The correlation of serum sCD40 and its ligand contents with renal injury in patients with preeclampsia

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ABSTRACT
Objective: To study the correlation of serum sCD40 and its ligand contents with renal injury in patients with preeclampsia. Methods: 68 patients with preeclampsia who were treated in our hospital between May 2012 and January 2016 were collected and divided into mild preeclampsia group (n=38) and severe preeclampsia group (n=30), and 57 health pregnant women who received antenatal care in our hospital during the same period were selected as control group. ELISA was used to detect serum contents of soluble CD40 (sCD40) and its ligand (sCD40L) as well as renal injury indexes; automatic biochemical analyzer was used to test the contents of renal function indexes; color Doppler diasonograph was used to detect renal aortal hemodynamic parameters. Results: Serum sCD40, sCD40L, BUN, β 2-MG, Scr and Cys C contents as well as urine KIM-1 and NGAL contents of severe preeclampsia group and mild preeclampsia group were significantly higher than those of control group (P<0.05), and serum sCD40, sCD40L, blood urea nitrogen (BUN), β 2 microglobulin (β 2-MG), serum creatinine (Scr) and cystatin C (Cys C) contents as well as urine kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) contents of severe preeclampsia group were significantly higher than those of mild preeclampsia group (P<0.05); blood flow peak acceleration time (AT) and resistance index (RI) levels of severe preeclampsia group and mild preeclampsia group were higher than those of control group (P<0.05) while peak systolic flow velocity (Vs) and end-diastolic flow velocity (Vd) levels were lower than those of control group (P<0.05), and the AT and RI levels of severe preeclampsia group were higher than those of mild preeclampsia group (P<0.05) while Vs and Vd levels were lower than those of mild preeclampsia group (P<0.05); serum sCD40 and sCD40L contents in patients with preeclampsia were correlated with the renal injury severity. Conclusion: Serum sCD40 and sCD40L contents significantly increase in patients with preeclampsia, are correlated with patients' renal injury, and can be used to evaluate the degree of renal injury.

1. Introduction

Preeclampsia refers to the hypertension, albuminuria and other manifestations in pregnant women with normal progestational blood pressure after 20 weeks of gestation, it is a pregnancy-idiopathic disease, and epidemiological survey shows that its clinical incidence is about 3.9% and it is one of the main diseases endangering maternal and child health[1,2]. Soluble CD40 (sCD40) and its ligand (sCD40L) is a pair of complementary transmembrane glycoproteins that play an important role in antigen presentation and autoimmunity, and in recent years, the relationship of abnormal sCD40/sCD40L with the occurrence and progression of preeclampsia has received more and more attention[3,4]. Both hypertension and proteinuria of preeclampsia can lead to kidney damage, renal damage degree is directly related to preeclampsia severity, but there is no clear report at present about the relationship between sCD40/sCD40L and renal damage degree in patients with preeclampsia. In the following study, the correlation of serum sCD40 and its ligand contents with renal injury in patients with preeclampsia was analyzed.
2. Information and methods

2.1. Clinical information

68 patients with preeclampsia who were treated in our hospital between May 2012 and January 2016 were selected, 38 patients with mild preeclampsia group were selected as mild preeclampsia group and 30 patients with severe preeclampsia group were selected as severe preeclampsia group. 57 health pregnant women who received antenatal care in our hospital during the same period were selected as control group. Mild preeclampsia group were 23–34 years old, the gravidity was 1–4 and (1.76±0.59) in average, and the parity was 1–3 and (1.25±0.33) in average; severe preeclampsia group were 25–35 years old, the gravidity was 1–3 and (1.65±0.56) in average, and the parity was 1–2 and (1.26±0.35) in average; control group were 24–32 years old, the gravidity was 1–4 and (1.68±0.52) in average, and the parity was 1–2 and (1.21±0.37) in average. Three groups of research subjects were statistically different in age, gravidity and parity distribution (P>0.05), all included pregnant women signed the informed consent, and the hospital ethics committee approved the study.

