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Serum ferritin as indicator of iron responsive anaemia in patients with rheumatoid arthritis

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SUMMARY In order to test the hypothesis that serum ferritin below 60 μg/l is a good indicator of iron deficiency in patients with rheumatoid arthritis peroral iron was given to 67 patients with active rheumatoid arthritis over a three month period. A rise in haemoglobin concentration was taken as evidence of iron responsive anaemia. In anaemic patients serum ferritin below 60 μg/l was a good indicator of iron responsive anaemia, with a predictive value of 83%. Although high plasma transferrin and low mean cell volume showed similar predictive values, more patients with iron deficiency anaemia could be diagnosed by serum ferritin measurements than by other conventional blood tests. In contrast, the predictive value of serum ferritin above 60 μg/l was low (50%). The test was of no predictive value in non-anaemic patients. In patients with anaemia and active rheumatoid arthritis serum ferritin is the best blood test currently available for the prediction of iron responsive anaemia.

Key words: iron deficiency.

In patients with active rheumatoid arthritis (RA) anaemia may be caused by the 'anaemia of chronic disorders' and iron deficiency. The differential diagnosis between these two types of anaemia is potentially important but may be extremely difficult unless bone marrow smears stained for iron are examined. The main reason for the difficulty is that the usual blood tests indicating iron deficiency (mean cell volume (MCV), mean corpuscular haemoglobin concentration (MCHC), serum iron) are affected similarly in the two types of anaemia. The magnitude of the problem is due to the fact that practically all patients with RA of a certain disease activity develop the anaemia of chronic disorders and up to 75% of the same patients also have iron deficiency.[1 2]

Serum ferritin is a good indicator of iron stores in the organism and is valuable in the diagnosis of iron deficiency anaemia. Since it is also an acute phase reactant it might a priori be of dubious value in RA.

In a previous study we showed that in patients with anaemia and RA serum ferritin levels below 60 μg/l indicated iron deficiency, as assessed by bone marrow examination, better than any other conventionally used blood test (MCV, MCHC, serum iron, plasma transferrin).[3] Similar results have been reported by others.[1 2 4 5]

The present study was undertaken to examine if serum ferritin in patients with RA could predict which patients would respond to iron therapy with a rise in haemoglobin (Hb) concentration.

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Materials and methods

Ninety one patients from the Department of Rheumatology, Hvidovre Hospital, who all had classical or definite RA according to the criteria of the American Rheumatism Association were treated with iron. Informed consent was obtained from all patients and approval obtained from the local ethical committee.

In 67 patients iron therapy was continued for the entire three months and laboratory values obtained before and after the therapy. There were 52 women and 15 men. Their ages ranged from 22 to 87 years (median 64 years). All the patients received various forms of antirheumatic therapy, including treatment with disease modifying drugs. No patients had

manifest bleeding or received blood transfusions during the study.

All patients received ferrous sulphate tablets equal to 200 mg of iron daily The iron was given irrespective of the presence of anaemia. Twenty five women and 10 men were anaemic at the start of the treatment, while 27 women and five men had Hb within the normal range.

Laboratory investigations before and after three months of iron therapy included Hb, MCV, MCHC, serum iron, plasma transferrin, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) in serum according to routine practice at the hospital laboratory. Serum ferritin was measured with a radioimmunoassay kit from Clinical Assays, Cambridge, Mass., USA; the coefficient of variation was 8%

A Student's *t* test, Fishers's test, and Spearman's correlation test were used for the statistical analyses.

Results

The predictive values of the laboratory variables for changes in Hb in anaemic patients are given in Table 1; all changes in Hb were included. Serum ferritin <60 μg/l predicted an increase in Hb during iron therapy in 83% (19/23) of the patients, while Hb decreased in 50% (6/12) of the patients with serum ferritin ≥60 μg/l ($p<0.01$). In non-anaemic patients serum ferritin had no predictive value. Hb increased in 61% (11/18) of the patients with serum ferritin <60 μg/l and decreased in 40% (4/10) of patients with serum ferritin ≥ 60 μg/l ($p>0.05$). In four patients with serum ferritin <60 μg/l the Hb was unchanged during iron therapy.

