Clinical Research

Elevated serum uric acid level as a predictor for cardiovascular and all-cause mortality in Chinese patients with high cardiovascular risk

Yongquan Wu, Meijing Li, Jue Li, Yingyi Luo, Yan Xing, Dayi Hu

Heart, Lung and Blood Vessel Center, Tongji University, Shanghai 200092, China

Objective  To assess the predictive value of serum uric acid levels for cardiovascular and all-cause mortality in a large prospective population based study.  Methods  The study was based on 3648 participants in Shanghai and Beijing, who were inpatients with high cardiovascular(CV) risk at baseline (2004.7 to 2005.1), and blood was taken. Follow-up for death from cardiovascular disease and any cause was complete until January 1, 2006.  Results  The mean follow-up was 1 years. There were 303 deaths during follow-up, of which 121 were cardiovascular. Crude mortality rates were 8.3 % for all patients, 6.8% for female patients (116/1715), and 9.7% (187/1933) for male patients. Among men, patients in the lower and higher uric acid groups had increased cardiac and overall mortality risks compared with patients in the normal uric acid groups. Similar relation was found in women but not statistically significant. After adjusting for other conventional risk factors (age, diabetes, hypertension, diuretic use and smoking), baseline uric acid level was still associated with increased risk for death from cardiovascular disease ($P=0.005$), or death from all causes ($P=0.014$)  Conclusion  Our data suggest that abnormal serum uric acid levels are independently and significantly associated with risk of cardiovascular and all-cause mortality. (J Geriatr Cardiol 2008; 5:15-20)

Key Words  epidemiology; uric acid; cardiovascular mortality ; all-cause mortality

Introduction

An epidemiological link between elevated serum uric acid and an increased cardiovascular risk has been recognized for many years.2,3 However, it has been argued that the relationship between serum urate concentration and death from cardiovascular disease may be spurious, since elevated serum uric acid is associated with many risk factors that predispose to cardiovascular disease-for example, hypertension, hyperlipidemia, diabetes, and male sex. Furthermore, urate concentration is also raised in patients with renal failure and in patients who are on diuretics-this might account for the link between urate and cardiovascular prognosis. Indeed, studies which performed multivariate analyses to examine whether urate level independently predicts poor cardiovascular prognosis have yielded conflicting results.4,7 Over recent years, there has been renewed debate about the nature of the association between elevated serum uric acid concentration and cardiovascular disease.1 This is an important question since an independent relationship between cardiac death and urate level would increase the validity of a large randomized controlled trial to test whether lowering urate with allopurinol would also lower cardiovascular mortality.

We investigated the predictive role of uric acid levels on the risk of future death from cardiovascular disease and death from all causes in 3648 Chinese patients with risk factors for cardiovascular disease.

Patients and methods

Study population

The investigation is based on a large-scale prospective epidemiological study in China. A total of 3,684 Chinese patients with two or more CV risk factors who attended the inpatients department at Tongji University Hospitals (Shanghai) and Beijing University Hospitals (Beijing) were sequentially enrolled in the study. All subjects were inpatients from the Coronary Care Unit, Intensive Care Unit. Departments of Cardiology, Endocrinology, Renal Disease, Neurology, Vascular Disease, etc, and were admitted to the hospital because of hypertension, hyperlipidemia, diabetes, acute coronary syndrome, renal disease, and other cardiovascular or metabolic diseases. All the patients were followed up for a median of 1 year. Follow-up information was obtained about cardiac death ($n=121$) and death causes not related to heart disease ($n=182$). Information about the cause of death was obtained from hospital or the relatives of the patients. The study was approved by the local ethics committee and written informed consent was obtained from all subjects.

