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Exercise associated hormonal signals as powerful determinants of an effective fat mass loss

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Abstract. Obesity management for achieving an effective weight loss includes dietary modification and exercise [resistance (strength), endurance (cardiovascular) or intervals training (high-intensity intermittent exercise)]. Regular exercise acutely increases fat oxidation, which induces loss of fat mass and increases energy expenditure. Moreover, it has a positive effect on the physical (improved insulin sensitivity, lipid profile, etc.) and mental health (mood, cognition, memory, sleep, etc.). Endocrine responses to muscle actions are affected by many factors, including the exercise muscle groups (lower and upper body), load/volume, time-under tension, and rest-period intervals between sets, training status, gender, and age. The aim of this review is to summarize, evaluate, and clarify the literature data focusing on the endocrine responses to different types of exercise, including the frequency, intensity, and type of movement with regard to the fat loss strategies. Many studies have investigated anabolic [growth hormone, insulin-like growth factor-1 (IGF-1), testosterone] and gluco- and appetite- regulatory (insulin, cortisol, ghrelin) hormone responses and adaptations of skeletal muscles to exercise. Muscle tissue is a critical endocrine organ, playing important role in the regulation of several physiological and metabolic events. Moreover, we are also describing the response of some other substances to exercise, such as myokines [irisin, apelin, brain-derived neurotrophic factor (BDNF), myostatin, and fibroblast growth factor 21 (FGF21)]. It is proposed that reducing intra-abdominal fat mass and increasing cardiorespiratory fitness through improving nutritional quality, reducing sedentary behavior, and increase the participation in physical activity/exercise, might be associated with clinical benefits, sometimes even in the absence of weight loss.

Key words: fat mass lose, exercise, lipid oxidation, catecholamines, cortisol, androgens, growth hormone, myokines

Introduction

There is widespread general consensus that life style changes are cornerstones of both the prevention and treatment of obesity and the metabolic syndrome (Kushner and Ryan 2014; Millen et al. 2014a). Recently, in the large population study (European Prospective Investigation into Cancer and Nutrition Study, EPIC) it has been shown that avoiding all the inactivities may theoretically reduce all-causes of mortality by 7.35% (95% CI: 5.88%, 8.83%); corresponding estimates for avoiding obesity [body mass index (BMI) >30] were

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Abbreviations: ACTH - adrenocorticotrophic hormone; BDNF - brain-derived neurotrophic factor; BMI - body mass index; CNS - central nervous system; CON - concentric contraction of muscles; GH - Growth hormone; ECC - eccentric contraction of muscles; FGF 21 - fibroblast growth factor 21; FM - fat mass; FFM - fat free mass; HIIT - high intensity interval training; HR - heart rate; IL - interleukin; IR - insulin resistance; PRL - prolactin; VO_2max - maximum oxygen consumption

3.66% (95% CI: 2.30%, 5.01%) (Ekelund et al. 2015). These results suggest that efforts to encourage even small activity increase in the inactive individuals may be beneficial for the public health. According to the American Heart Association/American College for Cardiology (AHA/ACC), the main strategy in management of the obesity prevention and treatment is the identification of patients who need to lose weight (BMI and waist circumference) (Millen et al. 2014b). A state-of-the-art guideline of AHA/ACC (Millen et al. 2014a) has recommended three treatment modalities to reach weight loss: dietary modification, comprehensive life style change (diet and exercise), and bariatric surgery. Therefore, the obesity management should not be focused only to the weight (and BMI) reduction; more attention should be paid to waist circumference, **the improvement in body composition,** which is focused on, at least, the maintaining or increasing of the fat-free mass (FFM) and decreasing the fat mass (Tsigos et al. 2011; Yumuk et al. 2014). Even more, the recent study have shown that long-term exercise (9 months of resistance training) may lead to an increase in the resting metabolic rate (RMR) ~5% on average. However, there exists a wide variability between individuals, which can be partially accounted to FFM and thyroid hormones changes (Aristizabal et al. 2014). Therefore, appropriate dietary regimen and physical activity may have benefits over their contribution to increased energy expenditure.

