Associations between Cardiovascular Risk Factors and Carotid Atherosclerosis in Middle-aged Japanese Men with Multiple Risk Factors

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Abstract: To examine the relationship between cardiovascular risk factors and prevalence of carotid atherosclerosis in Japanese middle-aged men with multiple risk factors, 110 Japanese men aged 36 to 60 yr were recruited based on the presence of all of the following factors detected during a screening survey: 1) body mass index (BMI) ≥ 25 kg/m²; 2) systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg; 3) serum levels of triglycerides (TG) ≥ 150 mg/dl and/or total cholesterol (T-Chol) levels ≥ 220 mg/dl and/or high density lipoprotein cholesterol (HDL-C) levels < 40 mg/dl; and 4) fasting serum glucose ≥ 110 mg/dl and/or hemoglobin A1C ≥ 5.6%. After adjustment for age and cardiovascular risk factors, the odds ratio (95% confidence interval) of carotid atherosclerosis associated with a 1-SD increment in HDL-C was 0.4 (95%CI: 0.2 to 0.9). We also detected a borderline association for anti-hypertension medication use, an indicator for advanced hypertension, with an odds ratio of 2.7 (95%CI: 1.0 to 7.4) after multivariable adjustment. The other risk factors, i.e. BMI, SBP, T-Chol, TG, diabetes, smoking and drinking status did not show significant associations with carotid atherosclerosis. In conclusion, low HDL-C and advanced hypertension were significant correlates of carotid atherosclerosis for middle-aged Japanese men with multiple risk factors.

Key words: Carotid atherosclerosis, Intima-media thickness, Cardiovascular risk factors, Multiple risk factors, High density lipoprotein cholesterol, Hypertension

Introduction

Multiple risk factor syndrome or metabolic syndrome is defined as a clustering of risk factors for coronary heart disease (CHD) and stroke, including abdominal obesity, dyslipidemia, hypertension and insulin resistance1–4). Epidemiological studies have shown that these syndromes are common among Japanese men5) as well as western populations6). Individuals with these syndromes were found to be likely to have carotid atherosclerosis7,8) and the components of metabolic syndrome to be associated with increased intima-media thickness (IMT) and stiffness8–10). Carotid atherosclerosis is reportedly a strong and independent predictor of morbidity and mortality associated with stroke and CHD11–14). In Japan, to prevent for ‘Karoshi’ (death due to
extremely hard work), the worker’s accident compensation insurance low was launched to provide the secondary health examination to the workers who had all of high levels of blood pressure, blood lipids, blood glucose, and BMI without history of stroke and heart disease in April of 2001. Carotid echography was included in this secondary health examination\(^5\).

In the study presented here, we sought to determine which cardiovascular risk factors were associated with carotid atherosclerosis in middle-aged Japanese male workers who undertook the secondary health examination.

**Methods**

**Subjects**

A cross-sectional study was conducted by the Transportation Bureau of a certain city. A total of 7,840 Japanese employees aged 18 to 68, underwent general health check-ups between September and October 2005. The results of these check-ups were used to select 110 men aged 36 to 60 yr (mean ± SD: 47.1 ± 7.2 yr), who met all of the following inclusion criteria: 1) body mass index (BMI) ≥ 25 kg/m\(^2\); 2) systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg; 3) serum levels of triglycerides (TG) ≥ 150 mg/dl and/or total cholesterol (T-ChoL) ≥ 220 mg/dl and/or high density lipoprotein cholesterol (HDL-C) < 40 mg/dl; and 4) fasting serum glucose ≥ 110 mg/dl and/or Hemoglobin A\(1C\) (HbA\(1C\)) ≥ 5.6%. These criteria were for the secondary health examination to the workers, provided by the worker’s accident compensation insurance law\(^5\).

Between September 2005 and March 2006, the 110 subjects underwent a secondary health examination to measure TG, T-ChoL, HDL-C, serum glucose, HbA\(1C\) as well as carotid ultrasonography. The subjects included 42 professional drivers (31 bus drivers and 11 subway operators). The remaining 68 subjects were non-drivers, such as technicians, conductors and clerical workers. The Ethics Committee of the University of Tsukuba approved the study protocol.

