Original article

Relationship between uric acid and hepatic steatosis among Koreans

K. Lee

Department of Family Medicine, Busan Paik Hospital, Inje University College of Medicine, 633-165, Kaegum-dong, Busan Jin-Gu, 614-735 Busan, Democratic People’s Republic of Korea

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Abstract

Aim. – The relationship between high uric-acid levels and hepatic steatosis, according to body mass index (BMI) categories, and their coexistence with the metabolic syndrome (MetS) were examined in the present study.

Methods. – The study involved a cross-sectional sample of 13,621 Koreans (7221 men and 6400 women) who visited a health checkup centre between 2005 and 2006. Hepatic steatosis was diagnosed using ultrasonography. Hyperuricaemia was defined as > 7 mg/dL for men and > 6 mg/dL for women. The MetS was defined as the presence of three or more MetS components—obesity (BMI ≥ 25.0 kg/m²), high blood pressure, elevated levels of triglycerides and glucose, and low levels of high-density lipoprotein (HDL)-cholesterol.

Results. – In total, 26.2% were diagnosed with hepatic steatosis, of whom 11.9% were non-obese (BMI < 25 kg/m²) and 52.5% were obese. Hyperuricaemia was associated with hepatic steatosis in non-obese (adjusted odds ratio [AOR] of 1.4 in men and 2.2 in women) as well as in obese individuals (AOR of 1.8 in men and 2.3 in women) after adjusting for age, other MetS components and liver function tests. The AOR (95% CI) for hepatic steatosis in obese individuals with hyperuricaemia compared with non-obese individuals with normal uric-acid levels was 7.7 (6.4–9.3) in men and 12.4 (7.8–19.5) in women. The adjusted age and liver-function test ORs (95% CI) for hepatic steatosis in those with hyperuricaemia and no MetS compared with those who had normal uric acid levels and no MetS were 2.0 (1.7–2.4) in men and 3.2 (2.1–4.9) in women. The ORs (95% CI) in those with hyperuricaemia and the MetS increased to 6.9 (5.5–8.8) and 15.2 (8.4–27.4) in men and women, respectively.

Conclusion. – Hyperuricaemia is independently associated with hepatic steatosis regardless of BMI category or the presence of the MetS in Korean adults. Further research into the causal relationship is needed.

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Keywords: Hepatic steatosis; Uric acid; BMI category; The metabolic syndrome; Korean

Résumé

Relation entre hyperuricémie et stéatose hépatique chez les coréens.

Objectifs. – Étudier les relations éventuelles entre l’hyperuricémie et la stéatose hépatique en fonction de l’indice de masse corporelle (IMC) et de la coexistence d’un syndrome métabolique dans un échantillon de la population coréenne.

Méthodes. – La population étudiée comportait 13 621 coréens (7221 hommes et 6400 femmes) suivis dans un centre de santé entre 2005 et 2006. Le diagnostic de stéatose hépatique a été porté par l’échographie. L’hyperuricémie a été définie par une uricémie supérieure à 7 mg/dL chez l’homme et supérieure à 6 mg/dL chez la femme. Le syndrome métabolique a été défini par la présence de trois ou plus des éléments suivants : obésité (IMC ≥ 25.0 kg/m²), hypertension artérielle, hypertriglycéridémie, hyperglycémie et HDL cholésterol bas.

Résultats. – Au total, 26.2 % des sujets présentaient une stéatose hépatique (11.9 % chez les sujets avec un IMC inférieur à 25 et 52.5 % chez les sujets obèses. Il existait une association hyperuricémie–stéatose chez les sujets de poids normal (odds ratio ajusté [AOR] 1.4 chez les hommes et 2.2 chez les femmes) et chez les obèses (AOR 1.8 chez les hommes et 2.3 chez les femmes) après ajustement pour l’âge, les éléments du syndrome métabolique et les tests fonctionnels hépatiques. L’AOR (intervalle de confiance à 95 %) de la stéatose chez les obèses avec hyperuricémie par rapport aux sujets de poids normal obèses avec uricémie normale était respectivement de 7.7 (6.4–9.3) chez les hommes et de 12.4 (7.8–19.5) chez les femmes. Ajustés pour l’âge et les tests fonctionnels hépatiques, les AOR (IC 95 %) des sujets avec stéatose et hyperuricémie sans syndrome métabolique par rapport aux sujets avec uricémie normale sans syndrome métabolique étaient de 2.0 (1.7–2.4) chez les hommes et 3.2 (2.1–4.9) chez les femmes. Les AOR (IC 95 %) des sujets avec hyperuricémie et syndrome métabolique passaient respectivement à 6.9 (5.5–8.8) chez les hommes et à 15.2 (8.4–27.4) chez les femmes.

