Does active rheumatoid arthritis affect intestinal iron absorption?

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SUMMARY One of the causes of anaemia in rheumatoid arthritis is thought to be defective iron absorption. In this study the ⁵⁹Fe absorption in patients with active rheumatoid arthritis is measured and correlated with the results for bone marrow iron stores (and in some cases with the iron stores in the terminal duodenum), which were assessed simultaneously with semiquantitative methods, and with the serum ferritin concentration. In 11 patients with rheumatoid arthritis and increased bone marrow iron stores, iron absorption was decreased. In five patients it was normal and in three further patients, whose bone marrow iron stores were depleted, iron absorption was maximally increased. According to the results both intestinal malabsorption and defective iron absorption can be excluded as causes.

Key words: anaemia, whole body counting.

One of the most common extra-articular features of active rheumatoid arthritis (RA) is anaemia, which is generally normocytic, normochromic, and at times slightly hypochromic. Its pathogenesis is complex and by no means clear.^{1,2} In addition, depending on the index of activity, patients with RA show a decreased serum iron concentration, decreased serum transferrin, and increased serum ferritin. Serum ferritin generally yields higher than normal baseline values in patients suffering from RA.^{3,4} Abnormal ferrokinetic parameters⁵⁻⁷ and heterotopic quantitative iron stores have been demonstrated in synovial tissue⁸ and lymph nodes.⁹

To what extent 'defective' iron absorption is causally related to the anaemia, the altered iron status, and the heterotopic pattern of iron stores associated with RA has been studied by various authors.¹⁰ The studies published to date, however, are either based on indirect or semiquantitative methods^{11,12} or appear to be inconclusive.^{13,14} Their results do not agree.

We have therefore measured whole body ⁵⁹Fe retention in 19 patients suffering from RA with varying bone marrow iron stores.

Patients and methods

PATIENTS

In 19 patients (12 female, 7 male, mean age 54 years, range 24–73) with active rheumatoid arthritis, all of whom fulfilled the criteria of the American Rheumatism Association, intestinal iron absorption was measured before starting treatment with gold, D-penicillamine or azathioprine, and corticosteroids. The duration of disease before the diagnostic absorption test and the other laboratory assays ranged from six months to several years.

Before our investigations 13 patients had received only non-steroidal antirheumatic agents, which were given in the form of suppositories on the day of the diagnostic test—four hours after administration of the nucleide at the earliest. One patient was given 40 mg prednisolone daily several days before and during the test period because symptoms could not be relieved with other measures. Five patients had previously received gold or azathioprine, or both. No patient had been given oral or parenteral iron therapy for a period of several months before our investigations. In no case did we find residual endothelial siderosis in the bone marrow. This specific heterotopic iron compartment in human bone marrow is commonly detected after intravenous administration of colloidal iron. The typical uniform granules representing non-ferritin iron in

lysosomes of endothelial cells disappear only one to three years after iron therapy has been stopped.¹⁵

CONTROLS

The controls were six patients with iron deficiency anaemia who did not suffer from arthritis and 20 healthy persons with normal iron intake (11 female, nine male); two further patients had iron overload owing to repeated transfusions. None of the controls received any drug.

TEST AND SOLUTION

We used the diagnostic ⁵⁹Fe absorption test¹⁶ using 10 µmol (0.56 mg) ⁵⁹Fe⁺⁺ labelled ferrous chloride with 100 µmol (17.6 mg) L-ascorbate in 0.001 N HCl administered orally with 100 ml water (distilled three times). The activity of the solution was relatively high at 0.19–0.37 MBq because not only was ⁵⁹Fe absorption measured with a whole body counter but also external organ measurement and articular ⁵⁹Fe deposits were recorded with variable detectors (unpublished data). Whole body activity is generally counted 14 days after oral administration of the nucleide and the iron absorption recorded as a percentage of the total administered dose of ⁵⁹Fe. This procedure is based on the assumption that unabsorbed ⁵⁹Fe has been completely eliminated by then. Recently we have begun to realise that intestinal iron absorption is a more complicated process than hitherto thought and includes such components as mucosal uptake, mucosal transfer, and mucosal elimination^{17 18} and continues over a long period of time.

The amount of ingested iron which after transient mucosal uptake is again actively secreted into the intestinal lumen can be measured by whole body counting and is referred to as postabsorption excretion (PAE). According to Björn-Rasmussen PAE can be expressed mathematically as the proportion of nucleide excreted from the 10th day after oral administration of radioiron until no more than basal losses can be measured (PAE₁₀).¹⁹ We were interested in measuring the regulatory capacity in all of its components and chose the time period from the seventh to the 14th day after nucleide administration for the PAE counts, though this is not strictly speaking representative.

