Clinical significance of serum total oxidant/antioxidant status for the disease activity in active rheumatoid arthritis

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Abstract: Background: Oxidative stress has been considered as an important pathophysiologic factor involved in development of rheumatoid arthritis (RA). The purpose of this study was to evaluate total serum oxidant/antioxidant levels in patients with active RA and analyze its significance in disease activity. Methods: A total of 112 patients with active RA and 52 healthy controls were enrolled. Serum total oxidant status (TOS), total antioxidant status (TAS) and oxidative stress index (OSI) were measured, and baseline characteristics were recorded. The DAS-28 scores were calculated as indicator of disease. Univariate analysis and multivariate logistic regression and receiver operating characteristic curve analyses were used to evaluate significance of TOS, TAS and OSI for indicator of disease of RA. Results: Both mean TOS (7.54±3.21 VS 5.73±2.81, P<0.05) and OSI (0.37±0.21 VS 0.23±0.16, P<0.05) of active RA patients were significantly higher than that of the controls whereas mean TAS of RA patients were remarkably lower than that of the controls (2.18±0.98 VS 2.52±0.81, P=0.031). In univariate analysis, OSI, TOS, ESR, CRP, CCP and RF were significantly correlated to the disease activity of RA. Patients with high disease activity (DAS-28>5.1) had significantly higher mean TOS (8.32±3.81 VS 5.88±3.12, P<0.05) and OSI (0.39±0.18 VS 0.25±0.11, P<0.05) than that of RA with low-moderate disease activity. OSI also was confirmed as an independent predictive indicator for disease activity of RA in multivariate analysis. Conclusions: Serum OSI level represents a useful indicator for disease activity in active RA patients, thereby helping the clinician to plan more appropriate therapeutic strategies.

Keywords: Rheumatoid arthritis, disease activity, serum total oxidant status, total antioxidant status, oxidative stress index

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory and autoimmune disease characterized by infiltration of inflammatory cells into the synovium, synovial hyperplasia and finally irreversible destruction of bone and cartilage [1, 2]. The prevalence of the RA is around 0.2-0.4% of population in China, which brings a considerable burden on patients, their families, and society [3, 4]. Stratification of the patients with different risk and early intensive treatment is important for improving clinical efficacy of RA [5].

Oxidative stress and severe systemic inflammation has been considered as important pathophysiologic mechanisms involved in development of RA [6, 7]. Oxidative stress occurs in response to the oxidative damage resulting from imbalance between antioxidant and scavenging ability and the active oxidants produced by a harmful stimulant [7, 8]. Reactive oxygen species (ROS), as the main active oxides, and accounts for more than 95% of total oxides. ROS has the potential to damage lipids, proteins and DNA in joint tissues [9, 10]. Previous reports showed that significant elevated ROS production in serum of RA patients comparing with healthy donors [11]. ROS are indirectly involved in joint damage as the secondary messengers in inflammatory and immunological cellular response in RA, which also can degrade directly the joint cartilage, influencing its proteoglycan and inhibiting its synthesis [9, 12]. Finding indicator inflecting oxidative stress sta-
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tus may be important for severity and disease activity evaluation in RA patients.

Therefore, the total oxidant status (TOS) is usually used to evaluate the overall oxidation state of the body while the total antioxidant status (TAS) is used to measure the overall antioxidant status [13, 14]. Furthermore, the oxidative stress index (OSI), which is calculated as the ratio of TOS to TAS, is considered as a more precise indicator of oxidative stress in the body because it can reflect imbalance between oxidation and antioxidant though comprehensive measurement TAS and TOS [15]. However, there was no data regarding the evaluation of TOS, TAS and OSI in patients with RA. In this study, we try to evaluate serum total oxidant/antioxidant status in RA patients though TOS, TAS and OSI measurement, and analyze the clinical significance of such indicator in RA.

Materials and methods

Patients

This prospective study enrolled 112 consecutive patients with active RA admitted to Department of Orthopedics and Traumatology in the Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine from June 1, 2014, to June 1, 2016. The diagnosis of RA was made by according to the criteria proposed by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) [16]. Patients with severe comorbidity, such as other ischemic diseases, severe cardiac or neurological disorders, malignant disease, chronic inflammatory disease, acute and chronic infective disease, preexisting organ failure, chronic obstructive airways disease and immunosuppressive disorders, were excluded from the study. Fifty-two healthy volunteers were enrolled as healthy controls. Written informed consent was obtained from individual patients and healthy subjects. This study was approved by the Ethics Committee of the Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine.

Clinical assessment

Demographic characteristics of all patients was recorded by one physician and furtherly check by another physician, such as age, gender, the duration of disease, medication and laboratory data including C reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and cyclic citrullinated peptide (CCP). The Disease Activity Score based on 28 Joints (DAS-28) were obtained to determine the activity of RA [17]. All patients received appropriate medical therapy and were followed though regular outpatient visiting. Outcome was assessed as disease activity representing though DAS-28 score. In details, the DAS-28 score >5.1 defined high disease activity whereas DAS-28 score 2.6-5.1 defined Low-moderate disease activity [18].

Measurement of TOS, TAS and OSI

The TOS and TAS level were measured according to Erel’s method [13, 14]. Approximately 5ml peripheral venous blood samples of all patients and controls were obtained and stored in a blood collection tube (BD Vacutainer). After centrifugation, the serums were decanted and measured immediately by a commercially available test kits (Rel Assay Diagnostics kit; Mega Tip, Gaziantep, Turkey) according to the manufacturer’s instructions and using their reagents and equipment. The results of TAS are expressed as mmol Trolox Eq/L while the result of the TOS are expressed as μmol H₂O₂ Eq/L. Oxidative Stress Index (OSI) values were calculated as the ratio of the TOS level to TAS level. Specifically, OSI (arbitrary unit) = TOS (μmol H₂O₂ Eq/L)/TAS (μmol Trolox Eq/L)×100.