The aim of this review was to summarize, evaluate, and clarify the literature data focusing on the endocrine responses to different types of exercise including frequency, intensity, and type of movement associated with the fat loss strategies. These endocrine responses to muscle actions may be also affected by other factors, including training status (Kraemer et al. 1998a,b), resistance exercise muscle groups (lower and upper body; e.g. (Hakkinen et al. 1998), load/volume (Gotshalk et al. 1997), time-under tension (Goto et al. 2009; Burd et al. 2012), and rest-period intervals between sets (de Salles et al. 2009), gender (Heavens et al. 2014), and age (Kraemer et al. 1998a).

The exercise intensity is one of the most important factors to determine the rate of the fat oxidation. Although, several studies have described the relationship between the exercise intensity and fat oxidation, this relationship was only recently studied in a wider range of intensities (Achten and Jeukendrup 2004). In absolute terms, carbohydrate oxidation increases proportionally with the intensity of exercise, whereas the rate of the fat oxidation initially increases, but at higher exercise intensities it decreases again (see Fig. 1). Maximal rates of fat oxidation have been shown to be reached at intensities between 59% and 64% of maximum oxygen consumption (VO_2 max) in trained individuals and between 47% and 52% of maximum oxygen consumption in a large sample of the general population (Achten and

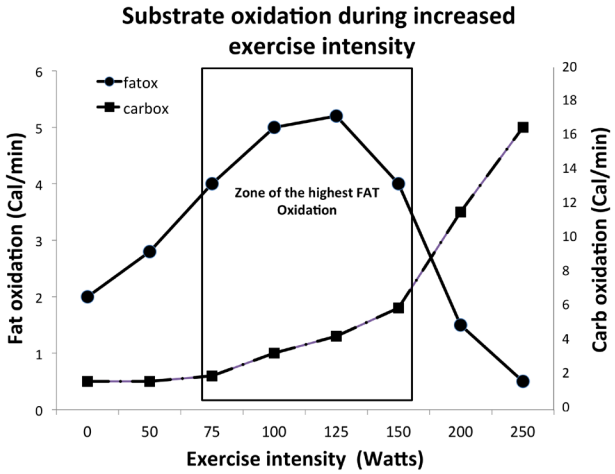

Fig. 1. Exercise intensity and fat oxidation. Fat oxidation increases from low to moderate exercise intensities, peaks at Fatmax, and decreases as the exercise intensity increases further (according Achten and Jeukendrup 2004).
Fatox - fat oxidation; Carbox - carbohydrate oxidation

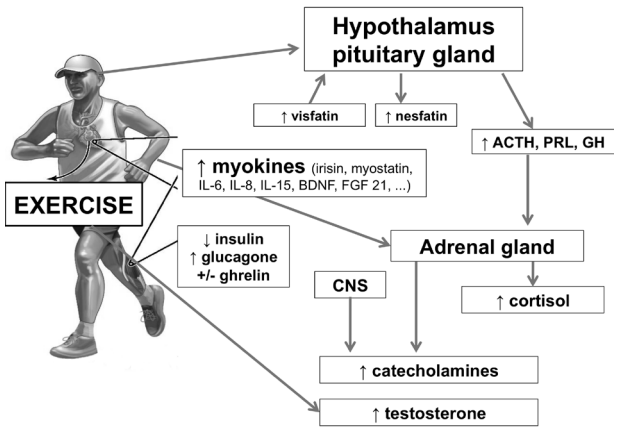

Fig. 2. Exercise induces a rise in many hormones and peptides. ACTH - adrenocorticotropic hormone; GH - growth hormone; PRL - prolactin; CNS - central nervous system; IL - interleukin; BDNF - brain-derived neurotrophic hormone; FGF 21 - fibroblast growth factor 21

Jeukendrup 2004). The mode of exercise can also affect the fat oxidation, whereas the fat oxidation is higher during running than cycling. Endurance training induces multitude adaptations that result in an increased fat oxidation. Ingestion of carbohydrate several hours before or on the commencement of exercise may significantly reduce the rate of the fat oxidation compared with fasted conditions, whereas fasting longer than 6 h optimizes the fat oxidation (Achten and Jeukendrup 2004).

