Biology of Sport, Vol. 23 N°1, 2006

PLASMA LEPTIN CONCENTRATIONS IN PHYSICALLY ACTIVE MEN AND WOMEN IN RELATION TO FAT MASS, FAT FREE MASS AND SELECTED BIOCHEMICAL VARIABLES

G. Lutosławska[1], B. Wit[2], E. Skierska[3]
Depts. of [1]Biochemistry, [2]Physiology, [3]Biology, Academy of Physical Education in Warsaw, Poland

Abstract. The plasma leptin concentration depends on many factors with a substantial role played by physical activity. The aim of this study was the evaluation of the effects of body fat and fat free mass as well circulating glucose and cortisol on plasma leptin concentrations in active men and women. A total of 26 physical education students (13 men and 13 women)- took part in the study. Their physical activity during the study was only thatrequired by theie study program. No one was engaged in high-performance sports. Fasting blood samples were taken from the antecubital vein into lithium heparin tubes and centrifuged to separate plasma specimens. Plasma leptin levels were determined using radioimmunoassay and commercial kits (Linco, USA). Cortisol was determined by means of ELISA method and IBL kits (Germany). Glucose was assayed by the oxidase method using Randox commercial kits (Randox Laboratories, Great Britain). Body fat was estimated using the BIA method (RJL System INC., USA). Despite the lack of difference in fat mass between sexes circulating leptin in women (6.5 $ng \cdot ml^{-1}$) was significantly higher than in men (2.4 $ng \cdot ml^{-1}$). Plasma leptin concentrations in both men and women were not correlated with circulating glucose and cortisol. Moreover, neither in men nor in women were they correlated with the percent of body fat. In contrast, in men plasma leptin levels were significantly correlated with fat mass expressed in kilograms ($r=0.56$; $p<0.05$). In women circulating leptin was significantly and inversely correlated with the ratio of fat-free mass to fat mass ($r=-0.71$; $p<0.006$). Our results indicate that the effect of body fat on plasma leptin concentrations differs in active men and women, probably due to pronounced fat-free mass effects on plasma hormone levels in women but not in men.

(Biol.Sport 23:73-84, 2006)

Key words: Physical activity – Gender – Anthropometric parameters – Biochemical variables

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Reprint requests to: Grażyna Lutosławska, PhD, DSc, Department of Biochemistry, Academy of Physical Education, 01-968 Warsaw 45, Box: 55, Poland;
E-mail: grazyna.lutoslawska@awf.edu.pl

Introduction

Leptin is a hormone secreted mostly by the adipose tissue [24,50]. Since 1994 when the leptin encoding gene was identified in humans and animals its biological role has been extensively studied. At present it is well documented that leptin plays a substantial role in the regulation of appetite, the onset of puberty and reproductive system function of both sexes [2,26,29,42]. Numerous data suggest that leptin affects carbohydrate and lipid metabolism. A bolus leptin injection into the rat and the elevation in its plasma level increases oxygen uptake and decreases RQ value, indicating the shift from carbohydrate to lipid whole-body utilization [23]. Similarly, other studies have shown that both in the liver and muscles leptin injection attenuates glycogen breakdown and in the liver, but not in striated muscle inhibits the activity of a key enzyme of oxidative carbohydrate metabolism – pyruvate dehydrogenase [5,36]. Moreover, it has been noted that leptin inhibits lipogenesis in the liver, striated muscles and adipose tissue, and in consequence increases the availability of free fatty acids to energetic processes [32,33].

Numerous studies have indicated that plasma leptin concentrations are positively correlated with body fat expressed both in kilograms and as the percent of body mass [3,6,45]. In addition, circulating leptin is under control of male and female sex hormones. It has been found that testosterone lowers and progesterone increases leptin concentrations in plasma [11,25,31,41]. Therefore, in women plasma leptin concentrations are higher than in men with similar body fat content. However, the mechanism of sex hormone action on circulating leptin is not fully elucidated. Rosenbaum *et al.* [39] have shown that sex-related differences in body fat distribution have a minor effect on circulating leptin in males and females. Recent studies have shown that leptin mRNA levels do not differ in male and female rats, thus sex-related differences in plasma leptin concentrations are probably due to the differences in leptin synthesis [10].