Statistical analysis

Analyses were performed with SPSS 20.0 (IBM, USA). P<0.05 (two sided) was considered statistically significant. Data for categorical variables are expressed as a percentage and continuous variables as mean ± SD. The X² test or Fisher’s exact test was used to compare categorical variables while continuous variables were analyzed by independent student’s t test. The odds ratio (OR) was determined using multivariate logistic regression analysis for variables with significant p values (P<0.05) on univariate analysis.

Results

Patient characteristics

A total of 112 RA patients and 52 healthy controls were enrolled in this study. There were 14
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### Table 1. Baseline clinicopathologic characteristics of the RA patients and the controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RA patients (n=112)</th>
<th>Controls (n=52)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>14 (12.5%)</td>
<td>4 (7.7%)</td>
<td>0.359</td>
</tr>
<tr>
<td>Age (y)</td>
<td>55.41±12.62</td>
<td>52.31±11.41</td>
<td>0.133</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>32.52±7.61</td>
<td>15.74±11.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>33.51±25.23</td>
<td>3.43±2.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCP (RU/mL)</td>
<td>341.21±127.4</td>
<td>14.20±9.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF-IgM (IU/mL)</td>
<td>153.63±98.2</td>
<td>10.33±7.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF-IgG (IU/mL)</td>
<td>113.7±88.6</td>
<td>9.2±3.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF-IgA (IU/mL)</td>
<td>136.8±89.81</td>
<td>12.4±8.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TOS (mmol Trolox Eq/L)</td>
<td>7.54±3.21</td>
<td>5.73±2.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAS (μmol H2O2 Eq/L)</td>
<td>2.18±0.98</td>
<td>2.52±0.81</td>
<td>0.031</td>
</tr>
<tr>
<td>OSI</td>
<td>0.37±0.21</td>
<td>0.23±0.16</td>
<td>&lt;0.001</td>
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</table>

RA, rheumatoid arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; TOS, total oxidant status; TAS, total antioxidant status; OSI, oxidative stress index.

### Table 2. Univariate analysis of risk factors associated with disease activity in RA patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low to moderate activity (2.6&lt;DAS-28&lt;5.1, n=39)</th>
<th>High activity (DAS-28&gt;5.1, n=73)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>ESR (mm/h)</td>
<td>21.32±8.71</td>
<td>77.81±36.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>22.66±5.81</td>
<td>62.62±15.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCP (RU/mL)</td>
<td>238.71±186.15</td>
<td>589.21±163.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF-IgM (IU/mL)</td>
<td>118.43±36.27</td>
<td>201.17±132.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF-IgG (IU/mL)</td>
<td>125.23±37.66</td>
<td>163.18±127.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF-IgA (IU/mL)</td>
<td>98.61±15.26</td>
<td>160.86±114.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TOS</td>
<td>5.88±3.12</td>
<td>8.32±3.81</td>
<td>0.001</td>
</tr>
<tr>
<td>TAS</td>
<td>2.12±0.87</td>
<td>2.24±0.95</td>
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RA, rheumatoid arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; TOS, total oxidant status; TAS, total antioxidant status; OSI, oxidative stress index.

Discussion

In this study, we prospectively evaluate the serum total oxidant/antioxidant status in patients with active RA through TOS, TAS and OSI measurement, and found that RA patients had a significant higher TOS and OSI level than healthy controls. Furthermore, high TOS and OSI level was significantly associated with high disease activity in RA patients.

All 112 patients were divided into two groups according DAS-28 score, in which, 39 patients (2.6<DAS-28<5.1) were consider as low to moderate disease activity group while 73 patients (DAS-28>5.1) were enrolled as high disease activity group. In univariate analysis, patient with high disease activity has significant higher mean ESR, CRP, CCP and RF than patients with low to moderate disease activity (All P<0.05, Table 2). However, there was no significant different in mean TAS between low to moderate disease activity group and high disease activity group (2.12±0.87 vs. 2.24±0.95, P=0.514) (Table 2).

A multivariate logistic regression analysis enrolled serum ESR, CRP, CCP, RF, TOS and OSI level to identify independent predictive factors for disease activity of RA. The result showed that serum OSI level (OR, 2.201; 95% CI, 0.712-6.835; P<0.05) and CRP level (OR, 3.872; 95% CI, 1.112-12.087; P<0.05) and CCP level (OR, 1.362; 95% CI, 0.981-2.514; P<0.05) and RF-IgA level (OR, 0.488; 95% CI, 0.172-1.231; P<0.05) were the independent predictive factors (Table 3).

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Several limitations may influence the interpretation of the results of this study. One limitation is limited subjects. A large-scale, multicenter, prospective study should be conducted to confirm results and obtain more definite evidence. Furthermore, we measured TOS, TAS and OSI according to Erel's method, which cannot precisely reflect true level in a sample [29]. At this point, the OSI can better reflect the oxidative stress status of a subject. Thus, the results of this study may not be comparable with those of other studies. Various furtherly validation studies may be required to confirm more definite significance of OSI in RA patients.

In conclusion, the serum TAS, TOS and OSI level is increased in patients with active RA. As a biomarker of oxidative stress and antioxidants, serum OSI level may be a useful independent predictor of disease activity for patients RA.

Disclosure of conflict of interest
None.
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