Acute exercise leads to an increase in the production and release of many hormones: catecholamines, growth hormone, glucagon, testosterone, adrenocorticotrophic hormone (ACTH), cortisol, and prolactin, whereas each of them has local as well as systemic effect (Galbo 1995; Ball 2015) (Fig. 2). Exercise induces a rise in catecholamines that has been observed across a wide range of exercise modalities (Christensen and Brandsborg 1973; Galbo et al. 1975); it is exercise- intensity dependent (Galbo et al. 1975) and is diminished with training (Winder et al. 1978; Zouhal et al. 2001). Therefore, it is lower in trained individuals than untrained ones (Jacob et al. 2002, 2004). Adrenergic receptor activation in adipose tissue is known to increase the lipolytic rate by liberation of non-esterified fatty acids (NEFAs) from triacylglycerol stores (Arner 2005). Therefore, it may be expected that elevation in the epinephrine and norepinephrine circulating levels may lead to an increase of NEFAs availability. During the later stages of the prolonged intermittent exercise (6 h) of moderate intensity, a shift in fuel utilization from carbohydrate to fatty acids may be expected (Spriet 2014 a,b). Arner et al. (1990) have demonstrated that during the exercise, β-adrenergic stimulation is the principal mechanism in the adipose tissue lipolysis activation.

Weight lifting during the dynamic resistance exercise necessitates a force production during the muscle shortening (concentric contraction; CON), whereas weight lowering (eccentric contraction; ECC) requires force production during the muscle lengthening. Actually, Kraemer and Castracane (2015) and Cadore et al. (2014) have reviewed the current knowledge regarding the different endocrine responses and adaptations to CON and ECC muscle actions. The review has been specifically focused on studies that have investigated anabolic [growth hormone (GH), testosterone, free testosterone, insulin-like growth factor I (IGF-1)] and gluco- and appetite- regulatory (insulin, C-peptide, amylin, cortisol, ghrelin) hormone responses and adaptations to ECC muscle actions compared with CON muscle actions. GH, IGF-I, and testosterone are known to have an important anabolic effect on protein synthesis and maintenance or improvement of the muscle mass, which is particularly important for moderate and older populations at risk for loss of muscle mass. These anabolic effects are very well described in the review of Kraemer and Castracane (2015). Collectively, many studies have suggested that resistance exercise training increases GH and testosterone concentrations in young and middle-aged men (Arazi et al. 2013) and GH in women (Seo et al. 2010). Thus, using the ECC resistance exercise in older populations should be considered as an important medical treatment option. The significant increases in GH, IGF-I, and testosterone, induced by ECC muscle actions with moderate loading, can be used to elicit anabolic hormone responses that are expected to lead to an improved muscle mass in the aging population, at risk for sarcopenia (Ali and Garcia 2014; Sato and Iemitsu 2015). Taking into account the specificities of aging, modified version of the High-Intensity Interval Training (HIIT) may be a time-saving and effective way for olders. It less fits to adults to stay in shape.

In the study of Shaner et al. (2014), **the effect of resistance exercise selection on the acute hormonal response**, using similar lower-body multi joint movement, free weight and machine weight exercises, has been examined. Ten resistance trained men completed 6 sets of 10 repetitions of squat or leg press at the same relative intensity separated by one week. The exercise increased the testosterone and GH levels immediately after, whereas their concentrations were greater in the squat than leg press procedure. GH levels were also greater in the squat than leg press 15 and 30 min after exercise (Shaner et al. 2014). Cortisol was higher after exercise, greater after the squat than leg press. Although, the total work (external load and body mass moved) was greater in the squat than leg press, rating of the perceived exertion did not differ between these modes. Free weight exercises seem to induce greater hormonal responses to resistance exercise than machine weight exercise, using similar lower-body multi joint movements and primary movers (Shaner et al. 2014). Recent studies have shown that sex steroidogenesis-related mRNA and protein expressions, 5α-reductase and aromatase cytochrome P-450 enzymes, were detected in the skeletal muscle, while testosterone, estradiol, and 5α-dihydrotestosterone (DHT), were locally synthesized in skeletal muscle from dehydroepiandrosterone (DHEA) (Larionov et al. 2003).

Important aspect of the exercise and training programs/protocols is the **frequency**. Koudourakis et al.

