Correlation study between blood uric acid levels and disease severity in patients with type 2 diabetes mellitus and carotid atherosclerosis

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Objective: To study the correlation between blood uric acid levels and disease severity in patients with type 2 diabetes mellitus and carotid atherosclerosis. Methods: A total of 106 patients diagnosed with type 2 diabetes in our hospital between March 2014 and February 2016 were selected as the T2DM group of the study, carotid ultrasonography was conducted to assess the conditions of carotid atherosclerosis, and 60 healthy volunteers receiving physical examination in our hospital during the same period were selected as the control group of the study. Serum was collected to determine the content of uric acid, endothelial injury markers, inflammatory mediators and lipid metabolism indexes. Results: Blood uric acid content of T2DM group was significantly higher than that of control group and blood uric acid content of T2DM group with carotid atherosclerosis was significantly higher than that of those without carotid atherosclerosis; serum ET-1, sTM, sEPCR and vWF content of high-quartile and middle-quartile patients were significantly higher than those of low-quartile patients while NO content were significantly lower than that of low-quartile patients; serum ET-1, sTM, sEPCR, vWF, NF-κB, TNF-α, IL-1β, IL-18, LPa, ox-LDL and ApoB content of high-quartile patients were significantly higher those of middle-quartile patients while NO and ApoA1 content were significantly lower than those of middle-quartile patients. Conclusion: Elevated serum blood uric acid levels in patients with type 2 diabetes mellitus can lead to the occurrence of carotid atherosclerosis, and the molecular changes involved in the process include the aggravation of endothelial injury, inflammation and lipid metabolism disorders.

1. Introduction

Type 2 diabetes is the most common endocrine disease in our country, patients are with elevated blood glucose levels and insulin resistance, and it will increase the risk of macroangiopathy and microvascular complications[1,2]. Carotid atherosclerosis is the common macroangiopathy in patients with type 2 diabetes, it is also the window that reflects the coronary artery and intracranial artery lesions, and both abnormal lipid and homocysteine metabolism and endothelial injury caused by inflammation and oxidative stress are associated with the formation of atheromatous plaque[3,4]. Studies in recent years have confirmed that hyperuricemia is a newly discovered risk factor for cardiocerebrovascular events[5,6], but the relationship between blood uric acid metabolism and carotid atherosclerosis in patients with type 2 diabetes mellitus has not been clearly reported yet. In the following study, the correlation between blood uric acid levels and disease severity in patients with type 2 diabetes mellitus and carotid atherosclerosis was analyzed.

2. Subjects and methods

2.1 Research subjects
A total of 106 patients diagnosed with type 2 diabetes in our hospital between March 2014 and February 2016 were selected as the T2DM group of the study, all patients were diagnosed with type 2 diabetes through sugar tolerance test, carotid ultrasonography was conducted to confirm the conditions of carotid atherosclerosis, and carotid intima-media thickness >1.2 mm was defined as carotid atherosclerosis. 60 healthy volunteers receiving physical examination in our hospital during the same period were selected as the control group of the study and excluded of carotid atherosclerosis through carotid ultrasonography. T2DM group included 65 male cases and 41 female cases that were (46.4±6.9) years old; control group included 36 male cases and 24 female cases that were (44.9±6.3) years old. The two groups of patients were not significantly different in general information (P>0.05).

2.2 Serum specimen collection and index detection methods

5ml of cubital venous blood was collected from T2DM group after diagnosis and centrifuged to get serum, then full–automatic biochemical analyzer was used to determine uric acid (UA), lipoprotein a (LPa), apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) content, and enzyme–linked immunoassortment assay kits were used to determine endothelin–1 (ET–1), nitric oxide (NO), soluble thrombaxone (sTM), soluble endothelial cell protein C receptor (sEPCR), von Willebrand factor (vWF), nuclear transcription factor–κ B (NF–κ B), tumor necrosis factor–α (TNF–α), interleukin–1β (IL–1β), IL–18 and oxidized low–density lipoprotein (ox–LDL) levels.

