Close Correlation of Intra-abdominal Fat Accumulation to Hypertension in Obese Women

Hideyuki Kanai, Yuji Matsuzawa, Kazuaki Kotani, Yoshiaki Keno, Takashi Kobatake, Yoshiyuki Nagai, Shigenori Fujioka, Katsuto Tokunaga, and Seiichiro Tarui

The relation between intra-abdominal visceral fat accumulation and blood pressure was investigated in 67 obese women (mean body mass index, 33.6±3.1; average age, 50±11 years). As an index of intra-abdominal fat accumulation, the ratio of the intra-abdominal visceral fat area to subcutaneous fat area was determined using a computed tomographic section at the level of the umbilicus. When the obese subjects were divided into a hypertensive group and a normotensive group, the ratio of the intra-abdominal visceral fat area to subcutaneous fat area in the hypertensive group was significantly higher (0.53±0.33 versus 0.29±0.12, p<0.01). Significant correlations between the ratio of intra-abdominal visceral fat area to subcutaneous fat area and systolic blood pressure (r=0.62, p<0.001) and diastolic blood pressure (r=0.53, p<0.001) also were found. However, no significant difference existed in either the body mass index or the waist-to-hip circumference ratio between the hypertensive and normotensive groups. Plasma renin activity, aldosterone, epinephrine, and norepinephrine levels were not significantly different between the two groups. Moreover, the correlation between the ratio of the intra-abdominal visceral fat area to subcutaneous fat area ratio and blood pressure was found independent of age and body mass index by multiple regression analyses. We conclude that intra-abdominal fat accumulation itself may play an important role in the pathogenesis of hypertension in obesity. (Hypertension 1990;16:484-490)

It has been noted that the incidence of circulatory and metabolic complications among comparably obese subjects differs depending on their body habits.1 We have developed a method to estimate fat distribution using computed tomography (CT) scan, which clearly distinguishes between subcutaneous fat and intra-abdominal visceral fat2 and have demonstrated a close correlation between intra-abdominal fat accumulation and metabolic disturbances.3 Further, using this method we reported that the accumulation of intra-abdominal visceral fat itself may reflect cardiac dysfunction and metabolic disorders better than subcutaneous fat.4-7 Therefore, we propose the existence of two types of obesity: visceral fat obesity, characterized by a pronounced accumulation of fat in the abdominal cavity, and subcutaneous fat obesity, characterized by an accumulation mainly in the subcutis (Figure 1). We also reported8 that this classification is more useful than other classifications of fat distribution,9-16 including the waist-to-hip circumference ratio, as we were unable to duplicate the correlation between waist-to-hip circumference ratio and metabolic disorders reported by Kissebah and others.10,11 In the present study, we evaluate the relation between intra-abdominal fat accumulation and blood pressure levels in obese Japanese women.

Methods

Subjects

The research subjects were 67 obese adult women aged 50±11 (range, 31–73) years who consulted our clinic in the Second Department of Internal Medicine, Osaka University Hospital, Osaka, Japan, for assistance in weight reduction. Obese patients whose body mass index (BMI) weight/height² [kg/m²]) was more than 30 were considered for the present study. Their mean BMI was 33.6±3.1 (30.0–44.3). Ten patients were taking antihypertensive medication prescribed elsewhere at the start of the study: two were treated with diuretics, one with a β-blocker, two...
with calcium antagonists, and five with combination therapy. None of the patients were taking any lipida
classifying or hypoglycemic agents. The body weight of
the research subjects was stable for at least 4 weeks
before they consulted our clinic, and the study was
performed within 1 week after consultation while the
subjects were maintained on a 2,000 to 2,400 kcal of
a weight-maintaining diet, with 60% of the calories
given as carbohydrate, 20% as fat, and 20% as
protein. None of the subjects engaged in a program
of vigorous physical exercise. All subjects gave in-
formed consent before the investigation.

