers of somatic growth than sexual maturation. Specifically, circulating ghrelin levels were inversely correlated with insulin-like growth factor-1 concentrations and with annual height and weight velocity in both sexes [4]. Accordingly, the decrease in circulating ghrelin levels at the onset of puberty is apparent [4, 34, 35], despite the fact that puberty is characterized by increased appetite and food intake [31] and ghrelin is known to stimulate appetite [28, 36]. Research suggests that there could be an increased sensitivity for appetite stimulation by ghrelin over puberty [31] and/or low ghrelin concentrations signal adequate nutritional status to support rapid somatic growth and development of reproductive capacity [4] to sustain growth in this period. In addition, elevated energy expenditure and, therefore, also an increased energy intake in physically active children during pubertal maturation are linked to higher circulating ghrelin levels in these children compared with physically inactive children [36]. Accordingly, it could be argued that regular physical activity still causes higher ghrelin levels during puberty to stimulate appetite and food intake to cover higher energy homeostasis [36]. This is supported by the finding that there is a negative correlation of cardiorespiratory fitness as measured by peak oxygen consumption with total ghrelin [37] and acylated and desacylated forms of ghrelin [38] in boys during puberty. However, different forms of ghrelin were not associated with directly measured physical activity intensities in pubertal boys with differing body composition [38]. Collectively, these results demonstrate that somatic growth and maturation are associated with ghrelin, which concentrations decrease with advancing age and puberty. However, further longitudinal studies throughout puberty in children with various physical activity and body composition levels are needed to better understand how physical fitness and activity may influence circulating ghrelin concentrations dur-

ing puberty in children with different body composition values before any definitive conclusions can be drawn.

In longitudinal investigations with growing and maturing athletes, total ghrelin levels have been studied in female gymnasts [35, 39] and male and female swimmers [40, 41]. It could be argued that regular sport training increases ghrelin levels to stimulate appetite and food intake to cover higher energy homeostasis in these young athletes [2, 42]. Ghrelin may act as a hormone signalling a need for energy conservation, and ghrelin secretion is triggered to counter a further deficit in energy storage to help to maintain body mass [2, 43]. Accordingly, higher basal ghrelin concentrations have been found in prepubertal and adolescent athletes when compared with untrained controls [34, 35, 44]. However, basal ghrelin levels decreased in both prepubertal rhythmic gymnasts and age-matched lean untrained controls over a 12-month study period [39], showing that an increasing age decreases ghrelin concentrations similarly in both groups despite large differences in daily energy expenditure [2, 36]. Therefore, ghrelin concentrations were still significantly higher in the rhythmic gymnasts when compared with untrained controls at both measurement times during prepuberty [39]. However, when rhythmic gymnasts and untrained controls reached puberty, ghrelin levels were decreased in both groups and were not different between groups with different energy expenditure levels [35]. Similarly, a significant decrease in basal ghrelin levels was observed in male swimmers after the evolution of puberty [41], while basal ghrelin levels were not changed in pubertal female swimmers with advancing pubertal maturation over a 2-year study period [40]. It can be suggested that basal ghrelin levels are higher in prepubertal children who participate in sport training in comparison with age-matched untrained controls, while basal ghrelin levels decrease when young athletes reach puberty even in the presence of chronically elevated energy expenditure [2, 36]. Furthermore, pubertal maturation appears to reduce circulating ghrelin concentrations in growing athletes of both sexes, despite heavy athletic activity [2, 36].

## Ghrelin Relationships with Adiposity and Energy Availability

Ghrelin levels are significantly lower in obese individuals [45–47] and substantially elevated in patients with anorexia nervosa [12, 48, 49], proposed as a likely adaptive mechanism response [12, 50]. Accordingly with these patterns, there is a negative association of ghrelin concentration with body mass [32, 51], body mass index [32, 52], total body fat mass [34, 51], visceral fat mass [53, 54] and total body lean mass [32, 55]. It has also been suggested that circulating ghrelin level could be regarded as a signal of decreased total body lean mass in healthy elderly females [56]. In addition, there are also studies to show an inverse correlation between ghrelin concentration and body height [32, 57, 58] and body height velocity [4] during growth in children.

