Fat Accumulation and Obesity-related Cardiovascular Risk Factors in Middle-aged Japanese Men and Women

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Abstract

Objective A cluster of multiple risk factors has been noted to constitute the background of cardiovascular disease. The purpose of this study was to evaluate the relationship between the visceral fat area (VFA) or subcutaneous fat area (SFA) and a cluster of obesity-related cardiovascular risk factors, including hyperglycemia, dyslipidemia and elevated blood pressure, in middle-aged Japanese men and women.

Methods A total of 571 subjects (m=434; f=137; age: 53±9 years) who underwent health examinations with evaluations of body fat distribution using computed tomography scans and assessments of 75-g oral glucose tolerance tests were enrolled in this study.

Results The VFA and SFA were linearly correlated with the number of risk factors in both men and women. The area under the receiver-operating characteristic curve of VFA (m=0.741, f=0.763) was significantly higher than that of SFA (m=0.636, f=0.689) with respect to the clustering of risk factors (one or more). The men exhibited larger VFA values and smaller SFA values than the women in similar body mass index (BMI) categories. Men with a VFA of ≥100 cm² irrespective of BMI and women with a VFA of ≥100 cm² and a BMI of ≥25 kg/m² demonstrated a high prevalence of diabetes mellitus and impaired glucose tolerance. Men and women with a VFA of ≥100 cm² irrespective of BMI demonstrated a high prevalence of type IIb dyslipidemia.

Conclusion These results suggest that the absolute value of VFA rather than SFA is more closely associated with a cluster of risk factors irrespective of sex and is a good marker for selecting subjects to whom weight reduction should be recommended in order to prevent cardiovascular disease in the general population.

Key words: visceral fat, metabolic syndrome, glucose tolerance, dyslipidemia

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Introduction

Preventing cardiovascular disease (CVD) is an important health issue in industrial countries. We introduced the computed tomography (CT) scan method for precisely evaluating body fat in obese subjects (1), which enabled clinicians to evaluate the amount of intra-abdominal visceral fat for the first time, and found that the accumulation of visceral fat rather than the total mass of body fat is more closely associated with the development of obesity-related disorders, including glucose intolerance, hypertriglyceridemia (2), elevated blood pressure (3), cardiac dysfunction (4) and coronary artery disease (5). Abdominal obesity [an increased waist to hip ratio: (W/H)] has been proposed to be a high risk factor of obesity associated with the development of CVD frequently accompanying cardiometabolic risk factors in Western countries (6-8). In general, Japanese individuals, especially women, have a smaller hip circumference than other ethnic populations worldwide. Therefore, the W/H has not been adopted as a marker of high-risk obesity in Japanese (9).

We propose that the visceral fat area (VFA) to subcutaneous fat area (SFA) ratio (V/S) is a better marker in obese...
Japanese subjects. Visceral fat comprises metabolically active adipose tissue. It is located in the mesentery and omentum, provides fatty acids and glycerol to the liver via the portal vein and secretes adipocytokines and other vasoactive substances that can influence the risk of developing metabolic syndrome. Excess visceral fat accumulation results in adipocyte dysfunction, i.e., the overproduction of plasminogen activator inhibitor type 1 and tumor necrosis factor-alpha, and the underproduction of defensive adipocytokines, such as adiponectin (10-12).

We previously demonstrated that the amount of visceral fat is rapidly reduced with weight reduction (13) and that improvements in elevated blood pressure and hypertriglyceridemia are closely associated with the reduction of visceral fat (14). We also previously reported that a decrease in visceral fat achieved within one year is correlated with a decrease in the number of metabolic risk factors (raised blood pressure, dyslipidemia and glucose intolerance) (15, 16) and an increase in the serum level of adiponectin (17).

These lines of evidence suggest that reducing the amount of visceral fat is beneficial for improving obesity-related disorders, possibly preventing CVD. This concept has also been adapted to mildly obese or nonobese overweight subjects with the clustering of risk factors known as metabolic syndrome (MetS).

