HIGH SERUM CALCIUM IN HUMAN BRUCELLOSIS: A CASE-CONTROL STUDY

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Abstract. In a retrospective case-control study of 58 cases of human brucellosis, adjusted mean serum calcium levels were found to be significantly higher in patients with brucellosis compared with controls: mean (95% confidence interval) = 2.39 (2.35–2.42) mmol/L versus 2.30 (2.26–2.34) mmol/L (P = 0.0012). The possible mechanisms underlying the cause of hypercalcemia in human brucellosis are discussed.

Hypercalcemia has been described in several granulomatous diseases including tuberculosis, sarcoidosis, and leprosy. Brucellosis is a chronic infection associated with granuloma formation. During clinical rounds, my colleagues and I postulated that human brucellosis, like other granulomatous diseases, is likely to be associated with hypercalcemia. This retrospective case-control was conducted to investigate this hypothesis.

PATIENTS, MATERIALS, AND METHODS

Fifty-eight patients who were diagnosed as having brucellosis and were seen at the Asir Central Hospital in Abha in southern Saudi Arabia from 1991 to 1995 inclusively were studied retrospectively. The cases were diagnosed on clinical grounds and confirmed by either blood cultures, bone marrow cultures, or an increasing titer in a standard tube agglutination test. The charts of these patients were reviewed with regard to age, sex, and total protein, albumin, serum calcium, and phosphate levels. Information for 58 randomly selected, age- and sex-matched controls without brucellosis who were seen during the same period were reviewed for the same parameters. Cases with abnormal calcium metabolism including renal diseases, malignancy, parathyroid disease, thyrotoxicosis, Addison's disease, and malabsorption, and those taking vitamin D or calcium supplements were excluded from both the study and control groups. This study was approved by the Research and Ethics Committee of Asir Central Hospital.

Total serum calcium was assayed by a calorimetric method using the automated Hitachi (Tokyo, Japan) 911 analyzer. The reagents used were obtained from Randox Laboratories (Crumlin, United Kingdom).

Serum calcium levels were adjusted for serum albumin levels by adding or subtracting 0.025 mmol/L of calcium for each gram/liter of serum albumin less than or in excess of 40 g/L, respectively.

The SPSS (SPSS, Inc., Chicago, IL) PC for Windows (Microsoft Corp., Redmond, WA) statistical software package was used to compute the mean and 95% confidence intervals. The unpaired Student’s t-test was used to compare the difference between means using the GraphPad Prism statistical software package. The significance level was P < 0.05.

RESULTS

Table 1 shows the demographic data and laboratory test results of both patients with brucellosis and the control group. There was no significant difference in total serum protein or phosphate levels between the groups although the total calcium × phosphate product levels were higher in the patients with brucellosis. The adjusted mean (95% confidence interval [CI]) serum calcium level was significantly higher in the patients with brucellosis compared with the controls: 2.39 (2.35–2.42) mmol/L versus 2.30 (2.26–2.34) mmol/L (P = 0.0012). The mean (95% CI) albumin level was significantly lower in patients with brucellosis compared with the controls: 35.26 (26.34–44.47) g/L versus 38.97 (33.02–40.18) g/L (P = 0.0008). Figure 1 shows the adjusted mean (95% CI) serum calcium levels in patients with brucellosis and the controls.

DISCUSSION

This case-control study has shown that adjusted serum calcium levels are higher in patients with brucellosis compared with the controls. To minimize bias, the patients and

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Brucellosis group [N]</th>
<th>Control group [N]</th>
<th>P (by unpaired t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of subjects</td>
<td>58</td>
<td>58</td>
<td>0.2956</td>
</tr>
<tr>
<td>Mean age in years (95% CI)</td>
<td>26.48 (20.98–31.99) [58]</td>
<td>27.85 (21.99–33.69) [58]</td>
<td>0.2956</td>
</tr>
<tr>
<td>Males</td>
<td>26 [58]</td>
<td>26 [58]</td>
<td>0.0012†</td>
</tr>
<tr>
<td>Females</td>
<td>32 [58]</td>
<td>32 [58]</td>
<td>0.0008†</td>
</tr>
<tr>
<td>Mean total protein in g/L (95% CI)</td>
<td>73.00 (66.98–79.02) [52]</td>
<td>70.00 (64.50–75.10) [58]</td>
<td>0.0008†</td>
</tr>
<tr>
<td>Mean albumin in g/L (95% CI)</td>
<td>35.26 (26.34–44.47) [58]</td>
<td>38.97 (33.02–40.18) [58]</td>
<td>0.0008†</td>
</tr>
<tr>
<td>Mean phosphate in mmol/L (95% CI)</td>
<td>1.22 (1.01–1.86) [20]</td>
<td>1.07 (0.58–1.69) [27]</td>
<td>0.1277</td>
</tr>
<tr>
<td>Mean adjusted calcium in mmol/L (95% CI)</td>
<td>2.39 (2.35–2.42) [58]</td>
<td>2.30 (2.26–2.34) [58]</td>
<td>0.0008†</td>
</tr>
<tr>
<td>Mean calcium × phosphate product level (total) in mmol/L (95% CI)</td>
<td>3.07 (2.43–3.70) [8.0]</td>
<td>2.54 (1.56–3.51) [8.0]</td>
<td>0.3004</td>
</tr>
</tbody>
</table>

* CI = confidence interval.
† Significant P value.
controls were matched for age and sex. Cases with known abnormal calcium metabolism were not included in both groups. The patients and controls were admitted to the hospital during the same period; therefore, the laboratory techniques used in the assessment were applicable to both. The mechanisms causing higher serum calcium levels in patients with brucellosis are likely to be similar to those seen in other granulomatous diseases, including tuberculosis\(^1\) and sarcoidosis,\(^2\) mainly through vitamin D hypersensitivity. Activated macrophages in the granulomas of patients with these diseases have been shown to have 1-alpha-hydroxylase activity, which converts 25-hydroxy-vitamin D\(_3\) to 1,25-dihydroxy-vitamin D\(_{3}\).\(^6,7\) Bone involvement in tuberculosis has been described as a possible cause contributing to hypercalcemia.\(^8\) Brucellosis is known to involve the bones and joints. However, it is difficult in this retrospective study to assess the possible role of bone involvement in brucellosis in causing higher serum calcium levels. The hypoalbuminemia observed in patients with brucellosis is consistent with results from previous studies, which have shown involvement of the liver in brucellosis, leading to abnormal liver function test results.\(^9,10\) It is worth noting the higher phosphate levels and the higher total calcium \(\times\) phosphate product levels in patients with brucellosis compared with controls, although these differences are not statistically significant. The higher calcium \(\times\) phosphate product levels could explain tissue calcification, which is known to complicate brucellosis granulomas.

In conclusion, this case-control study has provided evidence of higher serum calcium levels in patients with brucellosis. However, prospective studies are needed to investigate the possible role of macrophages and vitamin D metabolites or bone involvement in this hypercalcemia and to ascertain the clinical significance of these higher serum calcium levels.

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REFERENCES