Diet-induced weight loss in obese individuals has been accompanied by increases in circulating total ghrelin concentrations [59]. For example, plasma ghrelin levels increased by 17% in overweight women who reduced their body mass by 4.5% after 10-week body weight loss intervention programme [60], while a 6-month supervised weight loss programme that caused 17.4% body weight loss induced 24% increase in ghrelin levels [61]. In addition, short-term diet-induced body weight loss in obese subjects resulted in higher total ghrelin concentrations, which remained elevated also over weight maintenance periods of 6 and 12 months [59]. Similarly, long-term exercise intervention together with diet-control investigations has demonstrated that total ghrelin levels increase in response to exercise-induced body weight loss in obese subjects and not because of food restriction per se, acting via a negative feedback loop that regulates body mass [7, 62]. It has been suggested that changes in total ghrelin concentrations appear to be most sensitive to changes in body mass resulting from overall energy deficit, independent of specific effects of nutritional intake and/or physical exercise [7, 62]. There are studies to demonstrate that manipulations in food intake and exercise energy expenditure show a close relationship between circulating ghrelin

and energy availability [63, 64]. For example, Scheid et al. [64] measured total ghrelin, energy balance and body composition parameters before and after 3-month intervention period in exercising women and found that circulating ghrelin does not play a role in the adaptive changes associated with exercise training when exercise occurs in the absence of body weight loss. However, fasting ghrelin level increased when body mass is lost and may respond to even smaller changes in energy availability [64]. In addition, the change in total ghrelin level was inversely correlated with the change in body mass, body mass index, lean body mass and energy availability after diet- and exercise-associated weight loss [64]. In contrast, no impact of aerobic training on acylated ghrelin levels was observed in overweight and obese men [65]. It has been suggested that differences in body fat mass loss, exercise volume and duration, and gender may influence possible differences in ghrelin responses to weight reduction [59]. In addition, King et al. [66] showed that equivalent energy deficits induced by food restriction or physical exercise have markedly different effects on appetite, energy intake and acylated ghrelin concentrations. While food restriction elicited a rapid increase in appetite and energy intake and these responses appear to be related to postprandial suppression of acylated ghrelin, acute energy deficits induced by vigorous intensity exercise session did not alter appetite or energy intake and may be related to the failure of acute exercise to induce compensatory acylated ghrelin responses [66]. These results together suggest that changes in body mass are needed before any changes in circulating ghrelin levels could be seen in untrained individuals.

## Ghrelin Responses to Acute Exercise

There are a number of studies including athletes that have investigated the influence of acute bout of exercise on total ghrelin [37, 67–82] and on acylated ghrelin [66, 83–98] concentrations. Different investigations with healthy untrained individuals [37, 67, 68, 78] and also well-trained endurance athletes [71, 74, 82] would suggest that exercise-induced acute negative energy balance may not be sufficient to alter total ghrelin response. Conversely, however, there are studies demonstrating that total ghrelin level increased [69, 70, 72, 73] or decreased [75–77, 80, 81] as a result of short-term exercise session. In addition, studies with acylated ghrelin have mostly reported significant suppression [83, 84, 86, 89, 90, 94–98] or no change [66, 85, 92] in measured acylated ghrelin concentration after acute exercise. However, there are also studies that have observed significant postexercise increase in acylated ghrelin concentration [91, 93]. Accordingly, acute exercise studies have demonstrated different responses of different ghrelin forms to the acute exercise in subjects with different body composition and physical activity levels.

