Decrease in sE-Selectin after Pituitary Surgery in Patients with Acromegaly, Christoph Schmid,1 Peter Wiesli,2 René Bernays,2 Konrad Bloch,3 Jürgen Zapf,3 Cornelia Zwimpfer,1 Claudia Ghirlanda,1 and Michael Brändle1 (1 Department of Internal Medicine, Division of Endocrinology and Diabetes, 2 Department of Neurosurgery, and 3 Department of Internal Medicine, Division of Pneumology, University Hospital of Zurich, Zurich, Switzerland; * address correspondence to this author at: Department of Internal Medicine, Division of Endocrinology and Diabetes, University Hospital of Zurich, CH-8091 Zurich, Switzerland; fax 41-1-255-4447, e-mail peter.wiesli@DIM.usz.ch)

Adhesion of circulating leukocytes to endothelial cells is one of the initial events in the development of atherosclerosis (1). This process is mediated by cellular adhesion molecules such as sE-selectin, a specific product of endothelial cells. Circulating concentrations of soluble cell adhesion molecules may serve as surrogate markers for endothelial damage and early atherosclerosis (2–4). Increased serum concentrations of sE-selectin have been described in patients with insulin resistance (5, 6), diabetes mellitus (2, 7), hypertension (8), and sleep apnea syndrome (SAS) (9). In patients with acromegaly, impaired glucose tolerance, arterial hypertension, and SAS are frequent findings, and macrovascular disease is a common complication (10). The aim of this study was to measure sE-selectin in patients with acromegaly before and after pituitary surgery and to analyze whether sE-selectin concentrations are related to disease activity, insulin resistance, hypertension, or SAS in this particular group of patients.

All consecutive patients with newly diagnosed acromegaly who had been referred to the Division of Endocrinology and Diabetes at the University Hospital in Zurich between November 1999 and December 2002 were included. Serum sE-selectin concentrations were measured at diagnosis of acromegaly and 2–4 months after pituitary surgery. The Ethics Committee of the University Hospital of Zurich was contacted and decided that formal approval to measure sE-selectin was not necessary. Oral informed consent to determine additional laboratory values was obtained from all patients. A diagnosis of SAS was established by the simultaneous presence of two criteria: subjective hypersomnolence, defined as >10 points on the Epworth sleepiness scale, and an increased apnea–hypopnea index, defined as more than five apneic or hypopneic episodes per hour of sleep during an overnight sleep study. Insulin resistance was estimated by homeostasis model assessment (11).

All blood samples were drawn after an overnight fast. Serum concentrations of sE-selectin were measured by a commercially available ELISA (R and D Systems); the mean serum values in 130 healthy individuals provided by the manufacturer was 46.3 μg/L, and the upper limit of the reference interval was set at 60 μg/L. The intraassay CV was 4.8%, and the interassay CV was 7.3%. For measurements of insulin-like growth factor-1 (IGF-1), carrier proteins were removed by Sep-Pak® chromatography according to the instructions from the supplier (Waters Associates), and IGF-1 was determined by RIA (12). Growth hormone (GH) was determined by an IRMA (hGH-RIACT; CIS Bio international, Oris Industries) based on a sandwich technique using two monoclonal antibodies prepared against sterically remote antigenic sites on the hGH molecule. The intraassay CV was 2.1%, and the interassay CV was 4.5%. Insulin was measured by a solid-phase RIA (CIS Bio international, Oris Industries). The manufacturer-provided range of values for healthy individuals after an overnight fast was 30–138 pmol/L.

Data are presented as the mean (SD). Differences between values before and after pituitary surgery were analyzed with the two-sided paired t-test. Correlation coefficients between sE-selectin and insulin resistance, blood pressure, plasma glucose, and IGF-1 were assessed with the Pearson correlation formula; P values <0.05 were considered statistically significant. All statistical analyses were performed with SAS Software, Ver. 8.2 (SAS Institute Inc.).

Twelve patients (6 females and 6 males) with newly diagnosed acromegaly were included in the study. One patient with acromegaly and poorly controlled diabetes mellitus treated with insulin was excluded. The mean (SD) age at diagnosis was 49 (17) years, and the mean body mass index was 28 (3) kg/m2. Diagnosis of acromegaly was established by clinical findings, increased IGF-1 concentrations, and a lack of GH suppression to <1 μg/L during an oral glucose challenge test in all patients. Acromegalic symptoms had lasted for 7 (5) years. Magnetic resonance imaging revealed pituitary macroadenomas (≥10 mm in diameter) in 10 and microadenomas in 2 patients. Six (50%) patients met the definition of SAS, and eight (67%; all six patients with and two of the six patients without SAS) had hypertension, i.e., blood pressure ≥140/90 mmHg. Four (33%) patients had fasting plasma glucose concentrations >6 mmol/L, and nine (75%) had serum insulin concentrations >138 pmol/L. sE-Selectin concentrations were >60 μg/L in four (33%) patients. sE-Selectin concentrations were not different in patients with [48 (22) μg/L] and without SAS [53 (22) μg/L] and did not correlate with blood pressure or plasma glucose concentrations. However, there was a significant positive correlation between preoperative sE-selectin concentrations and serum IGF-1 concentrations and between preoperative sE-selectin concentrations and insulin resistance (r = 0.62, P = 0.03; and r = 0.65, P = 0.02, respectively).
All patients underwent transphenoidal pituitary surgery as primary treatment. Three patients had repeated surgery because postoperative tumor residuals were considered to be accessible for additional debulking by a recently introduced intraoperative magnetic resonance imaging technique (PoleStar N-10; Odin Medical Technologies). Transphenoidal surgery provided effective tumor debulking as documented by at least partial decreases in disease activity and serum IGF-1 concentrations. After neurosurgery, seven patients (58%) were cured as defined by clinical and biochemical criteria, i.e., age-adjusted serum IGF-1 concentrations within the reference interval and GH suppressed to <1 μg/L during the oral glucose tolerance test (Fig. 1, ○), an often cited definition of cure in patients with acromegaly (13). Five patients had persistent disease activity, as documented by nonsuppressible GH concentrations (Fig. 1, ●), although two of these had IGF-1 values within the age-adjusted reference interval.

