Soluble Intercellular Adhesion Molecule-1 Concentrations in Patients with Subacute Thyroiditis and in Patients with Graves’ Disease with or without Ophthalmopathy

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Abstract. Increased circulating soluble ICAM-1 (sICAM-1) levels has been previously reported in Graves’ disease (GD) patients with or without ophthalmopathy (GO) and in patients with toxic nodular goiter but not in patients with subacute thyroiditis. Conflicting results have also been reported about the usefulness of sICAM-1 levels as a marker for the activity of hyperthyroidism. We have therefore determined sICAM-1 levels by a sandwich enzyme linked immunosorbent assay (ELISA) method in 10 patients with subacute thyroiditis (Group 1), who are at the initial or acute phase of thyroiditis, in 10 hypothyroidic patients with Hashimoto’s thyroiditis (Group 2), in 10 patients with euthyroid nodular goiter (Group 3), in 10 patients with untreated GD patients with active ophthalmopathy (Group 4), in 10 hyperthyroid GD patients without clinical ophthalmopathy (Group 5), in 10 patients with GO who are euthyroid and treated with glucocorticoids for 3 months (Group 6) and in 20 normal subjects (Control Group). Groups 1, 2, 4, 5 and 6 (P<0.00001 for Groups 1, 4, 5, 6 and P<0.05 for Group 2) but not Group 3 showed increased sICAM-1 levels compared with the control group. However Groups 4 and 6 (patient with GO) showed significantly higher sICAM-1 levels (P=0.0003 for Group 4 and P=0.00013 for Group 6) than Group 5. Furthermore Group 4 showed slightly but not significantly higher sICAM-1 levels than Group 6. Mean sICAM levels were significantly decreased 3 months after glucocorticoid treatment (Group 6), but had not returned to normal levels. Three patients did not respond to steroid therapy and their sICAM-1 levels were not decreased. We concluded that patients with GO with or without hyperthyroidism and patients with subacute thyroiditis have elevated sICAM-1 levels. Moreover, sICAM-1 levels reflect the degree of inflammatory activity in the thyroid gland or orbital tissue independent of the thyroidal status, since we found elevated levels in both hyperthyroidism and hypothyroidism.

Key words: sICAM-1, Subacute thyroiditis, Graves’ disease, Ophthalmopathy

and seems to be a nonspecific inflammation marker [7, 8]. Release of cytokines, such as interferon (IFN), IL-1 and tumor necrosis factor (TNF), at sites of inflammation and immune response causes cell activation and results in augmented cellular expression of ICAM-1 [9, 10].

ICAM-1 is expressed on a variety of cells, including vascular endothelial cells, fibroblasts, thymic epithelial cells and thyroid follicular cells [10, 11]. Expression of ICAM-1 on focal clusters of dendritic cells in iodine deficiency goiters has also been demonstrated [12]. Elevated expression of this factor has been shown in several inflammatory tissues including thyroid and retroorbital connective tissue from patients with autoimmune thyroid disease [7, 11, 13], but conflicting results about the expression of ICAM-1 on thyroid epithelial cells have been reported. Some groups have shown that ICAM-1 was expressed on thyrocytes [11, 14], but others could not confirm these observations [15, 16].

Recently, in addition to the membrane bound ICAM-1, a circulating form of this molecule (sICAM-1) has been described [17, 18]. It has been suggested that soluble adhesion molecules function as competitive inhibitors of membrane-bound forms, thereby focusing cell adhesion at sites of inflammatory tissue activation [19]. In addition, soluble adhesion molecules may be of importance in preventing the activation of circulating leucocytes [7, 20].

