Coexistence of Visceral Fat and Multiple Risk Factor Accumulations is Strongly Associated with Coronary Artery Disease in Japanese (The VACATION-J Study)

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Aim: Multiple risk factor syndrome is a target for the prevention of coronary artery disease (CAD). A cluster of multiple risk factors, such as hypertension, glucose intolerance, and/or dyslipidemia, is encountered in Japanese without and with excess visceral fat. The present study investigated the relationship between multiple risk factor accumulation and CAD in Japanese without and with visceral fat accumulation.

Methods: The study subjects comprised 257 Japanese with suspected CAD (males/females = 153/104), who underwent 64-row multislice computed tomography (CT) coronary angiography and visceral fat area (VFA) measurement by CT. Based on the Japanese criteria for visceral fat accumulation, they were divided into those with VFA < 100 and ≥ 100 cm².

Results: In subjects with VFA < 100 cm², the age- and sex-adjusted odds ratios (ORs) for 2 and 3 risk factors were 5.33 (95% confidence intervals; 1.04-27.38, \( p = 0.0449 \)) and 4.07 (0.72-23.15, \( p = 0.1138 \)), respectively, compared with VFA < 100 cm² and 0 risk factor set at 1.0 (\( p = 0.0569 \) for trend). In contrast, the respective ORs for subjects with VFA ≥ 100 cm² were much higher [6.46 (1.25-33.44, \( p = 0.0261 \)) and 20.42 (3.60-115.73, \( p = 0.0007 \)) (\( p < 0.0001 \) for trend). The multivariate adjusted model demonstrated a significant relative excess CAD risk of 1.08 (\( p = 0.0484 \)) and 5.01 (\( p < 0.0001 \)) for the interactions of 2 risk factors and VFA ≥ 100 cm², and 3 risk factors and VFA ≥ 100 cm², whereas multiple risk factor accumulation was not related with the increase of CAD risk in subjects with VFA < 100 cm².

Conclusions: Coexistence of visceral fat and risk factor accumulations is strongly associated with CAD in Japanese.


Key words: Coronary artery disease, Visceral fat accumulation, Multiple risk factor accumulation

Introduction

A cluster of multiple risk factors (dyslipidemia, hyperglycemia, hypertension, and obesity) is a target for the prevention of coronary artery disease (CAD) in Japanese subjects¹. Obese East and South Asians...
including Japanese have a mild degree of adiposity compared with European and American subjects\(^5\). Different from the amount of total body fat, body fat distribution, especially the accumulation of visceral adipose tissue, has been found to be a major correlate of a cluster of metabolic abnormalities, referred to as metabolic syndrome\(^6\), however, subjects with a low body mass index (BMI) and multiple risk factors, such as essential hypertension\(^4,6\), glucose intolerance with a low capacity for insulin secretion\(^6,8\), and/or familial dyslipidemia\(^9\), are commonly encountered in the Japanese general population or patients with CAD.

**Aim**

In the present study, we assessed both the amount of visceral fat and coronary artery lesions by computed tomography (CT) scan, and investigated the relation between multiple risk factor accumulation and CAD in Japanese subjects with and without visceral fat accumulation.

**Subjects and Methods**

**Study Population**

The study subjects were 259 consecutive outpatients with suspected CAD, who underwent both fat CT scan and 64-row multislice computed tomography (MSCT) coronary angiography (Toshiba Aquilion 64 CT Scanner, Toshiba Medical, Tochigi, Japan; Lightspeed VCT, GE Healthcare, Waukesha, Wisconsin) at five centers across Japan (Osaka, Aichi, Miyagi, Hokkaido, Fukuoka) in 2010. The study subjects comprised 257 Japanese (males/females = 153/104), excluding 2 subjects with a poor MSCT coronary angiography image. The study was approved by the human ethics committee of each participating hospital and informed consent was obtained from each participant. This research (The VACATION-J study: Visceral Fat Accumulation and Coronary Artery Disease Investigation in Japanese)\(^10\) is registered with The University Hospital Medical Information Network, number UMIN 000002273

https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000002780&language=E.

**Anthropometry and Laboratory Tests**

Height and weight were measured in the standing position and BMI was calculated \([=weight (kg)/height (m)^2]\). Systolic and diastolic blood pressures (SBP and DBP) were measured with a standard mercury sphygmomanometer on the right or left arm after at least 10-minute rest in the standing position. Venous blood samples were collected in the standing position and used for measurements of glucose and lipids.