The results from the individual patients are given in Tables 2a, b, and c. In Table 3 are given the group means and SEM. There was no difference in serum ferritin between anaemic and non-anaemic patients, but serum ferritin increased during iron therapy. In the anaemic patients MCHC, serum iron, and plasma transferrin were lower than in non-anaemic patients, and ESR and CRP were higher. During iron therapy there was a decrease in plasma transferrin in both anaemic and non-anaemic patients. There was no change in the overall disease activity as judged by an unchanged ESR and CRP during the three months.

Discussion

This study has shown that in anaemic patients with RA serum ferritin levels below 60 μg/l indicate iron responsive anaemia with a rather high degree of accuracy (83%). Although MCV and plasma transferrin scored comparably high percentages, it is evident from Table 1 that serum ferritin would diagnose more patients with iron deficiency anaemia than any other blood test. If the simultaneous presence of low serum ferritin and high plasma transferrin were taken as evidence of iron deficiency anaemia, the predictive value would be further increased (to 91%), but again with a loss of the number of patients correctly defined as having iron deficient anaemia. None of the tests were of any value in predicting a negative response to iron therapy, and although low serum ferritin levels were found in several patients in the non-anaemic group, the predictive value was too low to be of any clinical value in predicting a rise in Hb concentration in this group of patients.

These results support our previous data which showed that serum ferritin was a good indicator of iron deficiency as assessed by bone marrow examination and further defined the clinical applicability of this blood test in terms of its ability to predict iron responsive anaemia in these patients.[3] These results and those reported by others[2 4] show that serum ferritin is the best blood test for evaluating the iron status in patients with RA. It needs to be considered whether it should replace bone marrow examination in this context.

It is not completely clear why serum ferritin values above 60 μg/l could not predict a negative

Table 1 *The predictive values of laboratory variables for a rise or decrease in Hb during iron therapy in anaemic patients with rheumatoid arthritis*

Predictive value of an abnormal test (Hb increase)		*Predictive value of a normal test (Hb decrease)*	
Serum ferritin<60 μg/l	19/23=83%	Serum ferritin≥60 μg/l	6/12=50%
Serum iron<9 μmol/l	20/28=71%	Serum iron≥9 μmol/l	2/7=29%
Plasma transferrin>36 μmol/l	12/14=86%	Plasma transferrin≤36 μmol/l	8/20=40%
MCV<80 fl	5/6=83%	MCV≥80 fl	9/28=32%
MCHC <19·0 mmol/l	9/13=69%	MCHC≥19.0 mmol/l	6/21=29%

Table 2a *Laboratory values before and after three months of iron therapy in anaemic women*