(2014) have studied different seasonal strength programs (high, moderate and low) on the androgen levels and performance parameters in professional players of soccer at the pre-season period, middle (mid-point), and end of the competition periods (end-point). In all groups, the performance parameters (VO_2max, squad-jump, countermovement-jump, 10 m and 20 m sprint) increased significantly until the mid-point. The performance further increased only in group with high strength intensity, i.e. only for jumping and sprinting ability between end-point vs. mid-point. Only the training program of high strength intensity increased the testosterone levels as well as the metabolic product of activated testosterone 3a-androstendiol glucuronide (3a-Diol-G) at all point-measurements. Marginal significant effect was detected in the second group (moderate) and non-significant effect in the third group (low). They also found a borderline significant negative correlation between 3a-Diol-G and VO_2max in the second group (moderate) at mid-point (Koundourakis et al. 2014). Authors´ findings have suggested that the volume of strength training combined with intensive soccer training may cause an elevation in circulating androgen levels parallel with the induction of performance capacity. These authors have also suggested that the elevation of endogenous androgens, as a result of the volume of strength training, may indicate that the only method to improve athletic performance is hard training. There are no substitutes or shortcuts available, i.e. if the body requires more androgens, it will produce them endogenously (Koundourakis et al. 2014). In another study (Smilios et al. 2014), hormonal responses to resistance exercise (4 sets of squat and 4 sets of leg-press exercises, 8 repetitions/set, 10-repetition) performed with maximum and submaximum movement velocities, have been reported. The first exercise protocol was performed at maximum velocity (Vmax), the second at 70% of Vmax with equal training volume (70%VmaxEV) to Vmax, and the third at 70% of Vmax (70%Vmax) with a 10.6% higher training volume to Vmax. Testosterone and GH increased after all exercise performances compared with baseline and were higher versus control values. Cortisol concentrations gradually decreased by 70%Vmax, 70%VmaxEV in control protocols following a typical circadian rhythm, but remained relatively constant in Vmax protocol (Smilios et al. 2014). GH was higher in 70%Vmax vs. Vmax, while cortisol was higher in Vmax versus 70%VmaxEV and control. The greatest reduction in vertical jump and increase in heart rate was observed after the VO_2max protocol. A hypertrophy type resistance exercise protocol, performed at the maximum movement velocity, increases testosterone and GH and generates a greater biological stress, as evident by higher cortisol concentrations and heart rate responses and a greater reduction in neuromuscular performance. However, a protocol performed at submaximum movement velocity, combined with greater training volume, stimulated to a greater extent the GH response with no effect on cortisol (Smilios et al. 2014).

Budnar et al. (2014) have examined acute hormonal response to the kettlebell swing exercise (12 rounds of 30 seconds of 16 kg kettlebell swings alternated with 30 seconds of rest) in ten recreationally resistance trained men. Testosterone was significantly higher immediately after than before the exercise and also 15 and 30 min after the exercise. GH was higher immediately after 15 and 30 min of the exercise than before. Cortisol was higher immediately after and 15 min after the exercise than 30 min after and before the exercise (Budnar et al. 2014). The above mentioned authors have concluded that the exercise protocol produced an acute increase in he hormones involved in the muscle adaptations and thus the kettlebell swing exercise might provide a good supplement to resistance training programs (Budnar et al. 2014). Testosterone peaked immediately after exercise and GH had longer-lasting peak, lasting up to the 15th min copying the short cortisol peak. Peake et al. (2014) have compared the isoenergetic high intensity interval training (HIIT) and work-matched moderate-intensity continuous exercise (MOD). They have found that plasma ACTH ($p=0.019$), cortisol ($p<0.01$), and GH ($p<0.01$) were all higher immediately after HIIT. They did not find any differences between HIIT and MOD training programs in plasma norepinephrine and interleukin-6 (IL-6) immediately after exercise. It has been suggested that short acute cortisol elevation after hard and intensive exercise might have positive effect on the health, in contrast to chronic elevated cortisol levels (Skoluda et al. 2011; Shaner et al. 2014). Acute resistance exercise program variables include: 1) choice of exercise; 2) amount of resistance used (boat); 3) volume (total number of sets, repetitions, and load); 4) the sequence of exercises performed and 5) rest intervals between sets and exercises (Kraemer et al. 2003; Kraemer and Ratamess 2005). It has to be mentioning that intensive aerobic exercise, specifically endurance sports such is marathon run as a "chronic long term stress" induces significant increase of serum cortisol and prolactin levels one hour after the race, whereas they return to baseline one week later. Total testosterone