A study by Dall et al. [68] reported no change in total ghrelin concentration after acute cycling exercise for 45 min at the intensity of anaerobic threshold in healthy middle-aged men. Similarly, total ghrelin levels remained unchanged after acute submaximal running workloads (50%, 70% and 90% of maximal oxygen consumption [$VO_{2MAX}$]) [78] and also after a single bout of treadmill running for 60 min [67] in healthy physically fit male individuals. In well-trained endurance athletes, a progressively intense intermittent exercise trial on treadmill at different exercise intensities (10 min at 60%, 10 min at 75%, 5 min at 90% and 2 min at 100% of $VO_{2MAX}$ [74] and 30 min on-water sculling exercise performed either below or above the intensity of individual anaerobic threshold [71] did not change total ghrelin concentration. It could be argued that acute exercise energy expenditure was not sufficient to alter total ghrelin response in these studies [1]. Accordingly, significant postexercise increases in total ghrelin concentration after prolonged 2-h endurance rowing at the intensity of 80% of individual anaerobic threshold [34] and after 3-h endurance cycling at the intensity of 50% of maximal aerobic power [69] have been observed in endurance-trained athletes. Assuming that the energy balance drives the ghrelin response to prolonged rowing

exercise with the estimated energy expenditure of 1200–1500 kcal, it was conceivable to see that the increased postexercise total ghrelin concentration was associated with the amount of work performed ($r = 0.75$; $p < 0.05$) in rowers [34]. Furthermore, it was argued that the reduced resting levels of total ghrelin may have influenced the significant exercise-induced increase in ghrelin concentration in rowers [34]. The results of these studies [34, 69] would suggest that a certain threshold reduction in energy availability should be reached before any significant postexercise increases in total ghrelin concentration occur and that the amplitude of the total ghrelin increase could be linked to the energetic status induced by acute exercise stress and the resting levels of ghrelin in athletes [1]. However, to what extent exercise intensity may influence total ghrelin response to acute exercise has not yet been determined, although it has been suggested that low- rather than high-intensity exercise with longer duration stimulates total ghrelin levels [70]. Specifically, Erdmann et al. [70] investigated the effect of exercise intensity and duration on total ghrelin release, hunger and food intake in normal-weight untrained healthy individuals. Total ghrelin concentrations were increased by 50–70 pg/ml as a result of prolonged low-intensity bicycling exercise with a duration of up to 2 h, while no changes in total ghrelin were observed during higher intensity exercise [70]. In addition, only 2-h prolonged aerobic exercise at the intensity of 50 W with an exercise energy expenditure of 340 kcal lead to an increase in food intake without having an effect on hunger sensations [70]. An increase in plasma ghrelin concentration during exercise without alterations of hunger sensations under similar conditions of low-intensity exercise and energy expenditure was also found in another study [79]. Nonetheless, the stimulation of food intake during prolonged exercise was most likely not due to changes in circulating total ghrelin levels [70]. These results together demonstrate that total ghrelin concentrations can be increased as a result of a low-intensity prolonged exercise session when the exercise energy expenditure is high enough also in untrained subjects.

There are studies to suggest that acute exercise stress could also result in a decrease of total ghrelin concentration [75, 77, 80, 81]. These studies have used more intensive exercise bouts including resistance exercise protocols [75, 77, 80, 81], and it has been suggested that glucoregulatory stress from the acute intense exercise could result in a suppression of circulating ghrelin during the recovery period from the exercise [74, 75]. Indeed, studies that have utilized more intensive exercise bouts have demonstrated that maximal exercise-induced large increases in insulin [74, 75] and growth hormone [75, 81] levels may suppress total ghrelin concentration during the recovery period. However, there are also investigations that contradict the results of these studies as exercise-induced increases in both total ghrelin and growth hormone values have been observed after prolonged low-intensity exercise in endurance-trained males [69] and also in overweight postmenopausal women [79]. Others have argued that postexercise ghrelin responses may be independent of changes in energy balance [6] and that acute exercise stress increases energy intake only some time postexercise [6, 83]. To this end, Broom et al. [83] investigated the effects of 1 h running at 72% of $VO_{2MAX}$ on total and acylated ghrelin concentrations. They found that total ghrelin was not changed, while acylated ghrelin was decreased as a result of exercise [83]. Accordingly, it has been argued that although there is a close relationship between total and acylated ghrelin concentrations [25–27], it cannot be excluded that after acute exercise this relationship may be somewhat different [42, 70, 83].

