Relationship between Hyperuricemia and Body Fat Distribution

Miho Hikita¹, Iwao Ohno¹, Yutaka Mori², Kimiyoshi Ichida¹, Takuo Yokose¹ and Tatsuo Hosoya¹

Abstract

Objective We investigated the relationship between serum uric acid (SUA) and body fat area, serum lipid level, insulin resistance, and metabolic syndrome in Japanese men.

Method We studied 508 Japanese men industrial workers who underwent an annual medical examination and agreed to participate in the CT scanning examination. Body fat area was measured at the umbilical level. Metabolic syndrome was defined by the presence of visceral fat accumulation (≥100 cm²) accompanied by two or more disorders; dislipidemia, hypertension, and hyperglycemia.

Results SUA was positively correlated with visceral fat area, subcutaneous fat area, serum total cholesterol level, serum triglyceride level, the Homeostasis Model Assessment index, and was negatively correlated with the high-density lipoprotein cholesterol level. In multiple regression analysis, the most influential factor for SUA was visceral fat area (p=0.0027), followed by the serum triglyceride level (p=0.0245). We clarified a higher SUA in the metabolic syndrome group as compared with the non-metabolic syndrome group: 6.67±1.14 mg, 6.09±1.14 mg, respectively (p<0.0001). The median SUA was elevated with increasing metabolic syndrome factors (p<0.0001).

Conclusion The present study indicated that SUA is related to visceral fat accumulation. Patients with metabolic syndrome revealed a higher SUA.

Key words: uric acid, metabolic syndrome, visceral fat obesity

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Introduction

Many previous reports have shown the relationship between obesity and lifestyle-related disease. Matsuzawa et al showed that visceral fat obesity caused the clustering of lifestyle-related diseases, leading to various vascular diseases, so they proposed the term 'visceral fat syndrome' for this condition (1-3). The term “metabolic syndrome” was proposed by the World Health Organization (WHO) in 1999 (4). The criteria for the diagnosis of metabolic syndrome were defined by WHO (4), the National Cholesterol Education Program (ATP III) (5), and the International Diabetes Federation (IDF) (6), and the Japanese criteria was published in 2005 (7).

In a previous study, we showed that hyperuricemia is closely related to obesity and the degree of body fat accumulation (8). We also reported that patients with hyperuricemia are complicated with various lifestyle-related diseases, and patients who have many lifestyle-related diseases show a higher SUA (9).

There are various hypotheses as to why obesity causes hyperuricemia: for instance, accelerated uric acid production coupled with the synthesis of triglyceride (10), underexcretion of uric acid into the urine caused by the effect of insulin on the urinary tubular tract (11-13).

Several epidemiological reports showed a significant relationship between SUA and cardiovascular and cerebrovascular disease. In particular, in patients with hypertension, SUA was defined as an independent risk factor for cardiovascular disease.

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Table 1.  Patient Characteristics by Quartile of Serum Uric Acid Level

<table>
<thead>
<tr>
<th>Serum uric acid (mg/dl)</th>
<th>All</th>
<th>Q1  (5.3)</th>
<th>Q2  (5.4−6.2)</th>
<th>Q3  (6.3−7.0)</th>
<th>Q4  (7.1+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subject</td>
<td>508</td>
<td>119</td>
<td>132</td>
<td>133</td>
<td>124</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.5±7.7</td>
<td>46.3±7.1</td>
<td>47.0±7.9</td>
<td>47.4±7.8</td>
<td>47.0±8.3</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24.9±5.4</td>
<td>24.5±6.1</td>
<td>24.4±3.2</td>
<td>25.0±4.5</td>
<td>26.0±3.6</td>
</tr>
</tbody>
</table>

Statistical analysis

The correlation between the two variables was assessed using Pearson’s correlation test. Differences between the two groups were assessed with the Mann-Whitney U test and those among multiple groups were assessed with Sheffe’s F test and analysis of variance. The correlation between the complication number of metabolic syndrome components and SUA level was assessed by Spearman’s correlation coefficient by rank. P<0.05 was considered statistically significant in all analyses.

Results

The characteristics of subjects are shown in Table 1. The subjects’ mean age was 47.5 years old (24-68 years). Their mean BMI was 24.9 kg/m^2. All subjects were classified into quartiles by SUA (Quartile 1 (Q1): SUA ≤ 5.3 mg/dl, n= 119; Quartile 2 (Q2): SUA 5.4-6.2 mg/dl, n= 132; Quartile 3 (Q3): SUA 6.3-7.0 mg/dl, n=133; Quartile 4 (Q4): SUA ≥
Figure 1. Relationship between the serum uric acid level and visceral fat area.

7.1 mg/dl, n=124.

No significant differences of mean age were seen in any quartile. Higher quartiles showed higher BMI, and a significant difference was seen between Q2 and Q4 (p<0.001).

We investigated the relationship between SUA and VFA. A significant correlation between SUA and VFA was seen (r=0.303, P<0.001); furthermore, a higher quartile of SUA showed a higher VFA (Fig. 1). A significant correlation was also seen between SUA and SFA (r=0.252, p<0.001) (Fig. 2); however, in the quartile analysis, a significant difference was only seen between Q4 and the other quartiles (Fig. 2). These results showed that the body fat area, especially VFA, was significantly related to SUA.

In the study of serum lipid and SUA, a significant correlation was seen between SUA and TC (r=0.158, p<0.001) and TG (r=0.189, p<0.001), and a negative correlation was seen between SUA and HDL (r=-0.019, p<0.001) (data not shown). These results suggested that serum lipids, and in particular TG, are significantly related to SUA.