as well as free testosterone levels dropped significantly one hour after the race but also returned to baseline one week later (Karkoulias et al. 2008). Recent data suggest that repeated physical stress of intensive training and competitive races among endurance athletes is associated with elevated cortisol exposure over prolonged periods of time. These findings may have important implications with regard to somatic and mental health of athletes (Skoluda et al. 2011) and may also lead to an unfavorable health effect (Trivax and McCullough 2012). Therefore, the free testosterone to cortisol (fTC) ratio has been proposed as biomarker for overreaching-overtraining (i.e., training stress or imbalance) and it is necessary for a moderately high diet of carbohydrates to be consumed to maintain validity of any observed changes in the ratio value (Lane et al. 2010).

In the study of Heavens et al. (2014), the effect of high intensity and short rest resistance exercise on testosterone levels and muscle damage markers in both men and women has been demonstrated. The data of this study indicate that within and between sexes, universal load prescription (as assigned in extreme conditioning programs) creates extreme ranges in individual training intensities. The exercise intensity has been proposed to be the main factor determining the degree of muscle damage. The purpose of that study was to examine markers of muscle damage in resistance-trained men and women from a high intensity and short rest resistance exercise protocol. It consisted of a descending pyramid scheme starting at 10 repetitions, decreasing 1 repetition per set for the back squat, bench press, and dead lift, as fast as possible. Women demonstrated significant increases in IL-6 immediately after exercise; creatine kinase 24 h after exercise; and myoglobin immediately after and 15 and 60 min after exercise and a greater relative increase when compared with men 15 and 60 min after exercise. Men demonstrated significant increases in myoglobin immediately after and 15 and 60 min, and 24 h after exercise; IL-6 immediately after and 15 min after exercise; and creatine kinase immediately after and 60 min and 24 h after exercise. Testosterone levels also peaked immediately after and 15 min after the exercise. There were significant sex interactions observed in creatine kinase immediately after, 60 min and 24 h after exercise and testosterone in all times measured after exercise. Women completed the protocol faster (5 min averaged) and at a slightly higher intensity, however, men performed significantly more work (14384 kg vs. 8774 kg averaged). Overall, women demonstrated a faster inflammatory response with increased acute damage, whereas men demonstrated a greater prolonged damage response (Heavens et al. 2014). Authors have concluded that the strength of conditioning professionals need to be aware of the level of stress to be exposed when creating such volitional high intensity metabolic type workouts and allow for adequate progression and recovery from such workouts. The significant differences in testosterone levels up to 24 h after exercise may explain why the weight training is more muscle hypertrophy effective in men, than in women.

Exercise and appetite hormones

Exercise has been shown to reduce the circulating **insulin** concentration (Ahlborg et al. 1974; Wahren et al. 1984), but the rate of muscle glucose uptake can increase by tenfold during exercise. It is also well known, that resistance training may improve the muscle insulin sensitivity and β-cell function in obese patients (Croymans et al. 2013). HIIE three times per week for 15 weeks compared to the same frequency of steady-state exercise was associated with significant reductions in total body fat, subcutaneous leg and trunk fat, and insulin resistance in young women (Trapp et al. 2008). A 35% rise in glucagon concentration was positively correlated with the exercise intensity increase (Galbo et al. 1975). The metabolic effect of **glucagon** is indirect; overall, an increase in contractile activity of muscle will accelerate the rate of glucose uptake and in an effort to maintain euglycemia hepatic glucose production is accelerated through an increase in glycogenolysis and gluconeogenesis. The interaction of post-exercise metabolic processes and increased amino acid availability maximizes the stimulation of muscle protein synthesis and results in even a greater muscle anabolism when dietary amino acids are not present. Hormones, especially insulin and testosterone, play an important role as regulators of muscle protein synthesis and muscle hypertrophy. Following exercise, insulin has only a permissive role on muscle protein synthesis, but it appears to inhibit the increase of muscle protein breakdown. Ingestion of only small amounts of amino acids, combined with carbohydrates, can transiently increase the muscle protein anabolism (Tipton and Wolfe 2001).