Different studies have demonstrated that relatively high-intensity exercise sessions (≥70% $VO_{2MAX}$) may suppress acylated ghrelin concentrations [99, 100]. Typically, this hormonal decrease coincides with a transient reduction in appetite during and immediately after the exercise [87, 88], while there are also studies that have found no changes in appetite as a result of acute exercise [89, 92, 101]. It is possible that the lack of commonly observed appetite suppression may be due to a difference in training status or fitness of studied subjects [89]. In accordance, there is an evidence to suggest that highly trained

individuals are more accustomed to exercise stress and therefore do not have as great hormonal, including acylated ghrelin, response to acute exercise as in untrained individuals [88, 99]. For example, Broom et al. [84] found that plasma acylated ghrelin and hunger ratings fell and remained suppressed for 1.5 h after 90 min running at the intensity of 70% of $VO_{2MAX}$ (≈70% decrease in acylated ghrelin) in healthy men. In other studies with endurance-trained men, circulating acylated ghrelin concentrations were decreased after 45 min of cycling at the intensity of ≈76% of $VO_{2MAX}$ (≈23% decrease in acylated ghrelin) [89] and after 20 km run (≈14% decrease in acylated ghrelin) [90]. Therefore, the suppression of acylated ghrelin in endurance-trained athletes was transient, with concentrations not different from baseline already after 30 [90] and 40 [89] min postexercise. A recent study by Mattin et al. [92] observed no significant changes in acylated ghrelin and appetite scores as a result of 60 min cycling at the intensities of 40% and 70% of $VO_{2MAX}$ in healthy men. Therefore, although not statistically significant, acylated ghrelin responded differently to exercise intensity, as serum levels decreased by ≈27% at the intensity of 70% of $VO_{2MAX}$ and increased by ≈12% at the intensity of 40% of $VO_{2MAX}$ [92]. Larson-Meyer et al. [91] also found a significant increase in acylated ghrelin immediately after 60 min running at the intensity of 70% of $VO_{2MAX}$ in female runners. Therefore, appetite was not affected by running exercise, and postexercise acylated ghrelin was not associated with appetite scores [91]. It was argued that the energy cost of the running exercise may promote increased acylated ghrelin secretion after exercise in these athletes [91]. The results also suggested that acylated ghrelin is not a major contributor to postexercise food intake, perhaps because the signal is dampened by increases in different anorexigenic peptides at the same time [91, 102]. In accordance, other studies have also argued that it is possible that the transient suppression of circulating acylated ghrelin that can be observed during acute exercise may be entirely unrelated to appetite regulation [50, 85]. These results together suggest that acylated ghrelin is responsive to different conditions and modes of endurance exercise, duration and intensity, but the direction of the hormone response can be varied [95]. The differences in acylated ghrelin responses to acute exercise can also be attributed to subject physical fitness, pre-exercise meal consumption and timing as well as the timing of the hormone measurements and possible environmental factors such as temperature and altitude [103]. There is a need for further investigations to elucidate the exact mechanisms regulating ghrelin synthesis and clearance during and after acute exercise.

## Chronic Exercise Training and Ghrelin Responses

Chronic exercise training perturbs energy balance and can potentially alter body mass and composition. There are a number of studies that have reported an increase in circulating ghrelin concentrations after long-term exercise interventions in previously untrained individuals [13, 43, 62, 104–108], while other studies have not found any changes in ghrelin concentrations as a result of prolonged exercise training [51, 109–111]. It appears that circulating ghrelin levels increase with body weight loss [62, 105, 107, 108] and decrease with body weight gain [12, 112]. Accordingly, data on ghrelin responses to prolonged exercise training are mainly available from obese individuals (i.e. individuals involved in weight loss programme) [62, 106, 107, 109, 113], whereas only limited data are provided for athletes [29, 30, 114–116]. Most of the previous investigations have studied total ghrelin response to prolonged exercise training [13, 29, 30, 43, 62, 108, 109, 114, 115], while relatively few intervention studies have measured acylated [111, 113, 116] or unacylated [23, 24] ghrelin concentrations separately. Currently, there appears to be only one published study that has investigated the response of acylated ghrelin to prolonged training period in athletes [116].

