Changes in Intra-Abdominal Visceral Fat and Serum Leptin Levels in Patients With Obstructive Sleep Apnea Syndrome Following Nasal Continuous Positive Airway Pressure Therapy

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Background—Obstructive sleep apnea syndrome (OSAS) is a common disorder in obese subjects. Visceral fat accumulation (VFA) is a better predictor of coronary heart disease than body mass index. Leptin is a hormone involved in the control of body weight and fat distribution. The effect of nasal continuous positive airway pressure (NCPAP) treatment on VFA and serum leptin levels in OSAS patients has not been known.

Methods and Results—VFA and subcutaneous fat accumulation (SFA) were assessed by CT before and after NCPAP treatment in 22 OSAS patients (mean apnea and hypopnea index \( >50 \) episodes/h). Serum leptin levels of another 21 OSAS patients were measured before and after 3 to 4 days of NCPAP to gain insight into the mechanism by which NCPAP affects fat distribution. VFA and SFA decreased significantly after 6 months of NCPAP treatment (236 ± 6 16 to 182 ± 6 14 cm\(^2\), \( P = 0.0003 \) and 215 ± 21 to 189 ± 18 cm\(^2\), \( P = 0.003 \), respectively). VFA decreased significantly in the body weight reduction group (\( n = 9, P < 0.01 \)) and the no body weight reduction group (\( n = 13, P < 0.03 \)). In contrast, SFA changed significantly in the body weight reduction group only (\( P < 0.01 \)). Leptin levels decreased significantly following 3 to 4 days of NCPAP (\( P < 0.01 \)), whereas body weight, fasting insulin, and cortisol levels did not change significantly.

Conclusions—Correction of sleep disordered breathing by NCPAP may be used to reduce VFA in OSAS patients. OSAS may have significant effects on the serum leptin levels. (Circulation. 1999;100:706-712.)

Key Words: obesity ■ sleep ■ metabolism ■ lipids ■ cardiovascular diseases

Obstructive sleep apnea syndrome (OSAS) is a common disorder. In fact, 25% of all men 30 to 60 years old meet the minimal criterion for OSAS (apnea and hypopnea index \( >5 \)).\(^1\) Obesity clearly plays an important role in sleep-disordered breathing, and an increase of 1 SD in any measure of body habitus is associated with a 3-fold increase in the risk of an apnea-hypopnea score of 5 or higher.\(^1\) Therefore, \( >50\% \) of all obese men may have OSAS. Studies suggest that OSA is a risk factor for hypertension\(^2,3\) and myocardial infarction.\(^4\) However, the increase in the mortality rate in untreated patients with OSAS due to the cardiovascular diseases\(^5,6\) is controversial.\(^7\)

Obesity can be defined as an accumulation of excess body fat and is the most common nutritional disorder in humans. It is a major cause of mortality and morbidity through the development of metabolic disorders and cardiovascular disease. Extensive research into obesity has shown that the location of body fat deposits rather than their size is more important in determining the risk of developing of obesity-linked disorders.\(^8\) In fact, the accumulation of intra-abdominal visceral fat in the mesentery and omentum is a better predictor of coronary heart disease than the body mass index (BMI).\(^9\) Visceral fat accumulation (VFA) and fat around the neck\(^11,12\) are also risk factors for OSAS in obese patients.\(^10\)

Although the weight of most OSAS patients does not change significantly after nasal continuous positive airway pressure (NCPAP) treatment,\(^13\) the incidence of mortality in OSAS patients can be reduced with NCPAP treatment.\(^5\) We hypothesized that the location of body fat deposits in OSAS patients might be altered after long-term NCPAP treatment. Therefore, we investigated changes in the location of body fat in OSAS patients by abdominal CT. We also investigated the effect of NCPAP treatment on blood parameters because they

Received March 8, 1999; revision received May 13, 1999; accepted May 18, 1999.