Age	*Hb (mmol/l)** ♀*7·0–10·0** ♂*8·0–11·0*		*Serum ferritin (µg/l)*		*MCV (fl) 80–110*		*MCHC (mmol/l)* 19·0–22·0*		*Serum iron (µmol/l) 9·0–35·0*		*Plasma transferrin (µmol/l)* 21–36*		*ESR (mm/1st h)*		*Serum CRP (mg/l) 0–10*	
	month 0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3
44	6·3	8·4	5	23	76	79	18·0	20·8	<6·0	11·6	49	33	10	8	16	19
72	6·5	5·8	8	27	88	92	20·9	20·5	9·3	18·9	50	38	14	5	22	10
52	6·6	8·3	9	43	84	74	18·0	19·4	6·0	14·5	44	40	8	5	3	3
80	6·7	7·2	12	9	93	91	18·7	19·2	<6·0	<6·0	48	44	44	25	54	4
27	6·3	6·5	15	20	94	88	19·8	20·1	<6·0	7·9	40	42	85	68	121	139
63	6·7	6·0	17	48	80	88	19·5	17·6	<6·0	7·1	33	30	35	34	79	206
58	6·1	7·2	19	39	86	85	19·4	20·2	7·4	7·4	35	31	124	122	69	51
87	6·7	8·2	22	65	96	95	19·7	20·0	8·2	25·9	41	48	18	3	3	2
60	6·5	6·7	23	111	99	94	19·5	20·3	<6·0	<6·0	29	20	77	70	84	222
73	6·3	7·8	26	84	87	86	17·9	19·1	<6·0	<6·0	33	30	45	46	78	316
65	7·0	6·0	28	39	95	81	18·3	18·4	5·6	<6·0	33	33	37	46	90	44
65	6·8	7·6	29	90	78	81	18·4	19·8	7·4	3·2	32	21	20	30	60	75
78	5·3	6·6	31	34	102	92	19·3	17·8	5·6	5·5	39	34	60	49	—	—
75	5·6	7·2	32	59	110	90	17·0	18·8	6·1	9·7	29	23	60	48	—	—
51	5·9	5·6	39	93	79	77	19·0	19·3	<6·0	6·8	33	33	50	56	123	109
49	6·9	6·1	60	72	88	88	20·2	18·5	6·9	<6·0	31	32	80	70	134	133
72	6·9	8·0	81	127	91	95	19·3	20·1	13·4	13·1	—	28	42	45	48	37
56	5·9	5·6	85	143	95	89	20·0	20·1	<6·0	<6·0	26	25	140	130	258	280
69	6·5	7·5	90	115	90	89	19·9	19·1	6·5	8·9	39	38	117	63	59	16
41	6·4	5·5	98	123	92	86	18·0	16·0	<6·0	0·3	34	25	76	74	—	—
57	6·3	6·2	106	43	80	81	19·7	19·4	<6·0	<6·0	40	29	66	66	152	135
73	6·1	6·5	132	120	94	—	19·8	—	4·7	<6·0	30	30	130	116	198	125
72	6·2	5·6	169	174	86	80	17·8	19·2	6·6	<6·0	34	35	70	80	126	83
64	6·0	6·6	173	136	86	95	19·0	18·5	1·6	<6·0	23	28	87	61	205	132
80	4·9	5·7	295	610	89	104	16·3	14·6	1·6	4·4	21	26	63	63	—	—

*SI conversion; Hb—mmol/l×16·1=g/l; MCHC—mmol/l×1·612=g/dl; plasma transferrin—µmol/l×0·074=g/l.

Table 2b *Laboratory values before and after three months of iron therapy in non-anaemic women*

Age	*Hb (mmol/l)* ♀*7·0–10·0** ♂*8·0–11·0*		*Serum ferritin (μg/l)*		*MCV (fl) 80–110*		*MCHC (mmol/l)* 19·0–22·0*		*Serum iron (μmol/l) 9·0–35·0*		*Plasma transferrin (μmol/l)* 21–36*		*ESR (mm/1st h)*		*Serum CRP (mg/l) 0–10*	
	month 0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3
25	8·6	9·3	6	23	89	103	20·1	19·2	28·8	16·6	45	43	1	2	1	3
56	7·2	7·8	13	35	88	83	20·0	20·1	9·7	12·4	44	34	35	25	24	19
66	8·7	8·1	16	22	98	—	20·7	—	20·2	21·2	39	37	3	3	5	2
57	7·2	7·2	18	24	82	—	19·1	—	<6·0	—	35	—	47	47	98	82
40	7·2	8·6	18	56	81	92	19·3	20·8	<6·0	6·9	41	35	5	3	49	20
22	7·6	8·1	21	25	—	—	—	—	—	—	—	—	34	38	32	15
54	7·3	8·3	21	45	82	84	21·3	19·9	<6·0	<6·0	37	37	39	17	123	76
56	7·6	7·5	21	77	89	92	20·2	20·1	8·6	10·6	46	38	48	24	52	22
60	9·3	9·3	26	50	84	98	20·9	21·7	16·0	15·4	41	37	6	11	6	14
47	8·1	7·8	26	62	95	94	21·7	20·4	13·7	17·1	33	33	49	57	33	33
65	8·6	8·6	27	42	93	89	20·0	20·1	13·7	15·7	46	44	18	26	31	25
68	7·7	7·8	28	67	87	84	20·8	20·8	<6·0	12·4	46	41	38	38	18	12
69	7.5	6·9	30	73	104	106	—	20·9	13·2	11·8	36	32	48	69	40	122
34	7·1	7·0	31	81	84	85	19·8	19·3	<6·0	8·6	43	39	79	61	61	37
43	7·9	7·6	32	41	97	90	20·5	20·5	13·7	19·8	36	36	4	4	2	1
55	7·2	7·8	41	53	93	81	19·8	19·7	<6·0	<6·0	41	40	86	27	102	94
60	7·8	7·5	51	83	80	78	19·0	20·7	8·9	8·4	32	23	23	26	32	94
30	8·3	8·7	53	183	86	88	20·2	20·1	15·2	20·0	42	35	11	31	19	39
65	7·1	7·3	54	91	88	84	20·3	20·2	8·6	17·0	38	36	48	26	84	62
62	8·5	9·1	56	123	87	97	21·2	21·5	14·2	21·0	37	25	32	98	5	3
64	8·4	8·4	57	33	86	98	23·5	19·6	8·1	10·7	37	33	38	17	12	21
59	9·4	8·7	64	148	85	83	22·3	21.4	14·0	8·1	42	34	16	34	9	51
56	8·7	8·3	68	116	94	95	20·8	19·4	10·8	17·5	35	38	31	34	39	64
66	8·0	7·0	70	173	85	88	20·6	20·2	12·7	<6·0	35	29	20	77	43	84
67	8·4	9·0	85	146	89	97	20·4	21·0	6·6	13·9	46	46	44	40	27	13
76	7·1	7·7	91	51	99	95	19·7	20·8	14·3	10·8	37	41	38	50	30	24
57	7·5	8·5	100	179	92	83	20·3	21·2	13·4	24·6	40	41	11	7	4	3