Previous investigations have mostly found that total ghrelin concentrations increase during situations of body weight loss and suggest that weight loss is the most potential factor influencing ghre-

lin response to exercise training [13, 43, 62, 107, 108, 117]. In an earlier study, Leidy et al. [108] found that fasting ghrelin concentration was increased twofold in a group of normal-weight women who experienced weight loss (>1.5 kg) as a result of a 3-month energy deficit-imposing diet and 5-days-a-week exercise training intervention programme [108]. Therefore, body mass, body fat mass and resting metabolic rate significantly decreased before the increase in fasting ghrelin occurred [108]. It was suggested that circulating total ghrelin responds in a compensatory manner to changes in energy homeostasis in healthy young women and that ghrelin exhibits particular sensitivity to changes in body mass [108]. In another study, Foster-Schubert et al. [62] reported that total ghrelin levels increased by 18% in sedentary overweight postmenopausal women who lost more than 3 kg body mass after 1-year aerobic exercise training programme. Another 1-year moderate-to-vigorous intensity aerobic exercise for 45 min 5 days a week demonstrated that greater weight loss was associated with larger increases in total ghrelin concentrations in overweight and obese postmenopausal women [107]. Similarly, moderate-intensity aerobic exercise training 5 days a week for 12 weeks increased circulating acylated ghrelin concentrations in overweight and obese men and women [113]. In contrast to these findings, fasting acylated ghrelin concentrations decreased after a moderate dose (14 kcal/kg body mass weekly) but did not change after a low-dose (8 kcal/kg body mass weekly) moderate-intensity aerobic exercise training lasting 4 months in healthy nonobese older women [111]. It was argued that exercise training dose can have specific effects on acylated ghrelin that are not dependent on body weight or body fat mass loss [111]. However, there was a lack of acylated ghrelin level change in those participants who lost body weight or body fat mass as a result of 4-month training period [111]. In another study, Ravussin et al. [51] observed that neither positive energy balance caused by overfeeding nor negative energy balance induced by exercise training had a significant effect on total ghrelin concentration over a 100-day study period. The impact of negative energy balance on total ghrelin levels at the end of the investigation was smaller, due to the possible effect of accustomization [51]. Another study with a group of morbidly obese men and women demonstrated that fasting circulating total ghrelin levels remained unchanged despite 5% body weight loss induced by a 3-week integrated body weight reduction programme with exercise training [109]. The amplitude of ghrelin response to negative energy balance in these studies could be linked to the energetic status of studied individuals, which is attributable to specific body fat mass and exercise training characteristics. Accordingly, data regarding the influence of exercise training programme on circulating ghrelin in previously untrained individuals suggests that exercise training per se has no impact on circulating ghrelin levels and changes in ghrelin concentrations that are seen as a result of exercise training intervention take place as secondary changes to body weight loss [117].

Evidence suggests that the degree of negative energy balance and/or body weight loss threshold to increase circulating ghrelin concentrations has not yet been determined [1, 17]. In heavily exercising females, menstrual disturbances have been linked to an energy deficiency, where caloric intake is inadequate for exercise energy expenditure [12, 118]. These menstrual disturbances, together with an energy deficiency, are largely attributable to athletic events, where the emphasis is on the achievement of thin and lean physiques, which may require low body mass and body fat percent such as in gymnastics, figure skating and long-distance running [12]. Accordingly, higher ghrelin levels have been observed in amenorrheic athletes than in normally ovulating women who train [17, 119]. In fact, there are data to suggest that young female athletes with varying severities of menstrual disturbances can be distinguished from each other based on their circulating ghrelin levels [12, 48, 120, 121]. To this end, as energy deficiency increases in severity across the continuum of menstrual cycle disturbances, physically active women with amenorrhea have the lowest resting energy expenditure relative to lean body mass, together with the increased ghrelin levels [48, 121]. In contrast, physically active women with