Visfatin, also known as pre-B cell colony-enhancing factor (PBEF), is produced by the visceral adipose tissue. It belongs to adipokines that are associated with hyperlipidemia and insulin resistance (Berndt et al. 2005). The expression of visfatin is increased in individuals with abdominal obesity and type 2 diabetes (Fukuhara et al.

2005). There are limited data available, regarding the effects of ECC muscle action on adipokines. Recently, Jamurtas et al. (2013) have examined the effect of 45 min of downhill running on several adipokines, including adiponectin, resistin, and visfatin. **Adiponectin** and visfatin did not change following the ECC exercise. **Resistin** increased significantly in response to exercise, but this occurred only two days afterwards. Twelve-weeks of supervised exercise program (5 days per week, 60 min exercise at 85% of HRmax) resulted in body weight reduction improvement of physical fitness and decreased visfatin which correlates with the improved glucose tolerance (Haus et al. 2009). Similar results of decreased levels of visfatin after 12 weeks of aerobic training in adolescences have been published by Lee et al. (2010). Plasma visfatin increased after high-intensity exercise (running-based anaerobic sprint) in men. Therefore, it may sensitize tissues for post-exercise glucose uptake and glycogen restoration (Ghanbari-Niaki et al. 2010), a temporary and early postexercise anorexigenic metabolic state. Similarly, Ahmed et al. (2014) have found significantly increased serum visfatin after exhaustive exercise.

Nesfatin-1 is a neuropeptide, produced in the hypothalamus of mammals, which contributes to diminish hunger, a "sense of fullness", and thus a potential loss of body fat and weight (Oh et al. 2006). Increased AMP-activated protein kinase (AMPK) phosphorylation by central nesfatin-1 has been also responsible for the improved glucose uptake in skeletal muscles (Stengel et al. 2009). Mohebbi et al. (2015) have found decrease in the plasma levels of nesfatin-1 and leptin after exercise at the individual anaerobic threshold (IAT) intensity, which remained lower than baseline following 45 min of recovery. However, nesfatin-1 and leptin levels did not change significantly in any of the time courses of Fatmax intensity. Plasma epinephrine concentrations increased during exercise of both intensities only at the IAT. In addition, a significant correlation has been found among nesfatin-1 levels with insulin and glucose at basal and exercise conditions. These results have indicated that IAT has a greater exercise-induced appetite regulation effect compared with Fatmax. Ahmadizad et al. (2015) have studied effect of 6 weeks of high-intensity interval training (HIIT) and moderate-intensity continuous exercise training (MCT; 3 days per week followed by a week of detraining) on nesfatin-1 in 30 sedentary overweight men who were divided into three (n=10) body mass index-matched groups. They found that nesfatin increased significantly only with HIIT compared with the control group ($p<0.05$). After a detraining period, the plasma nesfatin-1 did not return to the pre-training levels in the HIIT group. HIIT seems to have better anorectic effects (as indicated by nesfatin) compared with MCT.

Ghrelin is an orexigenic hormone, produced primarily in the stomach fundus and less in other regions of the gastrointestinal track (Kraemer and Castracane 2010). When released in greater concentrations during fasting, ghrelin transmits a peripheral hunger signal via stimulation of the hypothalamic arcuate nucleus neurons in the hypothalamus which, in turn, increases the expression of neuropeptide Y and agouti-related peptide (Nakazato et al. 2001). Jurimae et al. (2007) have found no increase of plasma ghrelin concentration in neither of the exercise intensities in highly trained subjects. There were no changes found in the plasma leptin levels. GH increased significantly immediately after exercise and remained elevated during 30 min of recovery in both exercise conditions. Insulin decreased significantly immediately after exercise and remained significantly lower after 30 min of recovery in both exercise intensities. Baseline ghrelin was not correlated with the body composition, physical performance or blood biochemical data. The acute constant load sculling exercise above or below the individual anaerobic threshold that increased GH concentrations did not significantly increase the circulating plasma ghrelin levels. Similarly, Ozcan et al. (2015) did not find changes in leptin and ghrelin concentration after 16 weeks of aerobic exercise (AE) and core exercise programs (4 times per week) in sedentary middle-aged women. On the other hand, Thomas et al. (2012) have found higher ghrelin response to a single bout of high-volume resistance exercise associated with lower cortisol response only in obese individuals in comparison with the lean subjects. It has been suggested that the level of obesity and higher body fat percentage are important indicators of the hormonal response to exercise. Four weeks of cycling (30~min/day, 5 days/week) at 70%VO_2max led to a reduction of circulating leptin in obese adult males (48.0 ± 8.0 years) with type 2 diabetes, which was accompanied by a loss of body weight (Yamaguchi et al. 2011).

