Serum Leptin Concentrations in Relation to Body Fat, Gender, Sex Hormones and Metabolic Covariates in Thais†

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Abstract

In the present study, the relation of serum leptin to adiposity, gender and metabolic covariates in normal Thais was examined. Subjects consisted of 224 individuals aged between 20 - 79 years. Eighty two were men while 142 were women. Data were expressed as mean ± SEM.

Serum leptin was associated with total body fat assessed by dual-energy X-ray absorptiometry in both men ($r = 0.80$, $P < 0.0001$) and women ($r = 0.73$, $P < 0.0001$). Compared to women, serum leptin concentrations was lower in men ($P < 0.0001$). The difference still persisted after controlling the adiposity. Compared to premenopausal women, postmenopausal women had higher serum leptin independent of adiposity ($P < 0.0001$). In men, serum free testosterone was negatively associated with serum leptin ($r = -0.36$, $P < 0.001$) while there was no association between serum estradiol and leptin. The relation between serum FT and leptin in men no longer persisted after controlling for adiposity. Body fat was associated with fasting insulin levels in both men ($r = 0.26$, $P < 0.05$) and women ($r = 0.18$, $P < 0.05$). However, the association between fasting insulin levels and body fat in both men and women no longer existed after adjusting for leptin.

We concluded that serum leptin concentrations are associated with total body adiposity and serum leptin may mediate the effect of body fat on insulin sensitivity. There appears to be a sexual dimorphism of serum leptin unrelated to sex hormone status and the amount of body fat.

Key word: Body Fat, Leptin, Metabolic Syndrome, Insulin Sensitivity, Obesity

Body fat is genetically determined[1]. Recently, ob gene which is related to obesity in experimental animals was cloned[2]. Leptin, the product of ob gene, appears to regulate adiposity by modulating food intake and energy expenditure[3]. Experimental animals lacking the ob gene, the ob/ob mouse, have undetectable serum leptin and obesity. The phenotype can be reversed by leptin adminis-

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† Supported by 1997 Ramathibodi Hospital Research Grant.

tration[4]. In humans, however, leptin levels are high rather than low in obese subjects[5] suggesting a state of relative leptin resistance. A number of studies have found a strong positive relation between serum leptin and adiposity assessed by various methods[6]. There is also a sexual dimorphism of leptin levels with women having higher values than men[7]. Whether the basis for this gender-related difference is related to genetic, hormonal or other factors is still unknown.

It is well known that insulin resistance, one of the major components of the so called metabolic syndrome is related to body fat[8]. However, the mechanism for the relation is unclear. Since leptin is a humoral factor produced by adipose tissue it is probable that leptin may mediate the observed relation between adiposity and insulin resistance. In the present study, we examined 1) the relation between serum leptin and body fat in healthy Thai males and females, 2) the relations of sex hormones to serum leptin and 3) the correlation of body fat, insulin levels and other components of metabolic syndrome before and after controlling the effect of leptin.

MATERIAL AND METHOD

The subjects consisted of 224 individuals aged between 20-79 years residing in Bangkok Metropolitan areas recruited by direct contact flyers. Eighty two were men while 142 were women. None of the subjects were heavy smokers or consumed a significant amount of alcohol. Medical history-taking and complete physical examination were performed on volunteers to assess their health status. All were considered to be healthy.

Body fat was assessed by dual-energy X-ray absorptiometry. Briefly, the proportion of fat mass to fat-free mass was determined by the attenuation of the X-ray energy at measured areas containing only soft tissue (Rst) using a standard curve relating Rst to the ratio of fat mass to fat-free mass. The amount of fat mass was then determined by the product of this ratio with soft tissue mass. The *in vivo* coefficients of variation for fat mass was 2.4 per cent.

Fasting blood samples were obtained from subjects between 8.00 and 10.00 am. Samples were allowed to clot and after centrifugation serum was frozen at -20°C until measurement. Serum leptin (Linco, U.S.A.), free testosterone (FT) and estradiol (E_2) (Diagnostic Product Corp., U.S.A.) levels were measured by radioimmunoassay.

Data were expressed as mean ± SEM. The relations between leptin and variables including body fat and serum FT were determined by linear regression analyses. Partial correlation analyses or analysis of covariance were used to control the effect of body fat in analyses where body fat was considered a covariate. Relations among leptin, body fat and metabolic covariates were assessed by Pearson's correlation analyses. Differences among groups were assessed by the Student's *t* test.