2.2. Inclusion and exclusion criteria for preeclampsia

Inclusion criteria: (1) in line with the definition of preeclampsia in "Diagnostics" (2) systolic pressure ≥140 mmHg; (3) the urinary protein ≥0.3 g/24 h; (4) not associated with gestational diabetes, placenta previa, premature rupture of membranes or other pregnancy complications. Exclusion criteria: (1) associated with congenital heart disease; (2) associated with systemic infectious diseases; (3) with basic renal insufficiency; (4) with basic bleeding and clotting dysfunction; (5) with bad living habits such as smoking and drinking alcohol.

2.3. sCD40 and its ligand content

Immediately after inclusion, 1–2 mL peripheral venous blood was extracted from three groups of pregnant women, anti-coagulated, then let stand at room temperature for 10–15 min and centrifuged at low speed to get supernatant and freeze it at -20 °C for test. ELISA was used to determine serum sCD40 and sCD40L contents.

2.4. Renal function and renal injury indexes

Immediately after inclusion, peripheral blood serum and 24-hour urine were obtained from three groups of pregnant women with the same method, and detection indexes were as follows: (1) renal function indexes: fully automatic biochemical analyzer (Shenzhen Mindray Biological Medical Electronic Co., LTD., model BS-300) was used to detect serum blood urea nitrogen (BUN), β2 microglobulin (β2-MG), serum creatinine (Scr) and cystatin C (Cys C) levels. (2) Renal injury indexes: ELISA was used to determine the urine levels of kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL).

2.5. Renal blood flow parameters

Immediately after inclusion, color Doppler diasonograph (Shenzhen SonoScape Technology Co., LTD., model SSI-1000) was used to detect renal aortal hemodynamic parameters, including blood flow peak acceleration time (AT), peak systolic flow velocity (Vs), end-diastolic flow velocity (Vd) and resistance index (RI).

2.6. Statistical analysis

Data in the study was input in SPSS18.0 and analyzed by specially-assigned personnel, measurement data was in terms of mean ± standard deviation (x±s), comparison among three groups was by variance analysis, pair-wise comparison between groups was by LSD method, correlation was by Spearman correlation analysis and P<0.05 indicated statistical significance in difference.

3. Results

3.1. Serum sCD40 and its ligand contents of three groups of research subjects

Comparison of serum sCD40 and sCD40L contents among three groups of research subjects was as follows: differences in serum sCD40 and sCD40L contents were statistically significant among three groups of research subjects (P<0.05); serum sCD40 and sCD40L contents of severe preeclampsia group and mild preeclampsia group were higher than those of control group; serum sCD40 and sCD40L contents of severe preeclampsia group were higher than those of mild preeclampsia group, and differences were statistically significant (P<0.05), shown in Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>sCD40</th>
<th>sCD40L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia group</td>
<td>30</td>
<td>8.32±0.95*</td>
<td>7.11±0.85*</td>
</tr>
<tr>
<td>Mild preeclampsia group</td>
<td>38</td>
<td>3.04±0.35</td>
<td>2.85±0.34</td>
</tr>
<tr>
<td>Control group</td>
<td>57</td>
<td>1.26±0.14</td>
<td>0.97±0.09</td>
</tr>
</tbody>
</table>

Comparisons: Compared with control group, *P<0.05; compared with mild preeclampsia group, *P<0.05.

3.2. Renal function indexes of three groups of research subjects

Comparison of serum renal function indexes BUN, β2-MG, Scr and Cys C contents among three groups of research subjects was as follows: differences in serum BUN, β2-MG, Scr and Cys C contents were statistically significant among three groups of research subjects (P<0.05); serum BUN, β2-MG, Scr and Cys C contents
Comparison of renal aortal blood flow parameter levels of three groups of research subjects

Comparison of renal blood flow parameters AT, Vs, Vd and RI levels among three groups of research subjects was as follows: differences in AT, Vs and RI levels were statistically significant among three groups of research subjects ($P<0.05$). AT and RI levels of severe preeclampsia group and mild preeclampsia group were higher than those of control group while Vs and Vd levels were lower than those of control group; AT and RI levels of severe preeclampsia group were higher than those of mild preeclampsia group while Vs and Vd levels were lower than those of mild preeclampsia group. There was no significant change in differences among the three groups in AT, Vs, Vd and RI levels.

