Comparison of Circulating Adiponectin and Proinflammatory Markers Regarding Their Association With Metabolic Syndrome in Japanese Men

Kunihiro Matsushita, Hiroshi Yatsuya, Koji Tamakoshi, Keiko Wada, Rei Otsuka, Seiko Takefuji, Kaichiro Sugiuira, Takahisa Kondo, Toyoaki Murohara, Hideaki Toyoshima

Background—Anti-inflammatory and proinflammatory molecules purportedly play an important role in developing metabolic syndrome (MetS). However, little is known as to the relative importance of these molecules in the association with MetS.

Methods and Results—We studied 624 middle-aged Japanese men without medical history of cardiovascular disease or cancer and investigated the associations of circulating tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), and adiponectin with MetS. We used the respective definitions proposed by the National Cholesterol Education Program Adult Treatment Panel III (ATP-III), the International Diabetes Federation, and the Japanese Society of Internal Medicine. Decreased serum adiponectin was observed in those with any of the ATP-III–MetS components, whereas this was not the case with increased TNF-α, IL-6, or CRP. Adiponectin and CRP levels linearly deteriorated with an increasing number of ATP-III–MetS components (trend P<0.001, respectively). Significantly higher CRP and lower adiponectin levels were observed in those who met any MetS criteria, whereas increased TNF-α was observed in only those with ATP-III–MetS. Finally, odds ratios (ORs) for MetS prevalence of a 1-SD increase/decrease in log-transformed 4 markers were calculated with multivariate logistic regression analyses. Consequently, decreased adiponectin was associated most strongly with ATP-III–MetS (adiponectin: OR, 1.90 [95% CI, 1.44 to 2.51]; P<0.001; CRP: OR, 1.33 [95% CI, 1.01 to 1.74]; P=0.03; TNF-α: OR, 1.25 [95% CI, 0.94 to 1.67]; P=0.12; and IL-6: OR, 0.87 [95% CI, 0.63 to 1.19]; P=0.37). This result was not altered by using the other 2 criteria.

Conclusions—The present results raise the possibility that decreased serum adiponectin might be fundamentally involved in the development of MetS. (Arterioscler Thromb Vasc Biol. 2006;26:871-876.)

Key Words: cardiovascular disease prevention ■ inflammation ■ metabolic syndrome ■ risk factors

Metabolic syndrome (MetS) is a cluster of atherosclerotic cardiovascular disease (CVD) risk factors and is closely associated with insulin resistance.1 Recently, inflammation has been considered to be associated with the development of insulin resistance and MetS.2–4 When the National Cholesterol Education Program Adult Treatment Panel III (ATP-III) suggested functional criteria for MetS, it also listed the proinflammatory state as a part of MetS. However, ATP-III did not include inflammatory markers in its MetS criteria. This might be partly attributable to lack of an established inflammatory marker applicable for routine CVD risk evaluation at that time. Since then, abundant evidence has accumulated to show that C-reactive protein (CRP) is associated with MetS and predicts diabetes and CVD events independently of traditional risk factors.5,6 Consequently, it has been suggested that CRP be included in the criteria of MetS.7 However, some studies showed that other circulating inflammatory markers (eg, tumor necrosis factor-α [TNF-α] and interleukin-6 [IL-6]), were also associated with MetS8,9 and were somewhat superior to CRP in predicting CVD.10,11 Although inflammation putatively plays an important role in the development of insulin resistance and MetS, the feature of each of these inflammatory markers in relation to MetS has not been fully elucidated.

Meanwhile, an adipocyte-derived plasma protein, adiponectin, has also been considered as a key molecule in the pathogenesis of MetS.12,13 Adiponectin modulates not only glucose and lipid metabolism14 but also the immune system in various ways. For example, adiponectin inhibits expression of adhesion molecules and nuclear transcriptional factor κB signaling, a pivotal pathway in inflammatory reactions, in endothelial cells.15,16 It also inhibits TNF-α production and class A scavenger receptor expression in macrophages.17,18 Thus, adiponectin is currently recognized as an anti-
inflammatory adipocytokine. When contemplating the etiology of MetS, it is a major concern which state, declined anti-inflammatory (ie, hypoadiponectinemia) or increased proinflammatory, is the key to the development of MetS. However, to our knowledge, few studies have measured all these inflammation-related markers including adiponectin in a single group of subjects, so the feature of each marker in relation to the individual MetS components and MetS itself cannot be evaluated. Therefore, in the present study, we investigated the respective characteristics of TNF-α, IL-6, CRP, and adiponectin featuring MetS and evaluated their magnitude in relation to MetS.