We investigated the presence of three obesity-related cardiovascular risk factors based on the Japanese criteria of metabolic syndrome\(^11\): 1) hypertension (SBP \(\geq 130\) mmHg and/or DBP \(\geq 85\) mmHg, or regular treatment with anti-hypertensive agents), 2) dyslipidemia [representing hypertriglyceridemia (fasting or postprandial triglyceride (TG) of \(\geq 1.69\) or \(2.27\) mmol/L, respectively)\(^2\)], and/or low high-density lipoprotein-cholesterol (HDL-C \(< 1.04\) mmol/L), or regular treatment with hypolipidemic agents for high TG or low HDL-C], and 3) dysglycemia/impaired glucose tolerance [representing hyperglycemia (fasting or postprandial plasma glucose concentration of \(\geq 6.10\) or \(7.77\) mmol/L, respectively)\(^3\)], or regular treatment with anti-diabetic agents.

**CT Imaging, Data Acquisition and Data Analysis**

All MSCT angiograms were scanned by trained technicians. ECG monitoring was performed continuously during the examination. If necessary, a \(\beta\)-blocker was administrated to control the heart rate. First, a preliminary scan was performed during inspiratory breath-hold to gain a sagittal and coronal view for positioning the entire heart. A region of interest was positioned at the center of the ascending aorta; then, a test bolus of the iodinated contrast agent was injected intravenously with a saline push. The time interval between bolus injection and maximal enhancement in the ascending aorta was recorded, and the starting time of the enhanced scan was calculated as 3 seconds after transit time of the contrast agent. The contrast agent was injected, followed by a saline push, and the scan was started with a delay time determined previously with \(64 \times 0.625\) mm collimation. The gantry rotation time was 0.35 seconds, and the tube current was 800 mA at 120 kV with dose modulation of 70% to 80% of RR interval. The reconstruction increment was approximately 0.5 mm. The dataset with the best image quality containing the fewest artifacts was selected for visualization of each coronary artery. Visceral and subcutaneous fat areas (VFA and SFA) were computed, or measured manually using commercial software for CT scans taken at the umbilical level in a supine position \([120\) kV, 400 mAsec, section thickness of 5-10 mm, field of view of 400 mm, window width of 800-1000 Hounsfield units (HU)]\) based on the Japanese guideline for obesity treatment (Japan Society for the Study of Obesity, in Japanese). All MSCT angiograms were evaluated by at least two experienced...
The presence of stenosis with coronary plaque was evaluated visually using axial and cross-sectional images and curved multiplanar reconstructions. Coronary calcification was assessed in degrees: none, mild, moderate, severe. Intracoronary lesion was identified as atherosclerotic stenosis above 90% and/or severely calcified lesions of at least one segment of a major coronary artery confirmed by MSCT coronary angiograms, which is a candidate for revascularization. Subjects with intracoronary lesion were considered to have CAD (n=91; new lesions [n=37], previous lesions [n=54]). The combined radiation dose was estimated based on the dose-length product and ranged from 15 to 18 mSv.

**Statistical Analysis**

Significant level was set at $p < 0.05$. Data on TG levels showed a skewed distribution, and therefore were log-transformed before analysis. Continuous variables are presented as the mean±SD, and data from two groups were compared by the unpaired Student’s $t$-test. Differences in frequencies were examined by the $\chi^2$ test. For multivariate logistic regression, all models were age- and sex-adjusted. The multivariate-adjusted odds ratios (ORs) are presented together with 95% confidence intervals (CIs). The following variables were included in the analysis: VFA (VFA cutoff value: 100 cm$^2$), hypertension (yes or no), dyslipidemia (yes or no), and abnormal glucose level (yes or no) (Fig. 1). Each test was computed to assess the relative contribution of VFA (Fig. 1) in subjects with and without visceral fat accumulation to the association with the accumulation of multiple obesity-related cardiovascular risk factors (VFA cutoff value: 100 cm$^2$), according to the Japanese criteria$^{14}$ and our recent report$^{10}$. We also determined whether there was an additive association between visceral fat accumulation and the accumulation of three obesity-related cardiovascular risk factors. The relative excess risk due to the interaction was calculated by the following formula: odds ratio [(visceral fat accumulation + accumulation of three obesity-related cardiovascular risk factors) − odds ratio (visceral fat accumulation) − odds ratio (accumulation of three obesity-related cardiovascular risk factors) + 1.0], or [(visceral fat accumulation + accumulation of two obesity-related cardiovascular risk factors) − odds ratio (visceral fat accumulation) − odds ratio (accumulation of two obesity-related cardiovascular risk factors) + 1.0], as reported previously$^{19}$. All statistical analyses were performed with the Statistical Package for Social Sciences (version 11.0.1); SPSS, Chicago, IL.