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Circulation is available at http://www.circulationaha.org

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are thought to be closely related to mortality in obese individuals.\textsuperscript{14}

Leptin is a circulating hormone that is expressed abundantly and specifically in adipose tissue,\textsuperscript{15-18} although it is also secreted from human placenta.\textsuperscript{19} Leptin induces a complex response involving control of body weight and energy expenditure.\textsuperscript{15} It has been reported that leptin selectively decreases visceral adiposity in the rats.\textsuperscript{20} Because NCPAP treatment significantly reduced the visceral fat in OSAS patients in this study, we expected that serum leptin levels would increase after short-term NCPAP treatment. On the other hand, it has been reported that circulating levels of leptin decreased after 3 months of NCPAP treatment.\textsuperscript{21}

Therefore, the effect of NCPAP treatment on circulating leptin levels is not known. Thus, to better understand the effect of NCPAP on serum leptin levels, serum leptin levels were measured before and after 3 to 4 days and 1 and 6 months of NCPAP treatment.

\section*{Methods}

\textbf{Patients}

\textbf{CT Imaging Study}

The diagnosis of OSAS and the selection of NCPAP candidates (AHI>20) were performed as described previously.\textsuperscript{22,23} A total of 31 patients (29 males and 2 females) with OSAS were recruited for the study. Twenty-two patients received NCPAP treatment and 9 patients served as controls. Twenty-two patients with OSAS were treated with NCPAP for >6 months. Control subjects were also candidates for NCPAP treatment. Polysomnography was performed before NCPAP therapy and again on the first night of NCPAP therapy.

\textbf{Study of the Serum Leptin Measurement}

Serum leptin levels were measured in another 21 patients (all male) with OSAS (AHI>20), including some members of the treatment and control groups because the serum leptin measurements were started after the CT imaging studies. This study was approved by the local institutional ethics committee, and all of the patients gave their informed consent before the study.

\textbf{Measurement of Body Fat Distribution}

The amount of abdominal subcutaneous and visceral fat deposition was assessed by CT imaging (Figure 1). The area of the subcutaneous fat and visceral fat was measured in a single cross-sectional scan at the level of the umbilicus. An image histogram was computed for the subcutaneous fat layers in order to determine the range of CT numbers for the fat tissue. The total fat area was then calculated by counting the pixels that had intensities within the selected range of CT numbers. The intraperitoneal space was defined by tracing its contour on the scan image. The total area with the same CT numbers was assessed by the Friedwald formula.\textsuperscript{26} Apolipoprotein (apo) A-I, A-II, B, C-II, C-III, and E levels were determined by the tissue immunoactive method.

A 75 g oral glucose tolerance test (OGTT) was performed before and after >6 months of NCPAP treatment, and blood samples were collected at 0, 30, 60, 90, 120, and 180 minutes for the determination of glucose and insulin levels. Plasma glucose was assayed by the glucose oxidase method, and insulin was assayed by a double antibody radioimmunoassay (RIA). VFA and subcutaneous fat accumulation (SFA) were assessed by CT before and after >6 months of NCPAP treatment.

\textbf{Serum Leptin Measurement Group}

Serum leptin levels before and after 3 to 4 days (n=21), 1 (n=10), and 6 (n=13) months of NCPAP treatment were determined by the RIA for human leptin.\textsuperscript{19,27} The intra- and interassay coefficients of variation used in the leptin measurements were 5.3% (n=10) and 5.9% (n=10), respectively.\textsuperscript{27} At the same time, serum insulin and cortisol levels were also determined using the respective RIA. Leptin levels can change with food intake and BMI.\textsuperscript{13} Therefore, the leptin levels of the OSAS patients before the NCPAP treatment were measured after 3 to 4 days of hospitalization following the first polysomnography. The patients then returned to their homes and after 2 or 3 days came to our hospital again to be treated with NCPAP. The second measurement of leptin levels was taken following 3 to 4 days of NCPAP treatment. The OSAS patients ingested the same amount of food for the 3- to 4-day period without any changes in body weight when leptin was measured. As some patients were lost to follow-up, the leptin levels in the OSAS patients were measured after 1 (n=10) and 6 (n=13) months of NCPAP treatments. Blood for the leptin measurements was also drawn at 8:15 AM after an overnight fast. Previous studies have reported a significant correlation among serum leptin levels and SFA and total fat accumulation (TFA), but not with VFA.\textsuperscript{15,16} Therefore, we measured the VFA and SFA of all patients in the serum leptin measurement group before (n=21) and after (n=8) NCPAP treatment to understand the relation between serum leptin levels and various measurements of fat accumulation: VFA, SFA, and TFA.