Jurimae et al. (2006) have found no change in **adiponectin** levels in a single exercise session in male rowers immediately after the exercise. However, adiponectin was significantly increased above the resting value after the first 30 min of recovery (+14.7%; $p<0.05$). Similarly, **leptin** levels were unchanged immediately after exercise and significantly decreased after the first 30 min of

recovery (-18.2%; $p<0.05$). Plasma insulin levels were significantly reduced immediately after exercise and remained significantly lower during the first 30 min of the recovery period. Glucose increased with exercise and returned to the pre-exercise level after the first 30 min of recovery. Basal adiponectin was significantly related to VO_2max (r=-0.62; p=0.034).

Skeletal muscle is an endocrine organ

The mechanisms underlying the improvement of the human physical condition have been revealed: skeletal muscle synthesizes and secretes multiple factors and these muscle-derived factors, so-called **myokines**, have autocrine, paracrine, or systemic effects and exert beneficial effects on peripheral and remote organs. Many papers have been published about the skeletal muscle production of myokines [interleukins, transforming growth factor-β (TGF-β), myostatin, myonectin, angiopoietin-like 4, irisin, bone morphogenic factor, brain derived neurotrophic factor (BDNF), fibroblast growth factor 21 (FGF21), vascular endothelial growth factor (VEGF), follistatin-like 1), etc. (Pedersen et al. 2007; Pedersen and Febbraio 2008; Pedersen 2013). Thus, muscle tissue is a critical endocrine organ that serves in the regulation of several physiological and metabolic events (Pedersen 2013; Raschke et al. 2013; Makela et al. 2014). It has been suggested that both skeletal muscle and adipose tissue are functioning as integrated endocrine organs in response to an exercise stimulus (Pedersen 2013).

Irisin is a myokine secreted by contracting of the skeletal muscle, possibly mediating some exercise health benefits via browning of white adipose tissue. Bostrom et al. (2012) have documented a twofold increase in irisin levels in eight healthy middle-aged men after 10 weeks of supervised aerobic training. However, the increase in basal irisin levels needs to be supported by independent investigators who conversely have reported either a decrease (Norheim et al. 2014) or no change (Kurdiova et al. 2014b; Hecksteden et al. 2015) in plasma irisin following aerobic (Kurdiova et al. 2014a,b; Norheim et al. 2014; Hecksteden et al. 2015) and strength training programs (Hecksteden et al. 2015). Scharhag-Rosenberger et al. (2014) have investigated the effects of 6 month preventive resistance training program on the resting metabolic rate (RMR), fat free mass (FFM), and irisin in 74 sedentary, healthy male and female participants. Resistance training elicits an increase in RMR. However, in contrast to the currently discussed hypotheses, this increase does not seem to be mediated by training-induced changes in FFM or circulating irisin concentration, which evokes a doubt in the meaning of irisin for human energy balance (Scharhag-Rosenberger et al. 2014). Tanisawa et al. (2014) have found that serum irisin concentration negatively correlated with age and was not associated with the oxygen uptake peak (VO_2 peak). Loffler et al. (2015) have reported that irisin levels decrease in adults with age, they are higher in men than women, and they are higher in obese than lean control subjects. Irisin levels were closely correlated with muscle-associated bio-impedance parameters like fat-free-mass and body-cell-mass. They have identified a clear and immediate increase in serum irisin levels after acute strenuous exercise (cycling ergometry) and 30 min bout of intensive exercise in children and young adults, whereas longer (six weeks) or chronic (one year) increase in physical activity did not affect irisin levels. Hew-Butler et al. (2015) have described lower irisin levels in runners vs. non-runners before as well as after the VO_2 Peak test and lower irisin in non-runners after completion of the training program. None of these favorable exercise effects were positively associated with plasma irisin. Huh et al. (2015) have shown that circulating irisin increases immediately after HIIT, continuous moderate-intensity exercise (CME), and resistance exercise (RE) and declines one hour later. The increase was greater in response to resistance compared with either high-intensity intermittent exercise or CME. Change in irisin in response to exercise did not differ between individuals with and without metabolic syndrome. Whether increased irisin levels after exercise may contribute to the beneficial effects of exercise on patients with the metabolic syndrome remains to be studied further.