4. Discussion

There is systemic small artery contraction in patients with preeclampsia, activation of endothelial cells is the core mechanism of the disease, and the secretion of pro-coagulation materials can accelerate disease progression. sCD40/sCD40L are widely distributed in the endothelial cells and platelets, sCD40L can be combined with sCD40 to exert a series of effects such as prompting adhesion molecule, tissue and metalloproteinase generation through intracellular signaling pathways, which mediate endothelial cell damage, small thrombosis and so on together[5,6]. In the study, serum sCD40 and sCD40L contents of three groups of subjects were compared with control group, $P<0.05$; compared with mild preeclampsia group, $P<0.05$.

Table 2

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>BUN (mmol/L)</th>
<th>β 2-MG (mg/mL)</th>
<th>Scr (μmol/L)</th>
<th>Cys C (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia group</td>
<td>30</td>
<td>11.09±1.64*</td>
<td>8.95±0.97*</td>
<td>71.24±7.83*</td>
<td>1.67±0.19*</td>
</tr>
<tr>
<td>Mild preeclampsia group</td>
<td>38</td>
<td>5.27±0.59*</td>
<td>3.72±0.45</td>
<td>45.61±5.09*</td>
<td>1.23±0.15*</td>
</tr>
<tr>
<td>Control group</td>
<td>57</td>
<td>2.18±0.27</td>
<td>1.47±0.18</td>
<td>20.38±2.74</td>
<td>0.91±0.09</td>
</tr>
</tbody>
</table>

Compared with control group, $P<0.05$; compared with mild preeclampsia group, $P<0.05$.

Table 3

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>KIM-1 (ng/mL)</th>
<th>NGAL (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia group</td>
<td>30</td>
<td>9.83±0.96*</td>
<td>17.5±1.86*</td>
</tr>
<tr>
<td>Mild preeclampsia group</td>
<td>38</td>
<td>7.64±0.85*</td>
<td>13.68±1.74*</td>
</tr>
<tr>
<td>Control group</td>
<td>57</td>
<td>4.83±0.57</td>
<td>10.27±1.85</td>
</tr>
</tbody>
</table>

Compared with control group, $P<0.05$; compared with mild preeclampsia group, $P<0.05$.

Table 4

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>AT (s)</th>
<th>Vs (cm/s)</th>
<th>Vd (cm/s)</th>
<th>RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe preeclampsia group</td>
<td>30</td>
<td>0.08±0.01*</td>
<td>74.14±87.94*</td>
<td>27.48±3.01*</td>
<td>0.69±0.07*</td>
</tr>
<tr>
<td>Mild preeclampsia group</td>
<td>38</td>
<td>0.06±0.002*</td>
<td>77.55±8.03*</td>
<td>31.17±3.52*</td>
<td>0.64±0.07*</td>
</tr>
<tr>
<td>Control group</td>
<td>57</td>
<td>0.04±0.001</td>
<td>80.37±8.95</td>
<td>34.27±3.95</td>
<td>0.61±0.06</td>
</tr>
</tbody>
</table>

Compared with control group, $P<0.05$; compared with mild preeclampsia group, $P<0.05$. 3.4. Renal blood flow parameters of three groups of research subjects
detected at first, and the analysis results showed that compared with control group, the severe preeclampsia group and mild preeclampsia group were with higher serum sCD40 and sCD40L contents ($P<0.05$); the severer the preeclampsia condition, the higher the serum sCD40 and sCD40L contents. The above results confirm that sCD40 and sCD40L are the important causes of preeclampsia aggravation, which might be directly related to the roles of stimulating vascular endothelial cells and macrophages to release inflammatory mediators, aggravating the body’s hypercoagulability formation and so on.