An increased concentration of circulating sICAM-1 was demonstrated in patients with systemic sclerosis, malignant disease, insulin dependent diabetes mellitus and idiopathic pulmonary fibrosis [21–24]. Heufelder and Bahn [19] and recently De Bellis et al. [25] reported elevated circulating sICAM-1 levels in patients with Graves' disease (GD) with or without ophthalmopathy. They suggested that sICAM-1 levels may be a useful marker of endothelial and fibroblast activity. In contrast, Wenisch et al. [26, 27] reported that sICAM-1 levels could not be a useful clinical marker for disease activity in GD without ophthalmopathy. Although they observed significantly elevated sICAM-1 levels in untreated Graves' patients without ophthalmopathy, sICAM-1 levels were not decreased to normal after euthyroidism was achieved with antithyroid drugs. Moreover, only one study [19] reported the effect of glucocorticoid treatment on circulating sICAM levels in patients with Graves' ophthalmopathy. In this study elevated sICAM-1 levels were decreased to normal 3 months after glucocorticoid treatment. In addition no study reported on the sICAM-1 levels in patients with subacute thyroiditis.

We have therefore determined sICAM-1 levels in sera of patients with various thyroid diseases including Graves' disease with or without ophthalmopathy, Hashimoto's thyroiditis, subacute thyroiditis and euthyroid nodular goiter. A secondary aim of our study was to evaluate the modulator effect of glucocorticoid treatment on circulating sICAM-1 levels in patients with GO.

**Patients and Methods**

Sera were collected from the following groups of patients. None of the patients had any infectious, malignant disease or other autoimmune disease.

**Group 1**

Ten patients (7 females and 3 males, mean age: 31.2 ± 8.63 yr, range 28 to 41 yr) with subacute thyroiditis who are in the initial hyperthyroid or acute phase of the disease. The diagnosis of subacute thyroiditis was based on anterior neck pain, symptoms of hyperthyroidism, tenderness in the thyroid region, elevated erythrocyte sedimentation rate above 50 mm/h, elevated T4 and T3 levels, low thyroid 131I uptake (less than 1 at 24 h), fine needle aspiration biopsy or no uptake or patchy and irregular uptake on 99mTc thyroid scans.

**Group 2**

Ten patients (7 females and 3 males, mean age: 34.2 ± 3.36 yr, range 28 to 41 yr) with hypothyroidism due to Hashimoto's thyroiditis who are in the initial hyperthyroid or acute phase of the disease. The diagnosis of subacute thyroiditis was based on anterior neck pain, symptoms of hyperthyroidism, tenderness in the thyroid region, elevated erythrocyte sedimentation rate above 50 mm/h, elevated T4 and T3 levels, low thyroid 131I uptake (less than 1 at 24 h), fine needle aspiration biopsy or no uptake or patchy and irregular uptake on 99mTc thyroid scans.
Group 3

Ten patients (6 females, and 4 males, mean age: 31.0 ± 4.61 yr, range 22–37 yr) with euthyroid nodular goiter (6 had solitary and 4 had multinodular goiter). Cytological examination of FNAB showed the benign character of the disease in all patients.

Group 4

Ten patients (6 females, and 4 males, mean age: 31.2 ± 3.64, range 26 to 37 yr) with untreated Graves' hyperthyroidism and active ophthalmopathy. Graves’ disease (GD) was diagnosed on the basis of clinical and laboratory evidence of thyrotoxicosis, palpable diffuse goiter, homogenous thyroid scan and the presence of antithyroid antibodies. The ophthalmopathy-index score ranged between 2 and 6 in this group.

Group 5

Ten hyperthyroid GD patients (6 females and 4 males, mean age: 30.3 ± 8.48 yr, range 26 to 38 yr) without clinically significant ophthalmopathy.

Group 6

Ten patients (7 females and 3 males, mean age: 34.7 ± 4.39 yr, range 28 to 41 yr) with Graves' ophthalmopathy who were treated with glucocorticoid for 3 months. These patients were included in the study just after euthyroidism was achieved with antithyroid drugs. They are clinically and biochemically euthyroid and taking methimazole for the maintenance of euthyroidism. We administered daily doses of 60 mg prednisone for 2 weeks, 40 mg for 2 week, 30 mg for 2 weeks, 20 mg for 2 weeks, with subsequent tapering by 5 mg/week. GO lasted less than 4 months in both groups of patients (Groups 4 & 6). The ophthalmopathy index score ranged between 2 and 6 in this group.

