The relationship between serum levels of uric acid and prognosis of infection in critically ill patients

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INTRODUCTION

Uric acid is an end product of the metabolism of purine through the action of xanthine dehydrogenase or xanthine oxidase. It is present in blood and excretes in the urine. Normal levels of blood uric acid range from 0.09 to 0.42 mmol/L in adults, with slightly higher values for elderly patients. Since the fifties of last century, it has been found that the high level of serum uric acid is associated with a variety of illnesses including hypertension, atherosclerosis, vascular anomaly, hyperinsulinemia, and renal insufficiency. There are many studies on the correlation between serum uric acid and outcomes of patients. However, dispute over this issue still exists among different authors, because the results are influenced by many factors such as gender and use of diuretics. However, consensus has been reached in respect of hyperuricemia resulted from disturbance of purine metabolism, abnormal metabolism of energy and impairment of renal function for excretion of uric acid. When uric acid accumulates in blood vessels and deposits...
on the endothelium of vessels, the release of vasorelaxation factors is hampered,\[1\] and vascular contraction is interfered, leading to a series of pathophysiological process and dysfunction of internal organs especially the kidney. Moreover, serum uric acid usually precipitates inflammatory reaction under certain circumstances, and interferes the adhesion and aggregation of blood platelets onto the endothelium of blood vessels. Meanwhile, the serum level of uric acid usually reflects the activity of xanthine oxidase. Probably, uric acid itself is a kind of non-enzymatic antioxidant in a large proportion in blood. As an indicator for evaluating the oxidation-antioxidation status of organisms, uric acid possesses protective effect on vitamin C. Someone believes that low level of serum uric acid is not favorable to the outcomes of illness.\[16\]

A majority of patients in the intensive care unit usually have experienced a variety of pathogenic courses such as ischemia-reperfusion injury, inflammation and dysfunction of blood coagulation. Uric acid may be a factor involving in the above mentioned pathogenic courses, and may have potential value for the assessment of changes in clinical settings and prognosis of illness. For this reason, a retrospective investigation was carried out to explore the variation of serum uric acid levels in ICU patients with infection and the significance of serum uric acid in respect of prognosis of infection as well as the correlation between uric acid and many diseases.

**RESULTS**

Demographical and clinical data of patients

Among the 471 patients, 308 were male and 163 were female, with a mean age of 56.73±20.135 years (median 57 years). The average hospital stay was 29.69 days (median 20.00 days). Average APACHE II score was 14.68±6.136 (median 15). The underlying diseases, sites of infection and prognosis of the patients are listed in Table 1. Within 24 hours after admission, the major relevant laboratory results were as follows: uric acid 0.232±0.131 mmol/L (median 0.199), serum creatinine 77.540±76.823 μmol/L (median 59.000), blood urea nitrogen 7.139±5.827 mmol/L (median 5.600).

Correlation between uric acid and creatinine, blood urea nitrogen

Serum levels of uric acid correlated with both creatinine ($F=159.470, P<0.001$) and blood urea nitrogen ($F=165.059, P<0.001$) in linear pattern (Figures 1 and 2).

Correlation between uric acid and gender, underlying diseases

Patients were divided into two groups for comparison as per gender and the existence of underlying diseases, including hypertension, diabetes mellitus, coronary heart disease, cerebral infarction, neoplasm, pneumonia, compromised renal function, central nervous system infection and trauma. Student's $t$ test was used to compare the difference in distribution of SUA values in patients.

**METHODS**

From January 2003 through April 2010, the data of 471 patients with infection who had been admitted into ICU of Huashan Hospital Affiliated to Fudan University, Shanghai were collected. The inclusion criteria of patients were those with solitary or multiple sites of infection diagnosed upon admission or during hospital stay. Site of infection, underlying diseases, prognosis assessment, APACHE II score, length of hospital stay, and serum levels of uric acid, creatinine and blood urea nitrogen (BUN) detected within 24 hours after admission were documented.