2.3 Statistical methods

SPSS 16.0 software was used to input and analyze data, measurement data analysis between two groups was by t test, measurement data analysis among three groups was by variance analysis and P<0.05 indicated statistical significance in differences.

3. Results

3.1 Blood uric acid content in patients with T2DM and carotid atherosclerosis

Blood uric acid content of T2DM group was (302.52±41.25) μmol/L and blood uric acid content of control group was (163.55±22.42) μmol/L. After t test, blood uric acid content of T2DM group was significantly higher than that of control group, t=8.583, P<0.05. Blood uric acid content of T2DM group with carotid atherosclerosis was (389.52±45.82) μmol/L, blood uric acid content of T2DM group without carotid atherosclerosis was (224.52±35.49) μmol/L, and variance analysis showed that blood uric acid content of T2DM group both with carotid atherosclerosis and without carotid atherosclerosis were significantly higher than that of control group, and blood uric acid content of T2DM group with carotid atherosclerosis was significantly higher than that of those without carotid atherosclerosis.

3.2 Effect of different levels of blood uric acid levels on endothelial injury in patients with T2DM

Patients with T2DM were grouped according to the quartile of blood uric acid levels and divided into low–quartile, middle–quartile and high–quartile, and analysis of serum endothelial injury molecules ET–1, NO, sTM, sEPCR and vWF was as follows: serum ET–1, sTM, sEPCR and vWF content of high–quartile and middle–quartile patients were significantly higher than those of low–quartile patients while NO content were significantly lower than that of low–quartile patients; serum ET–1, sTM, sEPCR and vWF content of high–quartile patients were significantly higher than those of middle–quartile patients while NO content was significantly lower than that of middle–quartile patients. Differences in pair–wise comparison of serum ET–1, NO, sTM, sEPCR and vWF content were statistically significant among patients with low–quartile, middle–quartile and high–quartile blood uric acid (P<0.05).

3.3 Effect of different levels of blood uric acid levels on inflammatory factors in patients with T2DM

Analysis of serum inflammatory factors NF–κ B, TNF–α, IL–1β and IL–18 content of T2DM patients with low–quartile, middle–quartile and high–quartile blood uric acid was as follows: serum NF–κ B, TNF–α, IL–1β and IL–18 content of high–quartile and middle–quartile patients were significantly higher than those of low–quartile patients; serum NF–κ B, TNF–α, IL–1β and IL–18 content of high–quartile patients were significantly higher than those of middle–quartile patients. Differences in pair–wise comparison of serum NF–κ

Table 1.
Comparison of serum endothelial injury molecules among T2DM patients with different blood uric acid levels (pg/mL).

<table>
<thead>
<tr>
<th>UA levels</th>
<th>n</th>
<th>ET–1</th>
<th>NO</th>
<th>sTM</th>
<th>sEPCR</th>
<th>vWF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low quartile</td>
<td>33</td>
<td>7.51±0.84</td>
<td>35.14±5.61</td>
<td>48.65±6.14</td>
<td>189.34±22.15</td>
<td>82.35±9.41</td>
</tr>
<tr>
<td>Middle quartile</td>
<td>41</td>
<td>10.42±1.77&lt;0.05</td>
<td>22.77±3.28&lt;0.05</td>
<td>63.52±8.92&lt;0.05</td>
<td>276.41±32.46&lt;0.05</td>
<td>135.23±18.69&lt;0.05</td>
</tr>
<tr>
<td>High quartile</td>
<td>32</td>
<td>15.48±2.14&lt;0.05</td>
<td>14.62±1.95&lt;0.05</td>
<td>81.45±9.35&lt;0.05</td>
<td>386.55±41.48&lt;0.05</td>
<td>223.42±31.49&lt;0.05</td>
</tr>
</tbody>
</table>

*: compared with patients with low–quartile blood uric acid content, P<0.05; ▲: compared with patients with middle–quartile blood uric acid content, P<0.05.
k B, TNF- α, IL-1 β and IL-18 content were statistically significant among patients with low–quartile, middle–quartile and high–quartile blood uric acid (P<0.05).