Procedure

The blood pressure measurements were taken
from the right arm using a mercury manometer after
the subject had briefly rested in a sitting position.
Cuff sizes were selected based on upper-arm girth
and length. The diastolic blood pressure was re-
corded when the Korotkoff sounds disappeared
(phase five). The mean of three measurements was
used in the analysis. A systolic blood pressure of 160
mm Hg or more or a diastolic blood pressure of 95
mm Hg or more, or both, were defined as hyperten-
sive. The subjects meeting these criteria and those
maintained on antihypertensive agents were defined
as hypertensive. A systolic blood pressure less than
140 mm Hg or a diastolic blood pressure less than 90
mm Hg, or both, were defined as normotension. The
blood pressure levels that did not meet the criteria of
hypertension or normotension were defined as bor-
derline hypertension (between 140/90 and 159/94
mm Hg).

Anthropometric measurements included manual
measurements of the height to the nearest 0.1 cm and
weight to the nearest 0.1 kg. Circumferences of the
waist and hip were measured to the nearest 0.1 cm at
the level of the umbilicus and at the widest circum-
ference over the greater trochanters and were used
to calculate the waist-to-hip circumference ratio.
Triceps, subscapular, and periumbilical skinfold
thicknesses were measured to the nearest 1.0 mm
with calipers (Eiyoken-Type, Meikosha Co., Ltd.,
Tokyo), and the mean of two measurements of each
skinfold was used in the analysis. The body fat
distribution by CT scan was determined according to
the procedure of Tokunaga et al,2 by which the total
cross-sectional area, subcutaneous fat area, and in-
tra-abdominal visceral fat area were measured at the
level of the umbilicus. All CT scans were performed
with the subject in the supine position with use of a
General Electric CT/T scanner (General Electric
Co., Milwaukee, Wis.), and the ratio of the intra-
abdominal visceral fat area to subcutaneous fat area
(V/S ratio) was calculated. The V/S ratio was
adopted as an index of the relative increase of
visceral fat, as previously reported by us3-8 and
others.17-19

Blood was drawn after an overnight fast. Serum
triglycerides, total cholesterol, and uric acid levels
were determined by enzymatic methods. Serum high
density lipoprotein (HDL) cholesterol was measured
by the heparin-calcium precipitation method. A 75 g
oral glucose tolerance test also was performed, and
blood samples were collected at 0, 30, 60, 90, 120, and
180 minutes to determine glucose and insulin levels.
Plasma glucose was assayed by a glucose oxidase
method and plasma insulin by double antibody radio-
immunoassay. The plasma hemoglobin Alc level was
assayed by high-performance liquid chromatography
(HPLC). The plasma glucose area and insulin area
were determined by calculating the area under the
concentration curve (i.e., by multiplying the 30 min-
utes by the sum of half the fasting level, the levels at
30, 60, 90, and 180 minutes and 1.5 times the level at
120 minutes). The blood samples for plasma renin
activity (PRA), aldosterone, epinephrine, and nor-
epinephrine assays were collected with cold tubes
containing EDTA 2Na (1.5 mg/ml) and stored at
−80°C. PRA and aldosterone concentration were
determined by radioimmunoassay. Plasma epineph-
rine and norepinephrine were assayed by HPLC.

Statistics

Results are expressed as mean±SD. The signifi-
cance of differences between means for two groups
was determined by Student’s t test for unpaired data
after an analysis of variance. Linear regression anal-
ysis was used to study the relation between variances.
Multiple regression analyses were performed to
quantify the effects of age and BMI.
TABLE 1. Comparison of Age, Onset of Obesity, Body Measurements, and Fat Distribution Among Hypertensive, Borderline Hypertensive, and Normotensive Obese Women