The average value of serum uric acid was expressed as mean±SD. The different levels of serum uric acid were graded into groups. Correlation between serum uric acid and serum creatinine, blood urea nitrogen, length of hospital stay, APACHE II score was analyzed by using SPSS version 15.0 (SPSS Inc., USA). The difference in distribution of SUA values between different groups of patients was studied by using Student's $t$ test. The Chi-square test was used to compare the prognosis of patients among different groups.

**Table 1. Demographical and clinical data of patients**

<table>
<thead>
<tr>
<th>Items</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying disorders</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>95 (20.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41 (8.7)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>17 (3.6)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>59 (12.5)</td>
</tr>
<tr>
<td>Trauma</td>
<td>126 (26.6)</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>19 (4.0)</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Site of infection</td>
<td></td>
</tr>
<tr>
<td>Pneumonia/severe</td>
<td>408/23 (86.6/4.9)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>23 (4.88)</td>
</tr>
<tr>
<td>Central nervous system infection</td>
<td>60 (12.7)</td>
</tr>
<tr>
<td>Hepatobiliary system infection</td>
<td>8 (1.70)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>6 (1.27)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>4 (0.64)</td>
</tr>
<tr>
<td>Septicemia</td>
<td>19 (4.03)</td>
</tr>
<tr>
<td>Single site infection</td>
<td>416 (88.32)</td>
</tr>
<tr>
<td>Multiple sites infection</td>
<td>55 (11.68)</td>
</tr>
<tr>
<td>Prognosis</td>
<td></td>
</tr>
<tr>
<td>Completely healed</td>
<td>36 (7.6)</td>
</tr>
<tr>
<td>Improved</td>
<td>312 (66.2)</td>
</tr>
<tr>
<td>Remained unchanged</td>
<td>32 (6.8)</td>
</tr>
<tr>
<td>Dead</td>
<td>90 (19.1)</td>
</tr>
</tbody>
</table>
with or without certain characteristics. No difference was found regarding gender ($t=1.205, P=0.229$), coronary heart disease ($t=-1.450, P=0.148$), neoplasm ($t=-0.452, P=0.651$) and pneumonia ($t=-1.940, P=0.053$). The following diseases affected the distribution of uric acid values: hypertension ($t=-3.084, P=0.002$), diabetes mellitus ($t=-2.487, P=0.013$), cerebral infarction ($t=-3.061, P=0.002$), compromised renal function ($t=-4.547, P<0.001$), infection of central nervous system ($t=5.096, P<0.001$) and trauma ($t=2.875, P=0.004$).

**Relationship between uric acid level and prognosis of infection**

Patients were divided into different groups according to their SUA levels in step of 0.1 mmol/L for comparison of prognosis of infection between different groups. There was association between SUA level and prognosis of infection among different groups ($\chi^2=74.455, P=0.018$) (Figure 3). When the patients with compromised renal function, trauma, erythrocytosis, hypertension, diabetes mellitus and central nervous system infection were excluded, the correlation between serum level of uric acid and prognosis of infection disappeared ($\chi^2=60.892, P=0.100$) (Figure 4).

