Correlation between Diagnostic $^{59}Fe^{2+}$-Absorption and Serum Ferritin Concentration in Man

H. C. Heinrich, J. Brüggemann, E. E. Gabbe, and M. Gläser

with the technical assistance of

Fatima Icagic and Ellen Pape

Division of Medical Biochemistry, Institute of Physiological Chemistry, University Hospital Eppendorf, University of Hamburg

(Z. Naturforsch. **32 c**, 1023 – 1025 [1977] ; received July 29, 1977)

Iron Absorption, Serum Ferritin, Iron Stores, Iron Deficiency

A high correlation coefficient $r = -0.832$ ($P_{r \neq 0} < 0.0001$) was estimated in man for the inverse relationship between the diagnostic $^{59}Fe^{2+}$-absorption and the serum ferritin concentration which is very close to the correlation $r = -0.88$ as described for the relationship between the diagnostic $^{59}Fe^{2+}$-absorption and the diffuse cytoplasmic storage iron in the bone marrow macrophages. The increase of the diagnostic $^{59}Fe^{2+}$-absorption seems to be an earlier and more sensitive indicator of depleted iron stores whereas the serum ferritin decreases somewhat later during the development of iron deficiency.

Depleted iron stores are characterized and can be diagnosed by the increased ^{59}Fe-absorption from a small 10 μmol (= 0.56 mg) $^{59}Fe^{2+}$-dose [1, 2, 4] since a correlation coefficient of $r = -0.88$ was estimated for the inverse relationship between intestinal $^{59}Fe^{2+}$-absorption and the "Berlin-Blue"-reactive diffuse cytoplasmatic non-haeme storage iron in the bone marrow reticuloendothelial cells [3, 4]. The traditional invasive method of Berlin-Blue staining the bone marrow for assessing body iron stores is however refused by many patients and has the disadvantage of being at the best a semiquantitative and subjective method with a limited reproducibility and capacity which requires some experience for a relevant evaluation by the observer. In order to investigate the possibility of substituting this classical method of assessing body iron stores by the recently introduced quantitative and reproducible immunoradiometric assay for serum ferritin [5, 6] we have studied the correlation between the diagnostic $^{59}Fe^{2+}$-absorption and the serum ferritin concentration in subjects with well defined stages of iron stores or iron deficiency [2–4].

The ^{59}Fe-absorption from a diagnostic 10 μmol (= 0.56 mg) $^{59}Fe^{2+}$-dose was calculated from the whole body retention of absorbed ^{59}Fe which was

Requests for reprints should be sent to Prof. Dr. H. C. Heinrich, Universitäts-Krankenhaus Eppendorf, Physiologisch Chemisches Institut, Medizinische Biochemie, Martinistr. 52, *D-2000 Hamburg 20*.

Table I. Diagnostic $^{59}Fe^{2+}$absorption (in %) and serum ferritin concentration (in ng/ml) in subjects with normal Fe-stores, prelatent, latent and manifest iron deficiency. (n = number of subjects, $\overline{X}_g$ = geometric mean, $C_{S.D.}$ and $C_{S.E.}$ = coefficients of standard deviation and standard error.)

Subjects with	Totals n	Range	$\overline{X}_g$	$C_{S.D.}$	$C_{S.E.}$	Males n	Range	$\overline{X}_g$	$C_{S.D.}$	$C_{S.E.}$	Females n	Range	$\overline{X}_g$	$C_{S.D.}$	$C_{S.E.}$
normal Fe-stores															
$^{59}Fe^{2+}$-absorption	67	10 – 53	29	1.45	1.05	29	10 – 47	26	1.47	1.14	38	16 – 53	32	1.38	1.05
serum ferritin	67	27 – 221	83	1.77	1.07	29	28 – 221	106	1.77	1.11	38	27 – 185	69	1.65	1.08
prelatent Fe-deficiency															
^{59}Fe-absorption	31	52 – 100	76	1.20	1.03	4	55 – 100	77	1.30	1.14	27	52 – 96	76	1.19	1.03
serum ferritin	31	7.8 – 64	27	1.77	1.11	4	16 – 30	24	1.34	1.16	27	7.8 – 64	27	1.83	1.12
latent Fe-deficiency															
^{59}Fe-absorption	15	63 – 100	89	1.17	1.04	4	96 – 97	96	1.00	1.00	11	63 – 100	85	1.19	1.06
serum ferritin	15	5.3 – 32	14	1.58	1.13	4	5.3 – 14	9.6	1.50	1.22	11	9.5 – 32	16	1.51	1.13
manifest Fe-deficiency															
^{59}Fe-absorption	45	63 – 100	87	1.17	1.02	11	71 – 100	91	1.13	1.04	34	63 – 100	86	1.17	1.03
serum ferritin	45	2.7 – 12	6.0	1.40	1.05	11	2.7 – 12	5.1	1.44	1.12	34	3.4 – 10	6.3	1.38	1.05