RESULTS

In men, serum leptin was strongly associated with total body fat (Fig. 1) Likewise, there

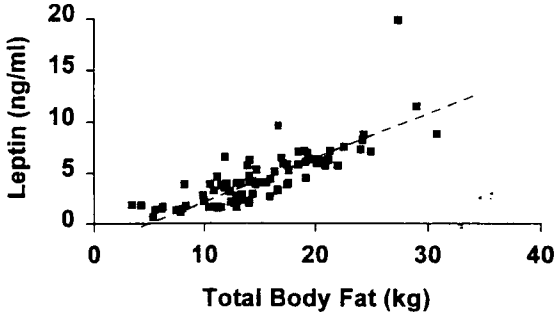

Fig. 1. Relation between serum leptin and total body at in males. Serum leptin concentration was significantly associated with total body fat ($r = 0.80$, $P < 0.001$).

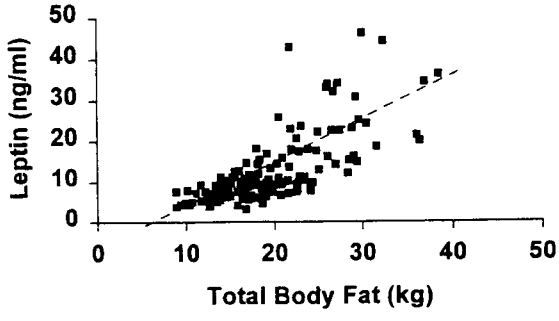

Fig. 2. Relation between serum leptin and total body fat in females. Serum leptin concentration was significantly associated with total body fat ($r = 0.73$, $P < 0.001$).

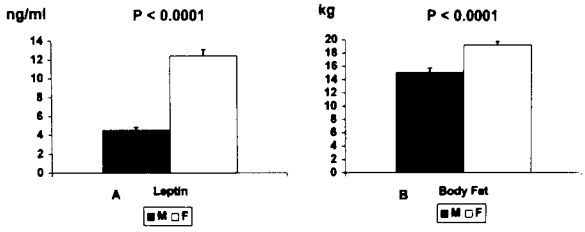

Fig. 3. Comparisons of serum leptin and total body fat between males and females. A, serum leptin was significantly higher in females ($P < 0.0001$). B, Body fat was also higher in females ($P < 0.0001$). After controlling the difference in body fat, the difference in serum leptin between males and females still persisted ($P < 0.0001$).

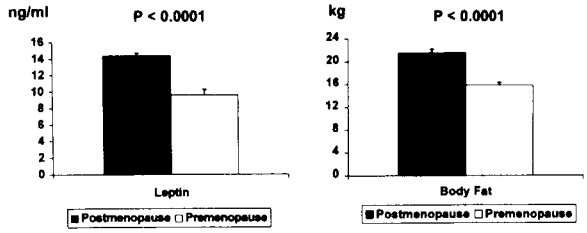

Fig. 4. Comparisons of serum leptin and total body fat between pre- and postmenopausal women. A, postmenopausal women had higher serum leptin ($P < 0.0001$). B, total body fat was higher in postmenopausal women ($P < 0.0001$). The difference in serum leptin between pre- and postmenopausal women no longer existed after controlling the difference in body fat.

Table 1. Correlation coefficients among serum leptin, body fat and metabolic covariates in males.

	Leptin	Insulin	Uric acid	Cholesterol	LDL cholesterol	HDL cholesterol	Triglyceride
Insulin	0.26 ($P < 0.05$)						
Uric acid	0.26 ($P < 0.05$)	0.06 (NS)					
Cholesterol	0.21 (NS)	0.14 (NS)	0.08 (NS)				
LDL cholesterol	0.14 (NS)	0.13 (NS)	-0.03 (NS)	0.93 ($P < 0.001$)			
HDL cholesterol	-0.18 (NS)	-0.29 ($P < 0.01$)	-0.1 (NS)	-0.1 (NS)	-0.13 (NS)		
Triglyceride	0.30 ($P < 0.01$)	0.24 ($P < 0.05$)	0.34 ($P < 0.01$)	0.22 ($P < 0.05$)	-0.08 (NS)	-0.32 ($P < 0.01$)	
Total body fat	0.80 ($P < 0.001$)	0.27 ($P < 0.01$)	0.37 ($P < 0.001$)	0.18 (NS)	0.13 (NS)	-0.27 ($P < 0.05$)	0.31 ($P < 0.01$)

was a positive correlation of serum leptin to total body fat in women (Fig. 2). Compared to women, serum leptin concentrations were lower in men (Fig. 3A). It is likely that this difference may be due to lower total body fat in men (Fig. 3B). Nevertheless, the gender-related difference still persisted after controlling the degree of adiposity ($P < 0.0001$). Concerning the effect of estrogen deficiency, postmenopausal women had higher serum leptin concentrations (Fig. 4A) and body fat (Fig. 4B) compared to premenopausal women. The difference in serum leptin no longer existed after adjusting the total body fat. In men, serum FT was negatively associated with serum leptin ($r = -0.36$, $P < 0.001$) while there was no association between serum E_2 and leptin. Nevertheless, after controlling the effect of body fat, the relation between serum FT and leptin in men no longer persisted.

