

Physical Activity and Obesity Related Hormones

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Article information	Abstract
<p>Article history: Received: 4 Jan 2012 Accepted: 26 Apr 2012 Available online: 29 Dec 2013 ZJRMS 2014 Aug; 16(8): 6-11</p> <p>Keywords: Physical activity Exercise Obesity Hormones</p> <p>*Corresponding author at: Cellular and Molecular Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: hedayati@endocrine.ac.ir</p>	<p>Probably, obesity can be considered as the most common metabolic disorder. In other words, the control of metabolism is disrupted in this condition. The most important metabolic control is performed by hormones. Today, adipose tissue is considered as an active tissue in secretion of hormones. In obesity, in addition to adipose tissue hormones, effective neuropeptides on appetite are interfered. There are 4 main approaches in the management and treatment of obesity including nutrition and diet therapy, physical activity, medical and surgical approaches. The specialists and obese patients prefer the first and second approaches. Physical activity helps to control and treat this disorder by influencing on obesity-related hormones. The main obesity-related hormones are ghrelin, agouti, obestatin, leptin, adiponectin, nesfatin, visfatin, tumor necrosis factor, interleukin-6, and resistin. In this review, the effect of physical activity on 10 major obesity-related hormones has been discussed.</p>

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Introduction

Obesity is an increasing metabolic complication which has influenced developed and developing countries. Obesity has genetic origin with central and environmental factors and is also related to lifestyle. Lifestyle-related factors such as diet, socio-cultural issues and physical activity are responsible for the increased prevalence of this complication in recent years [1]. Alignment of body weight is a very complex and precise controlled process and the peptides which are generated in brain and stomach play an important role in this process [2]. Adipose tissue is as an endocrine organ, a complex and highly active metabolic that in addition to the transmission of afferent messages from different hormonal systems and the central nervous system, causes the secretion of secreted factors with endocrine functions. These factors include leptin, adiponectin, resistin and other adipocytokines [3]. Brain regulates energy homeostasis in response to adipose tissue signals, the gastro-intestinal (GI) path and its connection with central nervous system (CNS) which is considered as an important role in appetite regulation [2]. Furthermore, obesity is a condition that is introduced by the characteristics of a mild systemic inflammation. Inflammation is the main mechanism of atherosclerosis and insulin resistance. In this situation, inflammatory markers such as pre-inflammatory cytokines and acute-phase proteins will be increased in blood [4]. The results of the studies have demonstrated that production of high volume of inflammatory cytokines such as interleukin-6

(IL-6), TNF- α (Tumor Necrosis Factor- α) and CRP (C-Reactive Protein) by the adipose tissue play a role in causing insulin resistance, diabetes and the metabolic syndrome [5]. The aim of the present study is a brief review on the effects of physical activity and 10 major obesity-related hormones.

Materials and Methods

In this study, PubMed and Google Scholar databases were searched between 2000-2012. Key words used for search were physical activity, exercise, training, obesity, adipokine, hormone, leptin, adiponectin, nesfatin, visfatin, ghrelin, obestatin, AgRP (Agouti-Related Peptide), IL-6, TNF- α , resistin. Initially, 142 articles were obtained by screening the titles and abstracts, papers with similar results were omitted, finally this review was written based on 50 articles.

Results

Ghrelin: Due to the effects of ghrelin on appetite and weight controlling, different researches have reported various results about the effect of exercise on ghrelin levels in plasma and various tissues. Some studies have shown that weight loss caused by exercise and the subsequent reduction in BMI (Body Mass Index) due to negative energy balance can alter the plasma levels of ghrelin [6]. Ghanbari-Niaki et al. evaluated the effect of 6

weeks of aerobic exercise on plasma ghrelin levels and soleus muscle of rats. Blood samples were prepared 48 h after the last session of exercise and in the status of satiety (4 h of food deprivation). Ghrelin levels in plasma and muscle of rats was decreased after 6 weeks of resistive exercise; also, at the end of the exercise program, no differences were found between plasma levels of glucose, insulin, and weight of subjects in control and experimental group [7].

