Study of the correlation of serum selenium level with Behcet’s disease

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Abstract

Background: Selenium, like other trace elements and antioxidant enzymes, is known as an antioxidant and immunomodulator trace element. Due to recent evidence for selenium deficiency in Behcet’s syndrome, this study is to evaluate the correlation of serum selenium level with Behcet’s disease (BD).

Materials: This case–control study was conducted on 46 BD patients and 46 healthy controls in a rheumatology research centre. The case and control groups were both age- and race-matched. Serum selenium level was then measured by atomic absorption spectrometry Shimadzu AA-680. Average serum levels of both groups were then compared and analyzed using t-test.

Results: Mean serum selenium levels of patients appeared to be 66.4 ± 15.38 µg/L which was significantly lower than that in the healthy controls (86.87 ± 17.18 µg/L) (P < 0.005). Taking physician global assessment of disease activity into account, significant difference was detected between the patients with active disease (66.57 ± 15.21 µg/L) and those in the inactive state (65.83 ± 14.75 µg/L). Regardless of the findings mentioned above, serum selenium level was meaningfully elevated among the patients with ocular involvement (P < 0.001).

Conclusions: These findings demonstrated that selenium serum level among BD patients was lower than that in healthy controls, whereas among the patients with ocular involvement it was higher than those not involved.

Key words: Behcet’s disease, ocular involvement, selenium.

INTRODUCTION

Behcet’s disease (BD) is a chronic systemic disease with various manifestations in multiple organs like mucosa, skin, eyes and joints, along with cardiovascular, nervous and gastrointestinal systems.1 The etiology and pathogenesis of Behcet’s disease is still unknown and its diagnosis is based on clinical practice. Despite the initial report of BD half a century ago by Hulusi Behcet, and disease activity being measured by the Behcet Disease Current Activity Form (BDCAF), which is in accordance with a combination of the Iranian Behcet disease dynamic assessment measure (IBD-DAM) and the European criterion, clinical characteristics that may help predict the fluctuating clinical course of the disease have not yet been identified. Laboratory parameters of importance in this regard include enhanced level of circulating pro-inflammatory cytokines, increase in the level of myeloperoxidase resulted from neutrophil hyperactivity, inflammatory
response to different auto-antigens like endothelial antigens, auto-antibodies such as heat shock protein, auto-antibodies against oxidized low-density lipoproteins (LDL), and auto-antibodies against retinal S-antigen as an index of Behcet ocular involvement.\textsuperscript{2,3} However, to-date none of the laboratory parameters have been found to correlate with the disease activity. In recent studies, the role of reactive oxygen species, including superoxide, hydroperoxide, hydroxyl radicals and nitric oxide, were emphasized in autoimmune diseases. These elements are essential to activate the process of producing pro-inflammatory cytokines.\textsuperscript{4} Various studies have been done on the activity level of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) and have strengthened the role of free radicals in the pathogenesis of BD.\textsuperscript{5,6} Trace elements of zinc and selenium are used as cofactors by the above-mentioned enzymes. The first observations of selenium-mediated immune system were made through tracing radioactive selenium administrated to a dog in 1959,\textsuperscript{7} and the discovery of the biological function of selenium as a part of GSH-Px in 1973.\textsuperscript{8} Also, a variety of studies have dealt with the correlation of zinc serum/plasma levels in BD, where a decline in the plasma level of zinc has been noted in all cases.\textsuperscript{5,6} In most cases, relation of zinc with CuZn : SOD and CuZn : GSH-Px enzymes has been highlighted,\textsuperscript{5,6,9} while the exact mechanism for the role of zinc and selenium in BD is not well understood. In one study conducted in 2004, the effect of daily administration of 200 mg selenium in the well-being of rheumatoid arthritis patients was undertaken,\textsuperscript{10} whereas in other studies, zinc intake, as a contributing drug with rising effect, alongside the patient’s main drugs, was underlined.\textsuperscript{5,11} This study is to determine if there is any correlation between selenium serum levels and disease activity in BD patients referred to the Rheumatology Research Centre of the Medical University of Tehran. If selenium turns out effective in BD with regard to recurrences and ocular involvement, interventional studies will be needed to confirm the effect of selenium for patient treatment.