\textbf{Data Analysis}

The data were presented as mean±SEM and were tested by nonparametric methods. The differences in the VFA of OSAS patients before and after >6 months of NCPAP treatment were tested for significance with the Wilcoxon signed-rank test. As body weight reduction has a significant effect on the VFA and SFA,\textsuperscript{28} we divided the CT imaging group into 2 groups: those who showed a significant body weight reduction (BWR; a decrease in BMI ≥1 kg/m\textsuperscript{2}, n=9), and those with no weight reduction (No-BWR; a change of BMI <1 kg/m\textsuperscript{2}, n=13). Differences among the values obtained from the 3 groups (control, BWR, and No-BWR groups) were tested for significance by the Kruskal-Wallis test and the intergroup differences among 3 groups were evaluated with the Mann-Whitney U test with a Bonferroni correction for multiple group comparison. The Wilcoxon signed-rank test was used to compare the results of VFA and SFA between first and second CT measurements in the OSAS controls. The Wilcoxon signed-rank test was also used to compare the results in the OSAS patients between before and after NCPAP treatment. Spearman rank correlation coefficients were calculated to analyze the correlation among leptin levels and VFA, SFA, TFA, insulin, and cortisol levels. A P<0.05 was considered to be significant.

\textbf{Protocol}

\textbf{Control and CT Imaging Group Before and After NCPAP Treatment}

Blood was drawn at 8:15 AM after an overnight fast before and after >6 months of NCPAP treatment. Serum triglyceride, total cholesterol, and other lipid measurements were then determined by enzymatic methods using commercial kits. LDL cholesterol was calculated by the Friedwald formula.\textsuperscript{26} Apolipoprotein (apo) A-I, A-II, B, C-II, C-III, and E levels were determined by the tissue immunoactive method.

\textbf{Results}

\textbf{CT Imaging Study}

\textbf{Patient Characteristics}

There were no significant differences between control OSAS and OSAS with NCPAP treatment with respect to age, BMI, blood pressure before the study, and respiratory parameters during sleep. Although we recommended that all patients reduce their body weight, some patients lost a significant amount of body weight (BMI change ≥1 kg/m\textsuperscript{2}, n=9) and...
others did not (BMI change <1 kg/m², n=13). Because this difference in body weight could affect the results, the OSAS patients with long-term NCPAP treatment were divided into 2 groups: BWR and No-BWR. The parameters of the 3 (control, BWR, and No-BWR) groups are shown in Table 1. The only significant difference between the BWR and the No-BWR group was the value of the lowest SaO₂ during sleep. None of the other parameters showed any significant differences among the 3 groups. Antihypertensive drugs were prescribed in 3 of 9 patients in the BWR group and 3 of 13 patients in the No-BWR group. During the study, none of the medications were changed in any of the patients.

Body Fat Distribution Before and After NCPAP Treatment

In the control group without NCPAP treatment, the amount of VFA and SFA did not change significantly over a period of >1 month (36±5.7 days; Figure 2). After >6 months of NCPAP therapy, VFA and SFA in OSAS patients decreased significantly (236±16 cm² to 182±14cm², P=0.0003 and 215±21 cm² to 189±18 cm², P=0.003, respectively), whereas body weight also decreased significantly after >6 months of NCPAP treatment. The VFA after NCPAP (BWR group: 236±21 days, No-BWR group: 237±10 days) decreased significantly in both the BWR and the No-BWR groups, whereas SFA did not decrease significantly in the No-BWR group (Table 2 and Figure 2).

75 g OGTT and Other Parameters

Serum glucose levels in 7 of 9 patients in the BWR group and 8 of 13 patients in the No-BWR group exceeded 200 mg/dL during the glucose tolerance test. In the BWR group, glucose levels during the glucose tolerance test, triglyceride levels, and several other serum lipid parameters decreased significantly but without any concomitant changes in the insulin levels, except for insulin levels at 180 minutes (Figure 3 and Table 2). In contrast, there were no changes in glucose and insulin levels during OGTT (n=12) or other lipid parameters.
in the No-BWR patients, although HDL and LDL cholesterol levels improved significantly. (Table 2).