Under these conditions the following standards hold for the diagnostic ⁵⁹Fe absorption test: <10%=suspected Fe malabsorption, acquired iron overload; 10–45% (24% in men; 32% in menstruating women)=iron absorption of healthy subjects; 50–100%=depleted iron stores; idiopathic haemochromatosis, iron loading anaemias.^{20 21}

WHOLE BODY COUNTER

A whole body counter is a large volume radio-

Table 1 Summary of experimental results

Group*	n†	7d-R‡ (%)	14d-R‡ (%) (NR‡ 10–45)	PAE‡ (%)	Hb‡ (g/l) (NR‡ 140±20) (♂ 160±20)	ESR‡ (mm/h) (NR≤20)	SI‡ (µmol/l) (NR 11–29)	TIBC‡ (µmol/l) (NR 43–72)	SF‡ (ng/ml) (NR 30–300)	Bone marrow iron (PBR)‡	RF‡ (No+ve/ No-ve)
A	11	14 (3.0)	10 (2.0)	29 (13.3)	109 (9)	65/94	7 (2.5)	51 (7.2)	331 (263.6)	↑	6/5
B	5		25 (6.1)		131 (18)	28/67	9 (3.6)	54 (10.7)	226 (177.5)	N(†)	3/2
C	(3)‡	(32 (2.5))	(29 (1.2))	(7 (1.5))							
ID	3	96 (6.4)	94 (5.7)	2 (1.7)	92 (19)	47/82	6 (0.9)	93 (14.9)	5 (2.0)	↓	2/1
NC	6	95 (2.7)	93 (2.3)	2 (1.6)	92 (19)	14/33	5 (2.6)	87 (9.7)	11 (6.5)	↓	
PT	20		29 (7.7)		146 (15)	8/15	21 (3.6)	56 (4.2)	153 (50.1)	N	
	2	13	9	31	91	19/36	14	21	1890	↑	

*A/B/C=patients with active rheumatoid arthritis; A=increased iron stores and anaemia; B=normal iron stores and anaemia; C=depleted iron stores with anaemia; ID=control group, iron deficiency anaemia; NC=normal controls; PT=polytransfused patients (iron overload due to repeated transfusions).
†n=number of patients; 7d-R=⁵⁹Fe retention after seven days; 14d-R=⁵⁹Fe retention after 14 days; PAE=postabsorption excretion; Hb=haemoglobin; ESR=erythrocyte sedimentation rate; SI=serum iron; TIBC=total iron binding capacity; SF=serum ferritin; PBR=Prussian blue reaction; ↑=increased, ↓=depleted, N=normal iron stores, semiquantitatively determined on bone marrow sections²¹; RF=rheumatoid factor; NR=normal range.
‡In two of the five patients ⁵⁹Fe retention was measured after 14 days only.
Values are mean (SD); ESR column shows values after one hour/after two hours.

activity detector (Frieske and Hoepfner) with four scintillator blocks (NaI crystals, 5 inches each) that can be moved in three dimensions by means of motors and can be fitted to the individual body geometry of the recumbent patient in a reproducible manner. Two scintillator blocks are located above and two below the patient.

ADDITIONAL DATA

The laboratory data shown in Table 1, including the haematological and morphological parameters, were obtained by routine laboratory methods. Serum ferritin was measured with the two site solid phase assay of the sandwich type (RIA-Gnost ferritin, Behring-Werke AG). The results were not corrected to the WHO standard.

STATISTICS

Student's *t* test was used for statistical evaluation.^{22 23}

Results

In 19 patients (seven male, 12 female) who were experiencing an acute attack of RA the ⁵⁹Fe absorption rates ranged from 7% to 99%, i.e., their absorption rates ranged from normal to maximum. No significant correlation could be established between the individual absorption rates and the severity of the anaemia (*p*=0.001).

Group A (Table 1) consisted of anaemic RA patients with raised serum ferritin values and accordingly large bone marrow iron stores. The mean iron absorption rate in this group of 10 (SD 2)% was below normal (see also Fig. 1).

