Red cell ferritin content: a re-evaluation of indices for iron deficiency in the anaemia of rheumatoid arthritis

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Abstract

In iron deficiency anaemia basic red cell content of ferritin is appreciably reduced. This variable was determined in 62 patients with rheumatoid arthritis to evaluate conventional laboratory indices for iron deficiency in the anaemia of rheumatoid arthritis.

For 23 patients with rheumatoid arthritis and normocytic anaemia irrespective of plasma ferritin concentration, red cell ferritin content did not differ significantly from that for non-anaemic patients with rheumatoid arthritis. For 27 patients with rheumatoid arthritis and microcytic anaemia, the mean red cell ferritin content for patients with a plasma ferritin concentration in the 13-110 μg/l range was appreciably reduced. It was indistinguishable from that for patients with rheumatoid arthritis and classical iron deficiency anaemia, indicated by plasma ferritin concentrations of less than 12 μg/l. In contrast, the mean red cell ferritin content for patients with rheumatoid arthritis, microcytic anaemia, and plasma ferritin concentrations above 110 μg/l did not differ from that for patients with rheumatoid arthritis and normocytic anaemia. Oral treatment with iron in patients with rheumatoid arthritis, microcytic anaemia, and appreciably reduced red cell ferritin concentrations was accompanied by significant increases in haemoglobin concentration (p <0·01), mean corpuscular volume (p <0·01), and red cell ferritin contents (p <0·05). This treatment, however, did not produce any appreciable change in haemoglobin concentration in patients with rheumatoid arthritis, normocytic anaemia, and normal red cell ferritin contents.

These findings suggest that the indices for iron deficiency in patients with rheumatoid arthritis and anaemia should include peripheral blood microcytosis together with a plasma ferritin concentration of less than 110 μg/l.

Introduction

Anaemia is common in patients with rheumatoid arthritis, and its severity generally parallels the activity of the disease.[1] This inflammatory activity also promotes changes in iron metabolism that result in low plasma iron concentrations, reduced transferrin saturation, and microcytic, hypochromic red cells.[2] In anaemic patients with rheumatoid arthritis these findings are equally consistent with the anaemia of chronic inflammation and

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that of iron deficiency.[2] The concentration of ferritin in plasma is useful in resolving this clinical dilemma, with values of less than 12 μg/l being diagnostic of iron deficiency.[3 4] As plasma ferritin is an inflammatory acute phase reactant its clinical value as an indicator for iron deficiency is limited in anaemic patients with rheumatoid arthritis and plasma ferritin concentrations above 12 μg/l.[5 6] In these patients a variable and wide ranging lower limit of plasma ferritin concentration has been arbitrarily set at 55-110 μg/l.[4 6 7] This indefinite limit makes the decision of whether to give iron to these anaemic patients difficult. Such uncertainties are relevant as indiscriminate treatment with iron should be avoided; iron may possibly augment the rheumatoid synovial inflammatory process,[8] and there is also a potential risk of penicillamine nephropathy due to variable absorption from iron penicillamine complex formation.[9]

Human peripheral blood cells contain measurable amounts of ferritin, and basic red cell content of ferritin reflects the state of body iron stores, being raised in pathological iron overload and considerably reduced in uncomplicated iron deficiency anaemia.[10-12] In the present study we measured laboratory variables, including basic red cell ferritin content, in a large unselected group of anaemic patients with rheumatoid arthritis to define those indices that discriminate true iron deficiency anaemia from the anaemia of chronic inflammation.

Patients and methods

Twelve men and 50 women, aged 16 to 83 years, with classical or definite rheumatoid arthritis, were available for study. They comprised 11 men and 39 women with anaemia as defined by the criteria of the World Health Organisation (haemoglobin concentration for men <13·0 g/dl, for women <12·0 g/dl) and one man and 11 women, with active rheumatoid arthritis but without anaemia, who were selected as controls. Of these patients, 20 were receiving penicillamine alone and the 42 others were receiving a combination of non-steroidal anti-inflammatory agents and either hydroxychloroquine,[3] intramuscular gold salts,[10] oral glucocorticoids,[9] or immunosuppressive agents.[13] No patient had received oral or parenteral treatment with iron in the preceding six months.

