Serum ferritin concentration as an index of storage iron in rheumatoid arthritis

D. P. BENTLEY AND P. WILLIAMS

From the Department of Haematology, Welsh National School of Medicine, and Department of Rheumatology, University Hospital of Wales, Cardiff

SYNOPSIS  Serum ferritin concentration has been compared with semi-quantitative histochemical estimates of bone marrow iron deposits in 60 anaemic patients with rheumatoid arthritis. There was considerable variation in the visual assessment of iron stores made by different observers. Serum ferritin appears to be a particularly sensitive index of iron status when stores are low. The best means of detecting iron deficiency in rheumatoid arthritis are discussed.

Anaemia is a frequent finding in patients with rheumatoid arthritis and its severity roughly parallels the activity of the disease (Nilssen, 1948; Jeffrey, 1953). This anaemia is often hypochromic and microcytic as a result of a reduced flow of iron to the erythroblasts. Iron supply to the marrow may be limited either by a reduction in whole body iron or by defective release of iron from the reticuloendothelial system into the plasma pool. The latter case is associated with stainable reticuloendothelial iron stores (Cartwright and Lee, 1971). Whichever is the underlying cause, serum iron concentration and transferrin saturation are reduced. In the individual patient with rheumatoid arthritis the mechanism responsible for sideropenia cannot be defined without examination of the bone marrow for reticuloendothelial iron deposits. Iron therapy in the face of defective reticuloendothelial release will only serve to increase these stores without improving the supply of iron for haemoglobin synthesis.

Serum ferritin concentration has been shown to give an accurate indication of the amount of storage iron in normal subjects and in patients with iron deficiency and overload (Jacobs, Miller, Worwood, Beamish, and Wardrop, 1972; Walters, Miller, and Worwood, 1973). The purpose of this study is to evaluate serum ferritin concentration as an index of iron stores in patients with rheumatoid arthritis and to establish the best means of detecting iron deficiency in these patients.

Subjects and Methods

Subjects  Fully informed consent was obtained from all subjects taking part in this study. Sixty patients (nine men and 51 women) aged 38-71 years with classical or definite rheumatoid arthritis (Ropes, 1958) were investigated. They all had a haemoglobin concentration of less than 11.5 g/dl either at the time of the investigation or in the previous 12 weeks. Only nine patients had received iron therapy in the 12 months before the study and only two were receiving treatment at the time of the investigation. None of the patients had received any other haematinic. Three patients had received blood transfusions in the previous 12 months. Treatment for rheumatoid arthritis was not modified in any way.

Methods  Blood samples were analysed by means of a Coulter S automatic cell counter. Serum iron concentration was measured by the method of Young and Hicks (1965) and total iron-binding capacity (TIBC) was measured using the method of Ramsay (1957). Serum ferritin concentration was measured by the immunoradiometric method of Addison, Beamish, Hales, Hodgkins, Jacobs, and Llewllin (1972). Bone marrow fragments were obtained by aspiration from the sternum and smears stained in a single batch by the prussian-blue reaction (Dacie and Lewis, 1970). Intracellular stainable iron was assessed independently by four observers who were unaware of any other clinical or laboratory informa-

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There was considerable variation in the results of independent grading of iron stores in the bone marrow smears examined by the four observers. The initial assessment gave unanimous agreement for only 20 (33%) of the bone marrow smears examined. There was complete agreement on 11 of the 13 smears thought to contain no iron. In three of the six marrows finally thought to contain grade 1 iron stores at least one observer at first considered there to be no stainable iron present, and even in two marrow smears with grade 2 staining one observer initially reported iron absent. No individual observer showed any consistent bias.

After final assessment 13 (22%) smears were graded 0, six (10%) grade 1, 36 (60%) grade 2, and five (8%) had grade 3 iron stores. The haematological data for these patients in relation to their stainable marrow iron are summarized in Table 1. In the women the mean values for haemoglobin concentration, mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), serum iron, and transferrin saturation showed no significant difference between each group. Their mean TIBC showed a progressive fall with increasing marrow iron and the mean value in groups 2 and 3 was significantly lower than that in group 0 (t = 6.635 and 4.135 respectively, \( p < 0.001 \)).

The serum ferritin concentrations for each group are shown in Figure 1. As stainable iron stores increase there is a progressive rise in serum ferritin concentration. The mean (± SD) serum ferritin concentration in patients without stainable iron (grade 0) was 38 (± 19) μg/l and in those with minimal (grade 1) stores it was 53 (± 21) μg/l. Patients with grade 2 stainable iron had a mean (± SD) serum ferritin concentration of 200 (± 142) μg/l. In the five patients with gross (grade 3) marrow iron staining the mean serum ferritin (± SD) was 698 (± 500) μg/l. In simple iron-deficiency anaemia serum ferritin concentration is generally less than

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\text{Table I } \text{Haematological data in patients with rheumatoid arthritis (mean ± SD)}
\]

