Correlation between serum sCD40L and sCD40 levels with disease progression and plaque property change in patients with ACS

Fa-Bing Zhao, Wei Yao
ICU, the Second People’s Hospital of Yichang Hubei Province, Yichang 443000, China

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ABSTRACT

Objective: To study the relationship of serum soluble CD40 (sCD40), soluble CD40 ligand (sCD40L) levels with disease progression and plaque property change in patients with acute coronary syndrome (ACS).

Methods: 156 patients diagnosed with acute coronary syndrome in our hospital between May 2014 and December 2015 were selected as the ACS group of the study, 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 levels of sCD40L, sCD40 as well as inflammation-related factors and plaque stability-related molecules.

Results: Serum sCD40 and sCD40L levels of ACS group were significantly higher than those of control group (P<0.05), serum sCD40 and sCD40L levels of non-ST-elevation myocardial infarction (NSTEMI) patients and ST-elevation myocardial infarction (STEMI) patients in ACS group were significantly higher than those of UAP group (P<0.05), and serum sCD40 and sCD40L levels of STEMI patients were significantly higher than those of NSTEMI patients (P<0.05); serum inflammation-related factors hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8) and IL-18 as well as plaque stability-related molecules matrix metalloproteinase 2 (MMP2), MMP9, lysophosphatidic acid (LPA) and angiopoietin-like protein 2 (Angptl2) levels of ACS group were significantly higher than those of control group (P<0.05) and positively correlated with sCD40L and sCD40 levels.

Conclusions: Serum sCD40L and sCD40 levels abnormally increase in patients with ACS and are closely related to the inflammatory cascade activation and plaque property change during disease progression.

1. Introduction

Acute coronary syndrome (ACS) is a common disease of cardiovascular system, coronary atheromatous plaque formation and property change is the pathological physiological basis of ACS, and ACS includes unstable angina pectoris (UAP), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) according to the degree of coronary lumen obstruction caused by atheromatous plaque from light to severe. During the UAP progression to NSTEMI and STEMI, inflammation is the important change throughout the various pathological links, and proinflammatory cytokines, chemokines, adhesion molecules and other inflammation-regulating molecules are associated with the development and change of ACS[1,2]. CD40 and its ligand CD40L are the important molecules that regulate inflammation and activate platelets[3]. In order to define the relationship between CD40/CD40L and the occurrence as well as development of ACS, the relationship of serum sCD40L and sCD40 levels with ACS progression and plaque property change was analyzed in the following study.

2. Materials and methods

2.1. Research subjects

156 patients diagnosed with acute coronary syndrome in our hospital between May 2014 and December 2015 were selected as the ACS group of the study, all patients were clearly diagnosed
with ACS after coronary angiography or percutaneous coronary intervention, 65 patients were with UAP, 49 patients were with NSTEMI and 42 patients were with STEMI, 93 patients were male and 63 patients were female, and they were 55–74 years old; 60 healthy volunteers receiving physical examination in our hospital during the same period were selected as the control group of the study, 38 patients were male and 22 patients were female, and they were 52–76 years old. The two groups of subjects were not significantly different in general information (P>0.05).

2.2. Serum sample collection methods

5 mL of peripheral venous blood sample was collected from ACS group immediately after they were admitted to hospital, 5 mL of peripheral venous blood sample was collected from the control group during physical examination, the blood samples were let stand at room temperature for 30 min, then placed in the centrifuge and centrifuged for 10 min at 3 000 r/min, and the upper serum was separated, transferred into the new EP tube and then stored in a -80 °C refrigerator.

2.3. Serum index detection methods

Serum samples were collected and thawed at 4 °C, and then enzyme-linked immunosorbent assay kits were to determine soluble CD40 (sCD40), soluble CD40 ligand (sCD40L), hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), interleukin-18 (IL-18), matrix metalloproteinase 2 (MMP2), MMP9, lysophosphatide acid (LPA) and angiopoietin-like protein 2 (Angptl2) levels. All the steps were in strict accordance with the kit instructions.

2.4. Statistical analysis

SPSS20.0 was used to input and analyze data, measurement data analysis between groups was by t test, measurement data analysis among groups was by variance analysis and P<0.05 indicated statistical significance in differences.

3. Results

3.1. Serum sCD40 and sCD40L levels

Analysis of serum sCD40 and sCD40L between ACS group and control group is shown in Table 1: serum sCD40 and sCD40L levels of ACS group were significantly higher than those of control group, and differences in sCD40 and sCD40L levels were statistically significant between the two groups (P<0.05); analysis of serum sCD40 and sCD40L among patients with different disease severity within ACS group is shown in Table 2: serum sCD40 and sCD40L levels of NSTEMI patients and STEMI patients were significantly higher than those of UAP group, serum sCD40 and sCD40L levels of STEMI patients were significantly higher than those of NSTEMI patients, and differences in pair-wise comparison of serum sCD40 and sCD40L levels were statistically significant among patients with different disease severity within ACS group (P<0.05).