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hypertensive group (n=33)</th>
<th>Borderline hypertensive group (n=9)</th>
<th>Normotensive group (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>53±10*</td>
<td>49±11</td>
<td>47±9</td>
</tr>
<tr>
<td>Age of obesity onset (yr)</td>
<td>25±7</td>
<td>27±9</td>
<td>27±9</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>163±16</td>
<td>145±9</td>
<td>125±11</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>100±8</td>
<td>89±4</td>
<td>76±8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>154.2±4.8</td>
<td>153.0±4.8</td>
<td>156.1±5.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.1±9.0</td>
<td>78.7±9.4</td>
<td>82.4±10.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.3±3.4</td>
<td>33.3±2.8</td>
<td>34.1±3.3</td>
</tr>
<tr>
<td>WHR</td>
<td>1.01±0.07</td>
<td>0.98±0.07</td>
<td>0.98±0.08</td>
</tr>
<tr>
<td>Triceps (mm)</td>
<td>32±8</td>
<td>31±9</td>
<td>31±7</td>
</tr>
<tr>
<td>Subscapular (mm)</td>
<td>41±8</td>
<td>41±10</td>
<td>40±9</td>
</tr>
<tr>
<td>Periumbilicus (mm)</td>
<td>41±8</td>
<td>45±8</td>
<td>45±11</td>
</tr>
<tr>
<td>V/S ratio</td>
<td>0.53±0.33†</td>
<td>0.40±0.12*</td>
<td>0.29±0.12</td>
</tr>
</tbody>
</table>

Systolic and diastolic blood pressures in the hypertensive group were evaluated in those who were not taking antihypertensive agents (n=23). All values are mean±SD. BMI, body mass index; WHR, waist-to-hip circumference ratio; V/S ratio, intra-abdominal visceral fat area/subcutaneous fat area ratio.

Results

Among the 67 obese research subjects, 33 subjects, including the 10 taking antihypertensive medication, were classified as hypertensive, 9 subjects as borderline hypertensive, and the remaining 25 subjects as normotensive by our criteria. The demographic data are presented in Table 1. These characteristics were compared among these three groups. A slight difference in the average age existed between the hypertensive and normotensive groups, but there was no significant difference in the age of onset of obesity. Neither the BMI nor skinfold thickness was significantly different between the two groups. The waist-to-hip circumference ratio did not differ in the two groups. On the other hand, the V/S ratio in the hypertensive group was significantly higher than in the normotensive group (0.53±0.33 versus 0.29±0.12, p<0.01). The V/S ratio in the borderline hypertensive group also was significantly higher than in the normotensive group. Among the 57 obese subjects who were not taking antihypertensive agents, there was a significant correlation between the V/S ratio and systolic blood pressure (r=0.62, p<0.001) and diastolic blood pressure (r=0.53, p<0.001) (Figure 2).

As the average age between the hypertensive and normotensive groups was slightly different, multiple regression analyses were performed to ascertain whether the V/S ratio had an independent correlation with systolic or diastolic blood pressure in the 57 subjects. Both the systolic and diastolic blood pressure

![Figure 2. Scatterplots showing correlation between the intra-abdominal visceral fat area/subcutaneous fat area (V/S) ratio and systolic and diastolic blood pressures (BP) in obese subjects not taking antihypertensive medication.](http://hyper.ahajournals.org/content/images/figure2.jpg)

TABLE 2. Effect of Body Mass Index, Ratio of Visceral Fat Area to Subcutaneous Fat Area, and Age on Blood Pressure in Obese Women as Determined by Multiple Regression Analyses

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Partial correlation coefficient</th>
<th>Multiple correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>-0.07</td>
<td>0.59*</td>
</tr>
<tr>
<td>Diastolic</td>
<td>-0.11</td>
<td>0.52*</td>
</tr>
</tbody>
</table>

Ten subjects who were taking antihypertensive agents were not included in these analyses (n=57). BMI, body mass index; V/S ratio, ratio of intra-abdominal visceral fat area to subcutaneous fat area.

*p<0.001.
Pr»-m«nop«B«l
Pott-mmpmad
FIGURE 3. Scatterplots showing correlation between the intra-abdominal visceral fat area/subcutaneous fat area (V/S) ratio and systolic and diastolic blood pressures (BP) in premenopausal (n=24) and postmenopausal (n=33) obese women not taking antihypertensive agents.

sures correlated significantly with the V/S ratio after adjustment for age and BMI (Table 2).

