Differences in Leptin Production by Regional Fat Mass in Postmenopausal Women

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Abstract. To investigate the differences in leptin production by regional fat mass, 76 postmenopausal Japanese women were enrolled in this study. Age, height, weight, and body mass index (BMI, wt/ht²) were recorded. Serum leptin levels were measured by RIA. Trunk fat mass, total body fat mass, and percentage of body fat were measured by dual-energy X-ray absorptiometry (DEXA). The ratio of trunk to leg fat mass (trunk-leg fat ratio), an index of body fat distribution, was also assessed by DEXA. Relationship of leptin levels with baseline characteristics and anthropometric variables were investigated by Pearson correlation test. Serum leptin levels were positively correlated with BMI ($r = 0.683$, $p < 0.0001$), total body fat mass ($r = 0.680$, $p < 0.0001$), trunk fat mass ($r = 0.632$, $p < 0.0001$), and percentage of body fat ($r = 0.624$, $p < 0.0001$). However, no significant correlation was observed between trunk-leg fat ratio and leptin levels ($r = 0.181$). Age and height were not correlated with leptin levels. Based on these results, we concluded that body fat distribution does not serve as a predictor of leptin levels in postmenopausal women.

Key words: Leptin production, Body fat distribution, Trunk-leg fat ratio

PLASMA leptin is a circulating hormone that is expressed abundantly and specifically in the adipose tissue. Leptin plays an important role in the regulation of energy homeostasis, as well as the neuroendocrine and reproductive system. It has been shown that serum leptin levels become elevated with increasing body mass index (BMI, wt/ht²) [1–3]. Obesity is defined as excessive accumulation of adipose tissue. Recent evidence indicates that location of body fat deposit rather than the degree of obesity may play an important role in the risk of developing various endocrine and metabolic diseases including insulin resistance, hyperandrogenism, and hyperlipidemia [4–7]. Thus, it is of interest to determine whether this relationship can be also observed in leptin production. However, only limited data are available with regard to the relationship between leptin production rate and the location of body fat deposit.

The present study investigated the difference in leptin production among regional fat mass tissue.

Materials and Methods

Full informed consent to evaluate anthropometric variables was obtained in accordance with institutional guidelines. The study was also conducted in accordance with the provisions of the Declaration of Helsinki. Subjects were 76 postmenopausal Japanese women (mean age, 61.7 ± 7.1 years old; range, 51 to 78). All women were randomly recruited at the Department of Obstetrics and Gynecology, Faculty of Medicine, Kagoshima University Hospital between April 2000 and July 2001. Subjects were undergoing screening for cervical, uterine, and ovarian cancers, and were deemed in apparent good health, based on medical clinical evaluation. None was taking hor-
mone replacement therapy. All women had experienced natural menopause. The subjects were judged to have entered menopause when they had not menstruated for at least 12 months prior to the investigation.

Age, height, weight, and body mass index (BMI) were recorded for each subject. BMI was calculated as weight (kg) divided by height squared (m²). Trunk fat mass, total body fat mass, percentage of body fat, and the ratio of trunk to leg fat mass (trunk-leg fat ratio) were measured by dual-energy x-ray absorptiometry (DEXA, Hologic Inc., Waltham, MA, USA). Body fat distribution was assessed by trunk-leg fat ratio [7]. The relationships of serum leptin levels with baseline characteristics and anthropometric variables were investigated by Pearson correlation test.

DEXA measurements were performed with a total body scanner and results were evaluated by the same examiner. This equipment uses switched pulsed stable dual-energy radiation of 70 KV and 140 KV, performing serial transverse scans from head to toe at 1.2-cm intervals, providing a pixel size of 1.9 mm × 1.2 mm. The radiation dose is 0.05–0.15 μGy. Reproducibility of total fat mass measurement was determined in 10 women each of whom were measured twice at 1-week intervals. The coefficient of variation in these women was 1.0%.

The measurements of serum leptin levels were made with a commercially available RIA kit based on a polyclonal antisera raised against full-length recombinant human leptin (Linco, St. Charles, MO). The interassay coefficient of variation was 11.9%, and the intraassay coefficient of variation was 4.8%. Recovery of recombinant leptin added to human serum was 91.7 ± 4.8% at 2 ng/mL, 97.6 ± 4.2% at 4 ng/mL, and 105.5 ± 4.9% at 10 ng/mL.

All variables were normally distributed, and were therefore modeled as continuous. Correlation with serum leptin levels were investigated using Pearson correlation test.

### Results

Table 1 presents the baseline characteristics, anthropometric variables, and serum leptin levels in 76 postmenopausal women. Trunk fat mass was approximately half of the total body fat mass. Mean

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.7 ± 7.1</td>
<td>(51–78)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>150.7 ± 5.3</td>
<td>(139–167)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.7 ± 7.4</td>
<td>(41–75)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.2 ± 3.1</td>
<td>(18.7–32.0)</td>
</tr>
<tr>
<td>Trunk fat mass (kg)</td>
<td>8.9 ± 3.1</td>
<td>(3.0–16.3)</td>
</tr>
<tr>
<td>Total body fat mass (kg)</td>
<td>19.7 ± 5.5</td>
<td>(8.7–32.5)</td>
</tr>
<tr>
<td>Percentage of body fat (%)</td>
<td>34.8 ± 5.8</td>
<td>(21.3–46.7)</td>
</tr>
<tr>
<td>Trunk-leg fat ratio</td>
<td>1.38 ± 0.39</td>
<td>(0.54–2.29)</td>
</tr>
<tr>
<td>Serum leptin levels (ng/mL)</td>
<td>9.2 ± 7.1</td>
<td>(1.8–48.3)</td>
</tr>
</tbody>
</table>

SD = standard deviation.