There is a wealth of studies concerning the associations between leptin synthesis and its plasma levels and other hormones. It has been noted that catecholamines diminish leptin synthesis in the adipose tissue and its concentrations in plasma [4,7]. Many data point out the close relationship between leptin and insulin concentrations in plasma as well at the association between circulating leptin and whole-body insulin sensitivity [1,19,43]. Thong *et al.* [49] have suggesed that insulin contributes to the mechanism by which adipose tissue-originated leptin regulates whole-body energy balance.

It is well known that regular physical activity affects leptin plasma levels. In physically active subjects circulating leptin is lower than in sedentary ones

[12,14,18,30,40]. However, it has been found that the effect of physical activity on plasma leptin is not due to the decrease of body fat but rather to the increase in overall leptin sensitivity [9,38].

Nevertheless, it is worth noting that the influence of physical activity on plasma leptin concentration is gender related. Hickey *et al.* [22] have shown that after 12 weeks of aerobic training plasma leptin levels were decreased by 17.5% in women but not in men, despite the lack of training effect on body fat content in both male and female subjects. Moreover, in professional female swimmers plasma leptin concentrations do not respond to intensive training, despite significant decrease in body fat [34]. In contrast, in male swimmers there were no changes either in plasma leptin levels or in body fat content during the same training period. Sudi *et al.* [47] have found that the percent of body fat does not affect circulating leptin in endurance-trained male athletes, but has a pronounced effect on plasma leptin in strength athletes.

Thus, physical activity effects on circulating leptin are related both to gender and to the mode of training.

Except for the above-mentioned Nolan study [34] there is no data concerning the association between plasma leptin levels, body fat as well as selected biochemical variables in active men and women.

The aim of this study was the evaluation of the relationship between body fat, fat free mass as well as circulating glucose and cortisol and plasma leptin concentrations in active women and men not engaged in professional sport.

Materials and Methods

Subjects: A total of 26 physical education students (13 men and 13 women) volunteered to participate in the study.. All participants were healthy non-smokers, not using any medications on a regular basis. All the women were regularly menstruating and not taking oral contraceptives. The mean menstrual cycle length was 28.4±2.1 days. None of the participants were engaged in high-performance sport. Their physical activity was only due to the study program and amounted to 3.5 h/week. Subject characteristic are presented in Table 1.

Analytical methods: Fasting blood was withdrawn from antecubital vein between 8:30-9:00 a.m. into heparinized tubes and centrifuged (15 min, 4000rpm). Plasma was stored at -20° until analyses. Glucose was determined using the oxidase method and commercial Randox kits (Randox Laboratories, Great Britain). The coefficient of variations (CV) for glucose assay equalled 4.5%. Cortisol was assayed using the ELISA method and commercial kits (IBL, Germany). Coefficient

of variation (CV) for cortisol determination equalled: 6.1%. Circulating leptin was determined using standard radioimmunoassay and Linco commercial kits (USA). The coefficient of variation for the leptin assay was 6%.

Body fat was estimated using the BIA method and BIA-101 equipment with Weight Manager 2A software (RJL System Inc., USA).

Statistical analysis: Data are presented as means ±SD. The Shapiro-Wilk was used to test data distribution. The comparison of circulating leptin between men and women was performed using non-parametric Mann-Whitney U test. Other comparisons were made by means of unpaired Student-t test. For the calculation of Pearson correlation coefficients plasma leptin levels were logarithmically transformed. Significance was set at $p<0.05$. All calculations were done using Statistica v. 6.0 (StatSoft,USA).

