The association between plasma uric acid level and cardiovascular events in patients with stable coronary artery disease: a short-term follow-up study

Murat Yalcin, Ejder Kardesoglu, Zafer Isilak, Ömer Uz, Murat Atalay, Mehmet Tezcan, Mehmet Uzun, Bekir Sitki Cebeci

Gulhane Military Medical Academy, Haydarpasa Training Hospital, Department of Cardiology, Istanbul, Turkey

ABSTRACT

Aim The association of uric acid (UA) level with major cardiovascular risk factors has been well-known. However, whether UA is a risk factor for coronary artery disease (CAD) still remains controversial. We aimed to examine the short term effect of plasma UA level on cardiovascular events (CVEs) in patients with stable CAD.

Methods The study included 147 consecutive patients with CAD. The patients were evaluated in two groups. Group 1: 101 (68.7%) patients with UA level higher than 6.5 mg/dL for females and 7 mg/dL for males (n= 38 and 63, respectively); Group 2: 46 (31.3%) patients with UA level lower than those values (n= 15 and 31, respectively). The patients were followed for 15.3 ± 5.5 months. Death, acute coronary syndrome, stroke and other cardiovascular hospitalizations were defined as CVE. The relationship between CVEs and plasma UA level was examined using the Cox-regression analysis.

Results The mean age was 63 ± 11 years [94 (63.9%) males, 53 (36.1%) females]. Forty-five (30.6%) had diabetes mellitus and 106 (72.1%) had hypertension. The mean UA level was 6.0 ± 1.5 mg/dL. In the follow-up, 23 (15.6%) had any defined CVEs. Only two patients died. No statistical significance was found in terms of the association between plasma UA level and CVEs (p = 0.61).

Conclusion In patients with stable CAD no relation between plasma UA level and CVEs in the short-term was found. However, this subject still needs further studies with longer follow-up period.

Key words: cardiovascular risk factor, gout, mortality
INTRODUCTION

Uric acid (UA) is an end-product of purine nucleotide metabolism (1). Any disorder of its metabolism leads to gout clinically (2). The association of gout and hypertension as well as vascular diseases results in directing the attention to the potential harmful effects of UA which may be seen even in patients without gout (3).

The association between increased UA level and cardiovascular risk factors has been convincingly demonstrated (4). However, whether UA is a risk factor or risk marker remains still controversial (5). Several studies reported UA as a risk factor in some selected patients (6). Indeed, the studies dealing with the association of UA and adverse cardiovascular events (CVE) were mostly conducted to very selected patients such as acute coronary syndrome with various follow-up periods (7). The number of studies for stable coronary artery disease (CAD) remained very limited (8). We think that this kind of studies should be continually carried out for different patient population or races. It will add new findings to the data pool regarding the association of UA and CVE, which has been still arguable.

The aim of this study was to investigate the relationship between the UA level and the cardiovascular events for short-term in patients with stable CAD, and to provide new findings about the association of UA and CVE.

PATIENTS AND METHODS

One hundred and ninety consecutive patients with CAD independently diagnosed by coronary angiography were enrolled. Exclusion criteria was; patients with the history of gout, previous coronary bypass surgery or percutaneous coronary intervention, acute coronary syndrome, reduced left ventricular systolic function, any cardiovascular disease other than CAD, reduced renal function (serum creatinine>1.40 mg/dl), any systemic or rheumatic disease, using any drugs affecting the UA level such as losartan, diuretics, and hormone replacement therapy etc. as well as alcohol intake.

All patients were informed about the study, and an informed consent was obtained. Before coronary angiography, their history and physical examination findings and serum UA levels were recorded. All coronary angiographies were assessed by two invasive cardiologists blind to the study. Any epicardial coronary artery stenosis less than 50% and/or any atherosclerotic lesion in any side branch smaller than 2 mm in diameter or supplying a small area of myocardium were accepted as noncritical CAD. Otherwise was considered as critical CAD. The severity of CAD was determined by the number of involved vessel.