Baseline measurements and definitions

Risk factors included obesity, smoking, diabetes,
hypertension, and lipid disorders. In all 3,684 subjects, blood was drawn under standardized conditions after an overnight fasting. Samples were centrifuged at 4,000 g for 10 minutes, divided into aliquots, and frozen at −70°C for later determination of uric acid levels (Uricase/POD Method, Boehringer Mannheim, Mannheim, Germany). Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were determined using standard laboratory techniques. The weight and height of subjects were measured while they were wearing light clothes and no shoes. Body mass index (BMI) was calculated as weight(kg)/height (m)². Obesity was defined as BMI over 30 kg/m². The presence of underlying coronary heart disease (CHD) was defined as a history of a physician-diagnosed heart attack, evidence of prior myocardial infarction by electrocardiogram and/or self-reporting of a prior coronary revascularization procedure (percutaneous coronary artery intervention [PCI] or coronary-artery bypass surgery [CABG]). Diabetes mellitus was defined on the basis of a non-fasting blood glucose level of 11.0mmol/L or greater, a fasting blood glucose level of 7.0 mmol/L or greater, or the use of insulin or an oral hypoglycemic agent. Hypertension was diagnosed in those with a history of systolic blood pressure (SBP)=140 mm Hg or diastolic blood pressure (DBP) =90 mm Hg or the current use of antihypertensive drugs to control hypertension (according to WHO criteria). Lipid disorder was defined as TC>5.7mmol/L, TG>1.7mmol/L, LDL-C>3.6mmol/L, or HDL-C<0.9mmol/L or treatment with lipid lowering agents. Participants who reported smoking at least 1 cigarette per day during the year before the examination were classified as current smokers.

### Statistical analysis

Statistical analysis was performed using SPSS 13.0 for Windows. Continuous variables are presented as mean values ;±ASD, and categorical variables are expressed as percentages (counts). Categorical variables were compared by Pearson’s chi-square test, normally distributed variables by t test. Multivariate Cox regression analysis was performed to test if urate level predicted cardiac death after adjusting for other conventional risk factors, including age, sex, diabetes, hypertension and smoking. Survival was assessed by Kaplan-Meier survival functions. A P value of <0.05 was regarded as statistically significant.

### Results

Of all the study patients, 1715(47%) were women and 1933(53%) were men. The mean age was 67.3 ;±11.4 (19 - 96) years. The median uric acid level was 322.2 ;±118.2 µmol/L. The uric acid levels of women were significantly lower than those of men (299.0 ;±111 µmol/L vs 342.7 ;±120.5 µmol/L, P <0.001). During follow-up (median 1 year) of 3648 patients, 303 patients died (121 cardiac deaths, 182 noncardiac deaths). Crude mortality rates were 8.3 % for all patients, 6.8% (116/1715) for female patients, and 9.7% (187/1933) for male patients. The baseline characteristics of the patients were shown in Table 1.

We divided the population into 3 groups: lower uric acid group (serum uric acid<268µmol/L for men and <178µmol/L for women), median uric acid group (268-488µmol/L for men and 178-387µmol/L for women), and higher uric acid group (>488µmol/L for men and >387µmol/L for women) according to the Chinese criteria. In men, the cardiac mortality rates were 5.4% for the lower uric acid group, 3.2% for the median uric acid group and 5.6% for the

### Table 1 Baseline clinical characteristics of male and female subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men(n =1933)</th>
<th>Women(n =1715)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>67 ;±12</td>
<td>68 ;±11</td>
<td>0.000</td>
</tr>
<tr>
<td>Serum uric acid level(µmol/L)</td>
<td>342.7 ;±120.5</td>
<td>299.0 ;±111</td>
<td>0.000</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>24.4 ;±3.53</td>
<td>24.4 ;±3.74</td>
<td>0.75</td>
</tr>
<tr>
<td>SBP(mm Hg)</td>
<td>138 ;±24</td>
<td>141 ;±23</td>
<td>0.04</td>
</tr>
<tr>
<td>DBP(mm Hg)</td>
<td>81 ;±13</td>
<td>80 ;±13</td>
<td>0.14</td>
</tr>
<tr>
<td>TC( mmol/L)</td>
<td>4.43 ;±1.11</td>
<td>4.86 ;±1.16</td>
<td>0.000</td>
</tr>
<tr>
<td>HDL(mmol/L)</td>
<td>1.15 ;±0.42</td>
<td>1.26 ;±0.39</td>
<td>0.000</td>
</tr>
<tr>
<td>Creatinine(µmol/L)</td>
<td>109 ;±92</td>
<td>90 ;±85</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>70.5</td>
<td>74.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetic use, %</td>
<td>36</td>
<td>42.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>27.8</td>
<td>27.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Death due to cardiac disease(%)</td>
<td>4.0</td>
<td>2.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Death of any causes(%)</td>
<td>5.6</td>
<td>4.3</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Data are expressed as percentages of patients or mean value ;±ASD; the P value is given for the comparison of men vs women.
higher uric acid group, respectively ($P<0.05$); and the all-cause mortality was 16.1%, 8.3% and 11.9%, respectively ($P<0.05$). In women, the cardiac mortality rates were 9.1% for the lower uric acid group, 2.1% for the median uric acid group and 2.8% for the higher uric acid group, respectively ($P=0.092$) and the all-cause mortality was 9.1%, 6.0% and 7.6%, respectively ($P=0.394$) (Table 2). Among men, patients in the lower and higher uric acid group had increased cardiac and overall mortality risks compared with those in the median uric acid group. Similar relation was found in women but not significant.