**Serum Leptin Level Study**

The serum leptin levels were measured in 21 OSAS patients (Age 52.2 ± 3.3 y, BMI 29.3 ± 1.1 kg/m², AHI before NCPAP treatment: 52.2 ± 3.3 episodes/h, and after 3 to 4 days: 29 ± 0.8 episodes/h). Five of the 21 OSAS patients were also in the CT imaging group. The 21 OSAS patients ingested the same amount of food during the 3 to 4 day treatment period without any changes in body weight. Serum leptin levels decreased significantly following 3 to 4 days of NCPAP treatment (before NCPAP: 26.2 ± 3.3 ng/mL, after NCPAP: 21.7 ± 3.0 ng/mL, P = 0.0096) (Figure 4).

There were no significant differences between the CT imaging group (n = 22) and the leptin measurement group (n = 21) with respect to age, BMI, and AHI before and after NCPAP treatment. Serum leptin levels correlated positively with the SFA and TFA before (n = 21, r = 0.81, P = 0.0003 and r = 0.75, P = 0.0008, respectively) and after (r = 0.71, P = 0.0016 and r = 0.66, P = 0.0034, respectively) 3 to 4 days of NCPAP treatment. However, leptin levels did not correlate with VFA before (r = 0.23, P = NS) or after (r = 0.18, P = NS) 3 to 4 days of treatment. Also, after 6 months of NCPAP treatment, serum leptin levels in the OSAS patients (n = 8) decreased significantly (P = 0.012) and serum leptin levels correlated significantly with SFA (n = 8, r = 0.79, P = 0.038) but not with VFA (n = 8, r = 0.17, P = NS).

The relation between the serum leptin levels and the fasting insulin levels or cortisol levels were as follows (n = 21 for both): before NCPAP treatment, insulin: r = 0.56, P = 0.012; cortisol: r = -0.79, P = 0.0004, and after 3 to 4 days, insulin: r = 0.48, P = 0.03; cortisol: r = -0.63, P = 0.0052. Neither fasting insulin levels nor cortisol levels changed significantly after NCPAP treatment (Figure 4).

After 1 month of NCPAP treatment, serum leptin levels decreased significantly without significant changes in BMI (n = 10, leptin: before, 27.4 ± 4.4 ng/mL; after, 20.8 ± 4.1 ng/mL, P = 0.028; BMI: before, 29.8 ± 2.2 kg/m²; after, 28.7 ± 1.8 kg/m², P = NS). After 6 months of NCPAP treatment, serum leptin levels decreased significantly (n = 13, leptin: before, 26.7 ± 3.6 ng/mL; after, 14.0 ± 2.4 ng/mL, P = 0.0046) in 6 of 13 patients who had significant weight reduction (BMI change ≥ 1 kg/m²). In addition, the leptin levels in 7 of 13 patients whose weight did not change significantly after 6 months of NCPAP treatment also decreased significantly (n = 7, leptin: before, 23.3 ± 3.7 ng/mL; after, 9.2 ± 1.9 ng/mL, P = 0.028, BMI: before, 27.4 ± 0.9 kg/m²; after, 27.3 ± 0.9 kg/m², NS).

**TABLE 1. Clinical Profiles of Patients With OSAS**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n = 9)</th>
<th>No-BWR (n = 13)</th>
<th>BWR (n = 8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.3 (3.4)</td>
<td>46.2 (3.7)</td>
<td>50.8 (3.7)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.6 (1.3)</td>
<td>28.5 (0.8)</td>
<td>31.2 (1.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>130.9 (6.3)</td>
<td>135.4 (3.8)</td>
<td>131.9 (4.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>82.8 (4.6)</td>
<td>88.4 (2.6)</td>
<td>83.4 (2.0)</td>
<td>NS</td>
</tr>
<tr>
<td>AHI, episodes/h</td>
<td>59.4 (6.9)</td>
<td>52.7 (5.0)</td>
<td>63.5 (5.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Lowest SaO₂, %</td>
<td>54.2 (4.1)</td>
<td>62.6 (4.4)</td>
<td>47.7 (4.1)*</td>
<td>0.047</td>
</tr>
<tr>
<td>SaO₂&lt;90%, % time</td>
<td>47.7 (8.1)</td>
<td>29.0 (5.8)</td>
<td>46.4 (4.1)</td>
<td>NS</td>
</tr>
<tr>
<td>SaO₂&lt;85%, % time</td>
<td>31.2 (7.3)</td>
<td>16.7 (4.6)</td>
<td>31.2 (7.3)</td>
<td>NS</td>
</tr>
<tr>
<td>CAHI, episodes/h</td>
<td>5.2 (0.9)</td>
<td>2.6 (0.9)</td>
<td>3.8 (1.1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