**Results**

**Patients’ Characteristics**

Table 1 summarizes the characteristics of all subjects and the subjects with VFA $<$ 100 cm$^2$ and $\geq$ 100 cm$^2$. There was a significant difference in the mean number of obesity-related CAD risk factors between the two groups; however, subjects with VFA $<$ 100 cm$^2$ had two or more CAD risk factors (57.5%). There was no significant difference in total cholesterol between the two groups.

**Odds Ratio of Multiple Obesity-Related Cardiovascular Risk Factors for CAD According to VFA**

To investigate the contribution of visceral fat accumulation and the cluster of dyslipidemia, hypertension, abnormal glucose level on CAD, the subjects were divided into two groups, those with VFA $<$ 100 and VFA $\geq$ 100 cm$^2$; the cutoff value was selected based on the Japanese criteria for visceral fat accumulation$^{14}$. The age- and sex-adjusted ORs of subjects with CAD and VFA $<$ 100 cm$^2$ with 2 and 3 risk factors were 5.33 (1.04-27.38, $p=0.0449$) and 4.07 (0.72-23.15, $p=0.1138$), respectively, compared to those with 0 risk factors and VFA $<$ 100 cm$^2$ (set at 1.0) (Fig 1) ($p=0.0569$ for trend). None of the subjects with excess visceral fat and CAD had 0 risk factors (OR; not determined). The respective ORs for subjects with VFA $\geq$ 100 cm$^2$ were much higher [6.46 (1.25-33.44, $p=0.0261$) and 20.42 (3.60-115.73, $p=0.0007$)] (Fig 1) ($p<0.0001$ for trend).

Surprisingly, the multivariate adjusted model demonstrated a significant relative excess CAD risk of 1.08 ($p=0.0484$) and 5.01 ($p<0.0001$) for the interactions of 2 risk factors and VFA $\geq$ 100 cm$^2$, and 3 risk factors and VFA $\geq$ 100 cm$^2$, although multiple risk factor accumulation was not related with the increase of CAD risk in subjects with VFA $<$ 100 cm$^2$. Thus, visceral fat accumulation acts in concert with CAD risk factor accumulation to increase the risk for CAD.

**Discussion**

The main finding of the present study was that: 1) coexistence of visceral fat and multiple risk factor accumulation is strongly associated with CAD in Japanese subjects, and 2) the ORs of CAD for subjects with VFA $\geq$ 100 cm$^2$ were significantly increased ($p<0.0001$ for trend) and additive. The exact mechanism of this additive effect of excess visceral fat on CAD, especially in subjects with the triad of the above risk factors is not clear. We can consider at least two possi-
Another possibility is that the presence of excess visceral fat results in dysregulated production of adipocytokines. Lee et al. reported that the interaction of visceral adiposity with the severity of CAD correlated with serum levels of pro-inflammatory cytokines (lipocalin-2 and MCP-1). Recent reports also found that increased deposition of visceral abdominal plus epicardial fat is associated with an enhanced cardiovascular disease risk profile. There is also tight linkage between metabolic syndrome based on visceral fat accumulation and sleep-disordered breathing (SDB), especially obstructive sleep apnea (OSA) (often referred to as “Syndrome Z”). Abdominal visceral fat accumulation is also associated with increased deposition of epicardial fat, inflammation and CAD. Subclinical CAD is increased in patients with increased abdominal visceral fat compared to those without visceral fat accumulation. These findings are consistent with the notion that increased visceral fat might increase the severity of individual risk factors, especially serum TG. One is that the severity of each risk factor might be higher in subjects with the triad of these risk factors and excess visceral fat compared to those without visceral fat accumulation. Among subjects with three obesity-related risk factors, only serum TG was significantly higher in subjects with VFA ≥100 than VFA <100 cm² (2.28 ± 1.40 versus 1.56 ± 0.74 mmol/L, p = 0.024). However, there were no significant differences between subjects with VFA <100 and ≥100 cm² in the severity of each factor, i.e., SBP, DBP, HDL-C, glucose level and frequency of medical treatments (data not shown). It is possible that this single difference is a significant contributor to the development of CAD, although this needs to be confirmed in future studies.

