Leptin, Heart Disease and Exercise

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Abstract: Obesity is a complex disorder characterized by the accumulation of excess adipose tissue. Discovery of the hormone leptin in 1994 catalyzed the field of obesity research by demonstrating the existence of an afferent hormonal signal from adipose tissue to the central nervous system. Leptin the product of the ob gene is a proteohormone with a molecular mass of 16 kDa that is thought to play a key role in the regulation of body weight. Leptin increases energy expenditure by enhancing sympathetic nervous activity and lypolysis. It also suppresses appetite by acting on the hypothalamus. In recent years the potential participation of leptin has been reported to increase arterial pressure and heart rate by peripherally or centrally mediated mechanisms. The finding that leptin is linked to heart disease risk, strongly suggests that fat may be important in heart disease risk. Leptin deficiency and resistance to the effects of leptin are each associated with weight gain. Leptin resistance is much more common than leptin deficiency in human obesity. There are receptors for leptin on the endothelium and on vascular smooth muscle cells. Accordingly, leptin can exert receptor mediated influence on vessel tone and growth. In cell culture, leptin stimulates vascular smooth muscle proliferation. Vascular calcification is also accelerate by leptin in experimental models. Additionally, leptin induces oxidative stress in endothelial cells. Accordingly, it is possible that the high level of leptin observed in obesity could contribute to its adverse effects on cardiovascular health. Diet and exercise have been shown to reduce leptin levels regardless of weight loss. Exercise training induced reduction in leptin levels have been attributed to alterations in energy balance, improvements in insulin sensitivity alterations in lipid metabolism and unknown factors. This article considers leptin function and the impact that exercise has on blood leptin concentrations.

Key words: Leptin %Risk factor %Exercise

INTRODUCTION

Obesity is an increasing prevalent metabolic disorder affecting not only the developed but also developing countries [1]. In fact obesity can be described as the "New World Syndrome" that is one of the most severe problems for the modern day health industry. Its prevalence has been rose in all age groups in the world [2]. Statistical data reveals that the problem of obesity has increased from 12-20% in men and from 16-25% in women [2, 3]. Resent studies suggest that nearly 15-20% of the middle aged European population are obese [2, 4]. In USA alone it is responsible for as many as 300000 premature deaths each year [2]. The cause of obesity are varied and have both central and peripheral origins [4]. The pathogenesis of obesity is multi-factorial incorporating both genetics and lifestyle, while heredity explains 30% to 70% of obesity cases (Table 1) [1, 5]. The contribution from lifestyle factors such as diet and satiety may be predominantly responsible for the recent dramatic increase in the prevalence of obesity [1, 2]. Lack of exercise and poor diet are the primary causes of clinical obesity in developed countries [4].

In the United States, despite the fact that consumption of fat has been reduced dramatically over the last thee decades, a decrease in incidence of obesity has not occurred [1]. This is likely attributable to maintenance of food intake with an increase in total calories and also reduced physical activity.

Obesity, in simple terms, may be defined as a state of imbalance between calories ingested versus calories expenditure which would lead to excessive or abnormal fat accumulation. Body mass index (BMI) s a measure of weight corrected for height and which reflects the total body fat and has been the most accepted parameters for defining over weight [5].

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Table 1: Some important causes and precautionary measures of obesity

<table>
<thead>
<tr>
<th>Causes</th>
<th>Management</th>
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<tbody>
<tr>
<td>Sedentary lifestyle</td>
<td>Physical activity</td>
</tr>
<tr>
<td>Food availability</td>
<td>Diet control</td>
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<td>High fat diet</td>
<td>Behavioral therapy</td>
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<td>Hereditary</td>
<td>Medication</td>
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<tr>
<td>Drug induced weight gain</td>
<td>Surgery</td>
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</tbody>
</table>

Table 2: Obesity-associated diseases and risk factors

<table>
<thead>
<tr>
<th>Main disease</th>
<th>Related disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular diseases (CVD)</td>
<td>Hypertension, Coronary heart disease, Cerebrovascular disease, Varicose veins, Deep venous thrombosis</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>Breathless, sleep apnea, Hypoventilation syndrome</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>Hyperlipidemia, Diabetes mellitus, Insulin resistance, Menstrual irregularities</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Fatty liver and cirrhosis, Hemorrhoids, Hernia, Colorectal cancer, Gallstones</td>
</tr>
<tr>
<td>Malignancies</td>
<td>Breast cancer, Endometrial cancer, Prostate cancer, Cervical cancer</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Pregnancy stress, Arthritis and bone mass</td>
</tr>
</tbody>
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BMI = weight (kg)/hight $^2$ (m$^2$)

There is a very good correlation between BMI and the percentage of body fat in large populations [2].