### Table 1
Comparison of serum sCD40 and sCD40L levels between ACS group and control group (x±s).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>sCD40</th>
<th>sCD40L</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS group</td>
<td>156</td>
<td>42.69±6.69</td>
<td>27.51±3.46</td>
</tr>
<tr>
<td>Control group</td>
<td>60</td>
<td>14.52±1.76</td>
<td>6.79±0.89</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>15.918</td>
<td>22.597</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Table 2
Comparison of serum sCD40 and sCD40L levels among patients with different disease severity within ACS group (x±s).

<table>
<thead>
<tr>
<th>ACS severity</th>
<th>n</th>
<th>sCD40</th>
<th>sCD40L</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAP patients</td>
<td>65</td>
<td>22.67±3.97</td>
<td>14.21±1.86</td>
</tr>
<tr>
<td>NSTEMI patients</td>
<td>49</td>
<td>37.69±5.68</td>
<td>24.28±3.26</td>
</tr>
<tr>
<td>STEMI patients</td>
<td>42</td>
<td>58.14±8.93</td>
<td>38.19±4.68</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>13.589</td>
<td>16.320</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

: compared with UAP patients, P<0.05; : compared with NSTEMI patients, P<0.05.

3.2. Serum inflammation–related factor levels

Analysis of serum inflammation-related factors hs-CRP, TNF-α, IL-8 and IL-18 between ACS group and control group is shown in Table 3: serum hs-CRP, TNF-α, IL-8 and IL-18 levels of ACS group were significantly higher than those of control group, and differences in hs-CRP, TNF-α, IL-8 and IL-18 levels were statistically significant between the two groups (P<0.05). Correlation analysis between sCD40L as well as sCD40 levels and inflammation-related factor levels is as follows: serum sCD40L and sCD40 levels were positively correlated with hs-CRP, TNF-α, IL-8 and IL-18 levels.

### Table 3
Comparison of serum inflammation-related factor levels between ACS group and control group (x±s).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>hs-CRP (mg/L)</th>
<th>TNF-α (μg/L)</th>
<th>IL-8 (μg/L)</th>
<th>IL-18 (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS group</td>
<td>156</td>
<td>27.85±3.76</td>
<td>136.67±16.72</td>
<td>64.86±9.38</td>
<td>49.14±6.71</td>
</tr>
<tr>
<td>Control group</td>
<td>60</td>
<td>5.62±0.77</td>
<td>42.57±6.78</td>
<td>17.93±2.67</td>
<td>22.14±3.47</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>26.584</td>
<td>18.598</td>
<td>13.589</td>
<td>16.320</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
3.3. Serum plaque stability–related molecule levels

Analysis of serum plaque stability-related molecules MMP2, MMP9, LPA and Angptl2 between ACS group and control group is shown in Table 4: serum MMP2, MMP9, LPA and Angptl2 levels of ACS group were significantly higher than those of control group, and differences in MMP2, MMP9, LPA and Angptl2 levels were statistically significant between the two groups \((P<0.05)\). Correlation analysis between sCD40L as well as sCD40 levels and plaque stability-related molecule levels is as follows: serum sCD40L and sCD40 levels were positively correlated with MMP2, MMP9, LPA and Angptl2 levels.

4. Discussion

Coronary artery atheromatous plaque formation and plaque property change is the pathophysiological basis of ACS, and plaque property change could lead to local plaque rupture, platelet activation and thrombosis, which cause the coronary lumen stenosis and lead to UAP, NSTEMI and STEMI[4]. In the development and change of ACS, the cascade activation of inflammatory response is in the each link, and the plaque formation and rupture, platelet activation and thrombosis are all associated with the excessive synthesis and infiltration of a variety of inflammatory media[5,6]. However, the key molecules that regulate the cascade activation of inflammatory response in patients with ACS remain unknown. CD40L is type 11 transmembrane protein in tumor necrosis factor superfamily, it is abundantly expressed on mononuclear macrophage, vascular endothelium and smooth muscle cell surface, and it can be combined with CD40L and then regulate immune response and inflammatory reaction\([7,8]\). In the study, analysis of serum sCD40L and sCD40 levels in patients with ACS showed that serum sCD40 and sCD40L levels of ACS group were significantly higher than those of control group \((P<0.05)\). This means that the elevated serum sCD40L and sCD40 levels are associated with the occurrence of ACS. Further analysis of serum sCD40L and sCD40 levels of patients with different disease severity within ACS group showed that serum sCD40 and sCD40L levels of NSTEMI patients and STEMI patients in ACS group were significantly higher than those of UAP group \((P<0.05)\), and serum sCD40 and sCD40L levels of STEMI patients were significantly higher than those of NSTEMI patients \((P<0.05)\). This means that the elevated serum sCD40L and sCD40 levels are associated with the development and change of ACS.