In the current study, we investigated the relationship between the VFA or SFA and a cluster of obesity-related risk factors and analyzed glucose tolerance and phenotypes of dyslipidemia in middle-aged Japanese subjects recruited from the general population.

Materials and Methods

Participants

The study group comprised 571 Japanese subjects [434 men (53±9 years), 137 women (54±8 years)] who underwent medical health checkups at institutions that participated in the Japanese Visceral Fat Syndrome (J-VFS) Study Committee of the Ministry of Health and Welfare of Japan. Informed consent was obtained from all subjects following the approval of the ethics committee of Osaka University. Each subject underwent both an oral glucose tolerance test (OGTT) and an evaluation of body fat distribution using a CT scan. The medical health checkup program known as ‘Ningen (Human)-Dock’ aims to promote public health through the early detection of disease and risk factors. Among the study population, 36 (6.3%), 24 (4.2%) and 17 (3.0%) subjects were under treatment for hypertension, dyslipidemia and diabetes mellitus (DM), respectively. Diabetic subjects treated with insulin were not included in this study. All subjects were not clinically normal; however, most were representative of the general or health conscious Japanese population.

Anthropometry and laboratory measurements

Anthropometric measurements were obtained in the standing position. The body mass index (BMI) was calculated as the weight divided by the square of the height in meters. Waist circumference (WC) was measured at the umbilical level in the late exhalation phase while standing, as previously reported (1). Blood pressure was measured in the sitting position. The CT scans were performed in the routine supine position. The VFA and SFA were measured on CT cross-sectional scans obtained at the umbilical level in the supine position (18) using a commercial software program based on the Japanese guidelines of obesity treatment (Japan Society for the Study of Obesity, in Japanese).

Laboratory measurements

Blood was withdrawn after an overnight fast. The plasma glucose and insulin concentrations at 0, 30, 60 and 120 minutes following the ingestion of 75 g of glucose were determined according to the glucose oxidase method and double-antibody radioimmunoassay, respectively. The sums of the glucose and insulin concentrations measured during the OGTT were calculated as Σ plasma glucose and Σ plasma insulin, respectively. Glucose tolerance was assessed according to the Japanese Diabetes Association criteria for 75-g OGTT. Therefore, subjects with a fasting plasma glucose level of ≥126 mg/dL and/or plasma glucose level at two hours following the ingestion of a 75-g glucose load (2-hour plasma glucose) of ≥200 mg/dL were classified as having DM, and subjects with a fasting plasma glucose level of 110-126 mg/dL and/or a 2-hour plasma glucose level of 140-200 mg/dL were classified as having impaired glucose tolerance (IGT). Furthermore, subjects with a fasting plasma glucose level of <110 mg/dL and a 2-hour plasma glucose level of <140 mg/dL were classified as having normal glucose tolerance. Insulin resistance was estimated according to the homeostasis model assessment of insulin resistance (HOMA-IR), defined as: fasting plasma glucose (mg/dL)×fasting plasma insulin (μU/L)/405.

The serum total cholesterol and triglyceride concentrations were determined using enzymatic methods. The level of high-density lipoprotein (HDL) cholesterol was also measured using an enzymatic method following heparin and calcium precipitation. The phenotypes of dyslipidemia were defined as follows: type IIa, serum total cholesterol ≥200 mg/dL and triglyceride <150 mg/dL; type IIb, serum total cholesterol ≤220 mg/dL and triglyceride ≥150 mg/dL; type IV, serum total cholesterol <220 mg/dL and triglyceride ≥150 mg/dL.