subtle menstrual disturbances and nonathletic controls present higher resting energy expenditure relative to lean body mass and lower ghrelin concentrations [48, 121]. Increased ghrelin levels in young female athletes with amenorrhea may have a role in reproductive system [12, 119, 120]. An inverse relationship between acylated ghrelin concentration and gonadal steroids was observed in athletes [48], and acylated ghrelin levels may differentiate between athletes who will or will not develop functional hypothalamic amenorrhea during heavy training [48, 119]. Accordingly, it is likely that high circulating ghrelin concentrations contribute to functional hypothalamic amenorrhea by altering gonadotropin-releasing hormone and luteinizing hormone pulsatility [119, 120]. Therefore, body fat mass has an important negative influence on basal ghrelin levels in amenorrheic athletes [48, 120]. An increase in energy intake in amenorrheic athletes induces a decrease in basal ghrelin concentrations, which is paralleled by increases in body mass and resumption of menses [119]. Accordingly, it appears that circulating ghrelin is a biomarker of energy imbalance across the menstrual cycle in female athletes [36, 122]. Since ghrelin levels are consistently elevated in energy deficiency such as functional hypothalamic amenorrhea, ghrelin could be an important marker of energy deficiency and chronic undernutrition [12] and should be measured to monitor the health of female athletes.

The mechanisms by which changes in energy balance and/or body mass impact on circulating ghrelin levels are not fully understood [2, 36, 117]. It has been proposed that leptin, which levels directly correlate with body fat mass, may have an influence on circulating ghrelin concentrations [117]. Specifically, a negative association between circulating leptin and ghrelin concentrations has been reported [34], and an increase in circulating ghrelin levels in response to body weight loss may therefore occur as a result of a decrease in circulating leptin concentrations [117]. Therefore, alterations in ghrelin levels as a result of changes in body fat mass may therefore be secondary to changes in leptin [117]. In addition, insulin may also mediate some of the effects of body adiposity on circulating ghrelin [117] as circulating ghrelin concentrations are inversely correlated with insulin and insulin resistance values [123]. It has been suggested that relatively low ghrelin concentrations observed in obese individuals may be a result of insulin resistance that is a characteristic in obesity and which has an inhibitory effect on ghrelin concentrations, rather than excess body mass by itself [123]. Collectively, this may represent one mechanism by which insulin is implicated in the homeostatic regulation of energy balance [117].

Only few studies have investigated ghrelin response to different exercise training periods in adult male [30, 114–116] and female [29] athletes. Specifically, in male athletes, ghrelin responses to a weight reduction period before competitions in bodybuilders [30], an intensive training camp in football players [116] and a high-volume low-intensity endurance [114] and a high-volume low-intensity concurrent endurance and resistance [115] training periods in competitive rowers have been studied. In addition, ghrelin responses to intensified training period were also studied in female synchronized swimmers [29]. While studies with national-level male bodybuilders [30] and international-level female synchronized swimmers [29] demonstrated that total ghrelin levels increased together with a body weight reduction as a result of negative energy balance, no differences in total ghrelin concentrations together with no changes in body mass values were observed in competitive male rowers as a result of increased training volume [114, 115]. Accordingly, it can be speculated that body weight loss is also important to reduce total ghrelin concentrations in studied athletes. In contrast, circulating acylated ghrelin concentrations were significantly lowered during the 9-day intensive training camp, which tripled the training volume in male college-level footballers [116]. Therefore, no changes in body mass values were observed, and an increase in physiological stress was associated with a decrease in appetite [116]. It was suggested that an early-phase physiological stress response may decrease the acylated ghrelin concentrations in male athletes during an intensive training camp [116]. The reason for different results between this study with

other studies in athletes is not clear. It is possible that these discrepancies are due to factors related to the different modes of exercise, energy availability and competitive level of athletes. However, it is also likely that differences in dietary control, sample collection and assay procedures may also be implicated [117]. Clearly, further studies with elite athletes with different training programmes are needed before any definitive conclusions can be drawn.