The SCD40L in blood circulation is the trimeric peptide fragment of CD40L, and its combination with the CD40L on mononuclear macrophage, vascular endothelium and smooth muscle cell surface can directly trigger inflammation, which, on the one hand, can activate the secretion of a variety of inflammatory mediators, and mediate the inflammation in plaques through the infiltrated mononuclear macrophages in local plaque\([9]\), and on the other hand, can promote inflammatory cell infiltration to local plaque, and thus causes the cascade amplification of inflammatory response in the plaques\([10,11]\). The cascade activation and amplification of inflammatory response have played a crucial role in the progression of ACS, and in order to define the regulating effect of sCD40L and sCD40 in ACS patients on inflammation, serum inflammatory medium levels in ACS patients as well as their correlation with sCD40L and sCD40 were analyzed in the study. Hs-CRP and TNF-\(\alpha\) are the most common inflammatory media to evaluate the degree of inflammation, and they participate in each process of the inflammatory response; IL-8 is a proinflammatory medium with endogenous chemokine active, it can recruit inflammatory cells in local area and amplify inflammatory reaction, and it can also promote the interaction between blood coagulation factors and cytokines and promote thrombosis; IL-18 plays a regulatory role in both inflammation and immune response, and it can on the one hand, induce lymphocytes and natural killer cells to secrete interferon, and on the other hand, promote Th1 cells to differentiate and secrete a variety of pro-inflammatory media, eventually aggravating the inflammatory reaction in atheromatous plaque. In the study, analysis of the serum inflammation-related factors showed that serum hs-CRP, TNF-\(\alpha\), IL-8 and IL-18 levels of ACS group were significantly higher than those of control group \((P<0.05)\) and positively correlated with sCD40L and sCD40 levels. This means that the elevated serum sCD40L and sCD40 levels in patients with ACS can promote the cascade activation and amplification of the inflammatory response in the development and change of disease.

Excessively activated inflammation in patients with ACS is closely related to the plaque formation and plaque property change, and the plaque rupture caused by plaque property change can cause local platelet activation and thrombosis, thereby causing different levels of coronary artery stenosis and even obstruction. Plaque property change, therefore, is the key link causing the development and change of ACS, and the inflammatory cell infiltration and inflammatory factor secretion inside the plaques will affect the expression of a variety of molecules, thus causing the changes in internal structure and compositions of the plaques. The MMP2

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>MMP2 ((\mu g/L))</th>
<th>MMP9 ((\mu g/L))</th>
<th>LPA ((\mu mol/L))</th>
<th>Angptl2 ((\mu g/L))</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS group</td>
<td>156</td>
<td>38.49±5.12</td>
<td>56.38±7.83</td>
<td>4.27±0.61</td>
<td>127.95±15.62</td>
</tr>
<tr>
<td>Control group</td>
<td>60</td>
<td>15.25±1.77</td>
<td>24.51±3.27</td>
<td>2.21±0.32</td>
<td>52.32±6.74</td>
</tr>
<tr>
<td>(t)</td>
<td></td>
<td>13.285</td>
<td>11.926</td>
<td>9.173</td>
<td>12.673</td>
</tr>
<tr>
<td>(P)</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
and MMP9 in MMP family can degrade the collagen in the fibrous skeleton of atheromatous plaque, and inflammatory mediators have promoting effect on the expression of MMP2 and MMP9, which can reduce plaque stability and accelerate the development and change of ACS\cite{12,13}; LPA is the most simple water-soluble glycerol phospholipid in body structure, it is continuously produced when the low-density lipoprotein is oxidized into oxidized low-density lipoprotein and then deposits in atheromatous plaque and induces local thrombosis; Angptl2 is a new inflammation-regulatory molecule discovered in recent years, and it influences the synthesis and metabolism of a variety of ingredients in atheromatous plaque through the interaction with integrin, which, in turn, affect the plaque stability\cite{14,15}. In the study, analysis of the serum plaque stability-related molecules showed that serum MMP2, MMP9, LPA and Angptl2 levels of ACS group were significantly higher than those of control group (p<0.05) and positively correlated with sCD40L and sCD40 levels. This means that the elevated serum sCD40L and sCD40 levels in patients with ACS have promoting effect on the plaque property change in the development and change of disease.

Based on above discussion, it is concluded as follows: serum sCD40L and sCD40 levels abnormally increase in patients with ACS, and sCD40L/sCD40 have promoting effect the inflammatory cascade activation and plaque property change, thus accelerating the ACS progression.

References