The clinical data and laboratory characteristics of the patients are shown in Table 1.

Control group

Twenty healthy subjects (12 females and 8 males, mean age: 33.65 ± 4.17 yr, range 28–42 yr) with no history of thyroid disease were selected as a control group.

Serum levels of thyroid hormones and thyroid autoantibodies in different groups of patients are shown in Table 2. Blood samples were obtained from all patients and control subjects. Blood samples were collected from Group 6 patients before and at 3 months after the initiation of glucocorticoid therapy. All blood samples were centrifuged immediately and sera were stored frozen at -40 °C until sICAM-1 was analyzed. All patients and controls gave informed consent before enrollment and the protocol was approved by the Local Ethical Committee of Gülhane School of Medicine.

The degree of proptosis was measured with a Hertel exophthalmometer before and after gluco-

<p>| Table 1. Clinical data and laboratory characteristics of patients with subacute thyroiditis |
|--------------------------------------|-----------------|----------|---------|---------|---------|----------|----------|</p>
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>FT&lt;sub&gt;3&lt;/sub&gt; (pg/mL)</th>
<th>FT&lt;sub&gt;4&lt;/sub&gt; (ng/dL)</th>
<th>TSH (IU/L)</th>
<th>AMA (IU/mL)</th>
<th>ATA (IU/mL)</th>
<th>ESR (mm/h)</th>
<th>Thyroid uptake (¹³¹I, 24 h, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.4</td>
<td>6.3</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>70</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>2</td>
<td>17.1</td>
<td>6.5</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>110</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>3</td>
<td>16.9</td>
<td>7.9</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>100</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>4</td>
<td>16.7</td>
<td>8.2</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>110</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>5</td>
<td>14.3</td>
<td>6.8</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>90</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>6</td>
<td>11.9</td>
<td>7.4</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>86</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>7</td>
<td>16.2</td>
<td>6.2</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>75</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>8</td>
<td>7.1</td>
<td>3.4</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>80</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>9</td>
<td>8.7</td>
<td>4.0</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>110</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>10</td>
<td>12.9</td>
<td>3.0</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
<td>72</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

mean ± SD 13.82 ± 3.61 5.97 ± 1.86 – – – 90.3 ± 16.21 –

ESR, Erythrocyte sedimentation rate; AMA, Anti-microsomal antibody; ATA, Anti-thyroglobulin antibody; < 50, negative.
corticoid therapy in Group 6. Pabuşcu et al. [28], from our institution, evaluated the proptosis in a Turkish population without exophthalmos and found a mean value of 15.39 ± 2.79 mm. We therefore accepted 21 mm as the upper normal limit for proptosis (2 SD of normal limit).

All patients with GO who were treated with glucocorticoid were examined by the same ophthalmologist before and 3 months after glucocorticoid therapy. The results of examinations were summarized depending on the modified American Thyroid Association's (ATA) classification of ocular changes in Graves' disease [29]. We also estimated the ophthalmopathy-index score as previously described by Tallstedt et al. [30]. Four categories of findings (soft-tissue involvement, exophthalmos, extraocular-muscle involvement and sight loss) were scored from 1 to 3 according to their severity, giving a maximal overall score of 12. A score of 1 or more was considered to indicate the presence of ophthalmopathy [30].

The serum concentration of sICAM-1 was measured by a sandwich ELISA method as previously described by others [9, 19, 21], with kits supplied by T Cell Diagnostics Inc. (Cambridge MA, USA). All sera were run on the same assay. The sensitivity of the assay was 0.3 ng/mL. Intra-assay coefficients of variation were less than 5%.