Assessment of risk factors

We defined MetS according to the guidelines for the diagnosis of MetS in Japan (19), including abdominal obesity (a WC greater than or equal to 85 cm in men and greater than or equal to 90 cm in women) in addition to the presence of at least two of the following abnormalities: 1) hypertriglyc-
Table 1. Clinical Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>men (n=434)</th>
<th>women (n=137)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>53.0±8.9</td>
<td>54.1±8.2</td>
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<tr>
<td>BMI, kg/m²</td>
<td>23.5±2.8</td>
<td>22.7±3.0</td>
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<tr>
<td>WC, cm</td>
<td>85.1±7.4</td>
<td>78.2±9.2</td>
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<tr>
<td>VFA, cm²</td>
<td>103.1±52.8</td>
<td>64.3±37.3</td>
</tr>
<tr>
<td>SFA, cm²</td>
<td>112.9±50.2</td>
<td>159.4±72.0</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 25 kg/m²),%</td>
<td>27.7 *</td>
<td>18.2</td>
</tr>
<tr>
<td>Visceral fat accumulation (VFA ≥ 100 cm²), %</td>
<td>47.7 §</td>
<td>16.1</td>
</tr>
<tr>
<td>Dyslipidemia, % (under treatment, %)</td>
<td>41.2 (3.9)</td>
<td>15.3 (5.1)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>198.1±31.6</td>
<td>206.8±32.0</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>136.6±91.5</td>
<td>93.0±66.1</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>51.5±14.6</td>
<td>66.9±17.1</td>
</tr>
<tr>
<td>Hypertension, % (under treatment, %)</td>
<td>33.9 (6.5)</td>
<td>28.5 (5.8)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>122.8±16.9</td>
<td>116.8±20.4</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>72.9±12.0</td>
<td>68.4±14.0</td>
</tr>
<tr>
<td>Hyperglycemia, % (under treatment, %)</td>
<td>16.4 (3.5) *</td>
<td>8.0 (1.5)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>99.0±19.9</td>
<td>94.9±22.3</td>
</tr>
<tr>
<td>Fasting plasma insulin, μU/mL</td>
<td>5.9±3.8</td>
<td>5.7±3.6</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.5±1.3</td>
<td>1.4±1.0</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>17.7 §</td>
<td>3.7</td>
</tr>
</tbody>
</table>

BMI: body mass index, WC: waist circumference, VFA: visceral fat area, SFA: subcutaneous fat area, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment of insulin resistance. Continuous variables, results are presented as mean±SD or percent.

*p<0.05, **p<0.01, ***p<0.001, §p<0.0001 by Mann-Whitney U-test or chi-square test (compared with women)

Results

Clinical characteristics of the study participants

The descriptive characteristics of the study participants are shown in Table 1. The BMI, WC and VFA values were higher and the SFA values were lower in men than in women. Visceral fat accumulation (VFA ≥ 100 cm²) was identified in 47.7% of the men and 16.1% of the women. The systolic and diastolic blood pressures were higher in men than in women. The serum triglyceride levels were higher and the serum total cholesterol and HDL cholesterol levels were lower in the men than in the women. A total of 17.7% of the men and 3.7% of the women were diagnosed with MetS.

Relationships between the VFA or SFA and each risk factor

As shown in Table 2, simple regression analyses revealed that the systolic and diastolic blood pressure, levels of serum total cholesterol, triglycerides and fasting plasma insulin, Σ plasma glucose, Σ plasma insulin and HOMA-IR were positively and the HDL cholesterol level was negatively correlated with the VFA and SFA in men. The fasting plasma glucose level was positively correlated with the VFA but not SFA in men. In women, the systolic and diastolic blood pressure, levels of triglycerides and fasting plasma insulin, Σ plasma glucose and HOMA-IR were positively and the HDL cholesterol level was negatively correlated with the VFA and SFA. The total cholesterol and fasting plasma glucose levels and Σ plasma glucose were positively correlated with the VFA but not SFA in women.
In men, the proportion of risk factors in each SFA category was less than that observed in men. In women, the mean number of risk factors in each SFA category was greater than 1.0, even in the largest category of SFA. However, the slope was more gentle (Fig. 1B). In women, the proportion of subjects within each VFA category was widely distributed, with 48% having a VFA greater than 100 cm². In contrast, in women, the distribution of VFA was shifted to smaller values, with the frequency of subjects with a VFA greater than 100 cm² being only 16%.