There were correlations among components of metabolic syndrome such as fasting insulin levels, serum lipids and uric acids in both men (Table 1) and women (Table 2). Body fat was strongly

Table 2. Correlation coefficients among serum leptin, body fat and metabolic covariates in females.

	Leptin	Insulin	Uric acid	Cholesterol	LDL cholesterol	HDL cholesterol	Triglyceride
Insulin	0.18 ($P < 0.05$)						
Uric acid	0.35 ($P < 0.001$)	0.14 (NS)					
Cholesterol	0.12 (NS)	0.18 ($P < 0.05$)	0.24 ($P < 0.01$)				
LDL cholesterol	0.14 (NS)	0.19 ($P < 0.05$)	0.23 ($P < 0.01$)	0.96 ($P < 0.001$)			
HDL cholesterol	-0.28 ($P < 0.001$)	-0.32 ($P < 0.001$)	-0.20 ($P < 0.05$)	-0.38 ($P < 0.001$)	-0.48 ($P < 0.001$)		
Triglyceride	0.22 ($P < 0.01$)	0.29 ($P < 0.001$)	0.27 ($P < 0.001$)	0.22 ($P < 0.05$)	0.52 ($P < 0.001$)	-0.56 ($P < 0.001$)	
Total body fat	0.73 ($P < 0.001$)	0.37 ($P < 0.001$)	0.35 ($P < 0.001$)	0.24 ($P < 0.01$)	0.27 ($P < 0.001$)	-0.44 ($P < 0.001$)	0.31 ($P < 0.001$)

Table 3. Correlation coefficients between body fat and fasting insulin levels before and after controlling serum leptin in males and females.

	Males	Females
Before controlling for leptin	0.27 ($P < 0.01$)	0.37 ($P < 0.001$)
After controlling for leptin	0.06 (NS)	0.13 (NS)

associated with fasting insulin levels in both men and women. However, the association between fasting insulin levels and body fat in both men and women no longer existed after adjusting the serum leptin (Table 3).

DISCUSSION

Leptin, the translational product of ob gene, has been associated with obesity in ob/ob mice which do not produce leptin because of a non sense mutation in ob gene[3,4]. In humans, the role of leptin in obesity is not as straightforward as in mice. Obese subjects, instead of having low leptin levels, have higher leptin concentrations compared to lean subjects suggesting a leptin resistance[5]. However, this may just reflect the higher amount of leptin produced from more adipose tissue in obese subjects. In the present study, a positive association between serum leptin and body fat using DEXA was also confirmed. Although leptin resistance because of mutation in leptin receptors has been demonstrated in db/db mice[11,12], no mutation in leptin receptors has been detected so far in obese human subjects[13]. Moreover, in conditions with extreme leanness such as anorexia nervosa[9] and in distance runners[10], a positive relationship between serum leptin and body fat is still observed. These findings combined suggested that increased leptin in persons with higher body fat is more likely to reflect higher leptin production from more adipose tissue mass rather than leptin resistance.

There appeared to be a sexual dimorphism of serum leptin in the present study as well as others [6,7,14]. Although males of comparable weight were generally observed to possess lower body fat than females, the gender-related difference was not due to the difference in the amount of body fat per se. What underlies the higher levels of leptin in women is still unclear but may be due to genetic or hormonal factors. Considering the role of hormonal factors, our cross-sectional findings did not support the effect of sex hormones on serum leptin. Although postmenopausal women had higher serum leptin compared to premenopausal women, the difference could be explained by the difference in body fat alone. Similarly, although there was a negative association between serum free testosterone and leptin in men, the relation could also be attributed to the association between androgen and body fat alone. In IDDM, serum testosterone was also negatively correlated to leptin although the contribution of body fat was not investigated[15]. Longitudinal study of the response of serum leptin to the administration of

sex steroids should further resolve the issue.

