Relationship between the Serum Uric Acid Level, Visceral Fat Accumulation and Serum Adiponectin Concentration in Japanese Men

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Abstract

Objective  Visceral fat accumulation is an underlying component of the metabolic syndrome (MetS). Hypoadiponectinemia is one of the key molecules of the MetS. In the present study, we investigated the relationship between the serum uric acid level, visceral fat accumulation and serum adiponectin concentration in Japanese men.

Patients and Methods  The study group comprised 1,520 Japanese employed men (mean age: 45.6±10.4 years, ± SD), who had undergone an annual health check-up both in 2004 and 2005. In addition to parameters measured in the annual health check-up, visceral fat area (VFA) and serum adiponectin concentration were measured by the bioelectrical impedance analysis method and a sandwich enzyme-linked immunosorbent assay (ELISA) system, respectively.

Results  Visceral fat accumulation was identified in 56.1% of the subjects with hyperuricemia. There was significant positive correlation between visceral fat area and serum uric acid levels ($r=0.223$, $p<0.0001$), and negative correlation between serum adiponectin concentration and serum uric acid levels ($r=-0.198$, $p<0.0001$). The one-year change in VFA was associated with the one-year change in serum uric acid levels. Stepwise multiple regression analysis showed that VFA and the serum adiponectin concentration were significant explanatory variables for serum uric acid levels.

Conclusion  Hyperuricemia is significantly associated with visceral fat accumulation and hypoadiponectinemia in Japanese men.

Key words: uric acid, visceral fat accumulation, bioelectrical impedance analysis method, adiponectin, metabolic syndrome

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Introduction

The metabolic syndrome is a major target for the prevention of atherosclerotic cardiovascular diseases (1, 2). Visceral fat accumulation is associated with the development of metabolic disorders including glucose intolerance, dyslipidemia, elevated blood pressure, and atherosclerotic cardiovascular diseases (3-5). On the other hand, hyperuricemia is considered a component of the metabolic syndrome. Recent epidemiological studies have shown that hyperuricemia is a risk factor for atherosclerotic cardiovascular diseases (6, 7). In the global and Japanese guidelines for metabolic syndrome, hyperuricemia is stated as a metabolic disorder re-
related to the metabolic syndrome (1, 8).

The adipose-specific endocrine factor, adiponectin, exhibits anti-atherogenic, anti-diabetic and anti-inflammatory properties (9, 10), but the plasma level of this endocrine factor is low in obese subjects (11). Hypoadiponectinemia is associated with coronary artery disease, type 2 diabetes, essential hypertension, and metabolic syndrome (12-15) and seems to be a key molecule in the development of cardiovascular diseases in metabolic syndrome.

The association between hyperuricemia, visceral fat and hypoadiponectinemia has not been well investigated in the general population. The aim of the present study was to examine the relationship between the serum uric acid level, visceral fat accumulation and serum adiponectin concentration in Japanese employed men.

Materials and Methods

Subjects

Among 2,109 Japanese male subjects who were employees of the Amagasaki City Office, Hyogo (an urban area) and had undergone an annual health check-up both in 2004 and 2005, 1,520 subjects (mean age: 45.6±10.4 years, ± SD, range; 22-68) were recruited into the study. Subjects were excluded from the study if they did not agree to participate, had hepatic and/or renal dysfunction (AST ≥ 100 IU/L and/or ALT ≥ 100 IU/L and/or creatinine >1 mg/dL) or were being treated with anti-diabetic, anti-hypertensive, anti-hyperlipidemic, and/or hyperuricemic medications. Table 1 lists the basic anthropometric and metabolic characteristics of the subjects enrolled in this study.

### Table 1. Clinical Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th></th>
<th>n=1520</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.6 ± 10.4</td>
</tr>
<tr>
<td>Visceral fat area (cm²)</td>
<td>91.0 ± 37.0</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83.2 ± 7.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 ± 2.7</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>126.6 ± 16.6</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78.0 ± 12.1</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>161.4 ± 116.4</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>57.2 ± 16.3</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.09 ± 0.55</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.81 ± 0.10</td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>28.8 ± 31.8</td>
</tr>
<tr>
<td>Adiponectin (μg/mL)</td>
<td>7.13 ± 3.0</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.81 ± 1.24</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

BMI: body mass index, HDL: high density lipoprotein, γ-GTP: γ-glutamyltransferase