The UA levels were measured with photometric method (Abbott Architect C 8000). The study population was divided into groups according to their UA levels. Higher UA level group (Group 1) were composed of patients with a level of UA higher than 6.5 mg/dl for females and 7 mg/dl for males. Lower UA level group (Group 2) included the patients with a lower UA level than those values.

The cardiovascular events were described as death, acute coronary syndrome, stroke and any hospitalizations due to other cardiovascular causes (heart failure, any arrhythmia). At the end of the follow-up period, all patients were particularly inquired about these cardiovascular events via phone call and/or our hospital computer based recording system. The contact was lost with 43 patients, and the analyses were done for 147 patients.

The data were expressed as mean ± standard deviation. P values <0.05 were considered statistically significant. The cox-regression analysis was used to determine the relationship between serum UA levels and the risk of cardiovascular events. The chi-square and student-t test were used to compare the distributions and continuous variables respectively.

RESULTS

The mean age was 63 ± 11 years. Ninety-four patients (63.9%) were males and 53 (36.1%) were females. Forty-five patients (30.6%) had diabetes mellitus, 106 (72.1%) had hypertension. With regard to the severity of CAD, non-critical CAD was found in 54 (36.7%) patients, single-vessel disease in 22 (15.0 %), two-vessel disease in 20 (13.6%) and three-vessel disease in 51 (34.7%). The mean UA level was 6.0 ± 1.5 mg/dL. Group 1 (higher UA level group) comprised 101 (68.7%) patients including 38 (37.7%) females and 63 (62.3%) males, whereas group 2 (lower UA level group, n= 46, 31.3%) was composed of 15 (32.6%) females and 31 (67.4%) males. When compa-
ring the groups in terms of demographic, clinic characteristics as well as the severity of CAD, no statistically significant differences between groups except for the distribution of hypertension were not found (Table 1). Group 1 included 80.7% of patients with hypertension while 56.4% Group 2 (p < 0.005).

During the follow-up period, 23 (15.6%) patients had some cardiovascular event. Only two patients died. No statistical significance was found between serum UA level and the rate of cardiovascular events (p=0.61). Similarly, there was no statistically significant difference between groups in point of the distribution of cardiovascular events, 15 (14.9%) in Group 1, eight (17.4%) in Group 2 (p>0.05).

**DISCUSSION**

An increased UA level has been shown to be associated with the cardiovascular risk factors such as hypertension, metabolic syndrome, obesity and diabetes (4). In particular, its association of hypertension was obviously shown in large-scale studies (9). The mechanisms are quite complex, and still being studied. The UA level is increased by two main reasons; either increased the production or reduced the elimination (10). Reduced glomerular filtration rate, renal vasoconstriction, hyperinsulinemia, alcohol intake, tissue ischemia and oxidative stress increase the UA level (10). Estrogens have uricosuric effect, thereby causing higher UA level in postmenopausal women(11). During tissue ischemia, the production of UA raises, and leads to endothelial dysfunction (12). Endothelial dysfunction of peripheral arteries impairs the flow, and it results in the decrease of muscle glucose utilization (12). At the same time, higher UA causes inflammation and oxidative stress in adipose tissue (13). All these mechanisms account for the association of high UA level and metabolic syndrome (14). Higher UA level was clearly shown to be associated with higher C reactive protein level, coronary calcium score and carotid intima-media thickness (15,16).