Free T₃ (normal range: 2.2–4.7 pg/mL) and free T₄ (normal range: 0.85–2.67 ng/dL) were measured by radioimmunoassay (RIA) with reagents from Kodak Clinical Diagnostics Ltd. Amersham (Bucks, UK) (Kodak Amerlex-Mab f T₃ kit and Kodak Amerlex-Mab f T₄ kit, respectively). We determined serum TSH (upper reference limit 6.5 IU/L) by an immunoradiometric assay with reagents from Medgenix Diagnostic SA (Fleurus, Belgium; TSH immunoradiometric assay coated tube kit). Anti-microsomal and anti-thyroglobulin (Tg) autoantibodies were measured by a radiolabeled ligand assay with reagents from RADIM SA (Liege, Belgium; Anti-Tg antibody 125I coated tubes and TMAB 125I coated tubes, respectively). An antibody titer greater than 50 IU/mL is considered a positive antibody titer for the anti-Tg and anti-microsomal assay. All results are given as means ± SD. Groups were compared by corrected two-tailed Mann Whitney U test. sICAM-1 levels before and after glucocorticoid therapy was compared with the Wilcoxon Rank sum test.

### Results

As shown in Fig. 1 mean sICAM-1 levels were significantly elevated in patients with untreated Graves' hyperthyroidism with GO (Group 4, 549.50 ± 63.18 ng/mL, P<0.00001), Graves' hyperthyroidism without GO (Group 5, 376 ± 46.77 ng/mL, P<0.0001), subacute thyroiditis (Group 1, 424.0 ± 64.20 ng/mL, P<0.0001), Hashimoto's thyroiditis (Group 2, 239 ± 56.80 ng/mL, P=0.03), and euthyroid Graves' disease with GO (Group 6, 490.0 ± 64.83 ng/mL, P<0.0001) when compared to normal individuals (control group, 186.50 ± 53.29 ng/mL). No significant difference in sICAM-1 concentrations was observed between patients with euthyroid nodular goiter (Group 3, 220.0 ± 52.07 ng/mL) and the control group. Serum concentrations of sICAM-1 were highest in patients with ophthalmopathy (Groups 4 and 6) and subacute thyroiditis (all values > 2 SD above normal controls). Patients with GO (Groups 4 and 6) showed a significant increase in sICAM-1 levels (P<0.0003

### Table 2. Serum levels of thyroid hormones and thyroid autoantibodies in different groups of patients

<table>
<thead>
<tr>
<th></th>
<th>FT₃ (pg/mL)</th>
<th>FT₄ (ng/dL)</th>
<th>TSH (IU/L)</th>
<th>AMA (IU/mL)</th>
<th>ATA (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>13.82 ± 3.61</td>
<td>5.97 ± 1.86</td>
<td>&lt; 0.1</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Group 2</td>
<td>1.53 ± 0.39</td>
<td>0.47 ± 0.24</td>
<td>58.16 ± 15.18</td>
<td>2916.2 ± 1506.8</td>
<td>2520.9 ± 2400.5</td>
</tr>
<tr>
<td>Group 3</td>
<td>3.39 ± 10.2</td>
<td>1.59 ± 0.47</td>
<td>1.0 ± 1.0</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Group 4</td>
<td>19.04 ± 5.04</td>
<td>7.73 ± 2.51</td>
<td>&lt; 0.1</td>
<td>605.0 ± 439.7</td>
<td>272.5 ± 22.5</td>
</tr>
<tr>
<td>Group 5</td>
<td>18.1 ± 3.1</td>
<td>6.82 ± 2.30</td>
<td>&lt; 0.1</td>
<td>650.2 ± 238.6</td>
<td>216.2 ± 30.4</td>
</tr>
<tr>
<td>Group 6</td>
<td>3.02 ± 0.44</td>
<td>1.0 ± 0.61</td>
<td>0.18 ± 0.25</td>
<td>580.1 ± 186.2</td>
<td>186.3 ± 24.2</td>
</tr>
<tr>
<td>Control</td>
<td>3.65 ± 0.58</td>
<td>1.63 ± 0.44</td>
<td>1.0 ± 1.0</td>
<td>&lt; 50</td>
<td>&lt; 50</td>
</tr>
</tbody>
</table>

AMA, Anti-microsomal antibody; ATA, Anti-thyroglobulin antibody.
for Group 4 and $P=0.0013$ for Group 6) compared with hyperthyroid patients with Graves’ disease without ophthalmopathy (Group 5). Furthermore, sICAM-1 levels in untreated hyperthyroid GD patient with ophthalmopathy (Group 4) were slightly but not significantly elevated compared to those of euthyroid GD patients with ophthalmopathy (Group 6). There was no correlation between sICAM-1 levels and age, sex or thyroid hormone levels in any of the groups studied.