**DISCUSSION**

Studies$^{[4-9, 11-15, 19-20]}$ have shown that uric acid is an indicator of prognosis of many diseases including cardiovascular disorders, renal insufficiency, metabolic syndrome and diabetes mellitus. In a cohort of patients followed for 7.5 years, their serum uric acid was found to be an independent indicator of mortality. Moreover, the risk of death increased by 39% with an increase of 0.6 mmol/L in uric acid.$^{[15]}$ The present investigation did not show any direct correlation between the levels of serum uric acid and prognosis of infection. The possible reasons might be: 1) In a general ICU like ours, the...
patients admitted usually contracted more than one illness and were treated with different kinds of medicine which might lead to variation in uric acid since there must be interactions between different diseases and medications. The patients enrolled in the present study were different from those reported in the literature. 2) Under acute stress, disturbance of the internal milieu might alter the level of serum uric acid in patients with a given illness, which could result in a unique pattern of uric acid variation. In healthy subjects, the variation of levels of serum uric acid usually complies with normal distribution, whereas the result of our study showed a trend of deviation from normal distribution. It was likely due to the lower level of serum uric acid in those patients than that in the healthy subjects. The lower levels of uric acid in those patients might be a result of malnutrition and antioxidant consumption in the early stage of infection. The present study showed a linear correlation between serum uric acid and BUN and creatinine, suggesting the serum level of uric acid was influenced by many factors such as protein metabolism and renal function. The present study also showed that the distribution of serum uric acid levels revealed remarkable changes in patients with hypertension, diabetes mellitus, cerebral infarction, compromised renal function, central nervous system infection and trauma, whereas there were no noticeable changes in distribution of uric acid levels in patients with coronary heart diseases and neoplasm, which was in accordance with what was found in the literature.

Though the mechanism of variation in serum levels of uric acid in critically ill patients with infection is not fully understood, it is definitely due either to increase in uric acid production or to decrease in uric acid excretion, or due to both. In case of severe infection, ischemia and hypoxemia of many organs activate xanthine oxidase in the capillary endothelium to act upon xanthine and hypoxanthine and convert them into uric acid. Thus uric acid production is increased. Meanwhile, renal function is often compromised by severe infection leading to decrease in excretion of uric acid and further accumulation of uric acid in blood. Many studies reported that the serum levels of uric acid could reflect the severity and prognosis of sepsis. It was proved that hyperuricemia enhanced the production of pro-inflammatory mediators and in turn intensified the effect of endotoxin, which resulted in further exacerbation of systemic inflammatory response. Also the variation of serum levels of uric acid in septic patients was in a pattern of decrease and then in a pattern of increase. The more severe the infection was, the worse the internal milieu became. As a result, there was dysfunction of organs including impaired renal excretion and accumulated lactic acid that could compete with uric acid removal from the kidney, and the serum levels of uric acid increased gradually. Such hyperuricemia could no longer protect against oxidation stress. The non-survivors had a higher level of serum uric acid than the survivors. Similar phenomenon was found in the present study: the infection of central nervous system was closely related to the high level of serum uric acid, and the higher the level of serum uric acid, the poorer the prognosis. Renal insufficiency, trauma and infection themselves might cause hyperuricemia and death. When those confounding factors were excluded, the correlation between serum uric acid and prognosis of infection disappeared (P=0.100). In the present study, the observed unfavorable effect of infection on the prognosis might be attributed to impaired renal function, trauma and infection. Therefore, it could be postulated that the serum level of uric acid might be an indirect indicator of impaired renal function and oxidation stress, rather than a direct predictor for the prognosis of infection. This finding is really supported by other studies.

Certainly, the present study had some drawbacks. 1) As a retrospective analysis of data from ICU patients only, the evidence was not so solid as that in a prospective study, leading to limitation of extrapolation. 2) As an observation investigation, it was impossible to establish cause-effect relationship. 3) Since those patients usually had various underlying disorders, it was hard to perform stratification during analysis.

In summary, although the serum levels of uric acid vary markedly in many disorders such as hypertension, diabetes mellitus, cerebral infarction, renal insufficiency, central nervous system infection and trauma, there is no direct correlation between serum levels of uric acid and the prognosis of infection. The assessment of infection and prediction of prognosis for ICU patients are always major concerns for clinicians. Despite the fact that no conclusion could be made regarding the relation between serum uric acid and the prognosis of severe infection, the pathophysiological changes caused by uric acid during sepsis do exist and have been further confirmed. The potential value of intervention is still unknown. This is an area that warrants further basic and clinical research.

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indirectly to the subject of this article.

Contributors: Zhu HC proposed the study, and wrote the first draft. All authors contributed to the design and interpretation of the study and to further drafts.

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