Twelve weeks of aerobic exercise on a treadmill with moderate and severe intensity led to significant increase in ghrelin gene expression of gastrocnemius muscle and increase in ghrelin levels of plasma containing acyl in mouse [8]. In a review article, the effect of performing sport exercising on ghrelin was evaluated and concluded that weight loss caused by exercise increases blood ghrelin levels and people who lose more weight as a result of exercise, have higher blood levels of ghrelin compared to control group and those who lose less weight [6]. The plasma ghrelin levels can be regulated by the hormones such as insulin and metabolites such as glucose. Another study evaluated the plasma ghrelin response to the cons. Furthermore, after practicing and consumption of oral sugar after a session of aerobic activity in young academic men. The results showed that a session of aerobic activity led to significant increase in ghrelin levels and plasma growth hormones compared to resting time. Also, the levels of plasma cortisol and insulin were significantly decreased immediately after exercise and glucose was decreased immediately after exercise, but the decrease was not statistically significant [9].

We can conclude that the reduction in plasma glucose and insulin in the subjects can lead to increased plasma levels of ghrelin and ghrelin expression. Ghrelin response is different to various body exercise (acute and chronic) with different exercising methods and possibly exercises volume can play an important role in this field. Therefore it seems that ghrelin is very sensitive to changes in body weight and ghrelin increase is a compensatory response to weight loss. In other words, prolonged exercise leads to an increase in plasma ghrelin levels if weight loss occurred [6].

AgRP (Agouti-Related Peptide): Perhaps the most important aspect of AgRP function is its role in stimulation of food intake. Researchers believe that AgRP is the mediator of the effect of ghrelin on food intake. Chen et al. confirms the theory and demonstrated that by peripheral ghrelin injection of AgRP which its tonic effect on NPY-1 and AGRP-1 transgenic mouse does not occur. So, ghrelin calls AGRP to perform its role in food intake [10]. There are limited studies about tissue and plasma AGRP peptide response to physical activity and sports such a session or as exercises. Evaluation of the effect of one session of circular resistance exercise on AGRP in male students showed that serum AGRP levels are increased immediately after exercise. However, in this study, unlike previous research on animal models that showed fasting leads to increased AGRP, the controls which were fasting for 12 h showed no increase in AGRP [11]. In another study, the effect of 6 weeks of treadmill

running on resting levels of ghrelin, AGRP, ATP, and glycogen in the soleus muscle of rats were studied. The results of this study relatively confirm the primary hypothesis about the role of AGRP as a part of the glycogen over compensatory mechanism and applying ghrelin function by AGRP. In other words, the analysis of intracellular energy sources can be one of the possible mechanisms of changes in AGRP caused by exercise. Ghrelin decrease compared to AGRP demonstrated high sensitivity of this peptide compared to AGRP towards changes in muscle glycogen levels [7]. Fasting causes the energy negative balance in the body; in response to it, AGRP secretion of hypothalamic arcuate nucleus increases energy balance between food intake behavior and stimulated appetite. In the latest conducted study by Ghanbari-Niaki et al. AGRP response to a session of circular resistance exercises with different intensity which was evaluated in young academic women. The results of this study showed that AGRP expression of lymphocytes was increased in all given intensity (60, 40, 1-RM80, and a combination of intensity), and the highest expression was observed in 60% group. This led to increase and decrease of AGRP in plasma and lymphocyte, respectively and the most AGRP lymphocyte decrease was observed in 60% group. It should be noted that the lowest levels of lymphocyte and plasma GH was observed in the same group. Interestingly, lymphocyte ATP levels remained unchanged, but in spite of the decrease in glycogen levels, the high level of glycogen in 60% of resistance group was observed [12].

Obestatin: Obestatin which is mainly secreted by the stomach fundus cells and is secreted into blood and plays an important role in the regulation of food intake and body weight is known by Zhang et al. in mice stomach [13]. Zhang named this peptide as obestatin due to its inhibitory effect on appetite control. Although obestatin and ghrelin are both released from similar glandular cells, but have different secretory ratios so that total ghrelin ratio in blood is 10 to 20 times of obestatin [13]. Obesity and weight gain leads to decreased levels of plasma ghrelin and obestatin. In one study, three groups of women with normal weight, overweight and women with complications of anorexia nervosa were studied. The results showed that fasting plasma obestatin level of people with anorexia is significantly higher than those with normal weight. Plasma obestatin level in obese women is significantly lower. A similar pattern is seen for ghrelin levels [14]. Due to the effects of obestatin on energy balance, levels of this peptide may be affected by physical activity and causes changes in appetite and weight. It seems that the type, duration and intensity of exercises likely impact on obestatin levels [15]. About the effect of long-term resistive activities, Ghanbari-Niaki et al. evaluated the effect of 6 weeks of running on the total obestatin level of fundus and intestine [16]. The results indicated significant decrease of obestatin levels of fundus and small intestine in exercised rats and no significant change in the total plasma obestatin. This decrease was followed by significant increase of liver glycogen and plasma growth hormone and also