Percent Body Fat =
1.2(BMI) + 0.23 (age)-10.8 (gender)-5.4

Where, Gender = "1" for men and "0" for women

Obesity and Diseases: The metabolic effects of obesity have made this highly prevalent disease one of the most common risk factors for diabetes, hypertension and other cardiovascular diseases and osteoarthritis [2, 6, 7]. Epidemic logical studies underlined that Obesity represents a significant risk for the development of cancer (Table 2) [4, 8].

In addition, uncorrected obesity dramatically enhanced the propensity of other metabolic disorders such as hyperlipidemia, hyperuricemia and low plasma high-density lipoprotein cholesterol (HDL), collectively known as the metabolic syndrome [2, 3, 5, 7, 9].

Leptin and its Functions: Leptin (from Greek leptos-thin) was discovered in 1994 following the isolation of the ob gene [10]. The discovery of leptin has led to numerous experiments to better understand its function [11]. Leptin is a proteohormone with a helical structure similar to cytokines and a relative mass of 16 kDa [12]. The circulation leptin concentration is usually proportional to total adipose tissue mass, i.e. increased in obese and decreased in lean subjects [8]. Serum leptin levels are 2-3 times higher in women than in men even when adjusted for age and BMI [13].

Adipose tissue is the major source of leptin expression, however, other sites have been identified, including skeletal muscle, mammary, epithelium, heart, the fondues of the stomach, liver, gastric epithelium [11, 14] and the brain [12, 15]. It appears that leptin is not stored in any significant quantities. No large storage organelles for leptin have been found in adipocytes [12, 16]. And, studies looking at the kinetics of leptin synthesis and secretion in response to known secretagogues found no evidence of leptin release from stored sytolitic pools [12]. Thus, increases in leptin release are due to an increase in leptin expression. The leptin receptor (with long and short isoforms) is a member of the cytokine family of receptors and is expressed in a variety of tissues including the hypothalamic nuclei [15, 17]. Neurons in the arcuate, ventromedial and dorsomedial hypothalamic nuclei that are sensitive to leptin express neuropeptides/neurotransmitters that are associated with central regulation of energy balance [11, 12, 18].

Numerous factors alter leptin synthesis and secretion including genetics, various nutrients, sex hormones, insulin, catecholamines, fat free mass, fat stores and energy balance [12, 19].

Leptin has been implicated in regulating an array of physiological processes such as appetite, metabolic rate, reproduction and immunity [20, 21]. It is thought that a major role of leptin is to relay information to signal traducing receptors in the hypothalamus concerning the status of energy stores and thus aid in reduced feeding [11, 22]. In fact leptin acts on the central nervous system, in particular the hypothalamus, suppressing food intake...
and stimulating energy expenditure [18]. In mice, mutations of the ob gene (and subsequent lack of leptin production) cause hyperphagia and early and rapid onset of obesity. However, this mutation is quite rare in humans [12]. Obese individuals often have increased leptin concentrations and leptin administration shows only very limited effects [23]. Recent data have indicated that this is likely the results of desensitization for the leptin signal, a phenomenon now often referred to as leptin resistance [24].

Leptin and Heart Disease

Many studies have shown that weight gain is an independent predictor of diabetes mellitus and cardiovascular disease (CVD) in human [7]. Numerous peripheral effects of leptin suggesting its involvement in glucose and lipid metabolism, angiogenesis and blood pressure regulation [8].

Recent data suggests that hyperleptinemia, secondary to increased fat cell mass and other factors, may contribute to the development of the insulin resistance syndrome, including increasing blood pressure [24] through the effect on sympathetic tone, insulin sensitivity and number of other hormonal interactions [25]. Higher leptin levels in essential hypertension and noninsulin-dependent diabetes mellitus (NIDDM) may suggest a possible role for leptin in the development of atherosclerotic heart disease [7].