Results

Table 1
Subject characteristics (mean ±SD)

	Women (n=13)	Men (n=13)
Age (years)	22.0±1.1	22.1±1.5
Body mass (kg)	59.5±5.7[a]	75.9±6.1
Body height (cm)	166.5±4.8[a]	181.4±5.9
Fat free mass (kg)	46.6±2.8[a]	65.4±5.4
Fat		
kg	12.0±1.8	10.7±1.9
%	20.2±2.1[a]	13.9±2.2
FFM/FM*	3.9±0.8[a]	6.0±1.1
VO_{2max} (ml/kg/min)^	45.0±6.9[b]	51.5±8.2

*- Fat-free mass to fat mass ratio; ^ for cycle ergometer exercise;
a- $p<0.001$; b- $p<0.05$ – significantly lower in comparison to men

Subject characteristics: Body mass and fat free mass in women was significantly lower in comparison to men ($p<0.001$) (Table 1). Body fat expressed in kilograms did not differ between gender, however expressed as the percent of body mass was significantly higher in women than in men ($p<0.001$). Fat-free mass

to fat mass ratio as well as maximal oxygen uptake in women was significantly lower as compared to men ($p<0.001$ and $p<0.05$, respectively).

Table 2
Plasma leptin, cortisol and glucose concentrations in men and women (mean ±SD)

	Women (n=13)	Men (n=13)
Leptin ($ng \cdot ml^{-1}$)	6.5±1.4*	2.4±0.8
Cortisol ($nmol \cdot l^{-1}$)	385.1±144.4	453.3±117.8
Glucose ($mmol \cdot l^{-1}$)	4.7±0.6	5.0±0.6
Leptin (log_{10})	0.812±0.099*	0.380±0.151

*- significantly higher than in men ($p<0.001$)

Biochemical parameters: There were no differences between men and women in plasma cortisol and glucose concentrations. On the contrary, circulating leptin in women was significantly higher than in men ($p<0.001$) (Table 2).

Table 3
Pearson correlation coefficients between plasma leptin concentrations (log_{10}) and anthropometric and biochemical variables

	Women (n=13)	Men (n=13)
Fat (kg)	0.14	0.56*
(%)	0.22	0.33
Fat-free mass (kg)	-0.19	0.19
FFM/FM[a]	-0.71^	-0.38
Cortisol	0.25	0.32
Glucose	0.01	0.31

[a] – Fat-free mass to fat mass ratio; ^ - $p<0.006$; *$p<0.021$

Relationship between plasma leptin levels and anthropometric and biochemical variables: Leptin concentrations (log_{10}) in plasma were significantly correlated with body fat (in kg) only in men ($p<0.05$) (Table 3). Both in men and women circulating leptin was not correlated with the percentage of body fat, fat-free mass

and glucose and cortisol plasma levels. However, in women plasma leptin concentrations were significant and inversely related to fat free mass- fat mass ratio ($p<0.006$).

Discussion

The results of the present study are in agreement with the Nolan findings [34] and confirm that in active women plasma leptin concentrations are not related to body fat expressed both in kilograms and as the percent of body mass. However, in male participants plasma leptin levels were correlated with fat mass, but not with the percent of body fat. The above data show that regular physical activity markedly affects the association between circulating leptin and body fat and its effect is gender-specific and more pronounced in male subjects than in their female counterparts.

However, the reason for this finding could be only tentatively speculated. Nevertheless, it is worth noting that leptin receptors were identified in a skeletal muscles [48], the tissue which elicits many adaptative responses to regular physical activity. It is well known that muscle insulin sensitivity as well as glucose uptake in active subjects is significantly higher than in inactive ones [28]. Taking into account the well documented association between insulin sensitivity and plasma leptin concentration [44], it cannot be excluded that striated muscles in active subjects affect circulating leptin to a much greater degree than in sedentary ones, probably partially due to muscles greater mass in the former than in the latter.

Furthermore, in the rat it has been demonstrated that the increase in triacylglycerol content in the muscle brings about the elevation in circulating leptin together with depressed leptin-stimulated lipid oxidation [46]. These results suggest that greater intramuscular lipid stores depress muscle leptin sensitivity and cause compensative increase of its secretion from adipose tissue. A similar phenomenon occurs when whole-body insulin sensitivity is impaired resulting in elevated insulin secretion and concentrations in plasma [17,37]. Thus, it seems feasible that whole-body leptin sensitivity in men may be of importance in the regulation of its plasma concentrations.

