Iron-Deficiency Anemia Is Associated with High Concentrations of Transferrin Receptor in Serum

Kari Punnonen,1,3 Kerttu Irjala,1 and Allan Rajamäki2

We evaluated the use of transferrin receptor (TfR) in serum as an index of iron deficiency in 19 patients diagnosed as having iron-deficiency anemia, in 17 patients with anemia of chronic disease, and in a control group of 19 nonanemic patients who underwent elective ocular or nasopharyngeal surgery. The assessment of iron status of the anemic patients was based on the presence of stainable iron on bone marrow examination. In the patients with iron-deficiency anemia, the serum TfR concentration was 5.3 ± 1.8 mg/L (mean ± SD), significantly higher than in the control group (1.7 ± 0.5 mg/L) or in the patients with anemia of chronic disease (1.6 ± 0.4 mg/L). This study suggests that serum TfR measurement is a reliable index of iron depletion and potentially of importance in the diagnosis of iron-deficiency anemia.

Indexing Terms: bone marrow staining/transferrin

Iron-deficiency anemia can be caused by dietary deprivation of iron or by iron malabsorption and may be the first clinical sign of increased blood loss. Quite often, iron-deficiency anemia warrants extensive investigations of the gastrointestinal tract, given the relatively high probability that ulcers or malignant tumors are the cause of excessive blood loss. The distinction between iron-deficiency anemia and the anemia that accompanies infection, inflammation, or malignancy is not clear; the commonly used laboratory tests do not necessarily distinguish these common causes of anemia (1, 2). Conventional laboratory indices of iron status include serum iron, transferrin-total iron-binding capacity, transferrin saturation, and ferritin. Although each of these measurements has merit, no single determination gives a reliable index of iron status (2–4). High sensitivity as well as specificity are of special importance for a test of iron status, because further identification of the cause of depletion of iron stores requires tedious clinical and laboratory investigations. The absence of stainable iron on bone marrow examination is generally regarded as the only reliable index of iron deficiency.

Iron delivery to erythroblasts is mediated by the interaction of plasma transferrin with cell surface transferrin receptors (TfRs) (5, 6). The TfR protein has two identical polypeptide chains, 95 kDa each, and is present on the surfaces of virtually all cells. In normal adults, however, −80% of the receptors are in the erythroid marrow (5). The number of TfRs on the cell surface reflects the iron requirement (7). Deprivation of iron results in prompt induction of TfR synthesis (7). Soluble TfR has been identified in human serum and plasma; it is a truncated form of tissue receptor, with the truncation occurring at a site just beyond the cell membrane (8). Recently, serum concentrations of TfR have been suggested as a reliable index of iron depletion (2, 6, 9–13). In earlier studies of iron depletion, the iron status was not confirmed by bone marrow examination. Therefore, we analyzed serum TfR in a group of anemic patients, and correlated the TfR concentrations with the type of anemia and presence of stainable iron in bone marrow.

Subjects and Methods

Patients. A total of 36 anemic patients participated in this study. Bone marrow examinations were performed on all patients to identify the type of anemia and to study the iron stores. All procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983. On the basis of bone marrow examinations, 19 patients (13 women and 6 men) who fulfilled the morphological criteria of iron deficiency and who had no stainable iron on bone marrow examination were defined as having iron-deficiency anemia. For a control group, we used 19 age- and sex-matched patients (13 women and 6 men) who underwent elective ocular or nasopharyngeal surgery. No bone marrow examinations were performed on these patients but, to exclude patients with anemia or acute inflammation, we checked their hemoglobin, erythrocyte indices, erythrocyte sedimentation rate, and serum C-reactive protein concentrations and found them to be within the reference intervals. Another 17 anemic patients (10 women and 7 men) were selected on the basis of bone marrow examinations to form the group defined as having anemia of chronic disease. These patients had stainable iron on bone marrow examination (median storage iron 2+, range 1+ to 4+ on a scale from 0 to 4+), and their sideroblast count ranged from 5% to 15%. Of the 17 patients with chronic disease, 8 had recurrent or chronic infections, and the remaining 9 patients had other conditions related to miscellaneous chronic diseases.

Methods. Bone marrow was aspirated from the sternum, and smears were stained by the May–Grünwald–Giemsa method (stain provided by Orion Diagnostica, Helsinki, Finland); the iron stores were stained by the Prussian blue method. Blood counts were measured with an automated analyzer (Technicon H*2; Miles, Tarrytown, NY). Serum TfR was assayed with a commercially available kit based on a polyclonal antibody in a sandwich enzyme immunoassay format (Clinigen™;

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R&D Systems, Minneapolis, MN). The reference range provided by the kit manufacturer for TfR analysis is 1.54 ± 0.43 mg/L (n = 1000). Ferritin was measured (reference range 15–306 μg/L for men, 5–103 μg/L for women, according to the manufacturer) with an IRMA (Spectria™; Orion Diagnostica). Transferrin was measured [reference range 2.1–3.4 g/L for men, 2.0–3.1 g/L for women (14)] with a Behring Nephelometer (Behringwerke, Marburg, Germany) and antibodies provided by Dakopatts (Glostrup, Denmark). Serum iron (reference range 10–40 μmol/L) was measured with an Iron FZ assay (Hoffmann-LaRoche, Basel, Switzerland), based on a guanidine hydrochloride/ferrozine reaction. The transferrin index (TI) was calculated as iron (μmol/L)/transferrin (g/L), as recently suggested by Beilby et al. (15).