On entry into the study patients were assessed according to standard haematologic variables together with plasma iron, transferrin, and ferritin concentrations and red cell ferritin content. Disease activity was arbitrarily assessed by means of joint counts, duration of morning stiffness, global assessment by a single examiner, and determination of erythrocyte sedimentation rate (westergren).

Anaemia was microcytic (mean corpuscular volume <80 fl) in 27 of the 50 anaemic patients and normocytic (mean corpuscular volume 80-95 fl) in 23. For analysis these patients were arbitrarily divided into four groups according to whether their plasma ferritin concentration was 12 μg/l or less (group 1), 13-55 μg/l (group 2), 56-110 μg/l (group 3), or above 110 μg/l (group 4).

After three months 12 patients with microcytic anaemia and 19 patients with normocytic anaemia were evaluated again according to the described clinical, haematological, and iron variables. During this period seven patients with microcytic anaemia and plasma ferritin concentrations below 55 μg/l (groups 1 and 2) and nine with normocytic anaemia and plasma ferritin concentrations of 55-110 and above μg/l (groups 2 to 4) were given ferrous sulphate 350 mg daily. Three patients taking penicillamine and oral iron separated the iron and penicillamine doses by at least six hours.[9]

Basic red cell ferritin content and plasma ferritin concentration were assayed, as described in greater detail previously, with the hepatic ^{125}I ferritin immunoassay (Gammadab Travenol Laboratories Inc, Massa-

chusetts, USA).[14] Basic red cell ferritin content was expressed as attogram/cell (one attogram (ag) $=10^{-18}$ g), which for 17 normal men and 15 normal women ranged from 4-47 ag/cell, geometric mean 10·7 ag/cell.[14] To measure other biochemical variables standard techniques were used.[15 16] Peripheral blood haematological indices were determined by automated techniques in an Ortho ELT-800 Laser Analyzer (Ortho Diagnostic System Inc, Massachusetts, USA).

Statistical analysis was done with Student's t test. As with plasma ferritin concentration, red cell ferritin content is log normally distributed,[17] and for these variables statistical analysis was performed with log transformed data and results were transformed again as antilogs to recover original units of measurement.

Results

Of the 62 patients with rheumatoid arthritis whom we evaluated, 12 had normal haemoglobin concentrations. The mean basic red cell ferritin content of 6·5 ag/cell (range 2-30 ag/cell) for this group was

Table I also shows values for 27 patients with rheumatoid arthritis and microcytic anaemia. The haemoglobin and plasma iron concentrations and the degree of transferrin saturation for patients in each group did not differ significantly. The reduced mean corpuscular volume showed a progressive increase from mean 72 (SD 4) fl for patients with a plasma ferritin concentration below 55 μg/l (groups 1 and 2) to 77 (3) fl for patients with a plasma ferritin concentration greater than 110 μg/l (group 4, p<0·05).

The mean red cell ferritin content for all patients with microcytic anaemia was significantly lower than that for a normal population (groups 1 to 3, p<0·001; group 4, p<0·05), but only the patients with microcytic anaemia and a plasma ferritin concentration of less than 110 μg/l (groups 1 to 3) had mean red cell ferritin concentrations significantly lower than those for non-anaemic patients with rheumatoid arthritis or patients with rheumatoid arthritis and normocytic anaemia (p<0·05).

Table II shows the results of three months' treatment with oral iron in seven patients with microcytic anaemia and nine with normocytic anaemia and compares these findings with those from patients who did

TABLE I—*Geometric mean (range) ferritin values and mean (SD) haematological variables in anaemic patients with rheumatoid arthritis*