**METHODS**

This case–control study was carried out on 46 BD patients (meeting international criteria, including recurrent oral ophthus accompanied by two of the following parameters: genital ophthus, ocular involvement, cutaneous involvement or a positive pathergy test)\textsuperscript{12} and 46 healthy controls. Sampling was prepared constantly in Behcet’s disease unit of the Rheumatology Research Center. Owing to the fact that sex had no influence on BD and selenium serum levels,\textsuperscript{4} the subjects were not sex-matched. In addition, patients with any known disease (except BD in the case group) or pregnancy were excluded; those consuming laxative drugs, cholestramine, and wide-spectrum antibiotics, and those with a body mass index (BMI) < 19 were all excluded due to their influence on selenium serum levels. Patients and healthy controls were included in the study after completing an informed consent form provided by the Rheumatology Research Center. The questionnaires were completed at the time of the rheumatologist’s visit. To determine selenium levels, blood samples (5 cc) were taken with a VACUTAINER 21-gauge needle and stored in 7-cc tubes for trace elements custom-made for Behdarou Co., Tehran, I. R. Iran. After separating serum, Thompson and Allen’s technique was applied for the determination of selenium using atomic absorption spectrometry in the model of GBC AVANTA (GBC scientific equipment Ltd., Melbourne, Vic., Australia). The samples were prepared on a scale of 1 : 1 with 1% Troxon X-100 aqueous solution (Sigma Chemical Co., St Louis, MO, USA) and diluted nickel nitrate (Sigma), respectively. The samples were validated if their variances were < 10% for at least three estimations. The questionnaire was designed in the line of the study’s variables, including patient demographic data, active or inactive state of the disease based on GPA,\textsuperscript{2} ocular involvement, clinical signs, BMI, selenium serum level, blood sugar, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Some patients with retinal vasculitis or anterior/posterior uveitis were experiencing ocular involvement, while others were not. Selenium serum level of 86.8 μg/L was assumed as a normal limit. t-test, odds ratio (OR) and confidence intervals (CI) were used to make a comparison between active and inactive groups of cases and healthy controls.

**RESULTS**

Five out of 51 BD patients and one of the healthy controls were excluded from the study. Three patients were not included because of underlying diseases; and two other patients along with one healthy control were excluded due to BMI < 19. The case group consisted of 32 (69.6%) men and 14 (30.4%) women with a mean age of 39.2 ± 9.6 years, while the healthy controls included 26 (56.5%) men and 20 (43.5%) women.
with the mean age of 37.2 ± 12.1 years. Selenium serum levels in patients (66.4 ± 15.3 μg/L) versus healthy controls (86.89 ± 15 μg/L) were significantly different (P < 0.0005) (Table 1). Serum selenium levels in patients with active disease (19 patients, 66.6 ± 16.4 μg/L) compared with patients with inactive disease (27 patients, 66.4 ± 14.9 μg/L) was statistically different (P < 0.05) (Table 2). It is noteworthy that selenium serum levels in BD patients with ocular involvement (17 patients, 70 ± 17.7 μg/L) was outstandingly more than that in patients without ocular involvement (29 patients, 64.1 ± 13.5 μg/L) (P < 0.001) (Table 3).