The mean number of risk factors also increased with the VFA or SFA and elevated blood pressure. The error bars represent 95% confidence intervals. Kruskal-Wallis test for trend. *p<0.05, **p<0.01, ***p<0.001, f p<0.0001 according to the Mann-Whitney test. VFA: visceral fat area, SFA: subcutaneous fat area, M: men, F: women

Table 2. Correlation Coefficients of the Relationships between Visceral Fat Area, Subcutaneous Fat Area, and Various Parameters of the Metabolic Syndrome

<table>
<thead>
<tr>
<th></th>
<th>men (n=434)</th>
<th>women (n=137)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>VFA</td>
<td>SFA</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.291</td>
<td>0.158 **</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.309</td>
<td>0.145 **</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.165 ***</td>
<td>0.170 ***</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.316</td>
<td>0.223</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.335</td>
<td>-0.210</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>0.285</td>
<td>0.067</td>
</tr>
<tr>
<td>Fasting plasma insulin</td>
<td>0.237</td>
<td>0.385</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.237</td>
<td>0.322</td>
</tr>
<tr>
<td>Σ plasma glucose</td>
<td>0.352</td>
<td>0.128</td>
</tr>
<tr>
<td>Σ plasma insulin</td>
<td>0.156</td>
<td>0.290</td>
</tr>
</tbody>
</table>

VFA: visceral fat area, SFA: subcutaneous fat area, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment of insulin resistance, Σ plasma glucose: sum of the glucose concentrations during the oral glucose tolerance test, Σ plasma insulin: sum of the insulin concentrations during the oral glucose tolerance test.

*p<0.05, **p<0.01, ***p<0.001, f p<0.0001 by Pearson’s correlation coefficients.

Figure 1. Relationships between the (A) VFA or (B) SFA and the mean number of risk factors; men (n=434), women (n=137). Risk factors: hyperglycemia, hypertriglyceridemia/low high-density lipoprotein-cholesterol and elevated blood pressure. The error bars represent 95% confidence intervals. Kruskal-Wallis test for trend. *p<0.05, **p<0.01, ***p<0.001 according to the Mann-Whitney test. VFA: visceral fat area, SFA: subcutaneous fat area, M: men, F: women.

Relationships between the VFA or SFA and the cluster of risk factors

The proportions of subjects with zero, one, two or more risk factors of hyperglycemia, hypertriglyceridemia/low HDL cholesterolemia and elevated blood pressure were 37.1%, 39.2% and 23.7% in men and 59.1%, 30.7% and 10.2% in women, respectively. The frequency of obesity-related risk factors was higher in men than in women.

As shown in Fig. 1, each group was divided into 20-cm² categories of VFA or SFA. The mean number of risk factors significantly linearly increased with the VFA (p<0.0001 for trend) and was more than 1.0 at approximately 100 cm² for VFA in both men and women (Fig. 1A). In men, the proportion of subjects within each VFA category was widely distributed, with 48% having a VFA greater than 100 cm². In contrast, in women, the distribution of VFA was shifted to smaller values, with the frequency of subjects with a VFA greater than 100 cm² being only 16%.

The mean number of risk factors also increased with the SFA; however, the slope was more gentle (Fig. 1B). In women, the mean number of risk factors in each SFA category was less than that observed in men. In women, the mean number of risk factors did not reach 1.0, even in the largest category of SFA.

The area under the ROC curve (AUC) for VFA and SFA with respect to detecting the clustering of risk factors (one or more) was 0.741 (95%CI 0.697-0.782; p<0.0001) and
0.636 (95%CI 0.589-0.681; p<0.0001), respectively, in men. In women, the AUC for VFA and SFA with respect to detecting the clustering of risk factors (one or more) was 0.763 (95%CI 0.683-0.832; p<0.0001) and 0.689 (95%CI 0.604-0.765; p<0.0001), respectively.

**Associations between the VFA or SFA and BMI**

Each group was divided into 1.5-kg/cm² categories of BMI (Fig. 2). The mean values of VFA and SFA significantly increased with BMI in both men and women (p<0.0001 for trend). The men exhibited larger VFA values and smaller SFA values than the women in each BMI category.

