Very Low Levels of High-sensitivity C-reactive Protein are not Bimodally Distributed but are Significantly Related to Other Metabolic Risk Factors in Japanese

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Abstract

Background High-sensitivity C-reactive protein (hs-CRP) is an independent risk factor of diabetes and cardiovascular disease and it is proposed as a component of metabolic syndrome. Blood levels of hs-CRP are reported to be much lower in Japanese than in Westerners and bimodally distributed in Japanese.

Methods Very low levels of hs-CRP were examined using medical check-up data of 1,360 Japanese men and 821 women whose plasma levels of high-sensitivity C-reactive protein (hs-CRP) were below 10 mg/L.

Results The distribution of hs-CRP levels were skewed but not bimodal in both men and women and very low levels of hs-CRP were significantly related to waist circumference, systolic blood pressure, diastolic blood pressure, fasting glucose, triglycerides, and low-density lipoprotein cholesterol in both men and women. The area under receiver operating characteristic curve of hs-CRP for diagnosing metabolic syndrome and Spearman’s correlation coefficients between hs-CRP and components of metabolic syndrome were comparable to those of components of metabolic syndrome in both men and women.

Conclusion Very low levels of hs-CRP were not bimodally distributed but were significantly related to metabolic risk factors in Japanese.

Key words: metabolic syndrome, obesity, inflammation, CRP


Introduction

High-sensitivity C-reactive protein (hs-CRP) is reported as an independent risk factor of diabetes (1) and cardiovascular disease (2) and is proposed as a component of metabolic syndrome (2). Hs-CRP levels lower than 1 mg/L, those between 1 mg/L and 3 mg/L, and those higher than 3 mg/L are considered to be a low risk, an intermediate risk, and a high risk category, respectively in Western countries (3). But, hs-CRP levels and the degree of obesity in Japanese are substantially lower than those in Westerners (4-10). Yamada et al reported that median hs-CRP was 0.16 mg/L in Japanese men and 0.09 mg/L in women and that the distribution of hs-CRP was bimodal in Japanese though the reason for this peculiar distribution was unknown (4). To clarify this peculiar distribution of hs-CRP, we examined very low levels of CRP and their relation with other metabolic risk factors in Japanese.

Methods

Subjects

Between April 1 and September 30, 2008, 1,386 Japanese men and 837 women visited our medical check-up center for “Ningen Dock”, one of the medical check-up programs of our center. Visitors were all required to fill out a questionnaire designed by the Ministry of Health, Labor, and Welfare for the purpose of “Special Health Examination and Instruction” including history of cardiovascular disease (stroke, ischemic heart disease, and chronic renal failure), smoking status, antihypertensive and hypoglycemic medication, and alcohol consumption. Among these persons, 7 men
and 8 women without signed consent and 19 men and 8 women with serum levels of high-sensitivity C-reactive protein (hs-CRP) higher than 10 mg/L were excluded. Therefore, the present study was performed among 1,360 male and 821 female subjects. The protocol for the present study was approved by the ethics committee in Tachikawa Medical Center and signed informed consent was obtained from each subject.

Measurements

After an overnight fast, blood samples were withdrawn to measure serum levels of routine medical check-up markers: glucose, triglycerides, high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), hemoglobin A1c, uric acid, blood cell counts, electrolytes, liver and kidney function tests including gamma glutamyltransferase (GGT), alanine aminotransferase (ALT), and hs-CRP. Chemical measurements were all performed at BML Nagaoka (Nagaoka, Niigata, Japan) except for hs-CRP which was measured at BML General Laboratory (Tokyo, Japan) with nephelometry using N-latex CRP-2 (Siemens Healthcare Japan, Tokyo, Japan). The measurement limit of hs-CRP was 0.02 mg/L and the value of hs-CRP less than the measurement limit was considered as 0.01 mg/L. Body fat % was measured with bioelectrical impedance analysis using TBF-210 (TANITA, Tokyo, Japan). An average systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated from two measurements with the subjects in a sitting position after 5 minutes rest. Body weight was measured with the subjects wearing a lightweight hospital gown provided by our center and the weight of the hospital gown was subtracted from the measured body weight. Waist circumference (WC) was measured at the level of the umbilicus. Body mass index (BMI) was calculated as weight in kilogram divided by the square of height in meters.