<table>
<thead>
<tr>
<th>Marrow Iron Grade</th>
<th>No. of Patients</th>
<th>Haemoglobin (g/dl)</th>
<th>MCV (f/l)</th>
<th>MCH (pg)</th>
<th>Serum Iron (μg/l)</th>
<th>TIBC (μg/l)</th>
<th>Transferrin Saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Males</td>
<td>3</td>
<td>10.8 ± 0.78</td>
<td>78.0 ± 10.4</td>
<td>24.7 ± 3.2</td>
<td>34.7 ± 5.8</td>
<td>457 ± 146</td>
<td>7.7 ± 2.1</td>
</tr>
<tr>
<td>Females</td>
<td>10</td>
<td>11.9 ± 1.39</td>
<td>78.9 ± 6.9</td>
<td>25.4 ± 2.7</td>
<td>40.0 ± 15.8</td>
<td>399 ± 48</td>
<td>10.4 ± 4.5</td>
</tr>
<tr>
<td>1 Males</td>
<td>0</td>
<td>11.35 ± 1.30</td>
<td>86.3 ± 1.30</td>
<td>27.5 ± 2.5</td>
<td>53 ± 21.3</td>
<td>338 ± 62</td>
<td>15.8 ± 5.4</td>
</tr>
<tr>
<td>Females</td>
<td>6</td>
<td>10.9 ± 1.7</td>
<td>77.7 ± 3.1</td>
<td>24.5 ± 1.4</td>
<td>25.2 ± 9.4</td>
<td>300 ± 45</td>
<td>8.8 ± 3.3</td>
</tr>
<tr>
<td>2 Males</td>
<td>6</td>
<td>11.1 ± 1.2</td>
<td>84.0 ± 1.2</td>
<td>27.2 ± 3.5</td>
<td>38.5 ± 23.4</td>
<td>314 ± 46</td>
<td>12.3 ± 7.5</td>
</tr>
<tr>
<td>Females</td>
<td>5</td>
<td>11.72 ± 1.7</td>
<td>82.6 ± 9.4</td>
<td>27.2 ± 3.5</td>
<td>38.8 ± 30.9</td>
<td>290 ± 37</td>
<td>13.0 ± 8.2</td>
</tr>
</tbody>
</table>

Fig. Serum ferritin concentrations in patients with rheumatoid arthritis (--- mean value). Bone marrow iron stores are graded 0 to 3.

tion, and graded as follows: grade 0, no stainable iron; grade 1, trace amounts of iron; grade 2, clearly visible stainable iron; grade 3, gross stainable iron deposits. Marrow smears which contained no particles were not considered suitable for assessment. Where disagreement occurred the final grading was decided after further examination of the smears.

Results

There was considerable variation in the results of independent grading of iron stores in the bone marrow smears examined by the four observers. The initial assessment gave unanimous agreement for only 20 (33%) of the bone marrow smears examined. There was complete agreement on 11 of the 13 smears thought to contain no iron. In three of the six marrows finally thought to contain grade 1 iron stores at least one observer at first considered there to be no stainable iron present, and even in two marrow smears with grade 2 staining one observer initially reported iron absent. No individual observer showed any consistent bias.

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12µg/l (Jacobs et al, 1972) but in only three of the patients with no stainable iron was the serum ferritin concentration below this level. When stainable iron was visible in the marrow the serum ferritin concentration was always greater than 20µg/l.

Discussion

Iron-deficiency anaemia in patients with rheumatoid arthritis may be difficult to distinguish from the hypochromic, microcytic anaemia found in patients with any chronic inflammatory or malignant disease in whom serum iron concentration and transferrin saturation are reduced but in whom iron stores are normal or increased (Bainton and Finch, 1964). The examination of bone marrow particles for iron deposits has therefore been accepted as the only valid means by which iron status can be evaluated in patients with rheumatoid arthritis.

In normal subjects serum ferritin concentration correlates well with iron stores measured by the phlebotomy technique (Walters et al, 1973). The relationship of serum ferritin concentration with stainable marrow iron in the present study indicates a similar association with body stores. The low serum iron concentration and transferrin saturation at all levels of storage iron (table I) again demonstrates the poor mobilization of reticuloendothelial iron characteristic of chronic inflammatory disease (Cartwright and Lee, 1971).

There are a number of advantages in using the serum ferritin concentration as an index of storage iron. It is more sensitive than the histochemical quantitation of marrow iron; in many cases normal serum ferritin values were found when no stainable iron could be detected in the marrow and the routine use of the prussian-blue reaction for this purpose may well overestimate the incidence of iron depletion. Moreover, the visual grading of iron has a considerable observer error even when only four grades are used. There are clinical advantages in a quantitative technique over a subjective assessment and in addition to this a blood test is more likely to be acceptable to the patient than marrow aspiration.

The present data show that the conventional parameters of iron status may all indicate iron deficiency in the presence of normal or increased amounts of storage iron. In patients with a serum iron concentration of less than 60 µg/100 ml, a transferrin saturation of less than 16% or a TIBC in excess of 400 µg/100 ml the mean serum ferritin concentration was either normal or raised (table II).

It is suggested that the serum ferritin concentration should be used to assess iron status in patients with rheumatoid arthritis. In the anaemic patients with rheumatoid arthritis a serum ferritin concentration of less than 12 µg/l is a clear indication for iron therapy. Concentrations in the normal range exclude iron deficiency as a contributing factor to the anaemia. Serum ferritin concentrations in excess of 200 µg/l indicate adequate reticuloendothelial reserves and are a contraindication to iron therapy.

Table II  Mean (± SD) serum ferritin concentration (µg/l) in female patients with rheumatoid arthritis and other parameters suggesting iron deficiency

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Serum Iron &lt; 60µg/100ml</th>
<th>Transferrin Saturation &lt; 16%</th>
<th>TIBC &gt; 400µg/100ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin</td>
<td>207-1</td>
<td>194-6</td>
<td>46-8</td>
</tr>
<tr>
<td>±283</td>
<td>±291-7</td>
<td>±37-5</td>
<td></td>
</tr>
</tbody>
</table>

References

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