**Prevalence of MetS**

As shown in Fig. 3, the prevalence of MetS increased starting in the 40s in men, ranging from 17% to 24% between ages in the 40s and 70s. In contrast, the prevalence of MetS began to increase starting at the age of 50 by a lesser degree in women.

**Prevalence of IGT, DM and dyslipidemia**

Fig. 4 presents the prevalence of IGT, DM, type IIa dyslipidemia, type IIb dyslipidemia and type IV dyslipidemia with or without visceral fat accumulation (VFA ≥100 cm²) or obesity (BMI ≥25 kg/m²). The prevalence of IGT

![Figure 2](image)

**Figure 2.** Relationships between the VFA or SFA and BMI; men (n=434), women (n=137). The error bars represent 95% confidence intervals. Kruskal-Wallis test for trend. *p<0.05, ***p<0.001, §p<0.0001 according to the Mann-Whitney test. VFA: visceral fat area, SFA: subcutaneous fat area, BMI: body mass index, M: men, F: women

![Figure 3](image)

**Figure 3.** Age-specific prevalence of metabolic syndrome; men (n=434), women (n=137). M: men, F: women

![Figure 4](image)

**Figure 4.** Prevalence of IGT, DM, type IIa dyslipidemia, type IIb dyslipidemia and type IV dyslipidemia with or without visceral fat accumulation or obesity. Men (n=434), women (n=137). Scheffé post hoc test. *p<0.05, **p<0.01, ***p<0.001. IGT: impaired glucose tolerance, DM: diabetes mellitus, IIa: type IIa dyslipidemia, IIb: type IIb dyslipidemia, IV: type IV dyslipidemia, VFA: visceral fat area, BMI: body mass index, M: men, F: women
and DM was higher in men with a VFA of $\geq 100$ cm$^2$ irrespective of BMI and women with a VFA of $\geq 100$ cm$^2$ and a BMI of $\geq 25$ kg/m$^2$. The prevalence of type IIb dyslipidemia was significantly higher in the men with a VFA of $\geq 100$ cm$^2$ irrespective of BMI than in those with a VFA of $<100$ cm$^2$ and a BMI of $<25$ kg/m$^2$. The men with a VFA of $\geq 100$ cm$^2$ and a BMI of $\geq 25$ kg/m$^2$ and the women with a VFA of $<100$ cm$^2$ and a BMI of $\geq 25$ kg/m$^2$ exhibited a significantly higher prevalence of type IV dyslipidemia than those with a VFA of $<100$ cm$^2$ and a BMI of $<25$ kg/m$^2$.

The present study also found that the prevalence of DM diagnosed based on OGTT was high in the subjects with visceral fat accumulation irrespective of BMI. This result emphasizes the importance of evaluating the postprandial glucose and insulin levels in subjects with visceral fat accumulation. Substantial reports have demonstrated IGT determined based on the 2-hour plasma glucose concentration to be a risk factor for the development of CVD (25, 26). The diagnostic criteria for MetS do not include hypercholesterolemia (hyper-low-density lipoprotein (LDL) cholesterol) because MetS is considered to be a pathogenetic mechanism of CVD, independent of hyper-LDL cholesterol. The present study showed that subjects with visceral fat accumulation frequently have type IIb dyslipidemia as well as type IV dyslipidemia. Type III dyslipidemia resulting from high levels of chylomicrons and intermediate-density lipoproteins, known as broad beta disease or dysbetalipoproteinemia, was not distinguished from other types of dyslipidemia in this study. It is possible that the combination of MetS with hypercholesterolemia increases the risk of CVD.

One limitation of this study is that the enrolled subjects were health conscious enough to undergo both oral glucose challenge tests and evaluations of their body fat distribution using CT scans. However, the mean levels of BMI, glucose, blood pressure and lipids did not differ significantly from those observed in this generation of the Japanese population reported in many studies. The second limitation is that the subjects in this study were of working age, with a mean ± SD age of 53±9. We previously reported that the percentage of visceral fat increases starting in the 50s and 60s in obese women. Therefore, further analyses of the VFA, SFA and cardiovascular risk factors in elderly subjects should be conducted.

The authors state that they have no Conflict of Interest (COI).

References