In our study neither in men nor in women were plasma leptin levels correlated with fat-free mass. Literature data concerning this relationship are scarce and contradictory. Fernández-Real *et al.* [16] have found that circulating leptin is positively correlated with the fat-free mass in middle-aged men, but not in women in the similar age. On the contrary, Rosenbaum *et al.* [39] have noted a negative correlation between plasma leptin levels and fat-free mass in middle-aged men.

Consequently the association between fat-free mass and circulating leptin may vary, however, the reason for this discrepancy is unclear. But it could not be excluded that it is due to the differences in dietary habits of the participants, especially saturated fat intake. Numerous data have revealed that dietary saturated fat has the potential to modify cell membrane structure and fluidity and in consequence leptin receptor sensitivity to hormone action [21]. Chu *et al.* [5] have found a significant and negative correlation between plasma leptin concentrations and saturated fat intake. Thus, the results of the studies concerning the relationship between fat free mass and circulating leptin are contradictory when dietary habits of the participants are nor carefully controlled.

In female participants of the present study we a noted significant and negative correlation between circulating leptin and fat free mass/fat mass ratio. This finding suggests that plasma leptin levels in physically active woman depends on factor probably reflecting the relationship between leptin production in adipose tissue and muscle leptin sensitivity.

It is not clear why such a relationship was not found in men. It is worth noting that Fernăndez-Real *et al.* [15] have revealed a significant and negative correlation between leptin concentrations and whole-body insulin sensitivity both in men ($p<0.001$) and in women ($p<0.0001$). However, this relationship was much stronger in women than in men, probably as a consequence of greater insulin sensitivity in women as compared to men [35]. Concomitantly, Dubuc *et al.* [13] have shown that a decline in circulating leptin in women after 7 days of a low-calorie diet (68% of recommended intake) is significantly greater than in men. Moreover, Panarotto *et al.* [37] have found that plasma leptin concentrations in women are more closely related to circulating insulin than in men. Therefore, it could not be excluded that gender-related differences concerning the effects of fat free mass on circulating leptin in the present study resulted from differences in whole-body insulin sensitivity and possible differences in circulating insulin.

Data concerning glucocorticoids effects on plasma leptin concentrations in humans are scarce. In patients with Cushing's syndrome circulating leptin is elevated, but no correlation has been found between plasma leptin and cortisol levels [51]. However, it seems feasible that elevated leptin levels are a consequence of increased body fat but not due to increased plasma cortisol concentrations. On the other hand, Casabiell *et al.* [8] have shown the effects of glucocorticoids on leptin secretion is probably sex-dependent, since dexamethasone stimulates leptin secretion to a greater degree from isolated female than male adipocytes.

In the current study there were no correlation between plasma cortisol levels and circulating leptin suggesting that physiological cortisol concentrations did not affect plasma leptin concentrations.

A significant and positive correlations between plasma glucose and leptin levels has been found exclusively in sedentary men [13] and it at least partially reflects the relationship between plasma leptin and insulin levels [20]. No correlation between glucose and leptin concentration was found in both men and women in this study. However, it should be pointed out that physical activity not only lowers plasma leptin concentration but also affects mechanisms regulating its plasma levels. Sudi *et al.* [47] have noted that circulating leptin is correlated with plasma glucose and insulin levels in endurance but not in strength athletes. Male and female students participating in the present study were not engaged in high-performance sport, but solely attended sport classes provided by their study schedule. Hence, the results of our study can hardly be compared with those performed on professional athletes. Nevertheless, the lack of the relationship between plasma glucose and leptin concentrations in students may reflect the effect of regular physical activity on mechanisms regulating leptin secretion.

Summing up, it can be stated that in active men and women the percent of body fat did not affect plasma leptin levels. However, in men circulating leptin was correlated with fat mass expressed in kilograms. In contrast, in women plasma leptin concentrations were markedly correlated with the ratio of fat-free mass to fat mass, although neither of them was separately correlated with circulating leptin These data imply that mechanisms responsible for the regulation of plasma leptin levels in active subjects are gender-specific and in women probably muscle sensitivity to leptin is of greater importance than in men.

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Accepted for publication 3.10.2003

Acknowledgements

This study was supported by grant DS-37 and DS-50 from the Academy of Physical Education