Methods

Study Subjects
We studied a population of 2805 Japanese men in the year 2002, 35 to 66 years of age, belonging to a workplace in Aichi, Japan, who had no self-reported medical history of CVD or cancer and responded to a questionnaire about their lifestyle characteristics. They underwent an annual health checkup with a serological test and physical examination including blood pressure, height, and weight. The remaining serum was used for this study. Among initial samples, 624 participants provided enough serum to analyze for TNF-α, IL-6, CRP, and adiponectin, and were therefore used as subjects in the present study. Because it has been reported that extremely elevated CRP also predicts incident CVD,19 5 subjects with CRP of >10 mg/L, implying possible clinical inflammatory conditions, were included in the analysis. The study subjects were relatively older (49.8 versus 48.1 years; P<0.001) and showed less prevalence of ATP-III-MetS (11.5% versus 16.1%; P<0.001) than the remaining 2181 participants, whereas their mean body mass index (BMI) and the proportion of current smokers were comparable (23.3 versus 23.2 kg/m² and 34.9% versus 36.7%, respectively). All subjects provided their informed consent. The ethics committee of Nagoya University Graduate School of Medicine, Nagoya, Japan approved the study protocol.

Definition of the MetS
We basically used minimally modified ATP-III criteria of MetS so that those with ≥3 of the following components were considered as having ATP-III-MetS: (1) obesity as defined by BMI ≥25 kg/m² according to the criteria of the Japan Society for the Study of Obesity;20 (2) low high-density lipoprotein cholesterol (HDL-C) defined as HDL-C <1.036 mmol/L; (3) high triglyceride (TG) defined as TG ≥1.695 mmol/L or self-report of taking medication for hyperlipidemia; (4) high glucose defined as fasting glucose ≥6.10 mmol/L or self-report of taking medication for diabetes mellitus; and (5) elevated blood pressure defined as blood pressure ≥130/85 mm Hg or self-report of taking medication for hypertension.

To evaluate the consistency of our findings, we also used the criteria proposed by the International Diabetes Federation (IDF)21 and by the joint committee of 8 Japanese medical societies, including the Japanese Society of Internal Medicine (JSIM).22 Although we replaced waist circumference with BMI, specifically, those with obesity (BMI ≥25) plus ≥2 of the resting 4 components of the ATP-III criteria were considered as having IDF-MetS, for which high glucose was defined as fasting glucose ≥5.60 mmol/L or medication for diabetes. Participants who had obesity (BMI ≥25) plus ≥2 of the following 3 components were defined as JSIM-MetS: (1) HDL-C <1.036 mmol/L or TG ≥1.695 mmol/L or medication for hyperlipidemia; (2) fasting glucose ≥6.10 mmol/L or medication for diabetes; and (3) blood pressure ≥130/85 mm Hg or taking an antihypertensive.

Biochemical Analysis
Venous blood samples were drawn from each subject after 8 hours or overnight fasting. The samples were stored at ~80°C until biochemical assay. TG was determined enzymatically. HDL-C was measured by the phosphotungstate method. Glucose was enzymatically determined by the hexokinase method. TNF-α was measured by enzyme immunoassay with a minimum detectable level of 6 pg/mL (Dainippon Pharmaceutical Co, Ltd). Undetectable TNF-α values were recorded as 5 pg/mL, which was assigned to 5 subjects. High-sensitivity IL-6 was also measured by enzyme immunoassay (Dainippon Pharmaceutical Co, Ltd). High-sensitivity CRP was measured by latex nephelometry (BNII; Dade Behring Co, Ltd). Adiponectin concentrations were determined by ELISA (Otsuka Pharmaceutical Co, Ltd). Interassay coefficients of variation of each variable were as follows: TNF-α, <9.6%; IL-6, <7.5%; CRP, <4.0%; adiponectin, <8.6%.