unchanged ATP levels of fundus and small intestine and increased GH levels fundus and small intestine may lead to inhibition of obestatin levels of fundus and small intestine through negative feedback. Reinehr et al. studied the effect of a year of diet with high carbohydrates, low fat and physical activity on serum ghrelin and obestatin hormone levels in obese children with a mean age of 11.2 years and concluded that this situation results in decrease leptin and insulin levels and increase in obestatin levels after loss of body weight, while ghrelin levels did not significantly change. The researchers concluded that increased obestatin after weight loss may cause a mechanism to maintain weight loss [17]. Ghanbari-Niaki et al. studied the response of plasma obestatin to a session of circular resistive activity with different intensity in 20 physical education students. The findings showed that a session of circular resistive activity with different intensity does not affect on plasma obestatin [18]. Furthermore, the effect of 4 weeks of circular resistive activity with intensity of 40% and 80% one Repetition Maximum (1RM) on plasma and lymphocyte of young women was evaluated; plasma obestatin levels in 80% 1RM intensity was significantly decreased and changes of lymphocyte obestatin levels were not significant in any of the 2 groups of intensity. Given that the ratio of ghrelin to obestatin levels in 80% 1RM group was significantly increased, it seems that presumably due to energy decrease caused by exercise. Ghrelin production has turned to the production of ghrelin and the ratio of ghrelin to obestatin is increased. This increase is likely for stimulation of food intake and compensation of lost resources of energy [15]. This information confirms the theory of loss of energy resources and obestatin increase.

Leptin and Adiponectin: Leptin is mainly secreted by adipose tissue and acts via affecting on the CNS especially the hypothalamus, preventing from food intake and the stimulation of energy expenditure as a warning mechanism to regulate body fat. Several studies have examined the effects of exercise and diet on leptin. There are many reasons for leptin response to physical activity. One reason is the reduction in fat mass and subsequently changes in leptin levels, this can provide an explanation of how exercise affects obesity [19].

Other adipose tissue-derived hormone that regulates energy homeostasis and insulin action were detected by Do et al. and named as adiponectin [20]. The molecular mechanisms by which adiponectin increases insulin sensitivity is apparently dependent to pathway activity of AMP-activated protein kinase (AMPK) that directly increases glucose absorption in muscle and also fatty acid oxidation in muscle and liver. Thus, decreased levels of adiponectin are associated with increased insulin resistance [21]. There are few studies about effects of exercise on concentrations of adiponectin. For example, a program of aerobic exercise at three different intensities had no effect on adiponectin and its isomers [22]. While the evaluation of the effect of exercise with different intensities on HMW (high-molecular weight) and its ratio to total adiponectin ratio showed that HMW adiponectin concentrations was increased at all 3 groups

with low, moderate and severe intensity compared to control group after 12 weeks of exercise and this increase in moderate and severe intensity groups was significant compared to control group [23]. About the effect of acute aerobic exercise on adiponectin and leptin, it has been shown that a single session of aerobic exercise for 45 minutes with approximately 65% of maximum oxygen consumption did not significantly change serum adiponectin levels, but the index of insulin resistance was increased and insulin concentrations was significantly decreased immediately after exercise [24].

In another study, serum leptin after the resistive exercise with intensity of 30%, 55% and 80% was decreased as 10%, 7% and 13%, respectively, but the difference was not statistically significant [25]. In this study, the intensity of resistance exercise had no effect on insulin resistance. Also, serum adiponectin was increased immediately after resistance exercise; however, the intensity of resistance exercise had no significant effect on serum adiponectin concentration. The results of a study which compared the effect of selective aerobic activity and hypo-caloric diet on serum leptin concentrations in women showed that both selective aerobic activity and hypo caloric diet lead to decreased serum leptin concentrations and were followed with weight loss in both groups in comparison with control group. In this study, hypo-caloric diet probably causes energy loss from the body's internal energy resources (fat deposits) and reduced BMI was associated with decreased serum leptin levels. Also, the limitation of energy intake through hypo-caloric diet is more than energy consumed through and this may explain more decreases of leptin with hypo-caloric diet [26]. One reason of leptin decrease in response to resistance exercise could be that because resistance exercise leads to increased insulin sensitivity in muscle cells, thus, absorption of glucose in fat cells is decreased which results in a decrease in leptin secretion.