In patients with GO who are euthyroid (Group 6), sICAM-1 levels were measured before and 3 months after glucocorticoid treatment (Fig. 2). In 7 patients who responded to glucocorticoid therapy with a marked improvement in particularly soft tissue involvement. Mean sICAM-1 levels were significantly decreased 3 months after glucocorticoid treatment (from $490.0 \pm 64.83$ ng/mL to $344.50$ ng/mL).

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**Fig. 1.** Individual data for serum sICAM-1 concentrations in patients with subacute thyroiditis (Group 1), in hypothyroid patients with Hashimoto’s thyroiditis (Group 2), in euthyroid patients with nodular goiter (Group 3), in hyperthyroid patients with Graves’ disease (GD) and active ophthalmopathy (Group 4), in hyperthyroid patients with GD without ophthalmopathy (Group 5), euthyroid patients with Graves’ ophthalmopathy (Group 6) and in healthy controls.
± 109.1, z=2.19, P=0.02), but mean sICAM-1 levels after 3 months of glucocorticoid treatment were still significantly higher than those in normal subjects (z=−3.98, P=0.0001). Three patients responded poorly to steroid therapy. Mean proptosis values for the 10 patients were only significantly decreased in the right eye after glucocorticoid treatment (from 21.80 ± 2.74 mm to 20.90 ± 2.85 mm, z=−1.68, P>0.05 in the left eye; from 21.90 ± 2.77 mm to 20.60 ± 3.10 mm, z=−2.37, P=0.02 in the right eye) (Table 3). The ophthalmopathy index score at the beginning of the study was 3.6 ± 1.07. These values were decreased to 2.3 ± 1.56 (z=−1.96, P=0.05) at 3 months after therapy. sICAM-1 levels were not correlated with the ophthalmopathy-index score or proptosis in the GO group (Groups 4 and 6). No correlation was found between sICAM-1 levels and thyroid hormones (fT3, fT4), and anti-thyroid antibodies in any group.

**Discussion**

The major finding of this study was that sICAM-1 levels are elevated in patients with active ophthalmopathy with or without hyperthyroidism and in patients with subacute thyroiditis. Moreover, sICAM-1 levels were also elevated in hyperthyroid patients without clinical ophthalmopathy, even though at a lower concentration with respect to Graves' ophthalmopathy groups.

Elevated circulating sICAM-1 levels have been previously reported in Graves' disease patients with or without ophthalmopathy [19, 25, 27] and in patients with toxic nodular goiter [25, 27] but not in patients with subacute thyroiditis. Heufelder and Bahn [19] have previously reported elevated sICAM-1 levels in patients with invasive fibrous thyroiditis. Similarly, our patients with subacute thyroiditis who are at an initial or acute phase of thyroiditis have elevated sICAM-1 levels. The reason for elevated sICAM-1 levels in nonimmunologically mediated hyperthyroidism such as toxic nodular goiter and subacute thyroiditis is not clear. It is known that sICAM-1 expression

![Fig. 2. sICAM-1 serum concentrations in patients with Graves' ophthalmopathy (Group 6) before and 3 months after glucocorticoid therapy. Uninterrupted lines indicate patients with clinical response to therapy. Dashed lines represent 3 patients who respond poorly to steroid therapy.](image)