Statistical Analysis
All statistical analyses were conducted with the SPSS statistical package for Windows version 11.0 (SPSS Inc.). All continuous variables were shown by mean±SD, except for TNF-α, IL-6, CRP, and adiponectin. To approximate normal distribution, natural log-transformed values were used in the analysis, transformed back for data presentation, and shown as the geometric means and 95% CIs for those means. Partial correlation coefficients adjusted for age and smoking status (non-smoker or current smoker) were computed between inflammation-related markers and each MetS component. Continuous variables were compared by ANCOVA with age and smoking status as covariates. The test for trend was performed with a polynomial contrast procedure. To permit direct comparison between inflammation-related markers, odds ratios (ORs) for MetS prevalence of a 1-SD increase in log-transformed TNF-α, IL-6, and CRP and a 1-SD decrease in adiponectin were calculated with multivariate logistic regression analyses. ORs were evaluated in 2 models of independent variables in addition to age and smoking status as follows: model 1, each inflammation-related marker only; model 2, all markers together. All reported P values were 2-sided, and a P value of <0.05 was considered statistically significant.

Results
Characteristics of study subjects are shown in Table 1. The prevalence of ATP-III–MetS in this population was 11.5% (n=72), whereas that of IDF- and JSIM-MetS was 12.0% (n=75) and 8.5% (n=53), respectively. Geometric means (95% CIs) of TNF-α, IL-6, CRP, and adiponectin were 12.5 (12.2 to 12.8) pg/mL, 1.62 (1.54 to 1.70) pg/mL, 0.30 (0.27 to

TABLE 1. Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=624</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49.8±6.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.3±2.5</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>218 (34.9)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.49±0.35</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.42±0.88</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.48±0.98</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>125.4±16.1</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.6±11.9</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>51 (8.2)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>20 (3.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (1.1)</td>
</tr>
</tbody>
</table>

Values are mean±SD or number (%), as appropriate.
TABLE 2. Partial Correlation Coefficients Adjusted for Age and Smoking Status Between Inflammation-Related Markers and MetS Components

<table>
<thead>
<tr>
<th></th>
<th>Ln TNF-α</th>
<th>Ln IL-6</th>
<th>Ln CRP</th>
<th>Ln adiponectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.12†</td>
<td>0.08</td>
<td>0.25‡</td>
<td>−0.30‡</td>
</tr>
<tr>
<td>HDL-C</td>
<td>−0.11†</td>
<td>−0.09*</td>
<td>−0.19†</td>
<td>0.35‡</td>
</tr>
<tr>
<td>TG</td>
<td>0.09*</td>
<td>0.004</td>
<td>0.16†</td>
<td>−0.29‡</td>
</tr>
<tr>
<td>Glucose</td>
<td>−0.07</td>
<td>−0.09*</td>
<td>0.10*</td>
<td>−0.21‡</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>−0.01</td>
<td>−0.10*</td>
<td>0.07</td>
<td>−0.07</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.003</td>
<td>0.03</td>
<td>0.10†</td>
<td>−0.07</td>
</tr>
</tbody>
</table>

Correlation coefficients >0.20 are in boldface. *P<0.05; †P<0.01; ‡P<0.001.

Table 2 shows the partial correlation coefficients adjusted for age and smoking status between inflammation-related markers and MetS factors. The correlations were significant for BMI, HDL-C, TG, glucose, and BMI. Higher BMI, HDL-C, and TG were correlated with MetS, whereas adiponectin was negatively correlated with HDL-C.

Discussion

This is the first study to examine the relationship between inflammation-related markers and MetS prevalence among these inflammation-related markers. In the analysis with JSIM-MetS, only adiponectin was significantly associated with MetS in model 2 (OR, 1.57 [95% CI, 1.16 to 2.13]; P=0.004) compared to the ATP-III and IDF-MetS criteria. The results were not altered when independent variables were restricted to adiponectin and each of TNF-α, IL-6, and CRP (data not shown).

Separate analyses excluding 5 subjects with CRP >10 mg/L also provided quite similar results (data not shown).