In group C (Table 1) all patients were also frankly anaemic (mean Hb 92 g/l). The serum ferritin values, averaging 5 (2) µg/l, indicate iron deficiency. According to the cytological results the bone marrow iron stores were depleted. As expected,

⁵⁹Fe Whole Body Retention

Fig. 1 ⁵⁹Fe whole body retention in various groups. ○=⁵⁹Fe seven day retention; ●=⁵⁹Fe 14 day retention; —=percentage ⁵⁹Fe 14 day retention in healthy men, mean (SD)=24 (10)%; - - - =percentage ⁵⁹Fe 14 day retention in menstruating women, mean (SD)=32 (10)%; hatched area=⁵⁹Fe absorption range (R) in patients with depleted iron stores with and without anaemia=50% ≤R≤100%.²⁰ Groups A, B, C, ID, NC, PT are defined in Table 1. N=number of patients.

iron absorption was maximally increased to 94 (5.7)% (Table 1 and Fig. 1).

In group B (Table 1) the patients had a normal red blood count, normal serum ferritin values, and normal to slightly raised bone marrow iron stores. In these patients normal iron absorption rates were accordingly measured. A significant difference in this parameter was found between groups A and B ($p=0.0001$).

In some patients in groups A, B, and C (Table 1) and in all patients in the group ID gastroduodenoscopy was performed for diagnostic purposes.

Biopsies of three patients in group A (increased bone marrow iron stores) indicated the presence of large amounts of iron positive material in the duodenal villi. Otherwise this was found only in two patients with an iron overload due to transfusions. In two patients from each of the groups B and C and in all controls with iron deficiency anaemia (group ID) no iron could be demonstrated in the duodenal villi.

PAE of ^{59}Fe was higher in group A (mean (SD)=29 (13.3)%) than in groups B and C (Table 1). Thus in group A a considerable amount of temporarily retained iron must have been actively eliminated, whereas this did not occur in patients with RA who also had deficient bone marrow iron stores and in patients with simple iron deficiency anaemia (groups C and ID, both mean PAE=2%). Our patients with an iron overload due to transfusions had a PAE of 31%; this corresponds to the mean PAE of group A (29 (13.3)%, Table 1).

Radioiron absorption of our normal controls (group NC) with a mean (SD) of 29 (7.7)% correlated well with previously published data in this field.²⁰ Ranges of serum iron and total iron binding capacity values corresponded with the iron status and inflammatory activity of our patients. Intestinal iron absorption rates do not correlate with sero-reactions; seropositive and seronegative RA patients did not behave differently in regard to iron retention (Table 1).

Discussion

Rheumatoid arthritis is almost always associated with massive heterotopic iron deposits in the synovial tissue and the lymph nodes and, as long as no iron is lost owing to bleeding, correlates also with adequate to excessive bone marrow iron stores (Drews, unpublished data). Simultaneously the serum ferritin values are moderately to greatly increased and, depending on the disease activity, anaemia is observed, with typical haemoglobin values of between 90 and 120 g/l.

Various authors have published studies on iron

absorption in patients with RA with divergent results.

Jeffrey *et al* calculated the iron absorption rates of 15 patients with RA from the difference between the amount of orally administered ^{59}Fe and the amount of ^{59}Fe that was eliminated with the faeces over a period of 10 days.¹¹ The investigation showed an increase in iron absorption by a factor of almost three in patients with RA compared with normal subjects. In this study, however, the iron status of the patients was not sufficiently well defined.

Weinstein studied only the early plasma iron kinetics of orally administered ^{59}Fe in six patients with RA whose iron status was not classified in detail.¹² He did not find significant differences between these patients and six normal controls.

Boddy and Will measured the ^{59}Fe whole body retention rate of 15 patients with RA by whole body monitoring.¹³ The authors administered ^{59}Fe labelled iron in the ferric state, which is not readily bioavailable, and in a dose of 5 mg, an amount which is known to lead to a dose dependent decrease in the percentage of iron absorption.²⁰ Under these conditions it is impossible to achieve a broad range of up to 100% retention of the orally administered nucleide and the distinction between persons with depleted iron stores and normosiderotic or hyper-siderotic stores is less clear.

Boddy and Will did not find any significant difference in iron absorption between RA patients with normochromic, normocytic anaemia and their control group. Patients with hypochromic anaemia, to whom the authors imputed iron deficiency without assessment of their exact iron status, showed an average iron absorption of only 50% of that of a group of subjects with iron deficiency anaemia not suffering from RA.