3.4 Effect of different levels of blood uric acid levels on blood lipid metabolism in patients with T2DM

Analysis of serum lipid metabolism indexes LPa, ox–LDL, ApoA1 and ApoB among patients with low–quartile, middle–quartile and high–quartile blood uric acid was as follows: serum LPa, ox–LDL and ApoB content of high–quartile and middle–quartile patients were significantly higher than those of low–quartile patients while ApoA1 content were significantly lower than that of low–quartile patients; serum LPa, ox–LDL and ApoB content of high–quartile patients were significantly higher than those of middle–quartile patients while ApoA1 content was significantly lower than that of middle–quartile patients. Differences in pair–wise comparison of serum LPa, ox–LDL, ApoA1 and ApoB among patients with low–quartile, middle–quartile and high–quartile blood uric acid (P<0.05).

4. Discussion

Hyperuricemia is a new independent risk factor for cardio–cerebrovascular events discovered in recent years, and excessively accumulated uric acid in the blood circulation will increase the occurrence risk of atherosclerosis through a variety of links(7,8). The pathological features of atherosclerosis process are abnormal lipid metabolism and vascular endothelial injury under the action of inflammatory factors and oxidative stress products, and uric acid will cause impact on inflammation, lipid metabolism and processes. Studies have shown that hyperuricemia can aggravate the inflammatory response and increase the release of inflammatory mediators, it can also promote the generation of oxygen free radical and cause LDL modification into ox–LDL, and a variety of inflammation and oxidative stress products can cause endothelial injury and aggravate atherosclerosis[9,10]. In the study, the analysis of the blood uric acid content between patients with T2DM and health subjects showed that blood uric acid content of T2DM group was significantly higher than that of control group. This means that the uric acid metabolism is abnormal and blood uric acid content abnormally increases in patients with T2DM. Further analysis of the relationship between carotid atherosclerosis and blood uric acid content in patients with T2DM showed that the blood uric acid content of T2DM group with carotid atherosclerosis was significantly higher than that of those without carotid atherosclerosis. This means that the elevated blood uric acid levels will cause carotid atherosclerosis in patients with T2DM.

Endothelial injury caused by hyperuricemia is an important part that increases carotid atherosclerosis, and endothelial injury is accompanied by the change of ET–1, NO, sTM, sEPCR, vWF and other biochemical indicators. sTM, sEPCR and vWF are the specific molecules that reflect endothelial cell damage, sTM and sEPCR are the soluble fragments produced in the process of endothelial cell injury, vWF is the glycoprotein with adhesion function in endothelial cells, and the higher the content of these molecules in serum, the more severe the endothelial damage[11,12]. ET–1and NO is a pair of molecules regulating vasomotion, ET–1 has vasoconstrictor effect while NO has vasodilator effect, and they mediate endothelial injury and endothelial protection effect respectively[13]. In order to determine whether the increase of blood uric acid levels in patients with T2DM can cause endothelial injury, endothelial injury–related biochemical indexes in serum were detected and analyzed in the study, and the results showed that the higher the blood uric acid levels in patients with T2DM, the higher the serum ET–1, sTM, sEPCR and vWF content and the lower the NO content. This means that the increase of blood uric acid levels in patients with T2DM is directly related to endothelial injury, and the endothelial injury marker molecules ET–1, sTM, sEPCR and vWF content significantly increase while endothelial protection molecule NO content significantly decreases.

Table 2.
Comparison of serum inflammatory mediators among T2DM patients with different blood uric acid levels (pg/mL).