**Measurement of Carotid Atherosclerosis**

Three trained medical technicians performed ultrasoundographic scanning of the carotid arteries, using a real-time, B-mode ultrasound imaging unit (Vivid3; GE Healthcare, Milwaukee, WI) with a 6.7-MHz linear array probe (10 L (739 L), axial resolution: 0.1 mm; GE Healthcare). The imaging protocol involved obtaining a single longitudinal lateral view of the area of the right and left common carotid arteries (CCA). The maximum intima-media thickness (max-IMT) of the CCA was determined from the greatest thickness of the near and far walls on both sides of the CCA. Plaque was defined as any focal atherosclerotic change of the intima-medial layer of the CCA or internal carotid arteries including carotid bulb (ICA). We defined carotid atherosclerosis as a max-IMT in the CCA of ≥ 1.1 mm and/or plaque of ≥ 1.5 mm according to the modified criteria of several established epidemiological studies\(^{12, 16}\).

**Measurement of Cardiovascular risk factors**

Well-trained nurses measured SBP and fifth-phase DBP in the right arm using standard mercury sphygmonanometers with the subject in the sitting position after a 5-min rest.

For the measurement of serum lipids and glucose, blood was obtained from an antecubital vein, followed by separation of the serum. T-ChoL and HDL-C were then measured with the cholesterol oxidase method (Determiner C-TC; Kyowa Medex Co., Ltd., Tokyo, Japan) and the direct-homogeneous method (Determiner HDL-C; Kyowa Medex), respectively, using an automatic analyzer (AU5431; OLYMPUS Corporation, Tokyo, Japan). TG were measured with the glycerol 3-phosphoric acid oxidase method (Lipidos Liquid; TOYOBO Co., Ltd., Osaka, Japan) using the same analyzer as for T-ChoL and HDL-C. Serum glucose was measured with the hexokinase glucose-6-phosphoric acid dehydrogen enzyme (HK-G6PDH) method (L-type wako Glu2; Wako Pure Chemical Industries, Ltd., Osaka, Japan), also using the same analyzer. HbA\(1C\) was calculated with the immune coherent method (RAPIDIA Auto HbA\(1C\); FUJIREBIO INC., Tokyo, Japan) using the JCA-BM9020 analyzer (JEOL Ltd., Tokyo, Japan). Because the measurements of fasting serum lipids and fasting serum glucose values were also undertaken in the secondary health examination and these parameters were calculated by averaging the measurements obtained at the screening check-up and the secondary health examination to reduce their variabilities. Diabetes was defined as fasting serum glucose ≥ 126 mg/dl and/or HbA\(1C\) ≥ 6.1% and/or anti-diabetic medication use. An interview was conducted to ascertain smoking status (never, ex-, and current smokers) and drinking status (never, occasionally, and daily drinking).

**Statistical analysis**

Differences in age-adjusted mean values and proportion of baseline risk characteristics between the participants with and without carotid atherosclerosis were tested by means of the covariance and \(\chi^2\) test.

Odds ratios of carotid atherosclerosis associated with cardiovascular risk factors were calculated by using logistic regression models. The cardiovascular risk factors included age, BMI, SBP, T-ChoL, HDL-C, TG, diabetes, smoking and drinking status and current use of anti-hyper-
tensive medication. The SAS statistical package version 9.1 (SAS Institute Inc., Cary, NC) was used for all analyses. All p values for statistical tests were two-tailed, and values of p<0.05 were regarded as statistically significant.

Results

Table 1 lists the mean values and percentages of risk characteristics for the participants with and without carotid atherosclerosis. Carotid plaque or increased IMT were found in 29 of the 110 (26.4%) subjects. Those with carotid atherosclerosis had showed significantly higher mean values for age and border prevalence of anti-hypertensive medication use than did those without carotid atherosclerosis. The former also tended to show higher mean values of SBP, and the lower mean values of HDL-C.