Statistical analysis

Diabetes was defined as fasting glucose levels equal to or higher than 126 mg/dL or receiving hypoglycemic medication. Metabolic syndrome (MS) was defined by the revised National Cholesterol Education Program (NCEP) criteria (10) as three or more of five components in which the cut-off point of WC was modified for Japanese as 90 cm and SBP > 130 mmHg for blood pressure, triglycerides ≥ 150 mg/dL and/or HDLc < 40 mg/dL, and fasting glucose ≥ 110 mg/dL.Distribution of hs-CRP levels was plotted by gender. Means (SD) of components of MS, hs-CRP, GGT, ALT, LDLc and uric acid were calculated by quintiles of hs-CRP. Receiver operating characteristic (ROC) curve analyses for diagnosing MS and JMS were performed to obtain area under ROC curve (AUC) of components of MS, hs-CRP, GGT, ALT, LDLc and uric acid. Spearman’s correlation coefficients among components of MS, hs-CRP, GGT, ALT, LDLc and uric acid were calculated. Statistical analyses were conducted with Dr SPSS-2. p values of less than 0.05 were considered to be statistically significant.

Results

One thousand and three hundred sixty men aged [mean (SD)] 51.6 (9.3) years and 821 women aged 51.1 (10.1) were the subjects of the present study. Means (SD) and medians of basal laboratory data and prevalence of smoking, MS, JMS, diabetes, and cardiovascular disease are presented in Table 1. Prevalence of smoking, MS, JMS, diabetes, and cardiovascular disease were 34.3%, 13.5%, 12.1%, 4.7%, and 6.3%, respectively in men and 6.0%, 6.8%, 2.1%, 1.7%, and 3.4%, respectively in women. Figure 1 shows the distribution of hs-CRP by gender. The distribution of hs-CRP was skewed but not bimodal in both Japanese men and women, as shown in Fig. 1. Means (SD) of WC, SBP, DBP, fasting glucose, triglycerides, HDLc, hs-CRP, GGT, ALT, LDLc and uric acid were presented by quintile of hs-CRP by gender in Tables 2 and 3. WC, SBP, DBP, triglycerides, LDLc, and uric acid in quintile 2 (hs-CRP; 0.14-0.23 mg/L) were significantly higher than those in quintile 1 (hs-CRP; 0.02-0.13 mg/L), HDLc in quintile 2 was significantly lower than that in quintile 1, GGT and ALT in quintile 3 (hs-CRP; 0.24-0.37 mg/L) were significantly higher than those in quintile 1 and, fasting glucose in quintile 4 (hs-CRP; 0.38-0.72) was significantly higher than that in quintile 1 among men (Table 2). WC, SBP, DBP, fasting glucose, triglycerides, and LDLc in quintile 2 (hs-CRP; 0.09-0.16 mg/L) were significantly higher than those in quintile 1 (hs-CRP; 0.01-0.08 mg/L), GGT, ALT, and uric acid in quintile 3 (hs-CRP; 0.17-0.26 mg/L) were significantly higher than those in quintile 1, and HDLc in quintile 2 was significantly lower than that in quintile 1 among women (Table 3). AUC of metabolic risk factors for diagnosing MS and JMS are presented in Table 4. The AUC (95% confidence interval) of hs-CRP for diagnosing MS and JMS were 0.74 (0.70, 0.77) and 0.72 (0.68, 0.76), respectively in men and 0.72 (0.66, 0.78) and 0.76 (0.67, 0.84), respectively in women and these values were comparable to those of components of MS and other metabolic risk factors in both men and women. Table 5 presents Spearman’s correlation coefficients among WC, SBP, DBP, fasting glucose, triglycerides, HDLc, hs-CRP, GGT, ALT, LDLc, and uric acid. Correlations between hs-CRP and components of MS were comparable to those
Table 1. Basal Data