Patients with advanced chronic heart failure have increased serum concentrations of leptin and its soluble receptor. Leptin may participate in the catabolic cachexia in the course of chronic heart failure [26].

Leptin and C-reactive protein (an inflammatory predictor) levels are independently associated in normal human providing further evidence linking metabolic and inflammatory cardiovascular disease mechanisms [27]. The study by Sesso et al. [28] has clearly shown that elevated plasma C-reactive protein (CRP) was associated with the future development of hypertension in dose-dependent manner. These finding suggest that hypertension may be an inflammatory disease that is associated with obesity and the metabolic syndrome. This could represent a causative pathway by which inflammation predisposes to both arterial stiffness and hypertension as well as to cardiovascular and renal disease [6, 27, 29]. Furthermore, there may be hormonal pathway acting independently of either metabolic or inflammatory disturbances, with the finding that fasting serum leptin levels were independently associated with arterial distensibility [30-32]. The effect of obesity on vascular function may be mediated by the hormone leptin [33, 34]. Obese individuals have markedly increased leptin production probably as a consequence of resistance to its function [32, 35, 36]. However, the widespread distribution of functioning leptin receptors on vascular cells suggests that leptin also plays an important role in vascular physiology [25, 33]. In experimental models, leptin has been shown to have angiogenic activity [21], increase oxidative stress in endothelial cells [25] and promote vascular cell calcification [35] and smooth muscle cell proliferation and migration [21].

Leptin is also associated with increased heart rate and may contribute to platelet aggregation [31, 37, 38] and thrombosis [35].

Hyperleptinemia, universal in human obese population [39], has been deemed an independent risk factor for cardiovascular disease and, more specifically, a predictor of first myocardial infarction and an independent risk factor for ischemic and hemorrhagic stroke [22, 39].

The Effect of Exercise on Adipose Tissue Leptin Secretion:

Although the precise mechanisms that underlie leptin secretion are not fully understood, a link with negative energy balance, sympathetic activation, other hormones and metabolites has been observed [11, 40, 41].

The physiological stress of exercise is an obvious potential regulator of leptin secretion by adipose tissue. The attendant changes in fuel flux, systemic hormone concentrations and energy expenditure may influence plasma leptin concentration and presumably, leptin action.

There are many investigations that have examined the effects of exercise on leptin. There are several reasons why responses and adaptations to exercise may have important ramifications: exercise is Known to effectivel y reduce obesity (fat mass), thus if leptin levels are affected, this may provide some explanation of how exercise affects obesity [42].

Research on leptin and exercise has in general taken three traditional approaches: cross-sectional studies, acute (single-bout) exercise studies and exercise training. Studies investigating large databases have in general reported that the log of plasma leptin is inversely related to fitness [43, 44], but this relationship is generally not independent of adiposity. Exercise alters concentrations of certain hormones that may alter leptin concentrations, including insulin, cortisol, catecholamines, estrogen, testosterone and growth hormone [10, 11]. Additionally, the effects of exercise on leptin concentration may be the main result of the importance of exercise in heart diseases prevention and treatment.
Acute Effects of Exercise: The effect of physical exercise on leptin concentrations is currently controversial. Several investigators reported that exercise may result in reductions depending on duration and calorie expenditure whereas others have reported no change in leptin concentrations [14].

Elias et al. reported a decline in leptin concentrations in males (age-18-55) after a graded treadmill exercise test to exhaustion [11]. Essig et al. [45] stated lower leptin concentrations in trained males after 2 separate exercise tests, 800 and 1500 kcal treadmill run. These authors concluded that the decrease in plasma leptin concentrations after 48 hrs was preceded by a decrease in insulin concentrations.

Kraemer et al. have demonstrated that 30 min of exercise at 80% of VO2max is associated with reduced leptin concentration in postmenopausal females regardless of whether they are on or off hormone replacement therapy, but the reductions were due to the circadian rhythm of leptin as determined from the control trial samples from the same subjects [41]. Nine trained males completed 60 min of running at 70% of VO2max (energy expenditure 882.7±14.4 kcal). It showed that leptin concentrations were significantly lower immediately after exercise, 24 and 48 hrs during recovery [43]. Responses did not appear to be related to changes in insulin or glucose concentration. Blood samples were also collected from the same subjects after a short term maximal exercise test (energy expenditure 197.5±11.5 kcal) and leptin levels did not decrease immediately after or at 24 or 48 hrs post exercise.