*SI conversion: Hb—mmol/l×16·1=g/l; MCHC—mmol/l×1·612=g/dl; plasma transferrin—μmol/l×0·074=g/l.

Table 2c *Laboratory values before and after three months of iron therapy in anaemic and non-anaemic men*

Age	*Hb (mmol/l)* ♀*7·0–10·0** ♂*8·0–11·0*		*Serum ferritin (μg/l)*		*MCV (fl) 80–110*		*MCHC (mmol/l)* 19·0–22·0*		*Serum iron (μmol/l) 9·0–35·0*		*Plasma transferrin (μmol/l)* 21–36*		*ESR (mm/1st h)*		*Serum CRP (mg/l) 0–10*	
	month 0	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3
Anaemic men																
53	7·6	9·6	8	115	79	99	19·1	19·4	0·6	61·3	53	37	35	14	—	—
71	6·8	8·1	10	47	105	104	19·5	19·8	10·7	15·6	45	39	91	—	—	—
62	6·9	7·1	16	101	100	86	18·8	18·8	<6·0	<6·0	40	33	60	100	52	97
67	6·7	9·0	34	19	73	84	18·8	21·1	30·1	18·7	44	37	40	28	84	13
70	7·7	8·8	35	101	103	92	20·4	21·9	13·5	17·2	39	30	49	37	45	91
57	7·2	7·7	39	62	—	94	—	21·6	6·8	10·9	33	31	26	25	37	23
59	8·0	7·6	51	89	101	114	19·1	18·2	6·1	10·4	30	28	92	—	—	—
65	7·7	8·0	53	91	101	96	19·8	20·6	13·2	16·2	36	36	31	43	6	2
60	7·4	6·8	118	52	95	95	18·9	17·6	11·8	3·2	31	34	103	73	—	—
43	5·9	6·4	136	48	77	77	20·2	18·2	<6·0	<6·0	28	30	127	41	130	62
Non-anaemic men																
52	10·7	10·8	54	121	99	93	21·3	20·6	20·4	16·4	42	39	2	2	23	39
42	8·6	9·6	74	183	107	96	20·7	22·4	30·5	28·5	43	44	15	6	16	5
34	8.5	9·7	107	201	95	86	20·1	19·8	13·5	7·8	31	33	15	38	133	199
66	9·6	9·8	113	206	75	74	20·8	—	11·1	10·1	38	38	10	24	29	73
60	10·5	9·4	132	141	95	90	23·1	20·5	24·3	17·2	37	36	4	4	4	2

*SI conversion: Hb—mmol/l×16·1=g/l; MCHC—mmol/l×1·612=g/dl; plasma transferrin—μmol/l×0·074=g/l.