Relative to women athletes, a national team of female synchronized swimmers performed a 4-week intensified training period, where a baseline training load of about 22 h was increased by a 20.5% across the intensified training period, which caused a significant decrease in body fat percent from 17.3% to 16.4% in these elite female athletes [29]. In addition, a decrease in energy availability was observed, which was accompanied by an increase in ghrelin and decrease in leptin, reflecting a decrease in energy stores across the investigation period [29]. The results of the Schaal et al.'s [29] study demonstrate that a state of an increased fatigue and rather low energy availability in these elite female athletes was characterized by a significant increase in ghrelin levels shortly before the season's target competitions. Accordingly, it may be suggested that an increased ghrelin concentrations can be used as a marker of increased training stress and inadequate energy availability in elite female athletes.

In a study with male bodybuilders, 14 athletes were divided into seven competitors and seven control athletes, who were followed for 11 weeks before the national championships [30]. Competitors were able to significantly decrease their mean body mass by 4.1 kg during the 11-week period, whereas no changes in body composition or ghrelin values were observed in the control athletes [30]. In competitors' group, the energy deficit at about 536 kcal/day after the first 5-week period was already sufficient to cause a significant increase in total ghrelin concentrations, whereas no further increase in ghrelin levels was observed with the energy deficit reaching 978 kcal/day after 11-week preparatory period [30]. The athletes in the present investigation were competitive bodybuilders with a mean body fat percent of 9.6% at the beginning of the study and 6.5% at the end of the study [30]. It was argued that ghrelin secretion might have reached its limits at some point, and the negative energy balance of more than 900 kcal/day and a significant body weight loss of 2.4 kg in the second 5-week training period (between weeks 6 and 11) were not sufficient to further the significant total ghrelin increase in these athletes [30]. It was concluded that circulating ghrelin levels increase in well-trained bodybuilders with relatively low body fat percent but reach a plateau beyond which there is no further increase in total ghrelin levels, despite continuing negative energy balance and body weight loss [30].

In studies with male rowers, total ghrelin concentrations were measured after a reference week with usual training volume, after 2 weeks of high-volume training and after a recovery week with reduced training volume [114, 115]. In the first study, 90% of the trainings (rowing, running or cycling) were aerobic type of exercise and only 10% resistance type of exercise [114], while in the second study about 50% of the trainings were low-intensity resistance exercise and 50% aerobic type of exercise [115]. It appeared that fasting ghrelin concentrations were not increased as a result of the 2-week period of extended training volume in both studies [114, 115], while a decrease in fasting ghrelin was observed after a recovery week [115]. Although energy intake and energy expenditure increased significantly, the negative energy balance after the 2-week period of high-volume training and energy restriction was about 455 and 408 kcal/day in endurance [114] and concurrent resistance and endurance [115] training studies, respectively. It could be argued that during specific metabolic conditions resulting from the preceding high-volume training period with high energy expenditure, negative energy balance, temporarily restricted caloric condition in fasting state and probably relatively low body energy stores (i.e. low body fat percent) may all contribute to further exercise-induced effects on energy expenditure that leads to downregulation of ghrelin concentration in male rowers [114, 115].

