Relationships between baseline serum leptin levels and 2-year changes in body mass index, blood pressure and metabolic parameters in Japanese male adolescents and middle-aged men

Hiroshi HIROSE*,†, Ikuo SAITO*,†, Toshihide KAWAI*, Minako TSUJIOKA*,† Hiroshi KAWABE*† and Takao SARUTA*

*Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan, and †Health Centre, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

ABSTRACT

We and others have reported that serum leptin levels are positively correlated with body mass index (BMI), blood pressure and heart rate (HR) in cross-sectional clinical studies. However, only a few longitudinal studies have focused on the relationships between leptin, BMI and blood pressure. The present study was performed to elucidate the relationships between baseline serum leptin levels and 2-year changes in BMI, blood pressure, HR and metabolic parameters in 314 Japanese male adolescents aged 16–17 years and in 225 Japanese men aged 30–63 years. Height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, fasting plasma glucose (FPG), serum lipids [total cholesterol (TC), triacylglycerols (TG), high-density-lipoprotein cholesterol (HDL-C) and low-density-lipoprotein cholesterol (LDL-C)], uric acid (UA), insulin and leptin levels were measured in the morning after an overnight fast. In the male adolescents, serum leptin levels in 1996 (log [leptin'96]) were significantly correlated with BMI, SBP, mean blood pressure and HR in 1998 (r = 0.40, 0.13, 0.11 and 0.14, respectively). The percentage change in BMI per year (ΔBMI) was negatively correlated with log [leptin'96], even after adjustment for baseline BMI (r = −0.12, P = 0.030). In men aged 30–63 years, log [leptin'96] was also positively correlated with BMI'98, SBP'98, DBP'98, FPG'98, TC'98, log [TG'98], LDL-C'98 and UA'98 (all P < 0.05), and negatively correlated with HDL-C'98, ΔBMI, ΔFPG, ΔTC and ΔLDL-C. The relationship between log [leptin'96] and ΔTC was significant, even after adjustment for initial BMI (r = −0.15, P = 0.023). These findings therefore suggest that serum leptin levels are correlated with subsequent decreases in BMI and TC in Japanese men.

INTRODUCTION

Obesity is characterized by excessive accumulation of body fat and has become an important health problem in industrialized societies, as it is a risk factor for diabetes mellitus, hypertension, hyperlipidaemia and atherosclerotic diseases, due to insulin resistance and/or the resultant hyperinsulinaemia [1–4]. Obesity is known to be related to hypertension [5], although the mechanism(s) are not completely understood [6]. Animal studies have...
suggested that activation of the sympathetic nervous system is associated with obesity-related hypertension [7].

The mouse obese (ob) gene was identified using the positional cloning technique [8], and subsequent studies have revealed that the ob gene product, leptin [9], is expressed mainly in adipocytes and acts as a satiety factor that reduces food intake and increases energy expenditure via binding to its receptors [9–13]. Serum leptin levels have been reported to increase with degree of obesity [14–16], suggesting the occurrence of increased leptin resistance in obese subjects. Recent studies have indicated that human obesity is associated with marked sympathetic activation [17], and several animal studies have shown that leptin increases sympathetic nervous system activity [18,19] and arterial blood pressure [20,21].

We and others have reported that serum leptin levels are positively correlated with body mass index (BMI) [14–16,22], blood pressure [23,24] and heart rate (HR) [23,25] in cross-sectional clinical studies. To our knowledge, however, only a few longitudinal studies have focused on the relationships between leptin, BMI and blood pressure (e.g. leptin’s effects on weight change in Pima Indians [26]). The present study was therefore performed in order to elucidate the relationship between baseline serum leptin levels and changes in BMI, blood pressure, HR, plasma glucose, lipid profile, etc., in a 2-year follow-up study of Japanese male adolescents and middle-aged men.

Part of this work was presented at the 22nd Annual Meeting of the Japanese Society of Hypertension in Takamatsu on October 22, 1999, and at the 43rd Annual Meeting of the Japan Diabetes Society in Nagoya, on May 26, 2000.

METHODS

Subjects

The subjects of this study consisted of 314 Japanese male adolescents aged 16–17 years and 225 Japanese men aged 30–63 years in 1996, who came for annual medical check-ups in both 1996 and 1998. Subjects with diabetes mellitus, endocrine diseases, or significant renal or hepatic disease, and those taking antihypertensive drugs, systemic corticosteroids or lipid-lowering drugs, were excluded. This study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association, and the study protocol was approved by the Ethics Committees of Health Center and the Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan. Informed consent was obtained from each subject after full explanation of the purpose, nature and risk of all procedures used. Height, weight, blood pressure, HR, fasting plasma glucose (FPG), and serum total cholesterol (TC), triacylglycerol (TG; triglyceride), high-density-lipoprotein cholesterol (HDL-C), low-density-lipoprotein cholesterol (LDL-C), uric acid (UA), insulin and leptin concentrations were measured in the morning after an overnight fast.