0.33) mg/L, and 5.98 (5.77 to 6.20) µg/mL, respectively. The partial correlation coefficients adjusted for age and smoking status between inflammation-related markers and MetS factors are shown in Table 2. When the correlation was limited to a coefficient >0.20, CRP was correlated only with BMI, whereas adiponectin was negatively correlated with HDL-C, TG, glucose, and BMI. No MetS component was correlated with TNF-α and IL-6 with a correlation coefficient >0.20.

The adjusted mean value of each inflammation-related marker was compared between the subjects with or without each ATP-III–MetS component (Table 3). A significant difference in TNF-α level was seen only between the groups distinguished by TG level. Similarly, higher levels of IL-6 were observed in subjects with obesity. Elevated CRP levels were observed in those with high TG and obesity. However, significantly lower adiponectin concentrations were observed in those with any of the MetS components except for elevated blood pressure, even among those in whom a marginally lower adiponectin level was observed (P=0.06). Similarly, the difference in the adjusted mean value of each inflammation-related marker was evaluated among the 4 groups classified according to the number of clustering ATP-III–MetS components (ie, 0, 1, 2, and 3 to 5; Figure). In particular, the adiponectin concentration decreased linearly according to the number of MetS components (trend P<0.001), whereas the CRP concentration increased (trend P<0.001). However, TNF-α and IL-6 concentrations were not associated with the clustering of MetS components. Additionally, these 4 markers were compared between those with or without MetS defined by the 3 criteria (Table 4). Significantly higher CRP and lower adiponectin levels were observed in those who met any of the MetS criteria, whereas increased TNF-α was observed only in those with ATP-III–MetS.

Finally, the strength of association between each inflammation-related marker and MetS was evaluated by multivariate logistic regression analysis (Table 5). In both models of independent variables, adiponectin was consistently associated most strongly with either ATP-III or IDF-MetS prevalence among these inflammation-related markers. In the analysis with JSIM-MetS, only adiponectin was significantly associated with MetS in model 2 (OR, 1.57 [95% CI, 1.16 to 2.13]; P=0.004). These results were not altered when independent variables were restricted to adiponectin and each of TNF-α, IL-6, and CRP (data not shown).

Seperate analyses excluding 5 subjects with CRP >10 mg/L also provided quite similar results (data not shown).

**Table 3. Relationship Between Inflammation-Related Markers and ATP-III–MetS Components**

<table>
<thead>
<tr>
<th>MetS Component</th>
<th>n</th>
<th>Mean (95% CI)*</th>
<th>P</th>
<th>Mean (95% CI)*</th>
<th>P</th>
<th>Mean (95% CI)*</th>
<th>P</th>
<th>Mean (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>153</td>
<td>13.0 (12.3–13.8)</td>
<td>0.09</td>
<td>1.78 (1.61–1.97)</td>
<td>0.03</td>
<td>0.42 (0.36–0.50)</td>
<td>0.001</td>
<td>5.18 (4.83–5.57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>471</td>
<td>12.3 (11.9–12.7)</td>
<td>0.92</td>
<td>1.57 (1.48–1.66)</td>
<td>0.03</td>
<td>0.27 (0.24–0.30)</td>
<td>&lt;0.001</td>
<td>6.27 (6.02–6.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High TG</td>
<td>33</td>
<td>12.4 (11.0–14.0)</td>
<td>0.09</td>
<td>1.76 (1.41–2.19)</td>
<td>0.03</td>
<td>0.37 (0.25–0.54)</td>
<td>0.001</td>
<td>3.89 (3.34–4.53)</td>
<td>0.001</td>
</tr>
<tr>
<td>High glucose</td>
<td>591</td>
<td>12.5 (12.2–12.9)</td>
<td>0.92</td>
<td>1.61 (1.53–1.70)</td>
<td>0.45</td>
<td>0.30 (0.27–0.32)</td>
<td>0.30</td>
<td>6.13 (5.91–6.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>169</td>
<td>13.2 (12.5–13.9)</td>
<td>0.01</td>
<td>1.61 (1.46–1.77)</td>
<td>0.86</td>
<td>0.38 (0.32–0.45)</td>
<td>0.38</td>
<td>4.81 (4.50–5.13)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>455</td>
<td>12.2 (11.9–12.6)</td>
<td>0.01</td>
<td>1.62 (1.53–1.72)</td>
<td>0.86</td>
<td>0.27 (0.25–0.30)</td>
<td>0.001</td>
<td>6.49 (6.23–6.75)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Geometric means (95% CIs) adjusted for age and smoking status are shown.
initiation of insulin resistance, and hence MetS, has gained substantial currency, the present results raise the possibility that lowered protection against inflammation (ie, hypoadiponectinemia) is more potently associated with the development of MetS than proinflammatory proteins. Pleiotropic functions of adiponectin on lipid and glucose metabolism and NO synthesis may also contribute to a strong association between adiponectin and MetS. Pleiotropic functions of adiponectin on lipid and glucose metabolism and NO synthesis may also contribute to a strong association between adiponectin and MetS. However, evaluation of adiponectin might be useful to assess one’s metabolic state comprehensively as suggested previously. Nevertheless, further prospective studies would be necessary to confirm the stronger contribution of adiponectin to the development of MetS than inflammatory markers. If so, it would have great implications for the strategy of prevention or management of MetS and atherosclerotic disease, which predisposes toward suppression of inflammatory conditions rather than incitement of anti-inflammatory conditions.