## Conclusions and Future Directions

Energy homeostasis is regulated by a neuroendocrine system that also includes different appetite hormones including ghrelin. Ghrelin concentrations decrease during growth and pubertal maturation and are linked to nutritional status, with lower levels in obese and higher levels in underweight individuals. Therefore, basal ghrelin levels are elevated in growing athletes, while pubertal onset decreases ghrelin levels even in the presence of chronically elevated energy expenditure in young athletes. Since increased participation of children in competitive sport is evident, more research on the exercise-induced modification of the appetite hormones including ghrelin is warranted. It has to be considered that in those sport disciplines where heavy training with large energy expenditure starts at a relatively young age, there is a greater risk for developing the female athletic triad already during adolescent period. It can be suggested that growing and maturing athletes should be monitored at short intervals to better understand the influence of high athletic activity on hormonal markers including ghrelin that are involved in overall growth and energy homeostasis. Ghrelin can be used as an indicator of energy imbalance across the menstrual cycle in female athletes. Elevated ghrelin concentrations have been observed in female athletes with chronic energy deficiency, and ghrelin may differentiate between athletes who will or will not develop functional hypothalamic amenorrhea and be at risk for Relative Energy Deficiency Syndrome in Sport (RED-S). In addition, most of the investigations have studied the role of ghrelin in energy availability in different groups of obese individuals, while less studies have been done with athletes to investigate the possibility to use circulating ghrelin as a possible marker of training stress.

The current available information regarding the role of different forms of ghrelin concentrations in energy balance during acute exercise and prolonged training stress is not entirely clear. Acute exercise studies have demonstrated varied responses of different ghrelin forms to the acute exercise in individuals with different body composition and physical activity levels. Various investigations with healthy untrained individuals and also well-trained endurance athletes would suggest that exercise-induced acute negative energy balance may not be sufficient to alter total ghrelin and/or acylated ghrelin response. There are also studies that have argued that a certain threshold reduction in energy availability should be reached before any significant postexercise increases in total and/or acylated ghrelin levels occur and that the amplitude of the ghrelin increase could be linked to the energetic status induced by acute exercise stress and the resting levels of ghrelin in athletes. However, to what extent exercise intensity may influence circulating ghrelin response to acute exercise has not yet exactly been determined, although it has been suggested that low- rather than high-intensity exercise with longer duration stimulates ghrelin response. In contrast, different studies with acylated ghrelin have mostly reported significant suppression in measured acylated ghrelin concentration when performed at higher intensities. Therefore, the transient suppression of circulating acylated ghrelin that can be observed during acute exercise may be entirely unrelated to appetite regulation. The differences in ghrelin responses to acute exercise can be attributed to subject physical fitness, pre-exercise meal consumption and timing, the timing of the hormone measurements as well as sampling processing and assay protocols. Additional research is needed to elucidate the exact mechanisms regulating ghrelin synthesis and clearance during and after acute exercise.

Results regarding the influence of exercise training programme on circulating ghrelin are more consistent and mainly suggest that exercise training per se has no impact on circulating ghrelin levels, and changes in ghrelin concentrations as a result of exercise training intervention take place as secondary to body weight loss. Therefore, the majority of training studies have investigated the responses of total ghrelin concentrations, with relatively less studies measuring acylated ghrelin separately. Typically, circulating ghrelin levels increase with body weight loss and decrease with body weight gain. Data on ghrelin responses to prolonged exercise training are

mainly available from obese individuals, whereas only limited data are provided for athletes. It has been suggested that there is a negative energy balance and/or body weight loss threshold to increase circulating ghrelin concentrations that has not yet been exactly determined. It appears that basal and postexercise ghrelin responses without altering body mass are not sensitive enough to represent changes in training volume and energy availability in athletes. There is also some evidence to suggest that although ghrelin increases together with body weight loss in highly trained athletes with already relatively low body fat mass, there may be a plateau beyond which there is no further increase in circulating ghrelin concentrations despite continuing negative energy balance and body weight loss. Further investigations are needed to describe the exact role of ghrelin at different training conditions in athletes representing different sport events. Collectively, additional research including longitudinal studies in different populations with various body composition and physical activity patterns is warranted to better describe the role of ghrelin and its specific forms in conditions of energy deficiency, surplus and balance.

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