Nesfatin-1: Nesfatin-1 is one of the anti-appetite proteins, which was detected in 2006 by Oh et al. [27]. This protein is expressed in cells that control appetite in rats and inhibits food intake at night and prevent from weight gain in rats [27]. The studies show that nesfatin-1 is affected by several factors such as fasting, again nutrition after fasting, diabetes, and physical activity and in hungry status. In these situation gene expression of NPY-2 in paraventricular nucleus of hypothalamus and nesfatin-1 concentration are decreased [27]. By expression of NPY-2 in arcuate nucleus, neurons are inhibited by nesfatin-1 peptide [28].

In a study, the effect of 8 week of resistive exercise with intensity of 20 m/min on treadmill on expression of nesfatin-1 gene and changes of its concentration was evaluated in the liver of rats and reported increased expression of nesfatin-1 in liver and its changes in response to resistance exercise [28]. Some studies have shown that fasting has similar effects of physical exercise on energy resources, specially ATP and glycogen in liver and muscle and can lead to a decrease of 18% of nesfatin-1 levels. Furthermore, food intake for 12 h in fasted rats, turn decreased nesfatin-1 back to normal [29].

Therefore, considering to the suggested role of nesfatin-1 in energy balance and food intake behavior, it seems that evaluation of this peptide behavior especially in the tissue out of hypothalamus, under conditions of possible changes in energy states by physical activity and sport help to clarify its importance as a major or minor player in the regulation of energy.

Visfatin: Visfatin was identified first by Fokohara et al. This adipocytokine is mainly expressed in visceral fat in obese humans and mice. In fact, obesity leads to increased expression and plasma concentrations of visfatin in humans and animals [30]. Although visfatin function is not yet completely known, but visfatin may have dual role, one is the autocrine/paracrine function which facilitate distinction and differentiation of fat cells in visceral adipose tissue and the other is the endocrine role of visfatin which mediates insulin sensitivity in peripheral organs. So visfatin may facilitate glucose control and lead to the development of obesity [31]. Several studies have been performed about visfatin response to exercise in human [31, 32].

Haider et al. evaluated the effects of aerobic exercise for 4 months on an ergometer bicycle with an intensity of 60-70% heart rate reserve for 1 h per session on visfatin levels of 18 patients with type I diabetes. In the first 2 weeks of the program, the number of sessions from 2 times per week reached to 3 times per week. Initially, patients had higher plasma visfatin and glucose levels than the control group. Nevertheless, no correlation was found between visfatin levels and age and BMI of the studied subjects. After 2 and 4 months of exercise, visfatin levels in the experimental group was significantly decreased and the effect continued 8 months after the end of the exercise program, however, BMI, fasting glucose, glycosylated hemoglobin and lipoprotein were unchanged during exercise [32].

In another study, the effect of aerobic and resistive exercise on plasma level of non-diabetics obese women aged 50-55 years was evaluated and the results showed that visfatin level was significantly decreased after 12 weeks of exercise [31]. About visfatin response to resistance exercise in women, the results of another study showed significant decrease in plasma visfatin and glucose levels after 8 weeks of circular resistance exercise with intensity of 60-70% 1RM; while visfatin and insulin levels in the subjects of aerobic group (with an intensity of 80-85% heart rate reserve) was significantly decreased; also, body weight, BMI, percent of body fat and waist-hip ratio were significantly decreased in the experimental group than the control group [33].

TNF- α : TNF- α cytokine is produced as an inflammatory factor by NK cells, macrophages, and adipose tissue and is considered as one of the major intermediates of host defense against bacterial and viral infections [34]. TNF- α causes deterrence of lipoprotein lipase and stimulates lipolysis in adipocytes and leads to increase of unsaturated fatty acids in the blood which causes increased insulin resistance and diabetes [35]. Previous studies reported decreasing effect of long-term period of resistive and aerobic exercise on resting level of TNF- α

[36, 37]. While 1 study showed no effect of 10 weeks of resistive and aerobic exercise on resting level of TNF- α in man, Greiwe et al. reported decreased expression of this cytokine after 3 months of resistive exercise in old men [38]. Therefore, the difference in results can be due to duration of exercise methods, loading method, and the time of sampling.