Measurements

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR in subjects of both age groups were measured with an automatic electronic sphygmomanometer (BP-103i II; Nippon Colin, Komaki, Japan), twice in the sitting position after resting for at least 3 min, as described previously [22,23]. Plasma glucose and lipids were assayed by routine automated laboratory methods. Serum insulin concentrations were measured with a commercially available RIA kit from Eiken Chemical Co. (Tokyo, Japan), and leptin concentrations with an RIA kit from Linco Research Inc. (St. Charles, MO, U.S.A.), as described previously [22,23].

Statistical analyses

All statistical analyses were performed using the StatView* program for Macintosh (version 4.5-J; Abacus Concepts Inc., Berkeley, CA, U.S.A.). Because the serum leptin, insulin and TG levels were normally distributed after log transformation, the logarithms of these parameters were used for regression analyses. Data analysis included the calculation of Pearson’s correlation coefficients and partial correlation analyses. All data are expressed as means ± S.D., and P < 0.05 was considered statistically significant.

RESULTS

Relationships between baseline serum leptin and insulin levels, blood pressure, HR and metabolic parameters in a 2-year follow-up study of Japanese male adolescents

As shown in Table 1, the serum leptin levels in 1996 (log[leptin’96]) were significantly correlated with 1998 values for body weight, BMI, SBP, mean blood pressure (MBP) and HR. Moreover, log[leptin’96] was negatively correlated with the percentage change in BMI per year (ΔBMI) (Table 1 and Figure 1A; P < 0.001), but not with ΔSBP, ΔDBP or ΔHR. This negative correlation between log[leptin’96] and ΔBMI was significant, even after adjustment for baseline BMI (r = −0.12, P = 0.030).

As shown in Table 2, log[insulin’96] was also positively correlated with SBP’98, DBP’98, MBP’98 and HR’98 (all P < 0.05), and negatively correlated with ΔBMI and ΔHR (r = −0.11 and −0.15 respectively). However, the correlation of ΔBMI with log[insulin’96] was weaker than with log[leptin’96].
Figure 1 Negative correlations between baseline leptin levels and ∆BMI in 314 Japanese male adolescents (A) and in 225 Japanese men aged 30–63 years (B)
Table 3  Pearson’s correlations (upper) and partial correlation coefficients (lower) between baseline leptin levels and clinical parameters in 225 Japanese men aged 30–63 years

Regression coefficients are given for the correlation of each parameter with log[leptin‘96]. Significance: * P < 0.05, ** P < 0.01, *** P < 0.001.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1996 data</th>
<th>1998 data</th>
<th>Percentage change per year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>−0.01</td>
<td>−0.01</td>
<td>−</td>
</tr>
<tr>
<td>BMI</td>
<td>0.62***</td>
<td>0.59***</td>
<td>−0.16*</td>
</tr>
<tr>
<td>SBP</td>
<td>0.16*</td>
<td>0.18**</td>
<td>0.08</td>
</tr>
<tr>
<td>DBP</td>
<td>0.22***</td>
<td>0.22**</td>
<td>0.06</td>
</tr>
<tr>
<td>MBP</td>
<td>0.20**</td>
<td>0.21**</td>
<td>0.08</td>
</tr>
<tr>
<td>HR</td>
<td>0.04</td>
<td>0.03</td>
<td>−0.05</td>
</tr>
<tr>
<td><strong>After adjustment for baseline BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.06</td>
<td>0.06</td>
<td>−</td>
</tr>
<tr>
<td>BMI</td>
<td>−0.06</td>
<td>−0.06</td>
<td>−0.07</td>
</tr>
<tr>
<td>SBP</td>
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<td>0.02</td>
<td>−0.03</td>
</tr>
<tr>
<td>DBP</td>
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<td>0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>MBP</td>
<td>0.06</td>
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<td>−0.01</td>
</tr>
<tr>
<td>HR</td>
<td>0.13</td>
<td>0.07</td>
<td>−0.09</td>
</tr>
</tbody>
</table>

Table 4  Pearson’s correlations (upper) and partial correlation coefficients (lower) between baseline leptin levels and serum metabolites in 225 Japanese men aged 30–63 years