|                      | men            | women           | p    *
|----------------------|----------------|-----------------|------
| age years (years)    | 51.6 (9.3)     | 51.1 (10.1)     | 0.2  |
| body mass index (kg/m²) | 23.2 (2.9)   | 21.6 (3.0)      | <0.001 |
| body fat %           | 21.8 (4.9)     | 26.5 (5.7)      | <0.001 |
| waist circumference (cm) | 84.0 (8.0)   | 78.5 (8.6)      | <0.001 |
| systolic blood pressure (mmHg) | 121.9 (17.0) | 111.7 (16.4)    | <0.001 |
| diastolic blood pressure (mmHg) | 77.5 (10.5)  | 69.7 (10.1)     | <0.001 |
| fasting glucose (mg/dL) | 95.1 (13.3)   | 89.2 (10.7)     | <0.001 |
| triglyceride (mg/dL) | 119.4 (81.6)   | 83.3 (51.6)     | <0.001 |
| HDL cholesterol (mg/dL) | 57.7 (14.4)   | 66.8 (14.4)     | <0.001 |
| gamma glutamyltransferase (U/L) | 47.3 (42.8)  | 22.4 (19.6)     | <0.001 |
| alanine aminotransferase (U/L) | 25.4 (15.3) | 17.0 (9.4)      | <0.001 |
| LDL cholesterol (mg/dL) | 120.0 (29.4)  | 120.9 (28.9)    | 0.5  |
| uric acid (mg/dL)    | 6.2 (1.3)      | 4.5 (0.9)       | <0.001 |
| hemoglobin A1c %     | 5.1 (0.5)      | 5.0 (0.4)       | 0.02 |
| high-sensitivity CRP (mg/L) | 0.61 (1.03) | 0.39 (0.57)     | <0.001 |

HD: high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; MS, metabolic syndrome defined by revised NCEP definition; JMS, Japanese metabolic syndrome defined by the Examination Committee for Criteria of Metabolic Syndrome

* 2 sided t-tests for means and chi-square tests for %

Figure 1. Distribution of blood levels of high-sensitivity C-reactive protein in Japanese by gender. n: number of subjects, CRP: high-sensitivity C-reactive protein (mg/L)
among components of MS.

**Discussion**

For the past several decades, there was considerable effort to understand the underlying biology and to identify the risk factors of cardiovascular disease. As risk factors were identified, it became apparent that they tended to cluster in the same individual. Thus, the concept of insulin resistance syndrome (syndrome X) or metabolic syndrome emerged. Metabolic syndrome is a constellation of interrelated metabolic risk factors that appear to directly promote the development of diabetes and cardiovascular disease. The predominant underlying mechanisms of metabolic syndrome...
appears to be insulin resistance, abdominal obesity, and inflammation (15). However, in 2005, the American Diabetes Association and the European Association for the Study of Diabetes jointly stated that no existing definition of metabolic syndrome meets criteria as a syndrome (16) and there have been endless debates on pros and cons of diagnosing with this syndrome for individuals (17-20). We thought that metabolic syndrome might develop through adipose tissue disease (21) different from obesity and to be diagnosed with inflammatory, endocrine, metabolic, and histological tests. Criteria that regard obesity as an inevitable component of metabolic syndrome have a serious drawback because there is a substantial number of metabolically obese normal weight individuals (22) and only about one-third of the most insulin resistant individuals are actually obese (19). On the contrary, hs-CRP, a marker of inflammation, is an independent risk factor of cardiovascular disease and proposed as a component of metabolic syndrome (2). Studies with transgenic or diet-induced obesity animals indicate that the infiltration of activated macrophages into adipose tissue and accompanied inflammation, but not increased adipose tissue mass, increased adipocyte size, or increased visceral adipose tissue mass per se, are crucial for the metabolic consequences of obesity including insulin resistance (21). Thus, we prefer the concept of adipose tissue disease or adipopathy to the concept of obesity or adiposity (21).