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**Table 3. Individual responses to glucocorticoid treatment in 10 patients with Graves' ophthalmopathy (Group 6)**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Eye disease modified ATA class</th>
<th>Ophthalmopathy-index score</th>
<th>Proptosis (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
</tr>
<tr>
<td>1</td>
<td>III (IcIIIa)</td>
<td>III (IcIIIa)</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>III (IcIIla)</td>
<td>III (IcIIla)</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>IV (IcIIlaVa)</td>
<td>IV (IaIIlaIaVa)</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>II (Ic)</td>
<td>II (Ia)</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>II (Ic)</td>
<td>II (Ia)</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>IV (IcIIlaVa)</td>
<td>IV (IaIIlaIaVa)</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>II (Ib)</td>
<td>I</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>IV (IcIIlaIaVa)</td>
<td>IV (IaIIlaVa)</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>II (Ic)</td>
<td>II (Ia)</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>IV (IcIIlaIaVa)</td>
<td>IV (IcIIlaIaVa)</td>
<td>3</td>
</tr>
</tbody>
</table>

mean ± SD: 3.6 ± 1.07a, 2.3 ± 1.56b, 21.80 ± 2.74c, 20.90 ± 2.85d, 21.90 ± 2.77e, 2.60 ± 3.10f

P=0.05 for a vs. b, P>0.05 for c vs. d, P=0.02 for e vs. f.
sICAM-1 levels have been studied in one study so far [19]. They found normalization of elevated sICAM-1 levels after 3 months of steroid therapy. We found a decrease in sICAM-1 levels after 3 months of glucocorticoid therapy, but levels were still higher than those in normal individuals. Similarly, a sustained increase in sICAM-1 was observed even after clinical improvement in other inflammatory diseases [37, 38]. Although sICAM-1 levels were still higher after 3 months of steroid therapy, changes in sICAM-1 levels seem to be correlated with the degree of inflammatory activity in GO and the response to steroid therapy, although no direct relation was found between sICAM-1 and the ophthalmopathy-index score. But the observation of higher sICAM-1 levels in euthyroid patients with GO before and 3 months after steroid therapy suggest that sICAM-1 levels return to normal slowly. This may be due to the continuous presence of inflammatory cytokines causing ICAM-1 expression on endothelial cells.

sICAM-1 levels do not seem to be a useful marker of activity of hyperthyroidism or the thyroidal status since we could not find normal levels in patients with Graves’ disease when they became euthyroid with antithyroid therapy. Similar results have also been reported by Wenisch et al. [26, 27]. We also find slightly elevated sICAM-1 levels in hypothyroid patients with Hashimoto’s thyroiditis, supporting the view that sICAM-1 does not reflect the thyroidal status.

We found slightly elevated sICAM-1 levels in patients with Hashimoto’s thyroiditis when compared to those in control group. But some patients had levels overlapping those in controls. Similarly, Heufelder and Bahn [19] found elevated sICAM-1 levels in patients with Hashimoto’s thyroiditis. These elevated levels could be due to the immune process in Hashimoto’s thyroiditis. The finding of normal concentrations of sICAM-1 levels in patients with euthyroid nodular goiter also support the view that sICAM-1 levels could be a useful marker of the inflammatory activity in the thyroid gland or orbital tissue.

In conclusion, we demonstrate elevated sICAM-1 levels in patients with GO with or without hyperthyroidism and in patients with subacute thyroiditis. Although sICAM-1 levels had not returned to normal after steroid therapy, the decreases in sICAM-1 levels after steroid therapy suggest that is augmented in several inflammatory tissues [7, 31, 32] and therefore it seems to be a nonspecific inflammation marker. Increased sICAM-1 levels in subacute thyroiditis may therefore result from the inflammation and tissue damage observed in this disorder [33]. Another explanation is that thyroid hormones may make vascular endothelium active at unrelated sites or could prolong the metabolism of sICAM-1 and thereby cause an increase in sICAM-1 [27]. It is known that thyroid hormones influence the secretion and degradation of several proteins such as fibronectin, angiotensin-converting enzyme and factor VIII-related antigen [34, 35]. Shedding of the sICAM-1 into the circulation can therefore be explained as the results of proteolytic cleavage of the membrane bound molecule due to inflammation or the effect of thyroid hormones on vascular endothelium at unrelated sites [21]. The demonstration of shedding of several tissue-specific isoforms of the ICAM-1 molecule supports this view [36].