Results and Discussion

We analyzed serum TfR concentrations and performed conventional laboratory tests in anemic patients and correlated the results with the type of anemia and presence of iron in bone marrow. A total of 36 anemic patients participated in this study, and the results for blood counts and iron status markers are presented in Table 1. Common practice in Finland includes measuring the complete blood count, serum iron, transferrin, and ferritin when examining anemic patients. In patients with no chronic disease these values have been helpful in clinical decision-making. However, acute-phase responses make the interpretation of the laboratory data difficult, given that both serum ferritin and serum transferrin are acute-phase reactants, the former increasing and the latter decreasing in acute illness (3, 14, 16–18). Serum iron concentration is lower in patients with iron-deficiency anemia than in healthy subjects, but it cannot be used to distinguish iron-deficiency anemia from anemia of chronic disease. In the present study the mean serum transferrin concentration was slightly higher in the patients with iron-deficiency anemia than in the controls (Table 1), but the iron saturation of transferrin calculated as the TI is more useful than either serum iron or serum transferrin alone (15) (Fig. 1, top). The mean serum ferritin concentration was lower in patients with iron-deficiency anemia (9 ± 6 μg/L, mean ± SD) than in the controls (72 ± 89 μg/L, mean ± SD), but was significantly increased in the patients with anemia of chronic disease (288 ± 274 μg/L) (Table 1). Thus, the use of ferritin as a marker of iron deficiency is complicated by the acute-phase responses associated with chronic disease.

We evaluated the use of serum TfR as an index of body iron status in anemic patients and correlated the TfR concentration with the presence of iron stores in bone marrow. The individual values of transferrin, TI, ferritin, and TfR are shown in Fig. 1. In the patients who had anemia fulfilling the morphological criteria of iron deficiency anemia and no stainable iron on bone marrow examination, the serum TfR concentration was 5.3 ± 1.8 mg/L, significantly higher than that in the control group (1.7 ± 0.5 mg/L). In 18 of the 19 patients with iron-deficiency anemia, the serum TfR concentration was higher than in any of the control subjects. In the patients with anemia of chronic disease (and readily stain-

**Table 1. Markers of iron status in anemic patients and controls (mean ± SD).**

<table>
<thead>
<tr>
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<th>Controls</th>
<th>Iron-deficiency anemia</th>
<th>Anemia of chronic disease</th>
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<tbody>
<tr>
<td>n</td>
<td>19</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>138 ± 13</td>
<td>89 ± 19</td>
<td>103 ± 13</td>
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<tr>
<td>Mean cell volume, fl</td>
<td>91 ± 4</td>
<td>73 ± 9</td>
<td>90 ± 7</td>
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<tr>
<td>Iron, μmol/L</td>
<td>17.3 ± 6.3</td>
<td>4.3 ± 2.5</td>
<td>7.1 ± 4.0</td>
</tr>
<tr>
<td>Transferrin, g/L</td>
<td>2.5 ± 0.4</td>
<td>3.3 ± 0.5</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>TI*</td>
<td>7.1 ± 2.7</td>
<td>1.3 ± 1.0</td>
<td>3.7 ± 1.5</td>
</tr>
<tr>
<td>Ferritin, μg/L</td>
<td>72 ± 89</td>
<td>9 ± 6</td>
<td>288 ± 274</td>
</tr>
<tr>
<td>TfR, mg/L</td>
<td>1.7 ± 0.5</td>
<td>5.3 ± 1.6</td>
<td>1.6 ± 0.4</td>
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*μmol (Fe)/g (transferrin).
able iron in bone marrow), the serum TFR concentration was 1.6 ± 0.4 mg/L, essentially equal to that in the control group. The values in the control group were well within the reference range provided by the kit manufacturer. Earlier studies have varied considerably in the concentrations reported for serum and plasma TFR, apparently because of the different specificities of the antibodies they used (6).

Clearly, a more specific index of iron-deficient erythropoiesis is needed. Serum concentrations of TFR have been suggested to reflect the availability of iron for erythropoiesis (1, 10, 11). So far no published studies have correlated the serum TFR concentrations with the true iron status (based on bone marrow examination). In the present study, we found that high serum TFR concentrations could effectively identify the patients with true iron deficiency (confirmed on the basis of absence of stainable iron in bone marrow) and that serum TFR measurements could also distinguish patients with iron-deficiency anemia from those with anemia of chronic disease. TFR measurement seems to provide a means of identifying iron depletion even in patients with acute-phase reactions associated with inflammatory conditions (1, 2); however, the effectiveness of TFR measurements in identifying latent iron deficiency remains to be evaluated. Earlier studies reported increased TFR concentrations in association with, e.g., increased erythropoiesis, hemolytic anemias, and acute leukemias (2, 13, 19, 20). However, none of these conditions generally constitutes a clinical problem in the identification of iron-deficiency anemia. On the basis of the present study, consistent with other previous reports (1, 2, 10), we conclude that the serum TFR concentration is a useful serum marker of iron depletion.

References