Anthropometry and laboratory measurements

Anthropometric variables (height, weight and waist circumference) were measured in standing position. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height in meters (m²). Waist circumference (WC) at the umbilical level was measured with a non-stretchable tape in the late exhalation phase while standing in cm (16). Systolic and diastolic blood pressure values were measured in the sitting position to the nearest mmHg. VFA was determined by the bioelectrical impedance analysis (BIA) method, as reported previously by our group (17). Briefly, the voltage recorded at the flank to the flow of current between the umbilicus and the back correlates significantly with VFA and is not influenced by the amount of subcutaneous fat. We demonstrated previously that VFA estimated by BIA is significantly correlated with that determined by computed tomography (CT) (17). Serum concentrations of adiponectin were measured by a sandwich enzyme-linked immunosorbent assay (ELISA) system (adiponectin ELISA kit, Otsuka Pharmaceutical Co., Tokushima, Japan) (11). Serum uric acid level was determined by an enzymatic method using the uricase-peroxidase system. The value of hemoglobin A1c (HbA1c) was determined by high-performance liquid chromatography. Serum total cholesterol and triglyceride concentrations were determined by enzymatic methods. High-density lipoprotein (HDL) cholesterol was also measured by enzymatic method after heparin and calcium pre-
Table 2. Correlation Coefficients of Relationships between Serum Uric Acid Levels and Various Parameters of the Metabolic Syndrome Calculated from Data of 1,520 Japanese Men

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.063</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Visceral fat area</td>
<td>0.223</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.212</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.225</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.119</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.166</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.212</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>-0.009</td>
<td>N.S.</td>
</tr>
<tr>
<td>HbA1c</td>
<td>-0.040</td>
<td>N.S.</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.187</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>γGTP</td>
<td>0.301</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>-0.198</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

N.S.: not significant

Definition of hyperuricemia and metabolic syndrome

Hyperuricemia was defined as serum uric acid ≥ 7 mg/dL according to the 2002 guidelines of the Japanese Society of Gout and Nucleic Acid Metabolism (18). Metabolic syndrome was defined according to the recent report of the National Health and Nutrition Survey (2005) (19).

Statistical analysis

All statistical analyses were performed with Stat View-J 5.0 (Statistical Analysis System Inc., Cary, NC). Since triglyceride, g-glutamyltransferase (γGTP) and serum adiponectin concentration did not show Gaussian distribution; these three parameters were log-transformed before analysis. Pearson’s correlation coefficient was used to examine the relationship between serum uric acid and various metabolic parameters (Table 2, Fig. 1). Comparisons between changes in serum uric acid levels and changes in VFA were analyzed by Kruskal-Wallis test and Games-Howell test (Fig. 2). Stepwise multiple regression analysis was conducted to identify parameters that significantly contribute to serum uric acid levels (Table 3). Parameters with F value of >4.0 were subsequently entered into the regression analysis as independent variables. A P value less than 0.05 denoted the presence a statistically significant difference.

Results

Hyperuricemia (serum uric acid level ≥ 7 mg/dL) was detected in 17.4% (n=264/1,520) of the cohort. Of these subjects with hyperuricemia, 56.1% (n=148/264) had visceral fat accumulation (VFA ≥ 100 cm²). Of the subjects with hyperuricemia, 10.6% (n=28/264) had the metabolic syndrome while 23.5% (n=28/119) of subjects with the metabolic syndrome had hyperuricemia. We investigated the relationship between serum uric acid level and various parameters of the metabolic syndrome including VFA and serum adiponectin concentration. Table 2 lists the correlation coefficients for the relationships between serum uric acid levels and various clinical parameters. With regard to anthropometric parameters, serum uric acid levels correlated positively with BMI, WC and VFA. Furthermore, the serum uric acid level corre-
associated positively with creatinine (Cr) (20), systolic and diastolic blood pressure (21), serum triglyceride (20, 21) and γGTP (22), and negatively with adiponectin. Figure 1 shows scattergrams which demonstrate correlation between serum uric acid levels and visceral fat area (Fig. 1a) or serum adiponectin concentration (Fig. 1b).

Next, we investigated the correlation between the one-year change in VFA (ΔVFA) and change in serum uric acid levels (ΔSUA) within the same period in the 1,520 subjects (Fig. 2). We divided these subjects into six bins of ΔVFA (every 15 cm²). ΔSUA in subjects with decrease in VFA was significantly lower than that in the subjects with increase in VFA. Thus, ΔVFA was associated with ΔSUA.

Finally, stepwise multiple regression analyses of data of all subjects identified serum γGTP, creatinine, serum adiponectin concentration, VFA and diastolic blood pressure as significant explanatory variables for serum uric acid level (Table 3).

**Discussion**

In the present study, we demonstrated that 1) 56.1% of the subjects with hyperuricemia had visceral fat accumulation and the one-year change in VFA correlated significantly with the change in serum uric acid levels and 2) serum adiponectin concentrations was one of the significant explanatory variables for serum uric acid level.

Hyperuricemia is a complex disorder influenced by genetic (23) and environmental factors. Environmental factors such as purine-rich food and alcohol consumption, stress, and strenuous exercise are known to be associated with hyperuricemia (24-27). Hyperuricemia is also frequently accompanied by the metabolic syndrome including obesity, dyslipidemia, elevated blood pressure and insulin resistance (28-30). In global and Japanese guidelines for the metabolic syndrome, hyperuricemia is stated as a metabolic disorder related to the metabolic syndrome (1, 8).