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Significance of Visceral Fat in CAD

### Study Limitations

The present study has certain limitations. MSCT coronary angiography is not the "gold standard" for the evaluation of CAD; however, recent systematic review and meta-analysis have shown that it has high sensitivity (90%) and specificity (97%) compared with conventional coronary angiography in identifying significant stenosis in the coronary artery\(^{24, 25}\); therefore, we consider that the use of MSCT coronary angiography for the evaluation of CAD in this study was quite valid. The study included 257 subjects, with 91 diagnosed with CAD. Although we applied age- and sex-adjusted analyses, there is a need for separate studies of men and women. Such studies require more

### Table 1. Clinical characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Total ( (n = 257) )</th>
<th>VFA (&lt; 100 \text{ cm}^2 ) ( (n = 146) )</th>
<th>VFA (\geq 100 \text{ cm}^2 ) ( (n = 111) )</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ( (n = 93/18/74/30/17/6/12/3) )</td>
<td>66.4 ± 10.5</td>
<td>66.9 ± 11.2</td>
<td>65.6 ± 9.5</td>
<td>0.3190</td>
</tr>
<tr>
<td>Sex (male, %) ( n = 50/3/0/4/4/2 )</td>
<td>59.5</td>
<td>52.7</td>
<td>68.5</td>
<td>0.0109</td>
</tr>
<tr>
<td>Body weight, kg ( n = 42/4/1/3/1/2 )</td>
<td>62.5 ± 11.5</td>
<td>57.6 ± 9.9</td>
<td>68.8 ± 10.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2) ( n = 46/11/37/15/7/4/5/1 )</td>
<td>24.2 ± 3.6</td>
<td>22.7 ± 3.0</td>
<td>26.2 ± 3.3</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total fat area, cm(^2) ( n = 146 )</td>
<td>215.4 ± 115.5</td>
<td>143.2 ± 79.1</td>
<td>310.3 ± 82.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Visceral fat area, cm(^2) ( n = 112 )</td>
<td>97.3 ± 61.6</td>
<td>54.6 ± 27.1</td>
<td>153.4 ± 47.6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Subcutaneous fat area, cm(^2) ( n = 111 )</td>
<td>118.1 ± 72.7</td>
<td>88.6 ± 62.3</td>
<td>156.9 ± 67.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg ( n = 111 )</td>
<td>132.9 ± 18.7</td>
<td>132.0 ± 19.8</td>
<td>134.0 ± 17.3</td>
<td>0.6455</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg ( n = 111 )</td>
<td>75.4 ± 12.8</td>
<td>74.0 ± 13.0</td>
<td>77.0 ± 12.3</td>
<td>0.0398</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L ( n = 109 )</td>
<td>6.54 ± 2.49</td>
<td>6.36 ± 2.08</td>
<td>6.79 ± 2.93</td>
<td>0.1648</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L ( n = 106 )</td>
<td>5.09 ± 0.93</td>
<td>5.09 ± 0.92</td>
<td>5.08 ± 0.93</td>
<td>0.9340</td>
</tr>
<tr>
<td>Triglyceride, mmol/L ( n = 107 )</td>
<td>1.64 ± 1.12</td>
<td>1.40 ± 0.90</td>
<td>1.73 ± 1.09</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L ( n = 102 )</td>
<td>1.52 ± 0.43</td>
<td>1.63 ± 0.43</td>
<td>1.36 ± 0.39</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hypertension (under treatment), % ( n = 47/7/37/15/10/2/7/2 )</td>
<td>78.2 (57.2)</td>
<td>74.7 (53.4)</td>
<td>82.9 (62.2)</td>
<td>0.1136</td>
</tr>
<tr>
<td>Medications for hypertension (CA/ACEI/ARB/diuretics/( \beta )-blockade/( \alpha )-blockade/( \alpha \beta )-blockade/others) ( n = 92/7/17/5/1/1 )</td>
<td>62.6 (40.9)</td>
<td>53.4 (39.0)</td>
<td>74.8 (43.2)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Dyslipidemia (under treatment), % ( n = 93/18/74/30/17/6/12/3 )</td>
<td>35.4 (18.7)</td>
<td>32.9 (14.4)</td>
<td>38.7 (24.3)</td>
<td>0.3304</td>
</tr>
<tr>
<td>Abnormal glucose levels (under treatment), % ( n = 46/11/37/15/7/4/5/1 )</td>
<td>17.8</td>
<td>14.4</td>
<td>21.6</td>
<td>0.0021</td>
</tr>
<tr>
<td>Medications for hypertension (statin/fibrate/niacin/EPAAzetimibe/others) ( n = 42/4/1/3/1/2 )</td>
<td>28.1</td>
<td>39.7</td>
<td>44.1</td>
<td>0.0220</td>
</tr>
<tr>
<td>Number of obesity-related CAD risk factors ( n = 16/7/6/9/4/1 )</td>
<td>1.7 ± 0.9</td>
<td>1.6 ± 0.9</td>
<td>2.0 ± 0.9</td>
<td>0.0021</td>
</tr>
<tr>
<td>0 risk, % ( n = 27/15/9/16/5/1 )</td>
<td>10.5</td>
<td>14.4</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>1 risk, % ( n = 11/8/3/7/1/0 )</td>
<td>25.3</td>
<td>28.1</td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>2 risks, % ( n = 4/2/1/0 )</td>
<td>41.6</td>
<td>39.7</td>
<td>44.1</td>
<td></td>
</tr>
<tr>
<td>3 risks, % ( n = 1/0 )</td>
<td>22.6</td>
<td>17.8</td>
<td>28.9</td>
<td></td>
</tr>
<tr>
<td>Prevalence of CAD, % ( n = 146 )</td>
<td>35.4</td>
<td>29.4</td>
<td>43.2</td>
<td>0.0022</td>
</tr>
</tbody>
</table>