We already reported that an optimal cut-off point of hs-CRP as a component of MS may be 0.45 mg/L in men and 0.25 mg/L in women among Japanese (23). In the present study, we examined very low levels (0.02-0.72 mg/L in men and 0.01-0.52 mg/L in women) of hs-CRP among Japanese. The distribution of hs-CRP levels were skewed but not bimodal in both men and women contrary to the previously reported data (4) and very low levels of hs-CRP were significantly related with WC, SBP, DBP, fasting glucose, triglycerides, HDLc, GGT, ALT, LDLc, and uric acid in both men and women. The AUC of hs-CRP for diagnosing metabolic syndrome was comparable to those of components of MS and Spearman’s correlation coefficients between hs-CRP and components of MS were comparable to those among components of MS in both men and women.

Yamada et al reported that the distribution of hs-CRP was bimodal in Japanese though the reason for this peculiar distribution was unknown (4). Later, they reported that the distribution pattern of hs-CRP was different between the baseline data and the data after five years and median hs-CRP values were lower by 43% after five years than the baseline values in contrast to the changes in other risk factors (24). Therefore, it is possible that some measurement error might be involved in their data. There are substantial differences in median or geometric mean levels of hs-CRP among different studies (4-10) in Japanese and the differences mainly seem to result from different measuring methods because age and BMI among these study subjects were similar. Standardization of hs-CRP measuring methods may be mandatory to evaluate hs-CRP quantitatively among Japanese. As for gender differences in hs-CRP, Saltevo et al reported that the levels of hs-CRP were significantly higher in women with metabolic syndrome than in men with metabolic syndrome and, in subjects without metabolic syndrome, no gender differences in the levels of hs-CRP were found (25). Lakoski et al reported that women had substantially higher median hs-CRP levels compared with men (26). However, in Japanese, hs-CRP levels among women without metabolic syndrome were lower than those levels among men, but in subjects with metabolic syndrome, the gender difference in the levels of CRP might be obscured (5, 6). Thus, clustering of metabolic risk factors and weight gain may have stronger effects on hs-CRP in women than in men (5). Sekikawa et al reported that Japanese men had less subclinical atherosclerosis compared with the White counterparts, though the Japanese had a less favorable profile regarding many risk factors (27). However, in their study, BMI, WC, CRP, fibrinogen, and insulin were significantly lower and HDLc was significantly higher in Japanese men than in White men. Thus, the degree of obesity-related metabolic risk clustering through adipose tissue disease (21) may be substantially lower in Japanese than in White. Though hs-CRP levels are very low in Japanese compared with the standard in Western societies (3) where obesity prevails, women with hs-CRP values equal to or higher than 0.5 mg/L had a higher risk for cardiovascular disease than women with hs-CRP values lower