In keeping with previous reports, serum TNF-α and IL-6 were not well associated with MetS. Circulating TNF-α has been reported not to represent its biological function accurately because it may function as a paracrine. Although some investigators reported the significant association between TNF-α and MetS, this might be because of the inclusion of exclusively obese subjects. However, the association of IL-6 and insulin resistance seems more complex. IL-6 has been generally considered to play a role in developing insulin resistance. However, to the contrary, some investigators have insisted that IL-6 indeed prevents insulin resistance. In fact, IL-6–deficient mice demonstrated mature-onset obesity, and IL-6 overexpressed nonobese diabetic mice showed a retarded onset of diabetes compared with control mice. In the present study, serum IL-6 demonstrated a borderline quadratic association with clustering of MetS components rather than a linear association. This aspect was also demonstrated in a previous report and might reflect a complex association of IL-6 with MetS. Thus, circulating TNF-α and IL-6 at least might not be appropriate markers of MetS as suggested previously.

In the present study, CRP was more strongly related to MetS than TNF-α and IL-6, in agreement with previous reports. Serum CRP was associated with MetS, but not with fasting glucose and blood pressure, although a borderline elevation of CRP was observed in those with elevated blood pressure compared with those without it. The lack of correlation between CRP and fasting insulin has been reported previously. It is widely acknowledged that fasting glucose remains normal in the early stage of glucose intolerance.

### Table 4. Comparison of Inflammation-Related Markers Between Those With or Without MetS

<table>
<thead>
<tr>
<th>MetS Definition</th>
<th>n</th>
<th>Mean (95% CI)*</th>
<th>P</th>
<th>Mean (95% CI)*</th>
<th>P</th>
<th>Mean (95% CI)*</th>
<th>P</th>
<th>Mean (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNF-α, pg/mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP-III Present</td>
<td>72</td>
<td>13.5 (12.5–14.6)</td>
<td>0.04</td>
<td>1.73 (1.49–2.01)</td>
<td>0.34</td>
<td>0.46 (0.36–0.60)</td>
<td>&lt;0.001</td>
<td>4.57 (4.12–5.06)</td>
<td></td>
</tr>
<tr>
<td>ATP-III Absent</td>
<td>552</td>
<td>12.4 (12.0–12.7)</td>
<td>0.001</td>
<td>1.60 (1.52–1.69)</td>
<td>0.28</td>
<td>0.26 (0.26–0.31)</td>
<td>0.001</td>
<td>6.20 (5.97–6.43)</td>
<td></td>
</tr>
<tr>
<td>IDF Present</td>
<td>75</td>
<td>13.2 (12.2–14.3)</td>
<td>0.01</td>
<td>1.70 (1.46–1.96)</td>
<td>0.43</td>
<td>0.33 (0.33–0.55)</td>
<td>0.003</td>
<td>4.94 (4.46–5.47)</td>
<td>0.001</td>
</tr>
<tr>
<td>IDF Absent</td>
<td>549</td>
<td>12.4 (12.0–12.8)</td>
<td>0.13</td>
<td>1.61 (1.52–1.70)</td>
<td>0.51</td>
<td>0.26 (0.26–0.31)</td>
<td>0.003</td>
<td>6.14 (5.91–6.38)</td>
<td>0.001</td>
</tr>
<tr>
<td>JSIM Present</td>
<td>53</td>
<td>13.5 (12.2–14.8)</td>
<td>0.11</td>
<td>1.67 (1.40–1.98)</td>
<td>0.74</td>
<td>0.33 (0.33–0.60)</td>
<td>0.007</td>
<td>4.83 (4.28–5.46)</td>
<td>0.001</td>
</tr>
<tr>
<td>JSIM Absent</td>
<td>571</td>
<td>12.4 (12.1–12.8)</td>
<td>0.001</td>
<td>1.61 (1.53–1.70)</td>
<td>0.29</td>
<td>0.26 (0.26–0.32)</td>
<td>0.007</td>
<td>6.10 (5.88–6.33)</td>
<td></td>
</tr>
</tbody>
</table>