The pre- and postoperative findings are summarized in Table 1, and the IGF-1 and sE-selectin concentrations in each individual patient are shown in Fig. 1. IGF-1 decreased from 761 (328) to 267 (102) μg/L (P < 0.005).

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>P*</th>
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<tbody>
<tr>
<td>IGF-1, μg/L</td>
<td>761 (321)</td>
<td>267 (102)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.7 (0.9)</td>
<td>5.0 (0.9)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
<td>208 (125)</td>
<td>117 (37)</td>
<td>0.009</td>
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<tr>
<td>Insulin resistance, HOMA score</td>
<td>7.6 (4.5)</td>
<td>3.7 (1.1)</td>
<td>0.005</td>
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<tr>
<td>Blood pressure, mmHg</td>
<td></td>
<td></td>
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<tr>
<td>Systolic</td>
<td>141 (24)</td>
<td>130 (18)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diastolic</td>
<td>86 (13)</td>
<td>82 (6)</td>
<td>0.35</td>
</tr>
<tr>
<td>sE-Selectin, μg/L</td>
<td>50.6 (21.3)</td>
<td>42 (12.6)</td>
<td>&lt;0.01</td>
</tr>
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* Paired t-test.

Plasma glucose and serum insulin concentrations decreased in the same period (P < 0.005 and <0.01, respectively). Insulin sensitivity, as estimated by homeostasis model assessment, improved in 11 of the 12 patients. Systolic blood pressure was 141 (24) mmHg before and 130 (18) mmHg after the operation (P = 0.09), and diastolic blood pressure decreased slightly from 86 (13) to 82 (6) mmHg. sE-Selectin decreased in 10 of 12 patients, from 50.6 (21.3) μg/L before surgery to 42 (12.6) μg/L after surgery (P < 0.01).

Acromegalic patients exhibit many features of the metabolic syndrome, including arterial hypertension, insulin resistance, and a high frequency of macrovascular complications. Compared with patients with the metabolic syndrome, patients with acromegaly have less visceral fat and SAS is even more prevalent. Serum sE-selectin concentrations were often increased at diagnosis of acromegaly in our study, irrespective of SAS. In the preoperative condition, sE-selectin was positively correlated with IGF-1 concentrations and insulin resistance, suggesting that insulin resistance and GH excess are related to the increase in sE-selectin. We found no significant correlation between sE-selectin and blood pressure or fasting plasma glucose.

Increased sE-selectin has also been reported in patients with GH deficiency and could be reduced toward reference values with GH replacement (14). Thus, GH per se may not to be directly responsible for the high sE-selectin serum concentrations observed in acromegalic patients. Apparently both GH deficiency and GH excess lead to impaired endothelial function. Endothelial-dependent, flow-mediated dilatation was impaired in patients with active acromegaly and improved after successful treatment (15, 16), indicating that endothelial dysfunction may be reversible, at least to some extent. In our study, serum sE-selectin concentrations decreased after pituitary surgery along with an improvement of insulin sensitivity.

In conclusion, serum sE-selectin concentrations are of-
ten increased in acromegalic patients and decrease after pituitary surgery. sE-Selectin as an endothelial cell-specific product might be useful in the assessment of cardiovascular risk in patients with acromegaly. An improvement in sE-selectin concentrations may be related to decreased progression of macrovascular disease and normalization of long-term morbidity and mortality as observed after curative pituitary surgery (17–19).

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References


References


References


C-Reactive protein (CRP), the prototypical acute-phase protein, is produced by liver hepatocytes and regulated by cytokines, particularly interleukin-6 (1, 2). Circulating concentrations of CRP indicate inflammatory activity, and the recent development of highly sensitive CRP assays (3–5) has led to the discovery that slight increases in CRP (1–2 mg/L) are indicative of low-grade inflammatory processes that may be related to the pathophysiology of cardiovascular disease. More than a dozen population-based studies have demonstrated that increased CRP is an independent risk factor for future cardiovascular disease, with adjusted odds ratios >2.0 (6–9). The American Heart Association and the CDC have recommended measurements of CRP in clinical practice and called for additional population-based research (10).

A potential obstacle to the measurement of CRP (as well as other biomarkers) in large epidemiologic, community-based studies is the requirement for venous blood. Venipuncture is a relatively invasive procedure that must be performed by a trained phlebotomist (usually in a clinical setting), and it requires readily accessible facilities where blood samples can be promptly processed and stored under controlled conditions. Assays using whole blood dried on filter paper may provide a viable alternative: Several community-based applications have shown this to be a convenient and reliable means to facilitate sample collection, storage, and transportation, and laboratory methods have been validated for a growing number of analytes (11–16). “Guthrie papers” have been a core component of US hospital-based newborn-screening programs since the 1960s and are subject to a rigorous quality-control program (17).

Samples can be collected on filter paper easily by nonmedical personnel: The patient’s finger is pricked with a sterile, disposable lancet (commonly used by diabetics), and up to five drops of blood (~50 μL per drop) are spotted onto standardized filter paper (no. 903; Schleicher and Schuell) that is certified to meet perfor-