OSAS indicates obstructive sleep apnea syndrome; No-BWR, no body weight reduction group; BWR, body weight reduction group; BMI, body mass index; BP, blood pressure; AHI, apnea and hypopnea index; SaO₂, arterial O₂ saturation; CAHI, AHI after nasal continuous positive airway pressure treatment.

P < 0.05 vs No-BWR group.

Figure 2. Changes in the location of the body fat. A, In the control group without NCPAP treatment, amount of VFA and SFA did not change significantly after ~1 month (36 ± 5.7 days). B, After >6 months of NCPAP therapy, in the No-BWR group (237 ± 10 days), only VFA decreased significantly. C, BWR group (236 ± 21 days), amount of VFA and SFA decreased significantly. Dotted line represents the mean ± SEM.
This is the first study to suggest that NCPAP treatment may be used to reduce VFA in OSAS patients with or without significant changes in body weight. Excess VFA is associated with numerous metabolic and cardiovascular complications. Recent data suggest that OSAS is a common disorder and that 50% of all obese individuals have OSAS. Therefore, using NCPAP therapy to reduce VFA may lower the risk of VFA-associated diseases in large numbers of obese individuals.

A reduction in VFA has been reported to occur in conjunction with body weight reduction following diet and exercise. NCPAP treatment in OSAS patients results in an immediate increase in activity with an improvement in hypersomnolence during the day. This increase in activity may mimic the effects of exercise in OSAS patients.

The mechanisms underlying the decrease in VFA and the decrease in serum leptin levels without changes in body weight in OSAS patients are not clear at present. The relation observed among serum leptin levels and TFA, SFA, VFA, and serum fasting insulin levels corresponds to previous reports. No previous studies have examined the short-term effects of NCPAP treatment on serum leptin levels in OSAS patients.

Values are mean±SEM.
Before indicates before NCPAP treatment; After, after 8-month NCPAP treatment; T-chol, total cholesterol; TG, triglyceride; FPG, fasting plasma glucose; FPI, fasting plasma insulin; and apo, apolipoprotein.

*P<0.05, †P<0.01 vs before NCPAP treatment.

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Circulating levels of leptin have been re-

Figure 3. Seventy-five gram oral glucose tolerance test (OGTT). Open symbols represent blood glucose (insulin) levels during OGTT before NCPAP treatment. Closed symbols represent blood glucose (insulin) levels during OGTT after >6 months of NCPAP treatment. In BWR group (n=9) (B), glucose levels during OGTT decreased significantly but without any concomitant changes in insulin levels, except for value at 180 minutes. In contrast, this phenomenon was not seen in No-BWR group (n=12) (A). Insulin levels of some samples could not be measured because 2 samples at 180 minutes in No-BWR group and 2 samples at 90 minutes in BWR group were hemolysed. Values are mean±SEM. *P<0.05, †P<0.01.
reported to decrease after 3 months of NCPAP treatment. However, the changes in BMI were not accounted for in this study, and the number of study subjects (n=10) was small. Recently, it has been reported that leptin given to rats by osmotic minipumps for 8 days selectively decreases visceral adiposity. Because the VFA decreased following NCPAP treatment in our experiment, we expected leptin levels to increase. Instead, serum leptin levels decreased significantly after 3 to 4 days of NCPAP treatment. Three or 4 days of NCPAP treatment is too short a time interval to have any significant effects on body fat or the distribution of body fat. In this study, the OSAS patients ingested the same amount of food for a 3- to 4-day period without any changes in body weight. A more likely explanation for the reduction in serum leptin concentrations over this brief period would be the effects of NCPAP on sympathetic activation. Indeed, it has been reported that NCPAP decreases muscle nerve sympathetic activity and blood pressure during sleep. In addition, there is a report that muscle nerve sympathetic activity levels have a significant positive correlation with leptin concentration. On the basis of the results of our study, the decrease in sympathetic nerve activity from NCPAP therapy may decrease the leptin levels. Contrary to our results, several reports showed that leptin administration increased the sympathetic nerve activity. Therefore, the relation between sympathetic nerve activity and leptin levels in OSAS patients before and after NCPAP treatment should be studied further. NCPAP treatment may also evoke reflexes associated with increases in lung volume or increases in abdominal pressure and perhaps visceral blood flow. The increase in splanchnic venous volume, decrease in nocturnal blood pressure, and improvement in cardiac function may change blood flow in the body and this would have an effect on the leptin clearance. Another possible mechanism for the decrease in leptin levels after NCPAP treatment is the effect of the circadian rhythm on leptin levels.