In fully adjusted Cox models, baseline uric acid level was associated with increased risk for death from cardiovascular disease ($P=0.005$), or death from all causes ($P=0.014$).

The relationship between the urate concentration and death from all-cause in the study patients was graphically depicted by a Kaplan–Meier survival plot shown in Fig. 1. (log rank $P=0.029$).

![Figure 1](image-url)

**Figure 1** All-cause death rate at 1 year of the three groups. Subjects with lower or higher urate concentrations showed significant increased risk of death from all-cause in the patients with high cardiovascular risk.

### Discussion

The principal finding of this study is that in patients with 2 or more conventional cardiovascular risk factors, serum urate concentration lower or higher than the median level was associated with a statistically significant increase in relative risk of cardiac death and death of any causes even after adjusting for age and other risk factors for cardiovascular disease.

Serum uric acid was first reported to be a risk factor for atherosclerosis nearly half a century ago. Several prospective studies have shown an association between baseline hyperuricemia and incident coronary heart disease, cardiovascular disease, and death. Despite the strength of these associations, uric acid has not been established as a causal risk factor for cardiovascular disease. Instead, uric acid seems inextricably linked to hypertension, dyslipidemia, and disordered glucose metabolism, which play a causal role in the pathogenesis of cardiovascular disease. These studies suggested that uric acid may be merely a marker of risk for cardiovascular disease.

In 1996, Cappuccio proposed that uric acid was an independent risk factor of atherosclerosis or hyperuricemia was merely an indirect marker of adverse outcome by reflecting the association between uric acid and other CV factors. Culleton et al. reported in 1999 data from the Framingham study concerning the role of uric acid as an independent risk factor in coronary artery disease (CAD). They found an increased risk for adverse outcome after age adjustment only for women, which was not independently associated with death from cardiovascular disease or from all causes after additional adjustment for cardiovascular disease risk factors. In a stepwise Cox model, they identified diuretic use as the covariate responsible for rendering serum uric acid a statistically nonsignificant predictor of outcomes. They concluded that uric acid does not have a causal role in the development of coronary heart disease and that any apparent association with these outcomes is probably due to the association of uric acid levels with other risk factors. In contrast to those results, in the prospective observational study with CAD patients, Bickel et al. identified uric acid as an independent risk factor for adverse outcome in patients with CAD, although the use of diuretic treatment at baseline was tested in the stepwise Cox model. These findings are supported by the results of the First National Health and Nutrition Examination Survey (NHANES I) epidemiologic follow-up studies. In NHANES I study, no associations were seen among men, but were found among women, in whom serum uric acid levels were predictive of mortality from all causes and from ischemic heart disease. In the other follow-up study with an additional 5 years of follow-up and a nearly doubled number of deaths, increased uric acid levels were found to be independently and significantly associated with risk of cardiovascular disease.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cardiovascular death</th>
<th>All-cause death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men ($n=1933$)</td>
<td>Women ($n=1715$)</td>
</tr>
<tr>
<td>Lower uric acid</td>
<td>5.4%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Median uric acid</td>
<td>3.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Higher uric acid</td>
<td>5.6%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>
diovascular death in men and women. In our population-based study in subjects with high cardiovascular risk at baseline, we found a strong and significant association between baseline serum uric acid levels and risk of both cardiovascular and all-cause mortality among men. Male patients with lower or higher baseline serum uric acid level had increased cardiac and overall mortality risks compared with patients median uric acid level. Similar relation was found in women but not statistically significant. The unexpected insignificant relation between uric acid level and mortality among women is difficult to explain and may be the result of the disparity of criteria for uric acid by sex. Another possibility is that estrogen may affect the metabolism of serum uric acid and the event-free survival of women. However, evidence supporting this hypothesis was unavailable in the current study. In other studies, the risk of urate for outcome events increased along with the increase in serum uric acid level. But we found that patients with lower and higher serum uric acid levels had similar risk of cardiac and all-cause mortality, compared with patients who had median level of serum uric acid. We presumed there are two probable reasons to explain the discrepancy between our results and findings of other studies. On the one hand, prospective studies examining the relation between serum uric acid level to incident cardiovascular events differed substantially in study design. On the other hand, the management of current cardiovascular disease at the inception of each of those previous studies has also varied considerably.