Table 3 *Laboratory values before and after three months of iron therapy**

	Before iron therapy		*After three months of iron therapy*
Hb females (mmol/l)†			
anaemic	6·3±0·1	‡	6·8±0·2
non-anaemic	§7·9±0·1		§8·1±0·1
Hb males (mmol/l)†			
anaemic	7·2±0·2		7·9±0·3
non-anaemic	§9·6±0·5		§9·9±0·2
Serum ferritin (µg/l)			
anaemic	60±11		91±16
non-anaemic	50±6	‡	92±10
MCV (fl)			
anaemic	90±2		89±1
non-anaemic	90±1		90±1
MCHC (mmol/l)			
anaemic	19·1±0·2		19·2±0·3
non-anaemic	§20·6±0·2		§20·5±0·1
Serum iron (µmol/l)			
anaemic	8·2±1·2		13·0±2·5
non-anaemic	§14·6±1·2		14·8±1·1
Plasma transferrin (µmol/l)			
anaemic	36±1	‡	32±1
non-anaemic	§39±1	‡	§36±1
ESR (mm/1st h)			
anaemic	63±6		53±7
non-anaemic	§28±4		§30±4
CRP (mg/l)			
anaemic	87±12		90±17
non-anaemic	§37±6		§42±8

*Values are mean±SEM.
†SI conversion: mmol/l×16·1=g/l.
‡$p<0·05$ for difference between before and after iron therapy.
§$p<0·05$ for difference between anaemic and non-anaemic patients.

outcome of iron therapy. It must be appreciated, however, that the reference value used in this work, viz a rise in Hb concentration after iron therapy, may not be quite fair to the test, since a change in disease activity during the three months of iron treatment may also influence the Hb concentration in the individual patients. Actually, in five of the six patients who in spite of high serum ferritin values showed an increase in Hb concentration (data are missing for the sixth patient) disease activity decreased as judged from decreasing values for CRP, and consequently the recording of these patients as a failure regarding the predictive value of a high serum ferritin for no Hb response to iron therapy may not be correct. The strength of the design of this study is that it was shown that a low serum ferritin value could predict a positive outcome of iron therapy despite the presence of confounding factors influencing the Hb concentration in these patients.

Seventy five per cent of the anaemic patients and 50% of the non-anaemic patients showed a rise in Hb concentration after three months of iron therapy, and 87% of all patients showed an increase in serum ferritin values. Also a significant decrease in plasma transferrin values after treatment was noted (Table 3). This indicates that functional iron deficiency and iron deficiency anaemia were extremely common in our patients, in agreement with previous experience.[1–3] It also indicates that peroral iron is readily absorbed in these patients, despite the simultaneous presence of the anaemia of chronic disorders, which is believed to be associated with a decrease of iron absorption from the intestines.[6] The fact that no test could predict which of the non-anaemic patients would show an increase in Hb concentration is probably due to the fact that iron deficient erythropoiesis was not prominent in these latter patients. Thus they had normal values for MCV and MCHC and no significant increase in Hb concentration after treatment (Table 3).

This interpretation of our finding is not necessarily at variance with that of Bentley and Williams, who demonstrated a transient rise in Hb after parenteral iron treatment of patients with RA and anaemia.[7] They suggested that patients with RA may, as a rule, not be iron deficient, but that a relative iron deficiency in the bone marrow may exist due to excessive entrapment of iron in the inflamed synovial membrane.

In our previous study we found no correlation between serum ferritin and plasma fibrinogen, and in the present study no correlation between serum ferritin and CRP could be shown. It thus seems quite well documented that serum ferritin is not a conventional acute phase reactant, though it is increased in active RA per se. These findings constitute the basis for our proposal that serum ferritin levels below 60 µg/l may be used as a cut off point indicating iron deficiency in patients with RA regardless of the disease activity. This value is five times higher than the usual lower limit of serum ferritin indicating iron deficiency.[8] The peculiar role of serum ferritin, which is increased in active disease but does not follow the conventionally used parameters of disease activity, calls for further studies of the pathophysiology of serum ferritin in active RA.

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