Table 5. Spearman’s Correlation Coefficients among Metabolic Risk Factors

<table>
<thead>
<tr>
<th>WC</th>
<th>SBP</th>
<th>DBP</th>
<th>FG</th>
<th>TG</th>
<th>HDLc</th>
<th>GGT</th>
<th>ALT</th>
<th>LDLc</th>
<th>UA</th>
<th>hs-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC</td>
<td>0.341</td>
<td>0.326</td>
<td>0.260</td>
<td>0.270</td>
<td>-0.266</td>
<td>0.288</td>
<td>0.264</td>
<td>0.297</td>
<td>0.239</td>
<td>0.365</td>
</tr>
<tr>
<td>SBP</td>
<td>0.327</td>
<td>0.908</td>
<td>0.300</td>
<td>0.238</td>
<td>-0.062</td>
<td>0.203</td>
<td>0.253</td>
<td>0.268</td>
<td>0.184</td>
<td>0.221</td>
</tr>
<tr>
<td>DBP</td>
<td>0.300</td>
<td>0.926</td>
<td>0.296</td>
<td>0.228</td>
<td>-0.031</td>
<td>0.187</td>
<td>0.227</td>
<td>0.247</td>
<td>0.188</td>
<td>0.199</td>
</tr>
<tr>
<td>FG</td>
<td>0.275</td>
<td>0.238</td>
<td>0.226</td>
<td>0.179</td>
<td>-0.130</td>
<td>0.232</td>
<td>0.200</td>
<td>0.139</td>
<td>0.094</td>
<td>0.173</td>
</tr>
<tr>
<td>TG</td>
<td>0.388</td>
<td>0.213</td>
<td>0.224</td>
<td>0.165</td>
<td>-0.407</td>
<td>0.302</td>
<td>0.232</td>
<td>0.321</td>
<td>0.212</td>
<td>0.259</td>
</tr>
<tr>
<td>HDLc</td>
<td>-0.394</td>
<td>-0.027</td>
<td>-0.017</td>
<td>-0.093</td>
<td>-0.507</td>
<td>-0.069</td>
<td>-0.065</td>
<td>-0.158</td>
<td>-0.071</td>
<td>-0.243</td>
</tr>
<tr>
<td>GGT</td>
<td>0.333</td>
<td>0.302</td>
<td>0.317</td>
<td>0.257</td>
<td>0.382</td>
<td>-0.042</td>
<td>0.513</td>
<td>0.190</td>
<td>0.305</td>
<td>0.323</td>
</tr>
<tr>
<td>ALT</td>
<td>0.392</td>
<td>0.210</td>
<td>0.183</td>
<td>0.214</td>
<td>0.330</td>
<td>-0.210</td>
<td>0.533</td>
<td>0.189</td>
<td>0.273</td>
<td>0.199</td>
</tr>
<tr>
<td>LDLc</td>
<td>0.218</td>
<td>-0.005</td>
<td>-0.007</td>
<td>0.070</td>
<td>0.260</td>
<td>-0.208</td>
<td>0.082</td>
<td>0.153</td>
<td>0.155</td>
<td>0.203</td>
</tr>
<tr>
<td>UA</td>
<td>0.234</td>
<td>0.166</td>
<td>0.182</td>
<td>0.039</td>
<td>0.240</td>
<td>-0.121</td>
<td>0.242</td>
<td>0.206</td>
<td>0.125</td>
<td>0.245</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.369</td>
<td>0.207</td>
<td>0.184</td>
<td>0.134</td>
<td>0.268</td>
<td>-0.304</td>
<td>0.254</td>
<td>0.207</td>
<td>0.150</td>
<td>0.208</td>
</tr>
</tbody>
</table>

WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FG, fasting glucose; TG, triglycerides; HDLc, high-density lipoprotein cholesterol; GGT, gamma glutamyltransferase; ALT, alanine aminotransferase; LDLc, Low-density lipoprotein cholesterol; UA, uric acid; hs-CRP, high-sensitivity C-reactive protein

* Male data are in the lower left triangle (n = 1360) and female data are in the upper right triangle (n = 821).
than 0.5 mg/L even in the United States (28). Hs-CRP may reflect adipose tissue disease and relate to the clustering of metabolic risk factors even through very low levels as shown in the present study among Japanese.

**Limitations**

The present study was a cross-sectional study and the subjects were not a general population but visitors to our medical check-up center which is in a central city of a rural region in Japan. These conditions may influence the low serum levels of hs-CRP and the low prevalence of metabolic syndrome in our subjects. However, both the levels of hs-CRP in general populations and the prevalence of obesity are very low in Japan. Therefore, the present data may not represent a quite peculiar population in Japan and the conclusions may be relevant in other regions and populations in Japan.

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**References**