	No of patients	Plasma ferritin (µg/l)	Haemoglobin (g/dl)	Mean corpuscular volume (fl)	Plasma iron (µmol/l)	Transferrin saturation (%)	Red cell ferritin (ag/cell)
Normal values		20-200	{ women > 12, men > 13	80-95	7-32	18-45	10·7 (4-47)
Patients with rheumatoid arthritis and normocytic anaemia (n = 23)							
Group 2†	10	30 (16-54)	11·2 (0·8)	87 (6)	8 (3)	13 (5)	3·6 (2-18)
Group 3‡	4	79 (64-107)	10·5 (0·8)	89 (3)	9 (4)	17 (6)	4·8 (4-7)
Group 4§	9	223 (112-989)	10·5 (0·8)	87 (4)	9 (4)	19 (10)	8·7 (3-23)
Patients with rheumatoid arthritis and microcytic anaemia (n = 27)							
Group 1*	8	6 (2·5-12)	10·1 (1·1)	72 (4)	5 (3)	8 (5)	1·2 (0·5-4)
Group 2†	5	32 (23-53)	9·8 (1·6)	72 (4)	5 (3)	8 (6)	1·0 (0·5-3)
Group 3‡	7	86 (57-110)	10·0 (1·1)	75 (5)	7 (6)	15 (10)	1·5 (0·5-3)
Group 4§	7	235 (123-311)	10·7 (0·9)	77 (3)	5 (2)	11 (5)	4·4 (2-15)

Plasma ferritin concentrations: * ≤12 µg/l; † 13-55 µg/l; ‡ 56-110 µg/l; § >110 µg/l.
  Conversion: SI to traditional units—Iron: 1 µmol/l ≈ 5·6 µg/100 ml.

TABLE II—*Haematological variables before and after three months' treatment with oral iron in patients with rheumatoid arthritis and anaemia*

	Mean (SD)				Geometric mean (range)	
	Haemoglobin (g/dl)	Mean corpuscular volume (fl)	Plasma iron (µmol/l)	Transferrin saturation (%)	Plasma ferritin (µg/l)	Red cell ferritin (ag/cell)
Patients with microcytic anaemia						
Patients given oral iron (n = 7):						
Before	9·4 (1·7)***	70 (5)****	4 (3)	5 (4)	7 (2·5-24)*	1·2 (0·5-4)**
After	12·8 (1·4)***	82 (5)****	6 (3)	6 (4)	33 (19-92)*	5·6 (0·5-36)**
Patients not given oral iron (n = 5):						
Before	10·7 (0·6)	75 (3)	5 (3)	12 (9)	23 (9-53)	1·4 (0·5-3)
After	10·5 (1·5)	76 (6)	6 (3)	8 (4)	20 (5-38)	1·8 (0·5-3)
Patients with normocytic anaemia						
Patients given oral iron (n = 9):						
Before	11·0 (0·7)	88 (4)	9 (2)	15 (3)	50 (17-156)	6 (3-18)**
After	11·5 (0·8)	87 (4)	9 (2)	17 (4)	92 (30-319)	11 (5-24)**
Patients not given oral iron (n = 10):						
Before	11·3 (0·8)	82 (6)	8 (3)	15 (5)	114 (29-487)	7 (2-23)
After	11·9 (0·9)	89 (3)	8 (3)	17 (9)	108 (21-463)	9 (3-41)

Conversion: SI to traditional units—Iron: 1 µmol/l ≈ 5·6 µg/100 ml.
Significance of differences in: * plasma ferritin concentration, p<0·05; ** red cell ferritin content, p<0·05; *** haemoglobin concentrations, p<0·01; **** mean corpuscular volume, p<0·01.

not significantly different from that for a normal population (10·7 (range 4-47 ag/cell)).

Table I shows the variables conventionally measured to assess anaemia together with the red cell ferritin content for 23 patients with rheumatoid arthritis and normocytic anaemia. We did not identify any patients with normocytic anaemia and a plasma ferritin concentration of less than 12 µg/l. Findings from investigation of patients, when grouped according to plasma ferritin concentrations, did not show any significant difference for haemoglobin concentration, mean corpuscular volume, or degree of transferrin saturation. The mean red cell ferritin content for each of the three groups of patients with normocytic anaemia was not significantly different from that for the 12 patients with rheumatoid arthritis and a normal haemoglobin concentration.

not receive oral iron. There was no significant difference in variables of activity of the disease between the four groups and there was no significant change in these variables between groups before or after treatment with oral iron (data not shown).