E-mail addresses: kayoung.fmlky@gmail.com, fmlky@inje.ac.kr.

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1. Introduction

It is well known that hepatic steatosis is an additional feature of insulin resistance. The evidence also suggests that hepatic steatosis is predictive of coronary heart disease (CHD) risk [1,2]. Epidemiological studies have found that uric acid may be an independent risk factor for CHD [3,4]. Therefore, there appears to be a close relationship between hepatic steatosis and high uric-acid levels, as uric acid may play a role in insulin resistance [5]. However, the association between uric acid and hepatic steatosis remains controversial, and differs according to weight status. Most studies that have controlled for other metabolic risk factors suggest a positive relationship between serum uric acid and hepatic steatosis in obese individuals while, in non-obese individuals, uric acid is not consistently associated with the presence of hepatic steatosis [1,6,7]. Moreover, few studies have examined this difference in association with other metabolic abnormalities. Therefore, the objective of the present study was to clarify the relationship between high uric acid and the presence of hepatic steatosis according to body mass index (BMI) and the coexistence of the metabolic syndrome (MetS).

2. Methods

2.1. Study subjects

This study used data generated from 15,791 Korean adults (8667 men and 7124 women) who visited the Center of Health Promotion at the Inje University Busan Paik Hospital between March 2005 and June 2006. Subjects with evidence of excessive alcohol intake (≥ 20 g/day) and those with positive seromarkers for hepatitis B or C, biliary disease, liver cirrhosis or malignant disease were excluded, using surveys on alcohol intake, self-reported past medical history, laboratory tests and ultrasonography. Alcohol intake was assessed through two open questions: ‘How often did you have a drink containing alcohol per week in the past six months?’ and ‘How many glasses did you have on a typical day when you were drinking in the past six months?’ For the second question, one glass of alcoholic beverage was assumed to contain 10 g of alcohol. From the answers to these two questions, we calculated the subject’s daily intake of alcohol. After the exclusions, the present study comprised 13,621 adults (7221 men and 6400 women) with complete data for the analyses.

2.2. Measurements

Hepatic steatosis was diagnosed using abdominal B-mode ultrasonography (LOGIQ 7, 4 MHz transducer; GE Healthcare, Wauwatosa, WI, USA). The ultrasonography was carried out by experienced radiologists, who did not have access to the subjects’ clinical or laboratory test findings. Hepatic steatosis was assessed semiquantitatively, and graded from absent to severe on the basis of abnormally intense, high-level echoes arising from the hepatic parenchyma, liver–kidney differences in echo amplitude, echo penetration into the deep portion of the liver and clarity of the liver blood-vessel structure [8].

Body weight and height were measured in subjects while clothed in a light gown without shoes; these measurements were used to calculate the BMI (kg/m²). A BMI of ≥ 25 kg/m² was considered indicative of obesity [9]. Blood pressure (BP) measurements were taken with a standard manual sphygmomanometer with the subjects in a sitting position. Antecubital venous blood samples were taken from all subjects after a 12 h overnight fast. Levels of cholesterol, triglycerides (TGs), fasting glucose, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT) were measured using a biochemistry autoanalyzer (Toshiba 200-FR; Toshiba, Tokyo, Japan). The following criteria were used to define elevated uric-acid levels, the MetS components and abnormal liver-function tests: uric acid > 7 mg/dL for men and > 6 mg/dL for women [10]; BP ≥ 130/85 mmHg; fasting glucose ≥ 100 mg/dL; HDL cholesterol < 40 mg/dL for men and < 50 mg/dL for women; TGs ≥ 150 mg/dL [11]; AST > 42 IU/L; ALT > 45 IU/L; and GGT > 50 IU/L [10]. The MetS was defined as the presence of three or more of the following components: obesity (instead of central obesity); high BP; raised levels of TGs and glucose; and low HDL cholesterol levels [11]. The ethics committee of the Inje University Busan Paik Hospital approved the present study.