In principle it is possible with the diagnostic ^{59}Fe absorption test, which we used in all cases, to measure whole body retention scores up to 100% precisely and reproducibly with a whole body counter 14 days after nucleide administration, because of the very small oral dose of 10 μmol ^{59}Fe labelled ferrous chloride. If standardised test principles (see 'Patients and methods') are strictly adhered to it can be considered that the amount of iron absorbed depends on the available iron stores²¹; very few exceptions are known and these can be identified by the iron status of the blood and by histochemical investigations of bone marrow and Fe stores.

The question at issue is whether intestinal iron absorption of patients suffering from RA represents one exception that proves the rule.

Our results (Table 1 and Fig. 1) show that active RA is not accompanied by a defect in iron absorp-

tion, nor is such a defect responsible for the anaemia that is often associated with the disease. On the contrary, even in active RA there is an effective Fe absorption mechanism that compensates for iron deficiency by increasing the absorption rate. In cases of iron surplus, which is reliably reflected by the amount of iron confined to bone marrow macrophages, iron retention becomes protectively depressed. Accordingly patients with RA in group B fall within the 14 day iron retention normal range because during remission the anaemia is compensated for by use of the previously increased bone marrow iron stores (group B: mean (SD) 25 (6.1)%). From our results we infer that the degree of depression of iron absorption is related to the degree of severity of the anaemia in the patients with RA as long as the anaemia is exclusively related to the inflammatory process. This is always the case when utilisable iron is available in the bone marrow. If there is a negative iron balance, and if this is reflected as a depletion of iron stores, the organism adjusts iron absorption upwards to the highest physiologically possible degree, even during active disease.

The way the organism adjusts intestinal iron absorption rate to homeostatic requirements is not completely understood.¹⁴ Nevertheless, convincing positive correlation can be established between body iron stores and histochemically assessed iron content of mucosal macrophages in the upper intestine,^{24, 25} which favours the assumption that both iron compartments are connected in parallel. Thus the absorptive gut would be informed about actual iron requirements of the body and measurable postabsorption excretion of ingested iron would gain a morphological basis.

The parameter referred to here as PAE should not be regarded as established. It needs to be confirmed in a large group of subjects. We have used it in an 'abbreviated' form, because the PAE₁₀ defined by Björn-Rasmussen¹⁹ sometimes cannot be determined for certain until five weeks or more after nucleide administration.^{18, 25} As this would have postponed the beginning of therapy for an unacceptably long period the particular parameter PAE₁₀ (see 'Patients and methods') could not be established for our patients. Our measurements of PAE values are based on reports by Boender *et al*,²⁶ Boender and Verloop,²⁷ and Powell *et al*,²⁸ who all agree that orally administered non-absorbable radioisotopes are completely eliminated by one week after ingestion. Thus the difference in ⁵⁹Fe whole body retention measured between the seventh and the 14th day is an expression of a postabsorption phenomenon that corresponds to excretory processes involving mucosal iron in the

sense of Björn-Rasmussen.¹⁹ It must be presumed that a comparatively depressed ⁵⁹Fe absorption rate is associated with a high PAE and consequently iron ought to be detected histochemically in the mucosa of the small intestine. Our investigations of duodenal biopsy specimens indicate that only in RA patients with increased bone marrow iron stores can stainable iron be demonstrated in the duodenal wall. RA patients with normal or depleted iron stores had no mucosal iron. This agrees with studies of Astaldi *et al*, who did not find any iron positive villi in normosiderotic and hyposiderotic subjects in this section of the intestine, whereas hypersiderotic subjects did show mucosal iron.²⁹ We found in the duodenal biopsy specimens of hypersiderotic RA patients that lysosomal iron accumulations seen under the electron microscope and verified by means of x ray microanalysis are confined to perivascular and interepithelial macrophages in the tips of the villi of the terminal duodenum (unpublished results).

Occult intestinal bleeding is unlikely to influence PAE values of patients in groups A, B, NC, and PT as simultaneous Haemocult testing during measurement of ⁵⁹Fe absorption showed no positive reactions in stools. Some patients in group C and group ID had endoscopically verified slight intestinal bleeding; this could increase PAE. Median PAE (2%), however, corresponds well with PAE values of iron deficient patients without bleeding reported elsewhere.¹⁷ Possibly, intestinal irritation occurred in iron deficient RA patients (group C) owing to the use of non-steroidal drugs. The amount of drug induced blood loss, however, assessed by the ⁵¹Cr method hardly exceeds 3 ml a day,³⁰ which represents the detection limit of whole body counting over short time intervals.¹⁸ Thus our PAE data evaluated between day 7 and day 14 postabsorption would not be affected.

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