Discussion

Iron deficiency anaemia in patients with rheumatoid arthritis may be difficult to distinguish from the microcytic anaemia found in chronic inflammatory disease. In uncomplicated iron deficiency reduced marrow iron is a reliable index for this

deficiency. This reduction in stainable marrow iron correlates with both microcytosis and lowered plasma ferritin concentrations.[18][19] In addition, a plasma ferritin concentration of less than 12 μg/l is a clear indication for treatment with iron in an anaemic patient.[5][7] Plasma ferritin concentrations in patients with rheumatoid arthritis show, however, a less satisfactory correlation with bone marrow iron, as normal plasma ferritin concentrations are found with absent bone marrow iron.[3][4] Although a plasma ferritin concentration of less than 12 μg/l indicates iron deficiency, the diagnostic importance of concentrations above 12 μg/l is not entirely clear as the lower limit of plasma ferritin concentration for these patients has not been clearly defined.[3][4] Because of these conflicts other potential indices of iron deficiency in patients with rheumatoid arthritis need to be explored; in this study we evaluated basic red cell content of ferritin.

Basic red cell ferritin content reflects the rate of uptake of iron by marrow erythroid cells, which is dependent in part on the degree of transferrin saturation.[10-12] Thus in iron deficiency and, to a lesser degree, the anaemia of chronic inflammation, both characterised by low plasma iron concentration and reduced transferrin saturation,[2] basic red cell ferritin content is reduced.[11][12][20]

In the present study we determined the basic red cell ferritin content of patients with rheumatoid arthritis and indisputable iron deficiency anaemia as indicated by microcytosis and a plasma ferritin concentration below 12 μg/l.[3][4] The red cell ferritin content for this group was then compared with that for anaemic patients with rheumatoid arthritis and either normocytic or microcytic blood changes and variable plasma ferritin concentrations. The basic red cell ferritin content for patients with microcytic anaemia and plasma ferritin concentration in the range 13-110 μg/l was not significantly different from that for other anaemic patients with rheumatoid arthritis and classical iron deficiency or non-arthritic patients with iron deficiency anaemia.[20] Patients with microcytic anaemia and plasma ferritin concentrations above 110 μg/l showed appreciably higher values for mean corpuscular volume and a mean red cell ferritin content no different from that for patients with normocytic anaemia. In the patients with normocytic anaemia, the red cell ferritin for patients with plasma ferritin concentration above 110 μg/l was not significantly different from that for a normal population. In patients with this anaemia and a plasma ferritin concentration of 13-110 μg/l red cell ferritin content was significantly reduced compared with that for a normal population but not compared with that for patients with rheumatoid arthritis and normal haemoglobin concentrations.

These findings suggest that in anaemic patients with rheumatoid arthritis a plasma ferritin concentration in the 13-110 μg/l range, in itself, is not predictive for variables associated with iron deficiency anaemia—namely, pronounced microcytosis and a reduced red cell ferritin content. An explanation for this paradox may be that in patients with rheumatoid arthritis iron is redistributed into body compartments that sequester this metal, not altering plasma ferritin concentration but effectively reducing the amount of iron available for erythropoiesis. The degree of this iron compartmentalisation may determine the development of iron deficiency anaemia in patients with rheumatoid arthritis who have similar plasma ferritin concentrations. Sites for this abnormal distribution of body iron include lymph nodes[13] and synoviums.[21][22] A synovial iron content of 800 mg has been estimated to represent patients who have widespread active disease.[23]

Our findings suggest that the pragmatic clinical indicators for iron deficiency in anaemic patients with rheumatoid arthritis should include microcytosis together with a plasma ferritin concentration of up to 110 μg/l. The reduced red cell ferritin content in patients with normocytic anaemia and a plasma ferritin concentration ranging from 13 to 110 μg/l may simply reflect iron metabolic changes consequent on chronic inflammation. Only extensive formal studies evaluating the therapeutic effect of oral iron in these patients will resolve this uncertainty. The response to treatment with oral iron in the limited number of patients with anaemia and rheumatoid arthritis in this study was compatible with the above suggestions. Oral iron treatment did not have any significant effect on the haemoglobin or plasma ferritin concentrations or the red cell ferritin content of patients with normocytic anaemia. In patients with microcytic anaemia and appreciably reduced red cell ferritin concentration, treatment with iron resulted in an appreciable rise in haemoglobin concentration, which was accompanied by increases in red cell and plasma ferritin concentrations, independent of disease activity. These results suggest that more extensive trials are required to evaluate the effect of oral iron treatment in selected patients with rheumatoid arthritis and anaemia grouped according to the findings of this study.

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