The systemic small artery spasm, thrombosis, etc., in patients with preeclampsia can all directly affect kidney function and lead to its damage, and it is currently inconclusive whether sCD40/sCD40L is directly involved in renal injury in patients with preeclampsia[7]. In order to define the inner link between sCD40/sCD40L expression and kidney injury in patients with preeclampsia, the renal function of all groups of subjects was further tested in the study. Renal injury is mainly characterized by glomerular filtration function decline and the resulting abnormal blood and urine molecule contents, and numerous studies have confirmed that there are high levels of BUN and Scr in blood circulation of patients with chronic renal failure[7]. β 2-MG is a newly discovered factor closely related to the renal damage degree, and high level of β 2-MG is a sign of severe renal function injury[8,9]. Cys C is a sensitive index of early renal damage, and studies have confirmed that its levels rise as renal damage increases. It was found in the study that compared with control group, the mild preeclampsia group and severe preeclampsia group were with higher serum BUN, Scr, β 2-MG and Cys C contents ($P<0.05$), and the severer the preeclampsia, the higher the above index contents. Further correlation analysis showed that serum sCD40 and sCD40L contents in patients with preeclampsia were correlated with serum BUN, β 2-MG, Scr and Cys C contents. This indicates that the abnormally elevated serum sCD40 and sCD40L contents in patients with preeclampsia are valuable for evaluating renal damage degree.

There are also the factors in the urine closely related to renal damage, KIM-1 is the specific molecule of the renal tubular epithelial injury, its early levels rise in the blood, and its urine levels also increase when damage is increased[10]. When renal ischemic injury occurs, the NGAL content rises reactively in renal tubular epithelium, and it can reduce the glomerular ultrafiltration and reduce glomerular filtration[11,12]. The study of Huang et al confirms that urine NGAL content in pregnant women with preeclampsia is significantly higher than that in normal pregnancy pregnant women in the same period[13]. In the study, the contents of these kidney injury molecules were detected, and it was found that compared with control group, mild preeclampsia group and severe preeclampsia group were with higher KIM-1 and NGAL contents ($P<0.05$); the severer the preeclampsia, the higher the KIM-1 and NGAL contents, which is consistent with the above theory, and further confirms that the preeclampsia condition is consistent with the degree of kidney damage.

After the occurrence of preeclampsia, the renal small vessel spasm and perfusion reduce, and the renal blood flow and glomerular filtration decline sharply[14,15]. Renal function-sensitive index contents in serum and urine are the means that indirectly judge kidney damage, and color Doppler ultrasound measurement of renal blood flow parameters is the gold standard for specific diagnosis of kidney injury, and can confirm the illness severity[16]. Renal ischemic injury is mainly characterized by the increased peripheral vascular resistance, the decreased blood flow velocity, etc[17,18]. In the study, the renal blood flow parameters were compared among groups, and it was found that compared with control group, the mild preeclampsia group and severe preeclampsia group were with higher AT and RI levels, and lower Vs and Vd levels ($P<0.05$); the severer the preeclampsia, the higher the AT and RI levels, and the lower the Vs and Vd levels, confirming that there is decreased renal blood flow and increased blood flow resistance in patients with preeclampsia, and it is one of the most direct causes of renal injury.

It has been made clear the serum sCD40/sCD40L content change in patients with preeclampsia in the study, and the kidney injury-related parameter levels of all groups of research subjects were also detected. Spearman correlation analysis was used at last in the study to determine the inner link of serum sCD40/sCD40L content in patients with preeclampsia with kidney injury, and it was found that serum sCD40 and sCD40L content in patients with preeclampsia were directly correlated with the levels of renal function indexes, renal injury indexes and renal blood flow parameters. To sum up, it is concluded that serum sCD40 and sCD40L contents significantly increase in patients with preeclampsia, the specific increasing extent is consistent with the degree of renal injury, and they can objectively reflect the target organ injury in patients with preeclampsia.

References