The question that remains now is why urate appears to be independently associated with cardiac death. Is urate per se harmful to the coronary vessels? Or could it be that uric acid is a marker for some other biological process that accelerates death?

A link between elevated serum urate and cardiovascular disease may arise through its non-causal relationship with insulin resistance syndromes, where cardiovascular risk is mediated by other factors. A large body of evidence shows the association between uric acid and the metabolic syndrome of insulin resistance, obesity, hypertension, and dyslipidemia. Several studies have shown an inverse relation between uric acid excretion and insulin level. Insulin has also been found to promote the tubular reabsorption of sodium. Cappuccio and colleagues reported an association of hyperuricemia with increased renal tubular sodium reabsorption, thus providing a link with hyperuricemia, hypertension, and hyperinsulinemia.

Uric acid may also be an indicator for increased oxidative stress. Xanthine oxidase, a critical enzyme in the degradation of purines to uric acid, has been shown to be an important source of superoxide free radicals. The activity of xanthine oxidase increased during ischemia and intensifies during reperfusion in coronary endothelial cells. In animals, allopurinol limited infarction size and enhanced recovery of stunned myocardium, perhaps by limiting the generation of toxic free radicals. Clinically, hyperuricaemia occurs during interruption of limb arterial flow, after coronary angioplasty, during coronary artery bypass surgery, and in other hypoxic states.

There is thus increasing data suggesting that uric acid could be independently associated with cardiovascular disease. One of the possible mechanisms by which hyperuricaemia causes vascular disease is via endothelial dysfunction. Evidence for this hypothesis comes from four different types of data. Firstly, exogenous uric acid caused endothelial dysfunction when infused directly into the human brachial artery. Secondly, endogenous uric acid levels correlated with endothelial dysfunction in populations. Thirdly, the biological plausibility of the two above findings is increased by the following observations: uric acid was found to promote low-density lipoprotein (LDL) oxidation in vitro, a key step in the progression of atherosclerosis. In addition, uric acid could stimulate granulocyte adherence to the endothelium. A consistent relationship has also been noted between elevated serum uric acid concentration and circulating inflammatory markers. Moreover, urate could be phagocytosed by endothelial cells. Furthermore, Waring et al pointed out in an interesting review which discussed uric acid as a risk factor for cardiovascular disease, that uric acid could even traverse dysfunctional endothelial cells and accumulate as crystals within atherosclerotic plaques. Fourthly, three studies already showed that xanthine oxidase inhibition normalized endothelial dysfunction. However, allopurinol produces other non-urate effects which might be beneficial, i.e., allopurinol might be beneficial because of two distinct effects: it reduces uric acid per se and it also reduces oxidative stress because an ancillary property of xanthine oxidase is to make superoxide anions which normally degrade vascular nitric oxide. The fact that urate predicted cardiac mortality and the fact that allopurinol improved endothelial dysfunction made allopurinol an attractive possibility distinctly worthy of further investigation. There is evidence that intravenous allopurinol improved cardiac function post coronary bypass surgery.

Our findings suggest that uric acid is an important cardiovascular risk factor. Additional studies are required to assess whether the regulation of uric acid levels can actually reduce the risk of cardiovascular disease.

References


40. Duff GW, Atkins E, Malawista SE. The fever of gout: urate crystals activate endogenous pyrogen production from human