Data are the mean ± SD. *log-transformed. HDL: high density lipoprotein, CAD: coronary artery disease, CA: calcium channel antagonist, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, \( \beta \)-blockade, \( \alpha \)-blockade, \( \alpha \beta \)-blockade, EPA: eicosapentaenoic acid, SU: sulfonyl urea, \( \alpha \)GI: alpha glucosidase inhibitor, BG: biguanide, TZD: thiazolidinedione.

Obesity, representing abundant mesenteric fat tissue susceptible to hypoxic stress, was partly related with dysregulated production of adiponectin in OSA patients\(^{20}\). Further studies are needed to clarify the contribution of these mechanisms to an increased risk for CAD.

In conclusion, the coexistence of visceral fat and multiple risk factor accumulations is strongly associated with CAD in Japanese subjects. For clinically meaningful prevention of future CAD in Japanese, it may be useful to stratify subjects with multiple risk factors into those with or without visceral fat accumulation.
than 1,000 subjects because the frequency of CAD in women is relatively low, even in women with a cluster of risk factors (data not shown).

**Abbreviations**

CAD, coronary artery disease; BMI, body mass index; CI, confidence intervals; CT, computed tomography; HDL-C, high density lipoprotein-cholesterol; MSCT, multislice computed tomography; OR, odds ratio; SFA, subcutaneous fat area; TG, triglyceride; VFA, visceral fat area; WC, waist circumference.

**Declaration**

Ken Kishida and Tohru Funahashi are members of the “Department of Metabolism and Atherosclerosis”, a sponsored course endowed by Kowa Co. Ltd. and a company researcher is dispatched to the course. All other authors declare no competing interests.

**Authors’ Contributions**

A.H-S. and K.K. researched and analyzed data. K.K. wrote, reviewed and edited the manuscript. M.O. R.K. H.K. Y.N. A.N. and H.Y. recruited the patients and collected the data. T.Y. provided advice on CT analysis. T.O. provided advice on statistical analysis. T.N. Y.M. and S.S. contributed to the discussion. T.F. and I.S. contributed to the discussion and wrote the manuscript. All authors have read and approved the final version of the manuscript. The authors declare no conflicts of interest.

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