Brain-derived neurotrophic factor (BDNF) is synthesized mainly in the central nervous system, but also in the periphery by skeletal muscles (Mousavi and Jasmin 2006). Most of the BDNF that is produced by muscles is used locally at the neuromuscular junction (Fujimura et al. 2002; Matthews et al. 2009). In humans, BDNF release from the brain was observed at rest which increased 2- to 3-fold during exercise (Rasmussen et al. 2009). During the rest as well as exercise, the brain contributed by 70–80% of the circulating BDNF, while this contribution decreased following one hour of recovery (Rasmussen et al. 2009). Babaei et al. (2014) have described lower basal serum BDNF in the athletes group compared to controls. Serum BDNF was inversely correlated with VO_2max, but positively with BMI. Both

single acute aerobic and anaerobic activities elevated serum BDNF in athletes and sedentary groups compared with the rest. This study suggest that long-term habitual exercise is associated with lower peripheral BDNF and better intermediate with memory. However, acute form of intensive activity, either aerobic or anaerobic, are capable to elevate serum BDNF level in both sedentary and athletes. Tsai et al. (2014) have found elevated serum BDNF levels after an acute bout of 30 min of moderate intensity aerobic exercise in young adults with different cardiorespiratory fitness.

Eight-week endurance training program improved aerobic capacity and decreased fat mass, but had no effect on interleukin 6, **fibroblast growth factor 21 (FGF21)**, myostatin or irisin mRNA levels in muscle after training in obese non-diabetic male subjects. However, apelin mRNA levels increased twofold in muscle but not in adipose tissue (Besse-Patin et al. 2014). Moreover, **apelin** was significantly expressed and secreted in primary human myotubes and changes in the muscle apelin mRNA levels were positively related to whole-body insulin sensitivity improvement. Data of the recent study of Kim et al. (2013) have suggested that FGF21 may also be associated with exercise-induced lipolysis in addition to increased catecholamines and reduced insulin. They have found increased FGF21 levels in the serum of healthy male volunteers performing a treadmill run at 50 or 80% VO_2max (Kim et al. 2013).

Myostatin (growth differentiation factor 8) is a protein that is secreted as a growth differentiation factor, produced primarily in skeletal myocytes. Myostatin inhibits muscle differentiation and growth in the process, known as myogenesis. Therefore, it is a catabolic regulator of skeletal muscle mass growth. Saremi et al. (2010) have shown that creatine supplementation in conjunction with resistance training may lead to greater decreases in the serum myostatin levels, which may explain the increase in muscle mass that can be amplified by creatine supplementation (Saremi et al. 2010). For more details of muscle produced interleukins see the review of Pedersen (2013).

Conclusions

The regular exercise may acutely increase the fat oxidation, which decreases the fat and increases the muscle mass, resulting in increased energy expenditure. Endocrine responses to muscle actions are affected by many factors, including the exercise muscle groups (lower and upper body), load/volume, time-under tension, and rest-period intervals between sets, training status, gender, and age. The proper choice of the exercise type (resistance, endurance, combined, high intensity interval training), exercise intensity, volume, and load, should be considered individually to induce a proper endocrine responses to start and achieve successful fat loss. Moreover, exercise has a positive effect on the physical (improved insulin sensitivity, lipid profile, etc.) and mental health (mood, cognition, memory, sleep, etc.). Rather, it is proposed that reducing fat mass and increasing cardiorespiratory fitness through improving nutritional quality, reducing sedentary behaviors, and increasing participation to physical activity/exercise might be associated with clinical benefits, sometimes even in the absence of weight loss.

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