Insulin resistance and compensatory hyperinsulinemia is often associated with changes which increase the risk of coronary heart disease such as hypertension and dyslipidemia, the so called metabolic syndrome[16]. Although obesity is generally not considered a component of this syndrome, the degree of adiposity can modulate insulin resistance [17]. How increased body fat affects insulin resistance is unclear but proposed mechanism include pathways concerning free fatty acid metabolism[18]. As a humoral factor secreted from adipocytes, leptin is also likely to mediate the effect on body fat on insulin resistance. Indeed, in the present study, we showed that the strong association between fasting insulin levels, an index of insulin resistance, and body fat was abolished after adjusting the serum leptin in both men and women. The relation of serum leptin to insulin resistance independently of body fat has also been demonstrated in lean and obese subjects[19]. Moreover, chronic hyperinsulinemia has been shown to increase serum leptin *in vivo*[20]. On the other hand, leptin decreases insulin secretion *in vitro*[21] and modulates activity of insulin[22]. This evidence supports the notion that leptin may act as a counter regulatory hormone for insulin with effects ranging from decreasing food intake, reducing insulin secretion to inducing insulin resistance[23].

(Received for publication on October 20, 1997)

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รายงานการวิจัยเรื่อง ระดับเล็ปตินในเลือดและความสัมพันธ์กับปริมาณไขมัน เพศ ฮอร์โมนเพศ และปัจจัยทางเมตาบอลิกในคนไทย

บุญส่ง องค์พิพัฒน์กุล, พ.บ., รัชตะ รัชตะนาวิน, พ.บ.*, สุวรรณี ชั้นประเสริฐโยธิน, วท.ม.*, นพวรรณ เปียซื่อ, วท.ม.*, ละออ ชัยลือกิจ, วท.ม.**

เล็ปตินเป็นโปรตีนที่สร้างยีน ob ในเนื้อเยื่อไขมัน ผู้ดำเนินการวิจัยได้ทำงานศึกษาเกี่ยวกับความสัมพันธ์ระหว่างระดับเล็ปตินในกระแสเลือดกับปริมาณไขมัน เพศ ฮอร์โมนเพศ และปัจจัยทางเมตาบอลิกอื่นในคนไทย

ผลการศึกษาพบว่าระดับเล็ปตินในกระแสเลือดมีความสัมพันธ์กับปริมาณเนื้อเยื่อไขมันทั้งในเพศชาย ($r = 0.80$, $P < 0.0001$) และเพศหญิง ($r = 0.73$, $P < 0.0001$) ระดับเล็ปตินในเพศชายมีค่าต่ำกว่าเพศหญิงอย่างมีนัยสำคัญทางสถิติ ($P < 0.0001$) โดยไม่ขึ้นกับปริมาณไขมันที่แตกต่างกัน สตรีวัยหมดประจำเดือนมีระดับเล็ปตินไม่แตกต่างจากสตรีก่อนหมดประจำเดือน หลังปรับเกี่ยวกับปริมาณไขมันที่แตกต่างกัน ระดับเทศโทสเตอโรนในเพศชายมีความสัมพันธ์ในด้านลบกับปริมาณเล็ปติน ($r = -0.36$, $P < 0.001$) แต่ความสัมพันธ์นี้หมดไปเมื่อปรับเกี่ยวกับปริมาณไขมันที่เพิ่มขึ้นในชายที่มีระดับเทศโทสเตอรโรนต่ำ ระดับอินสุลินมีความสัมพันธ์กับปริมาณไขมันในเพศชาย ($r = 0.26$, $P < 0.05$) และเพศหญิง ($r = 0.18$, $P < 0.05$) แต่ความสัมพันธ์นี้หมดไปหลังปรับระดับเล็ปตินในกระแสเลือด

การศึกษานี้แสดงให้เห็นว่าระดับเล็ปตินในกระแสเลือดมีความสัมพันธ์กับปริมาณไขมันในร่างกายโดยที่เพศชายมีระดับเล็ปตินต่ำกว่าเพศหญิง ฮอร์โมนเพศไม่มีความสัมพันธ์โดยตรงกับระดับเล็ปตินที่แตกต่างกันในเพศชายและหญิง นอกจากนี้เล็ปตินอาจเป็นตัวกลางของระหว่างปริมาณไขมันที่เพิ่มขึ้นกับผลตอบสนองต่ออินสุลินที่ลดลง

คำสำคัญ : ไขมันในร่างกาย, เล็ปติน, กลุ่มอาการเมตาบอลิค, ความไวต่ออินสุลิน, โรคอ้วน

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