Table 1. Baseline characteristics, anthropometric variables, and serum leptin levels in postmenopausal women

Trunk-leg fat ratio was 1.38 ± 0.39 (range, 0.54 to 2.29). Serum leptin levels were 9.2 ± 7.1 ng/mL (range, 1.8 to 48.3 ng/mL).

Table 2 presents the outcome of Pearson correlation test. Leptin levels were positively correlated with BMI ($r = 0.683$, $p < 0.0001$), total body fat mass ($r = 0.680$, $p < 0.0001$), trunk fat mass ($r = 0.632$, $p < 0.0001$), and percentage of body fat ($r = 0.624$, $p < 0.0001$). However, there was no correlation observed between trunk-leg fat ratio and leptin levels ($r = 0.181$). Age and height were not correlated with leptin levels.

### Discussion

Trunk fat mass is composed of abdominal visceral and subcutaneous fat mass. There are reports indicating that trunk-leg fat ratio assessed by DEXA is highly correlated with abdominal visceral fat mass as measured by computed tomography [8, 9]. Thus, we can say that upper body fat distribution reflects abdominal visceral fat mass. In the present study, trunk fat mass was highly correlated with leptin levels. However, there was no correlation observed between trunk-leg fat ratio and leptin levels. These findings suggest that not abdominal visceral fat mass but abdominal subcutaneous fat mass has a major influence on leptin levels. Our speculation agrees with previous studies [10–14]. In one study, researchers found that the leptin secretion rate were higher in the subcutaneous than in the visceral region [15]. Taka-hashi et al. [16] reported that leptin levels showed a
LEPTIN PRODUCTION IN TRUNK FAT MASS

Table 2. Outcome of Pearson correlation test (n = 76)

<table>
<thead>
<tr>
<th></th>
<th>r with leptin levels</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.001</td>
<td>-0.225, 0.226</td>
<td>NS</td>
</tr>
<tr>
<td>Height</td>
<td>-0.097</td>
<td>-0.316, 0.131</td>
<td>NS</td>
</tr>
<tr>
<td>Weight</td>
<td>0.584</td>
<td>0.412, 0.715</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.683</td>
<td>0.541, 0.787</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trunk fat mass</td>
<td>0.632</td>
<td>0.474, 0.750</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total body fat mass</td>
<td>0.680</td>
<td>0.537, 0.785</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage of body fat mass</td>
<td>0.624</td>
<td>0.463, 0.745</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trunk-leg fat ratio</td>
<td>0.181</td>
<td>-0.047, 0.390</td>
<td>NS</td>
</tr>
</tbody>
</table>

r = Pearson correlation coefficient.  
NS = not significant.  
CI = confidence interval.

...positive correlation with subcutaneous fat area at the umbilical level but there was no significant correlation between leptin levels and visceral fat area in either non-obese or obese subjects. Subjects with relatively greater fat mass partitioned to the subcutaneous area would be expected to have greater serum leptin levels. In another study, serum leptin levels of subjects in the highest quartile of abdominal visceral fat area (154.5 ± 38.4 cm²) as estimated by computed tomography did not differ from those in subjects in the lowest quartile of abdominal visceral fat area (51.2 ± 20.1 cm²) [17]. These data and our observations agree with previous in vitro studies [18–20]. Leptin mRNA expression is lower in omental than in subcutaneous adipose tissue [18]. Abdominal subcutaneous to omental ratio of leptin mRNA expression is markedly higher in women (5.5 ± 1.1 fold) [20].

The greater leptin production rate in the abdominal subcutaneous fat mass appears to be at variance with reports indicating that excess visceral adipose tissue plays an important role in the occurrence of various endocrine and metabolic abnormalities [4–7]. In addition, abdominal visceral adiposity is associated with hyperinsulinemia which increases serum leptin levels [14, 21]. Possible explanations for this disparity may include the following: First, fat cell size and/or sympathetic innervation may differ between omental and abdominal subcutaneous fat mass [18]. Second, differentiation, growth, and properties may differ between abdominal subcutaneous and visceral fat mass [22]. Third, expression of leptin mRNA regulated by insulin may differ between abdominal visceral and subcutaneous adipose tissue in humans [23]. Finally, massive quantities of omental adipocytes may be insensitive to the putative regulatory function(s) of the obese gene product [24].

As indicated above, abdominal visceral adiposity is associated with insulin resistance, hyperinsulinemia, hyperlipidemia, and androgenic environment [4–7]. Abdominal visceral adiposity is a pathological condition caused by modern lifestyle including excess energy intake, while abdominal subcutaneous adiposity is not. Differing from insulin resistance, hyperlipidemia, and hyperandrogenism, leptin increase appears to play a more physiological role such as the regulation of energy homeostasis. Thus, higher leptin production in abdominal subcutaneous (physiological site) fat mass may be because leptin primarily is a physiological hormone. However, this study included only postmenopausal women. We have unpublished data indicating that correlation of leptin level with trunk-leg fat ratio is significant in premenopausal women, although the strength of correlation is weaker than that with trunk fat mass. This finding suggests that the difference in the expression of leptin mRNA between abdominal visceral and subcutaneous fat mass might be influenced by estrogenic status. Further study is necessary to elucidate this preliminary observation.
References