Many researchers have reported that acute aerobic exercise does not alter leptin concentrations [15, 46, 47]. Zoladz et al. [48] studied the responses of leptin in 8 healthy men following two incremental exercises. The maximal incremental exercise was performed in the fed state however the sub-maximal incremental exercise test up to 150 W was performed in a fasted state; the authors reported no significant changes in leptin concentrations.

Kraemer in a review study indicated that generally short-term exercises (< 60 min) and exercises that generated energy expenditure lower than 800 kcal do not modify the concentrations of leptin [11]. In fact exercises of very long duration that generate a sufficient energy imbalance suppress the amplitude of the diurnal rhythm of leptin [14]. It still needs to be determined how the hormones and the metabolites affecting the secretion of leptin work together and can lower the concentration of leptin under certain conditions, but not in others [49].

Effects of Training: Similar to the majority of acute exercise studies, exercise training interventions have suggested that exercise does not alter systemic leptin independent of changes in fat mass [26, 50]. Exceptions to this include work from the author's group, suggesting that plasma leptin may be reduced in exercise-trained females (but not males in an identical training program) despite stable fat mass [41, 51] and a study from saris' group suggesting that an independent effect of exercise on plasma leptin is detectable after 10 months of training [44]. It is important to note, that in early studies about leptin concentrations neither the acute exercise studies nor the training interventions controlled for energy balance and most sampled only a single fasting plasma leptin pre-and post intervention. Recently many studies have elegantly demonstrated the care that is necessary to study leptin-exercise interventions [11, 52]. Because leptin is actually sensitive to negative energy balance (fasting or caloric restriction), then it is important to design studies that can distinguish the effects of exercise per se from any attendant change in energy balance or, perhaps more specifically, energy availability.

In a study of adolescent female runners, Kraemer et al. [41] measured resting and post maximal exercise leptin concentrations over the course of a short track season. Resting leptin levels were not modified over the 7 weeks, nor were the acute responses to intense exercise despite a significant reduction in skin folds. Additionally short term training (60 min at 75% of VO2max during 7 successive days) does not modify leptin concentrations in healthy young and older males [53].

Merino et al. reported leptin concentrations were decreased after 3 weeks of a military training. The fat mass in this study was not measured, but the body weight remained stable [14].

Unal et al. [54] measured leptin concentrations in trained young male athletes (from different sports) and in healthy sedentary subjects. They noted a significant lower leptin after exercise and concluded that regular exercise, by reducing fat percentage, suppresses serum leptin levels.

Frank et al. [29] reported that regular, moderate exercise decreases fasting insulin and leptin concentrations in overweight / obese postmenopausal women and that the adoption of regular/ moderate intensity exercise may be particularly useful among post menopausal women who gain mass over time.

Finally, these findings suggest that by following the recommendations of $30 min of moderate intensity physical activity on most, or preferably all, days of the week [29], women may achieve a more desirable metabolic profile, especially with respect to carbohydrate and lipid metabolism.
Barbeau [55] indicated that the 8-month physical training doses prescribed to obese teenagers did not result in significant group differences in mean change in leptin, although there was large variability in individual response. The change in leptin was inversely associated with baseline leptin and change in cardiovascular fitness. They reported also: diet, physical activity level, visceral adiposity and glucose concentrations were not associated with leptin, neither at baseline nor in response to physical training over the 8-month intervention period, regardless of group membership, youths who had the lowest increase in cardiovascular fitness tended to have the highest increase in leptin.

**Effects of Resistance Exercise:** Information regarding the response of serum leptin to a single bout of resistance exercise is limited. In contrast to continuous running of moderate intensity, heavy resistance exercise is a potent nonoxidative stimulus that produces differential neural, metabolic and neuroendocrine responses [56]. One study reports reduced 24-hr serum leptin in diabetic not in healthy individuals [40] and other reports reduction of serum leptin levels 9-13 hrs post-exercise in healthy lean men [57]. There is an early study [58] concerning leptin levels in trained men with low fat mass plus large increase of muscle. The findings indicated that leptin correlated with BMI in overweight subjects, but this correlation was not observed either in athletes or in controls. The authors concluded: 1) regardless of the high BMI characteristics of body builders, no correlation was observed with leptin 2) trained state induced by resistance exercise does not influence leptin production independently of variations in body composition [58].