A significant correlation was also seen between SUA and HOMA index (r=0.152, p<0.001) (data not shown). This indicates a significant relationship between SUA and insulin resistance.

To examine the most influential parameters on SUA, multiple regression analysis was carried out. As shown in Table 2, the contributing factors to SUA were VFA (p=0.0027), followed by TG (p=0.0245).

Furthermore, we investigated the difference of serum uric acid in two groups: Metabolic syndrome group (MS: n=130) and non-metabolic syndrome group (NMS: n=372). In this study, mean SUA was significantly higher than that in the NMS group (6.67±1.14 mg, 6.09±1.14 mg, for each, p<0.0001) (Fig. 3).

In Spearman’s rank correlation coefficient analysis, the median SUA was elevated with increasing metabolic syndrome characteristics (p <0.0001) (Fig. 4).

**Discussion**

Upper-body obesity is considered to be a risk factor for coronary artery disease. Matsuzawa et al showed that visceral fat obesity (VFO) cause many lifestyle-related diseases based on insulin resistance, and accelerated the development of atherosclerotic diseases, as termed ‘visceral fat obesity syndrome’ (1-3).
Some investigators reported the relationship of body fat area and SUA. Matsuura et al. reported that patients with VFO (V/S ratio >0.4) show a higher urinary excretion of uric acid than those with subcutaneous fat obesity (SFO) (19); they therefore concluded that visceral fat accumulation is related to the overproduction of uric acid. Furthermore, Takahashi et al. reported that gout patients had a larger VFA than healthy subjects (20). They also reported that gout patients with the overproduction type had an increased VFA compared with the underexcretion type. In the present study, there were significant relations between SUA and both VFA and SFA; in particular, SUA was more closely related to VFA. Unfortunately, we did not examine the urinary uric acid level in the present study, and thus we could not assess the relationship between uric acid metabolism or the type of hyperuricemia and body fat area.

It is considered that the accumulation of visceral fat leads to insulin resistance, and a plurality of lifestyle-related diseases based on insulin resistance. The mechanism as to why visceral fat accumulation causes insulin resistance is thought to result from direct injury to the insulin receptor system by excessive free fatty acid in the portal vein (2). Several past studies have shown that hyperinsulinemia or insulin resistance decreased urinary uric acid excretion by the effect of insulin on urinary tubules (12, 13, 21). It is known that uric acid and sodium have a co-transporter system in the kidney (22). Ferrannini et al. reported that patients with essential hypertension show insulin resistance as determined by the glucose clamp test (23). DeFronzo showed that venous infusion of insulin decreases the urinary excretion of sodium (24). After these reports, Galvan et al. showed that elevation of the plasma insulin level decreases both the urinary fractional excretion of sodium (FENa) and uric acid (FEua) (12). Furthermore, Ter Maaten et al. showed a negative correlation between uric acid clearance and insulin resistance as determined by the glucose clamp method (13). These studies indicated that hyperinsulinemia or insulin resistance decreases
the urinary excretion of uric acid and causes hyperuricemia. From these results, it is considered that altered renal handling of uric acid and sodium due to an insulin effect lead to the coexistence of hyperuricemia and hypertension in a clustering of lifestyle-related diseases. As a significant correlation between insulin resistance measured by the HOMA index, and SUA was also seen in the present study, our results support that insulin resistance causes hyperuricemia.

Another reason why VFO causes hyperuricemia is as follows; in VFO patients, excessive free fatty acid in the portal vein accelerates the overproduction of very low-density lipoprotein that leads to hypertriglyceridemia. This also accelerates the de novo synthesis of ribose-5-phosphate to phosphoribosylpyrophosphate through the common metabolic pathway of NADP-NADPH, and as a result of this mechanism, uric acid production increases (10, 25). Tsutsumi et al reported that decreased activities of lipoprotein lipase and hepatic triglyceride lipase are seen in patients with gout (26). They considered that this might lead to a higher risk of coronary atherosclerotic diseases. In the present study, we concluded that the elevation of SUA is related to visceral fat accumulation and to the elevation of TG. In multiple regression analysis, the strongest correlation was seen between SUA and VFA (p=0.0027), followed by TG (p=0.0245). Other parameters, such as SFA, TC, the HOMA index, BMI and BP showed no significant correlation to SUA.

The criteria for the diagnosis of metabolic syndrome in Japan was defined in 2005 (7). In this criteria, SUA is not a diagnostic factor, because there is not enough evidence that it is an independent risk factor of cardiovascular disease, and they recommend that SUA should be used as a significant risk marker. Our results also suggest a relationship between SUA and metabolic syndrome. Recently, Kawamoto et al reported a significant relationship between SUA and metabolic syndrome in women (27). They also clarified that SUA was an independent risk factor for the incidence of carotid atherosclerosis, and concluded that SUA increases the risk of cardiovascular morbidity. By accumulation of clinical evidence, the significance of SUA in metabolic syndrome will become clearer. The improvement of insulin resistance might improve hyperuricemia and many lifestyle-related diseases, so we consider that treatment and education to decrease visceral fat accumulation is the most important for such patients.

In conclusion, 1) SUA was positively correlated with VFA, SFA, TC, TG, and HOMA index, and negatively correlated with HDL; 2) In multiple regression analysis, the most influential factor for SUA was VFA; 3) SUA was significantly higher in the metabolic syndrome group than in the non-metabolic syndrome group; 4) SUA was elevated with increasing metabolic syndrome characteristics. To clarify these mechanisms, more advanced study should be conducted, such as a prospective cohort study or a study on uric acid metabolism in many subjects.

References

18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF.