Table 2 shows the age-adjusted and multivariable-adjusted odds ratios (95% CI) for associations of carotid atherosclerosis with anti-hypertensive medication use, drinking and smoking status, diabetes and a 1-standard deviation (1-SD) increment in other cardiovascular risk factors. The multivariable odds ratio for a 1-SD increment in HDL-C (12mmHg) was 0.4 (95%CI: 0.2 to 0.9), while a 1-SD increment in age (7 yr) showed borderline significance of 1.7 (95% CI: 1.0 to 2.9), as did the association of anti-hypertensive medication use with carotid atherosclerosis with an odds ratio of 2.5 (95%CI: 1.0 to 6.0).

Table 1. Age-adjusted means and proportions of risk characteristics for subjects with and without carotid atherosclerosis

<table>
<thead>
<tr>
<th></th>
<th>Without carotid atherosclerosis</th>
<th>With carotid atherosclerosis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>81</td>
<td>29</td>
<td>0.004</td>
</tr>
<tr>
<td>Age, year</td>
<td>46.0</td>
<td>50.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29.1</td>
<td>28.4</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>146</td>
<td>150</td>
<td>0.09</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>94</td>
<td>94</td>
<td>0.88</td>
</tr>
<tr>
<td>Anti-hypertensive medication use, %</td>
<td>32</td>
<td>53</td>
<td>0.048</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl*</td>
<td>224</td>
<td>220</td>
<td>0.66</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl*</td>
<td>50</td>
<td>46</td>
<td>0.09</td>
</tr>
<tr>
<td>Triglycerides, mg/dl*</td>
<td>245</td>
<td>228</td>
<td>0.69</td>
</tr>
<tr>
<td>Anti-hyperlipidemic medication use, %</td>
<td>20</td>
<td>12</td>
<td>0.32</td>
</tr>
<tr>
<td>Serum glucose, mg/dl*</td>
<td>133</td>
<td>138</td>
<td>0.53</td>
</tr>
<tr>
<td>Hemoglobin A₁C, %*</td>
<td>6.3</td>
<td>6.7</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>54</td>
<td>56</td>
<td>0.82</td>
</tr>
<tr>
<td>Anti-diabetic medication use, %</td>
<td>23</td>
<td>33</td>
<td>0.28</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>51</td>
<td>62</td>
<td>0.37</td>
</tr>
<tr>
<td>Daily alcohol consumption, %</td>
<td>38</td>
<td>43</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Means of findings of the first and secondary health examinations.

Table 2. Age-adjusted and multivariable-adjusted odds ratios and 95% confidence intervals (95% CI) for association of carotid atherosclerosis with cardiovascular risk factors