Fatouros et al. [59] reported a decrease in plasma leptin concentration after resistance training (6 months, 3 days/week, 10 exercises/three sets) in fifty inactive men. These authors noted that this decrease was accompanied by reduce skinfold sum and BMI.

Zeferides et al. [19] examined the acute effects of maximum strength, muscular hypertrophy and strengthened endurance exercise protocols on serum leptin. The main findings of the study indicated that in normal individuals the three resistance exercise protocols elicit comparable serum leptin response and that a single bout of heavy resistance exercise protocols has on serum leptin compared with resting session. Then it appeared that differences in the configuration of the intensity, total work and rest interval among resistance training protocols do not affect acute serum leptin responses as they affect other hormonal responses. Ryan et al. [60] studied effects of 16 weeks of resistance training in obese postmenopausal females with and without weight loss, on plasma leptin and insulin action. Leptin concentration declined by 36% in the group that weight.

Changes in leptin levels were not related to alteration in resting metabolic rate or plasma catecholamines. However, the authors speculated that weight loss in the resistance training/weight loss subjects might mediate an increase in insulin action reported in the study [46].

**Effect of Caloric Restriction:** Many studies have shown that serum leptin levels in humans decline with weight loss [14]. Considine et al. for example, found that leptin fell 53% in obese subjects who lost approximately 10% of initial body weight in 8-12 weeks by consuming an 800 kcal/day leptin falls not only with long-term reductions in body weight (and fat) but also is response to short-term decreases in energy intake [61]. Two human studies of fasting, one of 36 hrs and the other of 52 hrs, found that leptin declined by 35 and 72%, respectively [62]. Such reductions are likely to be associated with a series of neurohormonal events that ultimately increase appetitive behavior and decrease energy expenditure in an effort to restore energy balance [7]. Leptin levels increase rapidly when caloric restriction is terminated [61]. Thus plasma leptin decreases markedly during short-term total fasting not in proportion to the loss in fat mass and returns to baseline concentrations with refeeding [13]. Furthermore, after a fast, refeeding a diet providing energy intakes considerably below requirements increases leptin concentrations and energy expenditure even with ongoing fat mobilization [9].

Klein et al. reported that compared with lean women, the fasting-induced decline in leptin production blunted in women with upper body obesity. The altered decline in attenuated decline in plasma insulin may be responsible for many of the alterations in the metabolic response to fasting associated with obesity [51].

Reseland et al. [63] concluded that long-term diet and exercise interventions may have direct effects on plasma leptin concentration beyond the effect expected due to changes in fat mass. Additionally the role of leptin in normalizing several starvation-induced neuroendocrine changes may have important implications for the pathophysiology and treatment of eating disorders and obesity.

**CONCLUSION**

The work of Hilton and Loucks is elegant and informative. The studies are useful in that they provide evidence of the limitation of studied using a single fasting blood sample to assess diet/exercise effects on systemic leptin. Both studies also make it clear that careful
consideration of energy balance is warranted when studying the biology of leptin. Because of differences in gender and design between these studies generalizations about the effect of exercise on leptin remain elusive. However, should the work of Hilton and Loucks [52] be confirmed (particularly in males), it will provide additional support for the hypothesis that leptin responds not to energy intake or exercise energy expenditure alone, but to the balance between the two. Because study findings suggest that 24-hr leptin levels may predict subsequent food intake [11], exercise-induced alterations in the 24-hr leptin rhythm can impact the regulation of energy balance in the organism over a period of days.

Although many studies have been published on the effects of exercise on leptin, numerous questions remain to be answered. There is a need to better define the relation of adiposity in both gender to leptin responses and adaptations to exercise. In order to determine the true dynamics of exercise-induced leptin responses, further studies should examine leptin concentrations for much longer periods after exercise. These studies should involve stringent controls for energy balance and more frequent sampling. There is a need for more studies to compare the effects of aerobic versus resistance exercise with or without diet regimen on leptin and other endocrine factors that may impinge on leptin regulation. It is important to indicate the relationship between leptin changes and the changes in some risk factors of coronary heart disease in obese individuals.

REFERENCES