The 57 subjects also were divided into a premenopausal group (n=24) with regular menstrual cycles and a postmenopausal group (n=33); the relation between the V/S ratio or waist-to-hip circumference ratio and blood pressure was evaluated in each group. In the 57 subjects, there was no one with pathological amenorrhea. Both the V/S ratio and the waist-to-hip circumference ratio in the postmenopausal group were slightly greater than in the premenopausal group, but the differences were not significant (V/S ratio, 0.48±0.31 versus 0.37±0.26; waist-to-hip circumference ratio, 1.00±0.07 versus 0.97±0.07). The correlation coefficient between the V/S ratio and blood pressure also was significant in both the premenopausal and postmenopausal groups (Figure 3). On the other hand, the correlation between the waist-to-hip circumference ratio and blood pressure was not significant in any group (Figure 4).

To investigate the pathogenetic relation of metabolic and hormonal factors to hypertension, we compared various metabolic characteristics among the hypertensive, borderline hypertensive, and normotensive groups excluding subjects who were taking antihypertensive medication (Table 3). There were no significant differences among these three groups in measured metabolic parameters concerning glucose and lipids metabolism. The hormonal factors relating to blood pressure regulation were also compared among these three groups (Table 4). No significant differences in PRA, aldosterone, epinephrine, or norepinephrine existed among these three groups.

Discussion
In the present study, which dealt with severely obese women, we found that intra-abdominal fat

FIGURE 4. Scatterplots showing correlation between the waist-to-hip circumference ratio (WHR) and systolic and diastolic blood pressures (BP) in premenopausal (n=24) and postmenopausal (n=33) obese women not taking antihypertensive agents.
TABLE 3. Metabolic Characteristics of Obese Subjects in Hypertensive, Borderline Hypertensive, and Normotensive Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hypertensive group (n=23)</th>
<th>Borderline hypertensive group (n=9)</th>
<th>Normotensive group (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>106±23</td>
<td>110±16</td>
<td>101±12</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma IRI</td>
<td>13±7</td>
<td>12±9</td>
<td>12±6</td>
</tr>
<tr>
<td>(microunits/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma glucose area</td>
<td>293±99</td>
<td>316±105</td>
<td>265±101</td>
</tr>
<tr>
<td>(mg·min/dl)×10⁻²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma insulin area</td>
<td>114±58</td>
<td>110±38</td>
<td>107±57</td>
</tr>
<tr>
<td>(microunits·min⁻¹·ml)×10⁻²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin Ace (%)</td>
<td>6.6±1.9</td>
<td>6.5±0.6</td>
<td>6.1±0.5</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>223±38</td>
<td>215±14</td>
<td>210±40</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>156±94</td>
<td>158±77</td>
<td>137±115</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>49±11</td>
<td>50±11</td>
<td>53±12</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.9±1.8</td>
<td>5.7±2.0</td>
<td>6.1±1.9</td>
</tr>
</tbody>
</table>

Ten subjects who were taking antihypertensive agents were not included in the hypertensive group. All values are mean±SD. IRI, immunoreactive insulin; HDL, high density lipoprotein.

accumulation had a close correlation with blood pressure elevation that was independent of age and BMI. As sex hormones are known to affect fat distribution,26 we divided the women into a premenopausal group and a postmenopausal group. The correlation between intra-abdominal fat accumulation and blood pressure was significant in both groups. These data suggest that intra-abdominal fat accumulation may play an important role in the pathogenesis of hypertension in adult obesity. No published report has examined this relation in this population, although some investigators reported this relation in healthy premenopausal women.21-23

Several reports on white women in Western countries found a strong correlation between the waist-to-hip circumference ratio and blood pressure.11,21-23 However, the present study did not find any significant correlation between the waist-to-hip circumference ratio and blood pressure in obese Japanese women. As no standardized level for measuring the waist and hip has been established, we also investigated the relation between blood pressure and the waist-to-hip circumference ratio using the minimum waist girth and maximum hip girth. Even this measurement, however, failed to show a significant correlation between the waist-to-hip circumference ratio and blood pressure (data not shown).