Whether UA is a risk factor for CAD has been an attractive subject for many years, but different results have been observed until now. In Framingham Heart Study, UA showed clear association with hypertension (17). In MRFIT study, UA and gout were independent risk factors for myocardial infarction in men followed for 6.5 years (18). In a systematic meta-analysis including the Framingham and MRFIT studies, Kim et al indicated that UA was a risk factor for CAD independent of traditional risk factors (6). The risk increase was more pronounced in women (6). All the studies mentioned above were done for the general population without CAD.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (n=101) (Mean ± SD)</th>
<th>Group 2 (n=46) (Mean ± SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 10</td>
<td>63 ± 11</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Gender Males (%)</td>
<td>62.3</td>
<td>67.4</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Females (%)</td>
<td>37.7</td>
<td>32.6</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.4 ± 6.4</td>
<td>168.1 ± 7.2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.9 ± 9.9</td>
<td>75.1 ± 12.2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2 ± 3.9</td>
<td>26.6 ± 3.8</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>150.6 ± 27.9</td>
<td>148.4 ± 24.2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>82.8 ± 9.0</td>
<td>81.0 ± 9.1</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>UA Level (mg/dL)</td>
<td>7.8 ± 0.9</td>
<td>5.1 ± 0.8</td>
<td>&lt; 0.05</td>
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<tr>
<td>Hypertension (No/%)</td>
<td>86 (85.1)</td>
<td>20 (43.5)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Diabetes mellitus (No/%)</td>
<td>35 (34.6)</td>
<td>10 (21.7)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Smoker (No/%)</td>
<td>29 (28.7)</td>
<td>19 (41.3)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>CVE (No/%)</td>
<td>15 (14.9)</td>
<td>8 (17.4)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>CAD Non-critical (No/%)</td>
<td>40 (39.6)</td>
<td>14 (30.4)</td>
<td></td>
</tr>
<tr>
<td>Single-vessel (No/%)</td>
<td>11 (10.9)</td>
<td>11 (23.9)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Two-vessel (No/%)</td>
<td>12 (11.9)</td>
<td>8 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Three-vessel (No/%)</td>
<td>38 (37.6)</td>
<td>13 (28.3)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. The demographic and clinic characteristics, and severity of coronary artery disease and the comparisons between the groups.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UA, uric acid; CVE, cardiovascular events; CAD, coronary artery disease
For patients with established CAD, in a sub-analysis of JCAD (Japanese Coronary Artery Disease) the study indicated that the UA level was an independent predictor of cardiovascular events in patients with severe coronary artery disease for a 3-year follow-up period (19). In our study, we failed to show this association for a short follow-up period of time. Our study population had various severity of CAD with shorter follow-up period of time. These might explain different results observed in two studies.

Ndrepepa et al. showed that elevated UA level was an independent predictor of short-term mortality in patients with acute coronary syndrome treated by percutaneous coronary intervention (7). The other study indicated that elevated UA level was an independent predictor of short-term mortality in patients with stable CAD treated by percutaneous coronary intervention (8). In our study, the population was totally different from that in such studies, thereby showing different results.

In our study, hypertension was more frequent in higher UA level group as shown previously (9). However, in our study UA had no predictive value for cardiovascular events in 15 months. It might be more difficult to account for these results than thought. One possible explanation might be that our patients had both critical and noncritical CAD. In addition, the limited number of events did not allow us to do any subgroup analysis to overcome that issue. Secondly, the unfavorable effects of UA could occur later, not within 15 months. Finally, an interesting study determined the risk of different threshold values for UA. Higher UA level (>3mg/dL) was shown to increase significantly the risk of developing renal disease, hypertension, diabetes than those in lower UA level (<3mg/dL) (20). Therefore, using different thresholds for UA might show different results. Unfortunately, the distribution of UA levels did not allow us to evaluate this issue.

The study had some limitations. The number of study population remained limited due to our strict inclusion criteria. In addition, we were not able to do any subgroup analysis such as age, gender or CAD severity groups etc due to a small number of cardiovascular events.

In conclusion, the UA level did not have any predictive value of cardiovascular events in patients with established stable CAD for short-term. It is clear that this subject still needs further studies.

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**TRANSPARENCY DECLARATIONS**

Competing interests: none to declare.

**REFERENCES**