Regression coefficients are given for the correlation of each parameter with log[leptin‘96]. Significance: * P < 0.05, ** P < 0.01, *** P < 0.001.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1996 data</th>
<th>1998 data</th>
<th>Percentage change per year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG</td>
<td>0.31***</td>
<td>0.22**</td>
<td>−0.14*</td>
</tr>
<tr>
<td>TC</td>
<td>0.22***</td>
<td>0.15*</td>
<td>−0.16*</td>
</tr>
<tr>
<td>logTG</td>
<td>0.32***</td>
<td>0.30***</td>
<td>0.02</td>
</tr>
<tr>
<td>HDL-C</td>
<td>−0.26***</td>
<td>−0.29***</td>
<td>−0.01</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.31***</td>
<td>0.17*</td>
<td>−0.15*</td>
</tr>
<tr>
<td>UA</td>
<td>0.24***</td>
<td>0.20**</td>
<td>−0.09</td>
</tr>
<tr>
<td><strong>After adjustment for baseline BMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG</td>
<td>0.16*</td>
<td>0.09</td>
<td>−0.09</td>
</tr>
<tr>
<td>TC</td>
<td>0.23***</td>
<td>0.15*</td>
<td>−0.15*</td>
</tr>
<tr>
<td>logTG</td>
<td>0.16*</td>
<td>0.16*</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL-C</td>
<td>−0.03</td>
<td>−0.05</td>
<td>−0.04</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.24***</td>
<td>0.14*</td>
<td>−0.08</td>
</tr>
<tr>
<td>UA</td>
<td>0.11</td>
<td>0.07</td>
<td>−0.07</td>
</tr>
</tbody>
</table>

The negative correlation between log[leptin‘96] and ΔTC was significant, even after adjustment for baseline BMI (Table 4; r = −0.15, P = 0.023).

Log[insulin‘96] was also positively correlated with SBP‘98, DBP‘98, MBP‘98 and HR‘98 (all P < 0.05), but the correlations were weaker than those with log[leptin‘96]. Log[insulin‘96] was not correlated with the percentage change per year in any of the parameters measured (results not shown).

**DISCUSSION**

The baseline serum leptin levels of both the male adolescent group and the adult and middle-aged men group in the present study were positively correlated with their BMI and blood pressure values 2 years later. In the adult and middle-aged men, log[leptin‘96] was also positively correlated with FPG‘98, TC‘98, log[TG‘98], LDL–C‘98 and UA‘98. Animal studies on the effects of leptin on the cardiovascular system have suggested that leptin activates the sympathetic nervous system [18,19], increases arterial pressure [20,21] and increases insulin sensitivity [27,28]. Serum leptin levels in our previous cross-sectional study [23] were also positively correlated with blood pressure. In that study, HR was correlated with leptin only in the adolescents, suggesting that leptin-induced activation of the sympathetic nervous system may contribute to obesity-related hypertension, especially in adolescents. We speculate that the aetiology in adult and middle-aged men may be more complicated because of confounding factors, including sodium retention, insulin resistance itself and/or atherosclerosis.

In the present study, baseline serum leptin levels in both the male adolescent group and the adult and middle-aged men group were negatively correlated with ΔBMI. These findings are partly compatible with the results of the 3-year follow-up study on Pima Indians [26], showing that the mean plasma leptin concentration was significantly lower in 19 weight gainers (> 3 kg/year) than in 17 weight-stable subjects (±0.4 kg) after adjustment for initial percentage body fat. Although it is unfortunate that we were unable to measure serum or urine catecholamines or basal metabolic rate in the present study, we hypothesize that high serum leptin levels increase basal metabolic rate and fat oxidation via increased sympathetic tone, especially in adolescents. In the adult and middle-aged men, however, a decrease in appetite caused by leptin, or merely a weight oscillation, may have been the main factor in the decline in BMI.

In the present study, serum leptin levels were negatively correlated with ΔTC, independent of baseline BMI, in men aged 30–63 years. Silver et al. [29] have suggested that defective HDL particle uptake and recycling in ob/ob hepatocytes (from leptin-deficient mice) play a role in the deterioration of plasma HDL protein and cholesterol levels. In the present study, log[leptin‘96] was negatively correlated with both HDL–C‘96 and HDL–C‘98, but not with ΔHDL–C. Instead,
Leptin, body weight and metabolic parameters

Figure 2  Negative correlations between baseline leptin levels and ΔFPG (A) and ΔTC (B) in 225 Japanese men aged 30–63 years

ΔLDL-C and ΔTC were negatively correlated with baseline leptin levels. We speculate that the effects of leptin on appetite and body weight may have been associated with later amelioration of glucose and lipid metabolism in the present study.

It is unclear if the results obtained here were related to alterations in the production or the clearance of leptin. High serum leptin levels in obese subjects suggest that they are attributable to increased secretion from an excess amount of fatty tissue. However, these obese subjects are supposed to show leptin resistance to some extent. Although the mechanism(s) of leptin resistance is not clear, recent studies in vitro have shown that leptin receptor (Ob-Rb) expression in neuroblastoma cells decreased too 18% of control levels following a 24 h incubation with 50 ng/ml leptin [30]. Other possible sites of leptin resistance are the blood–brain barrier [31] and post-receptor pathways, including STAT3 (signal transducer and activator of transcription 3) proteins [32].

To summarize, baseline serum leptin levels of male adolescents were negatively correlated with ΔBMI, even after adjustment for initial BMI. Also, the baseline serum leptin levels of adult and middle-aged men were negatively correlated with ΔBMI, ΔFPG, ΔTC and ΔLDL-C, and the correlation with ΔTC was significant even after adjustment for initial BMI. These findings suggest that serum leptin levels are correlated with subsequent decreases in BMI and TC in Japanese men.

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