Interleukin -6: Interleukin -6 (IL-6) is produced in many cells and some tissues such as adipose tissue and its production is increased in obesity [5]. Many researchers introduced IL-6 as a marker of insulin resistance and the factors involved in its incidence [39]. Various studies are performed in the area of the effect of exercise on these inflammatory parameters and most of them have shown that aerobic exercise has significantly decreased environmental inflammatory factors such as IL-6 and TNF- α in healthy people [40]. But another study showed non-significant decrease in IL-6 after resistive exercise [41]. Also Neubauer et al. reported increased plasma levels of IL-6 after resistive exercise [42].

Some studies evaluated the effects of resistive exercise on inflammatory indicators. In a study, the effects of 12 months of moderate-intensity resistive exercise on inflammatory parameters in obese women were studied and the results showed moderate resistive exercise keeps the level of inflammatory indicators low [43]. The effect of a 6-week resistive exercise with moderate and severe intensity on inflammatory marker IL-6 was evaluated in healthy young men and showed that IL-6 concentration was slightly increased in the post-test than pre-test. In addition, due to non-significant difference between the level of IL-6 in two experimental groups 1 and 2 in post-test, intensity of exercise most likely had no effect on plasma levels of IL-6 [44]. So, due to the lack of alignment in the results of researches in this area, it seems there is still no consistent information about the effect of resistive exercise in general and the effect of its intensity specifically on the important inflammatory markers. Moreover, severe contraction can affect on the production and secretion of IL-6, and express the damage caused by exercise as the initial stimulus of IL-6 production. Change in the plasma IL-6 during exercise could be related to the intensity and duration of physical activity, used muscle mass and resistive capacity of the people. Also, regular physical activity has a beneficial effect and can cause decreased systemic inflammation, so that consistently performing physical activity by overweight people can reduce levels of inflammatory cytokines and then improvements in insulin sensitivity.

Resistin: Resistin is a cysteine-rich peptide hormone which has 108 amino acids. The level of this hormone is high in diabetic and obese people. In humans, this hormone is mainly made in inflammatory cells and lipids [45]. Resistin cause disorder in glucose and lipid metabolism and leads to increasing the risk of atherosclerosis, also stimulates the pro-inflammatory cytokines and leads to increased vulnerability of atherosclerotic plaques [46]. About the effects of exercise on resistin levels, it has been reported that a session of submaximal aerobic exercise in healthy men and

overweight men does not significantly change the resistin levels until 48 hours after exercise [24]. Also, the effect of 8 months of aerobic exercise on decreasing resistin levels has been shown [47].

Another study showed significant increase in resistin after 8 weeks of aerobic exercise [48]. Camera et al. also reported that 10-day of severe resistive exercise in young men without exercise has increased the expression of resistin gene in adipose tissue [49]. In another study, resistin levels were not significantly different between athletes of resistive exercise who ran averagely 48 miles per week and sedentary healthy subjects and also the people who had decreased daily caloric intake to half [50]. So, we can conclude that the studies that evaluated the effect.

Discussion

The role of overweight and obesity has been demonstrated in cardiovascular disease and diabetes and the effects of adipose tissue hormones were studied in this disorder. Then, various interventions to manipulate hormones in adipose tissue were studied. Sports or physical activity interventions in changes of adipokines levels for weight loss and prevention of the consequences of overweight and obesity has been considerably noted. As described the effect of physical activity on changes of

adipokines levels, physical activity affects like a double-edged sword and depend on exercise type, intensity and duration could have positive or negative effects. For example, levels of ghrelin and agouti-like peptide which are appetizer can be reduced or obestatin which decrease appetite can be increased by appropriate physical activity. With appropriate adjustment of physical activity, leptin hormone can be reduced and adiponectin can be increased to improve the status of obesity and overweight through increased insulin sensitivity and increased oxidation of fat. Visfatin levels, tumor necrosis factor alpha, interleukin 6, resistin which mainly increase the obesity outcomes by increasing insulin resistance, inflammation, lipolysis and increased free fatty acid levels, all these hormones can be reduced through appropriate exercise protocol. However, lack of access to all published studies related to adipokines and physical activity and also limited studies performed about some adipokines, are considered as the limitations of this review article.

Authors' Contributions

All authors had equal role in design, work and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

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