**DISCUSSION**

The findings demonstrated that selenium serum levels in BD patients were less than that in healthy controls, revealing a significant difference (P < 0.0005). Dogan et al.\(^5\) in his study showed that selenium serum levels were 56.2 ± 7.02 and 92.11 ± 6.15 μg/L in their case and control groups, respectively (P < 0.001). Delibasy discovered that serum selenium levels were 54.24 ± 8.06 and 90.01 ± 9.94 μg/L in their case and control groups, respectively, which was significantly different (P < 0.001).\(^9\) As indicated in the studies above, reduced selenium serum levels in BD strengthens the role of selenium in the pathogenesis of inflammation, especially in BD. Nevertheless, the mechanism of action remains unknown and requires further investigation. Although selenium serum levels in patients were lower than healthy controls in Tuzun’s study, no significant difference was detected.\(^{11}\) In the study performed by Saglam, despite all the studies stated above, selenium serum levels in patients was more than that in healthy controls, although the difference was not significant.\(^{13}\) The findings of our study are consistent with the results of a number of other trials which similarly had patient sampling based on international criteria and utilized identical methods. Differences in the selection of patients seems to be responsible for differences in the results of other studies and those of the current study (in other studies patient selection was dissimilar to ours and international criteria were missing). On the other hand, ethnical and nutritional differences in selenium serum levels in BD might be responsible for the diversity of results. Selenium serum levels in healthy controls (86.8 ± 15 μg/L) in this study came so close to that reported by Moeen et al.\(^{14}\) for their controls in Tehran city (98.05 ± 13 μg/L).\(^{15}\) There is a significant difference between the selenium serum levels in BD patients and that of their healthy controls in the study that study.\(^{15}\) As far as our study is concerned, selenium serum levels in those with

**Table 1** Statistical indices for case and control groups by selenium serum level

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Serum selenium level (μg/L)</th>
<th>Odds ratio</th>
<th>95% CI (Mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>25</td>
<td>21</td>
<td></td>
<td>16.6</td>
<td>4.4–60.6</td>
<td>86.89 ± 15</td>
</tr>
<tr>
<td>BD patients</td>
<td>3</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
<td>66.45 ± 15.3</td>
</tr>
</tbody>
</table>

**Table 2** Statistical indices for case and control groups by the disease activity

<table>
<thead>
<tr>
<th>Disease state</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Serum selenium level (μg/L)</th>
<th>Odds ratio</th>
<th>95% CI (Mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>2</td>
<td>17</td>
<td></td>
<td>1.3</td>
<td>0.1–15.5</td>
<td>66.6 ± 16.4</td>
</tr>
<tr>
<td>Inactive</td>
<td>1</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td>66.4 ± 14.9</td>
</tr>
</tbody>
</table>

**Table 3** Statistical indices for case and control groups by ocular involvement

<table>
<thead>
<tr>
<th>Ocular involvement</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Serum selenium level (μg/L)</th>
<th>Odds ratio</th>
<th>95% CI (Mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>With</td>
<td>2</td>
<td>15</td>
<td></td>
<td>3.7</td>
<td>0.3–44.6</td>
<td>70.1 ± 17.7</td>
</tr>
<tr>
<td>Without</td>
<td>1</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td>64.1 ± 13.5</td>
</tr>
</tbody>
</table>
active disease (66.6 ± 16.4 μg/L) were higher than that for those with inactive disease (66.4 ± 14.9 μg/L), which was statistically significant (P < 0.05). On the other hand, a correlation as such was not investigated in other studies. Selenium serum levels in patients with ocular involvement (70.1 ± 17.7 μg/L) in our study appeared to be higher than that in those without ocular involvement (64.1 ± 13.5 μg/L), which was statistically significant (P < 0.001). This relationship was not dealt with in other studies as well. The findings obtained confirm the correlation of selenium with BD. Further study exploring the levels of antioxidant enzymes and other trace elements should be undertaken in order to authenticate the relation of selenium and BD. If the correlation is verified, pursuing interventional studies are advised so as to probe the curative effect of selenium in BD.

CONCLUSION

The findings here demonstrated that selenium serum levels in BD patients were lower than that in healthy controls, were higher in those with ocular involvement than those without. However, a significant correlation was detected between selenium serum levels and the intensity of BD activity which indicates that more studies are needed to determine the effective enzymes in the oxidative process along with interventional studies to discover the curative effects of selenium in Behcet’s Disease.

REFERENCES