<table>
<thead>
<tr>
<th></th>
<th>Age-adjusted odds-ratio (95%CI)</th>
<th>p-value</th>
<th>Multivariable odds-ratio (95%CI)*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 7 yr</td>
<td>0.8 ( 0.5 to 1.2 )</td>
<td>0.31</td>
<td>1.7 ( 1.0 to 2.9 )</td>
<td>0.051</td>
</tr>
<tr>
<td>Body mass index, 3.4 kg/m²</td>
<td>0.7 ( 0.4 to 1.1 )</td>
<td>0.11</td>
<td>0.4 ( 0.2 to 0.9 )</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic blood pressure levels, 12 mmHg</td>
<td>1.4 ( 0.9 to 2.2 )</td>
<td>0.10</td>
<td>1.3 ( 0.8 to 2.2 )</td>
<td>0.26</td>
</tr>
<tr>
<td>Anti-hypertensive medication use</td>
<td>2.5 ( 1.0 to 6.0 )</td>
<td>0.051</td>
<td>2.7 ( 1.0 to 7.4 )</td>
<td>0.054</td>
</tr>
<tr>
<td>Serum total cholesterol, 37 mg/dl</td>
<td>0.9 ( 0.6 to 1.4 )</td>
<td>0.66</td>
<td>1.1 ( 0.6 to 2.1 )</td>
<td>0.68</td>
</tr>
<tr>
<td>HDL-cholesterol, 12 mg/dl</td>
<td>0.7 ( 0.4 to 1.1 )</td>
<td>0.74</td>
<td>0.7 ( 0.4 to 1.3 )</td>
<td>0.23</td>
</tr>
<tr>
<td>Triglycerides, 186 mg/dl</td>
<td>0.9 ( 0.6 to 1.5 )</td>
<td>0.38</td>
<td>1.2 ( 0.5 to 3.4 )</td>
<td>0.68</td>
</tr>
<tr>
<td>Current smokers</td>
<td>1.5 ( 0.6 to 3.7 )</td>
<td>0.65</td>
<td>2.0 ( 0.7 to 6.0 )</td>
<td>0.20</td>
</tr>
<tr>
<td>Daily alcohol consumption</td>
<td>1.2 ( 0.5 to 2.7 )</td>
<td>0.85</td>
<td>0.9 ( 0.3 to 2.4 )</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*Adjusted for age, body mass index, systolic blood pressure levels, serum total cholesterol, HDL-cholesterol, triglycerides, smoking and drinking status, anti-hypertensive treatment and diabetes.
6.0) after age adjustment and of 2.7 (95% CI: 1.0 to 7.4) after multivariable adjustment. The other risk factors, i.e. BMI, SBP, T-ChoL, TG, smoking and drinking status and diabetes did not show significant associations with carotid atherosclerosis.

**Discussion**

The main finding of our study was the existence of associations of low HDL-C levels and anti-hypertensive medication use with a high prevalence of carotid atherosclerosis in Japanese middle-aged men with multiple risk factors. Since anti-hypertensive medication use reflects the presence of advanced hypertension, our results suggest that achievement of high HDL-C levels and control of hypertension may have greater beneficial effect than controlling other risk factors for the prevention of carotid arteriosclerosis development in Japanese middle-aged men with multiple risk factors.

Some previous studies have reported a similar association of low levels of HDL-C with carotid atherosclerosis [17-19]. A cross-sectional study of healthy, 55-to-74 yr-old Norwegian men and women indicated that, after adjustment for age, sex, SBP, HDL-C, TG and degree of stenosis, the odds ratio of carotid plaque associated with a 1-SD increment in HDL-C was 0.72 (95% CI: 0.53 to 0.97) [17]. A seven-year follow-up study of 25-to-82 yr-old Norwegian men and women with at least 1 plaque detected at baseline examination showed that higher levels of HDL-C were associated with slower plaque growth [18]. A community-based study of 60-to-74 yr-old Japanese men reported that the multivariate odds ratio for a maximum IMT ≥ 1.1 mm in the common carotid artery for a 14.7 mg/dl increase in HDL-C was 0.7 (95% CI: 0.6 to 0.8) [19].

In our study, use of anti-hypertensive medication was associated with carotid atherosclerosis. Again, this result does not imply that anti-hypertensive medication use induces carotid atherosclerosis, but simply indicates that the medication did not achieve good control of hypertension or the medication has been prescribed for the prevention of carotid arteriosclerosis development in Japanese middle-aged men with multiple risk factors.

The limitations of the study were first, its cross-sectional design and limited number of study subjects, so that longitudinal studies using larger samples are needed to confirm the relationship observed in our study. Second, dyslipidemia, one of the 4 criteria by which participants were selected included three parameters. The proportions of abnormal parameters among the subjects were 76% for high TG, 53% for high T-ChoL, and 23% for low HDL-C, all of which had the larger variabilities than BMI, blood pressure and glucose. The significant association between HDL-C and carotid atherosclerosis may be in part due to the larger variation.

In conclusion, low HDL-C and advanced hypertension were found to be associated with carotid atherosclerosis in middle-aged men with multiple risk factors, thus pointing to the importance of control for these risk factors to prevent atherosclerosis development.
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