2.3. Statistical analyses

The distribution of hepatic steatosis, hyperuricaemia, the MetS components and abnormal liver-function tests were compared between genders using a $\chi^2$ test. All analyses of the relationship between hyperuricaemia and hepatic steatosis were performed separately by gender. Logistic-regression analysis was used to analyze the independent relationships of high uric-acid levels and hepatic steatosis in each BMI category (non-obese and obese groups), and in a combined group of BMI and uric-acid categories (low uric acid and non-obese group, low uric acid and obese group, high uric acid and non-obese group, and high uric acid and obese group) after adjusting for age, the MetS components except for BMI category, and liver-function test categories (normal vs abnormal AST, ALT and GGT values). The interaction between the uric acid category and BMI category in the logistic-regression analyses for the presence of hepatic steatosis was analyzed. Likewise, the interaction between uric-acid category and the presence/absence of
Table 1
Clinical characteristics of the study participants by gender.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 13,621)</th>
<th>Men (n = 7221)</th>
<th>Women (n = 6400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic steatosis, total</td>
<td>3569 (26.2)</td>
<td>2525 (35.0)</td>
<td>1044 (16.3)</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m² (n = 4811)</td>
<td>2524 (52.5)</td>
<td>1802 (58.2)</td>
<td>722 (42.1)</td>
</tr>
<tr>
<td>BMI &lt; 25 kg/m² (n = 8810)</td>
<td>1045 (11.9)</td>
<td>723 (17.5)</td>
<td>322 (6.9)</td>
</tr>
<tr>
<td>Uric acid (mg/dL) &gt; 7 (M), &gt; 6 (W)</td>
<td>1477 (10.8)</td>
<td>1301 (18.0)</td>
<td>176 (2.8)</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m²</td>
<td>4811 (35.3)</td>
<td>3094 (42.8)</td>
<td>1717 (26.8)</td>
</tr>
<tr>
<td>BP ≥ 130/85 mmHg</td>
<td>3597 (26.4)</td>
<td>2297 (31.8)</td>
<td>1300 (20.3)</td>
</tr>
<tr>
<td>HDL (mg/dL) &lt; 40 (M), &lt; 50 (W)</td>
<td>2852 (20.9)</td>
<td>1211 (16.8)</td>
<td>1641 (25.6)</td>
</tr>
<tr>
<td>TGs ≥ 150 mg/dL</td>
<td>3313 (24.3)</td>
<td>2471 (34.2)</td>
<td>842 (13.2)</td>
</tr>
<tr>
<td>Glucose ≥ 100 mg/dL</td>
<td>2715 (19.9)</td>
<td>1713 (23.7)</td>
<td>1002 (15.7)</td>
</tr>
<tr>
<td>AST &gt; 42 IU/L</td>
<td>395 (2.9)</td>
<td>307 (4.3)</td>
<td>88 (1.4)</td>
</tr>
<tr>
<td>ALT &gt; 45 IU/L</td>
<td>1106 (8.1)</td>
<td>911 (12.6)</td>
<td>195 (3.0)</td>
</tr>
<tr>
<td>GGT &gt; 50 IU/L</td>
<td>2251 (16.5)</td>
<td>2028 (28.1)</td>
<td>223 (3.5)</td>
</tr>
<tr>
<td>MetS components ≥ three</td>
<td>2436 (17.9)</td>
<td>1593 (22.1)</td>
<td>843 (13.2)</td>
</tr>
</tbody>
</table>

All data are presented as n (%); *P < 0.05 using the χ² test; BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein cholesterol; M: men; W: women; TGs: triglycerides; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; MetS: metabolic syndrome (components: BMI ≥ 25 kg/m²; BP ≥ 130/85 mmHg; HDL < 40 (M), < 50 (W) mg/dL; TGs ≥ 150 mg/dL; and glucose ≥ 100 mg/dL).

the MetS was evaluated. In addition, the relationship between the uric-acid category combined with the presence/absence of the MetS (low uric acid with no MetS, low uric acid with MetS, high uric acid with no MetS, and high uric acid with MetS) and the presence of hepatic steatosis was analyzed using the logistic-regression analyses, after adjusting for age and liver-function test categories. Statistical significance was indicated at P < 0.05. All statistical analyses were performed using SPSS 14.0 KO for Windows software (release 14.0.2 [21 Apr 2006]; SPSS Inc., Chicago, IL, USA).