<table>
<thead>
<tr>
<th>UA levels</th>
<th>n</th>
<th>NF–κ B (ng/mL)</th>
<th>TNF–α (ng/mL)</th>
<th>IL–1 β (pg/mL)</th>
<th>IL–18 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low quartile</td>
<td>33</td>
<td>2.58±0.33</td>
<td>1.04±0.12</td>
<td>47.69±6.14</td>
<td>146.54±17.97</td>
</tr>
<tr>
<td>Middle quartile</td>
<td>41</td>
<td>4.13±0.56</td>
<td>1.57±0.18</td>
<td>55.36±6.65</td>
<td>183.34±22.63</td>
</tr>
<tr>
<td>High quartile</td>
<td>32</td>
<td>5.96±0.76</td>
<td>2.26±0.30</td>
<td>71.35±8.48</td>
<td>241.58±31.49</td>
</tr>
</tbody>
</table>

: compared with patients with low–quartile blood uric acid content, P<0.05; ▲: compared with patients with middle–quartile blood uric acid content, P<0.05.

Table 3.
Comparison of lipid metabolism indexes among T2DM patients with different blood uric acid levels.

<table>
<thead>
<tr>
<th>UA levels</th>
<th>n</th>
<th>LPa (μ g/mL)</th>
<th>ox–LDL (pg/mL)</th>
<th>ApoA1 (mg/mL)</th>
<th>ApoB (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low quartile</td>
<td>33</td>
<td>189.42±22.31</td>
<td>363.59±47.49</td>
<td>1.48±0.19</td>
<td>1.42±0.18</td>
</tr>
<tr>
<td>Middle quartile</td>
<td>41</td>
<td>263.56±32.59</td>
<td>492.52±62.47</td>
<td>1.14±0.13</td>
<td>1.85±0.23</td>
</tr>
<tr>
<td>High quartile</td>
<td>32</td>
<td>347.58±41.47</td>
<td>624.23±78.94</td>
<td>0.79±0.09</td>
<td>2.31±0.34</td>
</tr>
</tbody>
</table>

: compared with patients with low–quartile blood uric acid content, P<0.05; ▲: compared with patients with middle–quartile blood uric acid content, P<0.05.
Inflammation and abnormal lipid metabolism is an important part that causes atherosclerosis, and uric acid has regulating effect on inflammation and lipid metabolism. Nuclear transcription factor–κ B (NF–κ B) is an important transcription factor that regulates inflammatory mediator expression, and can start the expression of a variety of inflammatory factors such as TNF–α, IL–1β and IL–18, thus increasing the inflammation in arterial intima and atheromatous plaque, and accelerating the course of atherosclerosis[14,15]. In the study, the analysis of the content of inflammatory mediators in T2DM patients with different blood uric acid levels showed that the higher the blood uric acid levels in patients with T2DM, the higher the serum NF–κ B, TNF–α, IL–1β and IL–18 content. This means that the increase of blood uric acid levels in patients with T2DM is closely related to the excessive release of inflammatory mediators. Abnormal lipid metabolism can cause lipid to deposit in artery intima and form plaque, and the lipid components in plaque include LPa and ox-LDL; ApoA1 and ApoB are the important components carrying lipids, ApoA1 can carry the lipid in adjacent tissue to the liver and promote the lipid metabolism, and ApoB carries the lipid compositions, especially the LDL to adjacent tissue and is conducive to the oxidative modification of LDL into ox–LDL[16,17]. In the study, the analysis of the content of inflammatory mediators in T2DM patients with different blood uric acid levels showed that the higher the blood uric acid levels in patients with T2DM, the higher the serum LPa, ox–LDL and ApoB content and the lower the ApoA1 content. This means that the increase of blood uric acid levels in patients with T2DM is directly related to lipid metabolism disorders.

To sum up, elevated serum blood uric acid levels in patients with type 2 diabetes mellitus can lead to the occurrence of carotid atherosclerosis, and the molecular changes involved in the process include the aggravation of endothelial injury, inflammation and lipid metabolism disorders.

References