*Geometric means (95% CIs) adjusted for age and smoking status are shown.*
ance because the pancreatic β-cells compensate by increasing insulin output.32 CRP may have been reported to be associated with insulin resistance rather than decreased insulin secretion.33 Therefore, CRP may not have been associated with fasting glucose in the present study, which dealt mainly with an apparently healthy sample. Nevertheless, as proposed previously,7 CRP seemed appropriate for detecting MetS among representative inflammatory markers. However, given that adiponectin was more strongly associated with MetS than CRP, further studies would be needed to compare CRP with adiponectin as a MetS component.

From a different perspective, those with MetS showed an increase in serum CRP compared with those without MetS as well as a decrease in adiponectin. CRP has been practically established as a CVD predictor.34 In addition, adiponectin has been reported to predict myocardial infarction independent of traditional risk factors or CRP.35 Thus, these simultaneous deteriorations of CRP and adiponectin in MetS may, in part, explain the gap between the higher CVD risk observed in those with MetS and the estimated risk as the sum of the risk originating from each of the MetS components.36 These results underscore the importance of identifying MetS as a composite entity.

Some limitations of this study must be considered. First, the present cross-sectional study does not allow for inferring causality from the present results, which should be considered hypothesis generating and requiring confirmation by prospective studies. Second, BMI was used instead of waist circumference. Although BMI might not represent fat accumulation accurately, BMI of 25 kg/m² was nearly equivalent in a reference range, a systemic low-grade inflammatory state.40–42 Furthermore, modified ATP-III–MetS criteria with BMI as a substitute for waist circumference has predicted CVD in previous studies.38,39 Given these facts, we believe that this modification of MetS criteria would not change the main implications of the present study. However, confirmation by using waist circumference would be needed.

Third, no detailed inquiry was made regarding medications for hypertension, diabetes, or hyperlipidemia. Several mediators decrease CRP,40,41 and thiazolidinediones increase adiponectin.42 However, these effects would tend to bias the results toward null. In addition, controlling for medication intake did not affect the results (data not shown). Fourth, selection bias should be a concern. Because of serum amounts, we needed to restrict the subjects to 624 participants who were not equal in the prevalence of MetS to the remaining participants despite no difference in mean BMI and smoker rate. However, the present results obtained from relatively healthier subjects than the initial sample would provide important information particularly in terms of primary prevention. Finally, all results in the present study were Japanese males. Thus, the present results could not be simply extrapolated to female or other ethnic groups.

In conclusion, CRP and adiponectin were well associated with MetS among representative inflammation-related markers. In particular, adiponectin demonstrated a consistent relation to each MetS component and a stronger association with the MetS than TNF-α, IL-6, and CRP. The present results thus raise the possibility that adiponectin is a substantial key molecule in the development of MetS and may be a comprehensive marker of the MetS condition. Further prospective studies would be warranted to confirm these findings. If so, measures to increase circulating adiponectin might be crucial for the prevention or management of MetS.

Acknowledgments

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References


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