3. Results

Of the 13,621 subjects, 26.2% were diagnosed with hepatic steatosis by ultrasonography. Of the total number of subjects, 11.9% of the non-obese and 52.5% of the obese individuals had hepatic steatosis. The risk of hepatic steatosis was 1.8-fold higher in men compared with women (35.0% vs 16.3%, respectively; Table 1). However, the prevalence of hepatic steatosis in women increased sharply with age regardless of BMI category, so that the gender discrepancy decreased with age (Fig. 1). Furthermore, men were more likely to have hyperuricaemia, MetS components and abnormal liver-function test categories compared with women (Table 1). After adjusting for age, the MetS components (except for BMI category) and liver-function test categories, hyperuricaemia was found to be independently associated with the presence of hepatic steatosis in both the non-obese (adjusted odds ratio [AOR] of 1.4 in men and 2.2 in women) and obese (AOR of 1.8 in men and 2.3 in women) groups (Table 2). Obese men with hyperuricaemia compared with non-obese men with normal uric-acid levels had an AOR of 7.7 for hepatic steatosis, whereas the AOR in women of the same category was 12.4 (Table 2). However, there were no significant interactions between uric-acid category and BMI category in either gender. Hyperuricaemia was also significantly associated with hepatic steatosis regardless of the presence of the MetS. However, interaction between uric-acid category and presence/absence of the MetS was not significant across either gender. The adjusted age and liver-function test ORs for hepatic steatosis in those with hyperuricaemia combined with the MetS compared with the reference group (those with normal uric acid without the MetS) increased to 6.9 in men and 15.2 in women (Table 2).

4. Discussion

Many studies have examined the risk factors for hepatic steatosis and found that the MetS components are strongly associated with the presence of hepatic steatosis [12,13]. However, the relationship between elevated uric-acid levels and hepatic steatosis according to BMI category is not clear. In the present study of 13,621 Korean adults who visited a health checkup centre, there was a significant and independent relationship between increasing levels of uric acid and the presence of hepatic steatosis...
in non-obese as well as obese individuals, even after controlling for components of the MetS and liver-function tests. Indeed, these data show that the significant association between hyperuricaemia and hepatic steatosis remains consistent regardless of the subject’s weight status.

In contrast, previous studies have reported that high uric acid is not consistently associated with the presence of hepatic steatosis in non-obese individuals [1,6,7]. However, the pathophysiological mechanism of this difference in BMI category is uncertain. The discrepancy of results may perhaps be attributed to differences in study design and statistical analyses, such as the definition of hyperuricaemia, the risk factors adjusted for in the multivariate models, the classification of BMI category and the diagnostic criteria for hepatic steatosis using ultrasonography. In addition, some factors — which may be independent of BMI, but related to uric acid and hepatic steatosis — could be intermediaries along the causal pathway. There is, for instance, evidence that high uric-acid levels often precede high insulin levels [14], and insulin resistance has been found to be related to hepatic steatosis [6,7,12]. Although obese individuals are more likely to be insulin-resistant compared with normal-weight individuals, there are subsets of individuals who have ‘metabolically obese, but normal-weight’ (MONW) and ‘metabolically healthy, but obese’ (MHO) phenotypes [15,16].

According to the present study data, the strength of the relationship between uric acid and hepatic steatosis increases with the presence of the MetS. Specifically, the risk of hepatic steatosis in hyperuricaemia with the MetS increased up to sevenfold in men and 15-fold in women compared with the reference group, and the ORs were approximately three to five times greater than those of individuals without MetS, but with hyperuricaemia.

This study identified uric acid as a significant factor associated with hepatic steatosis across both BMI categories, and showed an additive effect between uric acid and the MetS. However, these data are not able to clarify the pathophysiological mechanism(s) behind these relationships. Generalization of the present results based on the BMI categories should also be considered with caution. As the data were obtained from Asians seeking health checkups, and as Asian populations have also been shown to have a greater percentage of body fat per given BMI value compared with Western populations [17], such relationships may not be observed in subjects of other ethnic backgrounds. This suggests that further research into the possible pathogenesis of these relationships in other populations is needed.

Nevertheless, the present study demonstrates the close relationship between high uric-acid levels and the presence of hepatic steatosis, regardless of weight status and the presence of the MetS. From this point of view, high uric acid can be considered an independent indicator of hepatic steatosis.

### 5. Conflicts of interest

None.

### References