In this study, the decrease in leptin levels continued after 1 and 6 months of NCPAP treatment and without significant changes in body weight. These results suggest that leptin resistance in obese OSAS patients may improve after NCPAP treatment. However, the mechanism for this improvement could not be determined in this study.

Studies suggest that VFA is closely correlated with HDL and LDL cholesterol levels. Patients with high VFA had low HDL and high LDL cholesterol levels. In this study, VFA decreased significantly following >6 months of NCPAP treatment while HDL increased significantly without a significant body weight change (Table 2). Thus, repetitive obstructive sleep apnea might have a significant effect on cholesterol metabolism during sleep, in addition to its effect on VFA (Table 2).

The effect of NCPAP treatment on glucose intolerance is unclear. One study reported that glucose intolerance in OSAS patients improved after long-term NCPAP treatment. Another report indicated that the relation between insulin resistance and sleep-disordered breathing was entirely dependent on body mass. The results of our experiment support the latter study.

The mechanisms that cause the differences between the BWR and No-BWR groups are unclear. Understanding this mechanism is very important because a significant BWR after NCPAP treatment could benefit patients by changing apolipoprotein levels and improving insulin sensitivity and hyperlipidemia in addition to changes in VFA (Table 2 and Figures 2 and 4). As reported in Pima Indians, long-term follow-up of serum leptin levels and body weight is important to understand the mechanisms that lead to the differences between the BWR and No-BWR groups in OSAS patients following NCPAP treatment.

This study has several limitations. The first major limitation was that this study had 2 groups: a CT imaging group without the serum leptin measurement and a leptin measurement group with NCPAP treatment. The members of each group were not the same. Therefore, a comparison of the 2 groups may be difficult to interpret. However, there were no significant differences between the CT imaging group (n=22) and the leptin measurement group (n=21) with respect to age, BMI, or AHI before and after NCPAP treatment. Therefore, these results would apply to all OSAS patients (AHI>20) who were candidates for NCPAP treatment.

Secondly, leptin levels were measured only once after 3 to 4 days of NCPAP treatment. However, our interassay coefficients of variation were within 6%. The leptin levels after 1 and 6 months of NCPAP treatment decreased significantly as those after 3 to 4 days of NCPAP treatment. Therefore, the decrease in the leptin levels over 3 to 4 days of NCPAP treatment should be significant, although the leptin levels change periodically.

In this study, NCPAP treatment in OSAS patients specifically reduced VFA. This reduction in VFA in these patients may lead to improvement of VFA-associated diseases. In the investigation of obesity-linked disorders, it is important to consider the existence of OSAS in obese patients not only because the prevalence of OSAS is so high but also because OSAS may have significant effects on adipocyte-derived signaling factors such as leptin.
Acknowledgments

We thank ShigeoYura and Hidenori Iwai for measuring the serum leptin levels. This study was supported in part by grant No. 09670608 from the Japanese Ministry of Education, Science, and Culture and the Japanese Ministry of Health and Welfare.

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Circulation. 1999;100:706-712
doi: 10.1161/01.CIR.100.7.706
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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