We found elevated sICAM-1 levels in GD patients with active ophthalmopathy with or without hyperthyroidism. But sICAM-1 levels were also elevated in hyperthyroid GD patients without clinical ophthalmopathy, though at lower concentrations with respect to GO groups. Similar results have been reported by De Bellis et al. [25]. Thus, elevated sICAM levels in GD patients with or without ophthalmopathy may originate in different cells involved in autoimmune processes both at orbital and thyroid levels [25]. Although conflicting results about the expression of ICAM-1 on thyroid epithelial cells have been reported [11, 14, 15, 16], increased expression of this factor has been shown in the interstitial and perimysial connective tissue surrounding extraocular muscle fibers from patients with GO [19].

No correlation was found between sICAM-1 and the ophthalmopathy-index score, thyroid hormones, or antithyroid antibodies in any group of patients. Similarly Heufelder and Bahn [19] found no correlation between sICAM-1 and TSI activity, but Wenisch et al. [26, 27] found a significant correlation between sICAM-1 and the antimicrosomal antibody, and the ophthalmic activity score, but not with anti-Tg levels. The reason for this difference among studies may be the population size or the severity of the disease.

The effect of glucocorticoid treatment on sICAM-1 levels has been studied in one study so far [19]. They found normalization of elevated sICAM-1 levels after 3 months of steroid therapy. We found a decrease in sICAM-1 levels after 3 months of glucocorticoid therapy, but levels were still higher than those in normal individuals. Similarly, a sustained increase in sICAM-1 was observed even after clinical improvement in other inflammatory diseases [37, 38]. Although sICAM-1 levels were still higher after 3 months of steroid therapy, changes in sICAM-1 levels seem to be correlated with the degree of inflammatory activity in GO and the response to steroid therapy, although no direct relation was found between sICAM-1 and the ophthalmopathy-index score. But the observation of higher sICAM-1 levels in euthyroid patients with GO before and 3 months after steroid therapy suggest that sICAM-1 levels return to normal slowly. This may be due to the continuous presence of inflammatory cytokines causing ICAM-1 expression on endothelial cells.

sICAM-1 levels do not seem to be a useful marker of activity of hyperthyroidism or the thyroidal status since we could not find normal levels in patients with Graves’ disease when they became euthyroid with antithyroid therapy. Similar results have also been reported by Wenisch et al. [26, 27]. We also find slightly elevated sICAM-1 levels in hypothyroid patients with Hashimoto’s thyroiditis, supporting the view that sICAM-1 does not reflect the thyroidal status.

We found slightly elevated sICAM-1 levels in patients with Hashimoto’s thyroiditis when compared to those in control group. But some patients had levels overlapping those in controls. Similarly, Heufelder and Bahn [19] found elevated sICAM-1 levels in patients with Hashimoto’s thyroiditis. These elevated levels could be due to the immune process in Hashimoto’s thyroiditis. The finding of normal concentrations of sICAM-1 levels in patients with euthyroid nodular goiter also support the view that sICAM-1 levels could be a useful marker of the inflammatory activity in the thyroid gland or orbital tissue.

In conclusion, we demonstrate elevated sICAM-1 levels in patients with GO with or without hyperthyroidism and in patients with subacute thyroiditis. Although sICAM-1 levels had not returned to normal after steroid therapy, the decreases in sICAM-1 levels after steroid therapy suggest that
sICAM-1 levels reflect the activity of GO, but sICAM-1 levels were not correlated with the thyroidal status, since elevated levels were observed both in euthyroid patients with GD and hypothyroid patients with Hashimoto’s thyroiditis. Circulating sICAM-1 levels may therefore be considered a specific marker of inflammatory activity in the thyroid gland or orbital tissue independent of the thyroidal status.

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References

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