In the present study, serum uric acid levels were significantly associated with visceral fat accumulation. Numerous epidemiological studies have shown a positive correlation between body weight and serum uric acid levels (31, 32). Recently, it was reported in a cross-sectional study that serum uric acid levels were associated with visceral fat accumulation (33). Compared with previous studies, the follow-

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**Table 3. Stepwise Multiple Regression with Serum Uric Acid Levels as the Dependent Variable, Calculated from Data of 1,520 Japanese Men**

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>Standardized regression coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>γGTP</td>
<td>0.399</td>
<td>0.045</td>
<td>0.232</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.677</td>
<td>0.302</td>
<td>0.209</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>-0.339</td>
<td>0.075</td>
<td>-0.111</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Visceral fat area</td>
<td>0.004</td>
<td>0.001</td>
<td>0.105</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.007</td>
<td>0.003</td>
<td>0.065</td>
<td>0.0112</td>
</tr>
</tbody>
</table>

Adjusted R²: 0.162

Not accepted variable (F value < 4.0) was Triglyceride.
ing features are unique to the present study; 1) inclusion of a large number (1,520 men) of general population, not hospitalized overweight or obese subjects, 2) measurement of VFA over two years in the same population using a new technique, the abdominal BIA method, and analysis of the relationship between one-year change in VFA and changes in serum uric acid levels, and 3) measurement of serum adiponectin concentrations in large number of subjects and analysis of the relationship between serum adiponectin concentration and serum uric acid levels. The present results suggest that a considerable number of subjects with hyperuricemia had visceral fat accumulation, and reduction of visceral fat may be associated with a reduction in serum uric acid level, at least in such subjects.

It is thought that serum uric acid level is determined by a balance among dietary purine intake, purine production in the liver and urinary excretion of uric acid. Several studies suggested that over-inflow of free fatty acid to the liver from accumulated visceral fat may be linked to de novo purine synthesis through the pentose phosphate pathway, which may accelerate the production of uric acid (34, 35), and that hyperinsulinemia associated with visceral fat obesity may reduce urinary urate excretion in parallel with a decrease in urinary sodium excretion (36). Recently, several studies reported that hyperuricemia is an independent risk factor for atherosclerotic cardiovascular diseases (37, 38), and experimental studies demonstrated that uric acid per se could cause dysfunction of vascular endothelial cells, proliferation of smooth muscle cells and stimulation of production of C-reactive protein from these cells (39, 40).

Accumulation of visceral fat causes adipocytokine dysregulation including hypoadiponectinemia, leading to hypertension, dyslipidemia, diabetes mellitus, and atherosclerosis. A subtype of hyperuricemia associated with visceral fat accumulation may be accompanied by adipocytokine dysregulation and multiple risk factors, leading to atherosclerotic cardiovascular diseases.

Serum γ-GTP, creatinine and diastolic blood pressure were associated with serum uric acid levels, as described previously (Tables 2, 3, ref. No. 20-22, 28-30). We also demonstrated in the present study that serum uric acid levels were negatively correlated with the serum adiponectin concentration and that the latter was one of the significant explanatory variables for serum uric acid levels. Interestingly, in the stepwise multiple regression analysis, both VFA and serum adiponectin concentration were significant explanatory variables of serum uric acid levels. When the interaction term (VFA x adiponectin) was entered into the model to analyze interaction effects between VFA and serum adiponectin, it was not a significant explanatory variable (data not shown).

These results suggest that hypoadiponectinemia per se could be associated with hyperuricemia, independent of visceral fat accumulation. Further studies are necessary to clarify the relationship between uric acid metabolism and adiponectin. It is possible that visceral fat accumulation and hypoadiponectinemia independently cause insulin resistance and reactive hyperinsulinemia (41). Therefore, secondary hyperinsulinemia may lead to hyperuricemia via increasing reabsorption of uric acid in kidney. When the subjects with renal dysfunction (1< Cr <2 mg/dL) were included, standardized regression coefficient for serum creatinine was further elevated (standardized regression coefficient: 0.251), suggesting that renal dysfunction considerably affects the serum uric acid level. Moreover, the present study also suggested that subclinical renal dysfunction (serum creatinine; up to 1 mg/ dL), which is often accompanied with the metabolic syndrome, has an impact on serum uric acid levels (Tables 2, 3).

Recently, we demonstrated that a reduction of visceral fat was significantly associated with a decrease in the number of metabolic risk factors such as elevated blood pressure, dyslipidemia, and glucose intolerance (42). Considered collectively with the results of the present study, we suggest that intervention strategies directed towards reduction of visceral fat could result in reduction of the total number of metabolic risk factors, including hyperuricemia.

In conclusion, hyperuricemia is significantly associated with visceral fat accumulation and hypoadiponectinemia in Japanese men.

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