Why were the results between Japanese and Caucasian women different? The significant correlation between waist-to-hip circumference ratio and blood pressure in Caucasian women may be due to the correlation between the V/S ratio and waist-to-hip circumference ratio.16 In any case, the V/S ratio as an index of intra-abdominal fat accumulation might be the best topographic predictor for morbidity in obesity, including hypertension and metabolic disorders. Therefore, the correlation between the waist-to-hip circumference ratio and blood pressure may have the same implications as the correlation between the V/S ratio and blood pressure in Caucasian subjects. On the other hand, as reported previously,4 the correlation between the V/S ratio and waist-to-hip circumference ratio in obese Japanese women was not as strong as in Caucasian women. (In the present study, r=0.10, NS.) Consequently, a close correlation between the waist-to-hip circumference ratio and blood pressure in Japanese subjects would not be expected.

For the present, it remains to be determined exactly why intra-abdominal fat accumulation is associated with hypertension, although the following hypotheses are proposed. Adipocytes in the abdominal cavity are known to be metabolically active and highly sensitive to lipolytic stimulation by catecholamines and to lipid mobilization.20 It has been shown that the blood flow rate through mesenteric adipose tissue is greater than the blood flow rate through inguinal subcutaneous adipose tissue in rats.24 Also, we have reported that cardiac output in obese subjects, as estimated by echocardiography, was increased in proportion not only to body weight but also to the V/S ratio.6,25 These data suggest that the blood flow through adipose tissue in visceral fat obesity may be greater than in subcutaneous fat obesity for the same body weight. The greater degree of volume overload in the former may be related to hypertension in obesity.

A number of reports have demonstrated that intra-abdominal fat accumulation is associated closely with metabolic disorders such as insulin resistance, glucose intolerance, and hyperlipidemia.3-5,7,8,21-23 Reaven26 has proposed a syndrome (with resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased plasma concentration of very low density lipoprotein triglyceride, decreased plasma concentration of HDL cholesterol, and high blood pressure) as the syndrome X that tends to occur in the same individual and may be of enormous importance in the genesis of coronary artery disease.26 This syndrome has a similar feature to visceral fat obesity as this type of obesity fre-
quenty is associated with both metabolic disorders and hypertension. Blood pressure in visceral fat obesity may be increased by various metabolic aberrations, including hyperinsulinemia, insulin resistance, or arteriosclerotic vascular changes that are accelerated by aging or hyperlipidemia.\textsuperscript{14-27} However, we did not find a significant difference in these metabolic factors between hypertensive and normotensive groups, suggesting that neither these nor any metabolic measure in the present study was directly related to the pathogenesis of hypertension in obesity.

As a factor that promotes both intra-abdominal fat accumulation and high blood pressure, an increased androgenic activity may be proposed as a candidate.\textsuperscript{20} However, we found a significant correlation between the V/S ratio and blood pressure in both premenopausal and postmenopausal women. As the postmenopausal group is naturally more androgenic than the premenopausal group, the significant correlation between the V/S ratio and blood pressure in both groups suggests that the correlation is independent of any androgenic influence. Further study is required to clarify the pathogenetic relation between intra-abdominal fat accumulation and high blood pressure.

In conclusion, the V/S ratio showed a close correlation with blood pressure in obese subjects independent of BMI and age, whereas the correlation between waist-to-hip circumference ratio and blood pressure was not significant in these Japanese subjects. There were no significant differences in either metabolic or hormonal factors measured here among the hypertensive, borderline hypertensive, and normotensive groups. These data indicate that intra-abdominal fat accumulation itself may play an important role in the pathogenesis of high blood pressure in obesity. Therefore, it will be necessary for the prevention and treatment of hypertension in obesity to clarify the pathogenesis of visceral fat accumulation and to find the most effective method of reducing it.

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