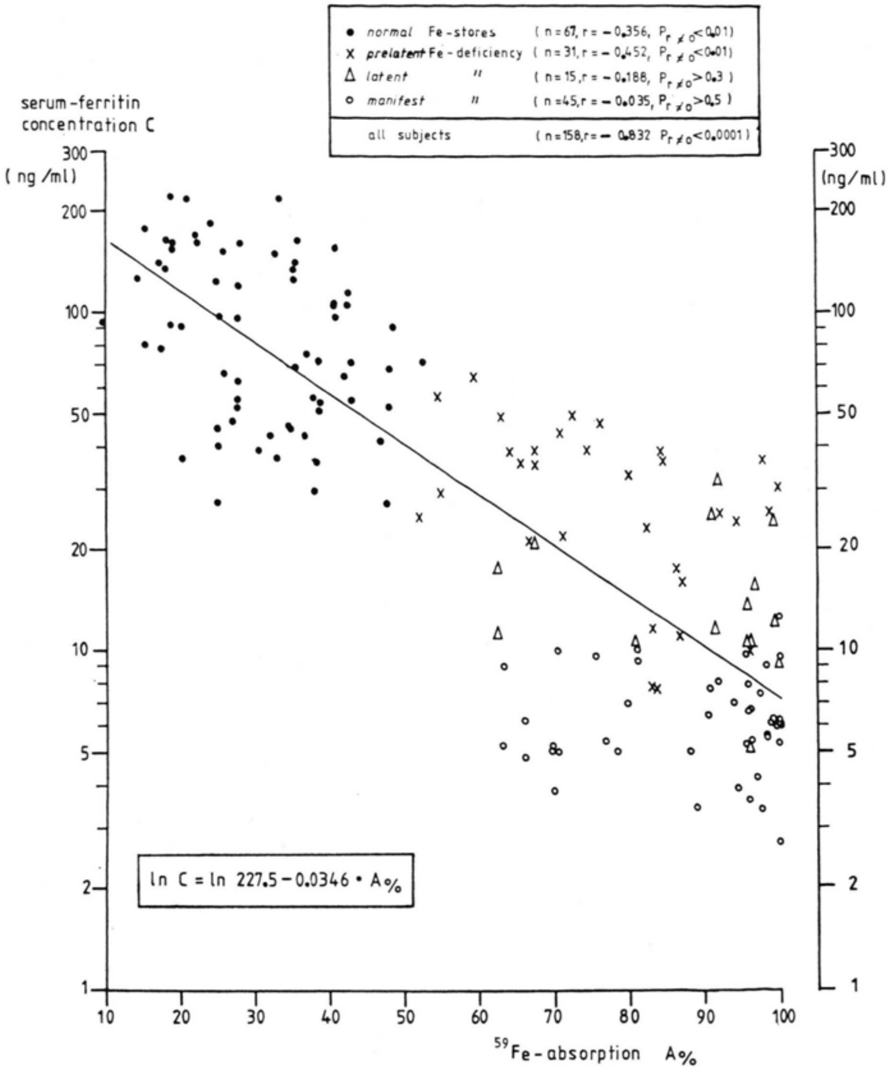

Fig. 1. Correlation between diagnostic $^{59}Fe^{2+}$-absorption and serum ferritin concentration.

measured in starved subjects after 14 days within the 4π-counting geometry of a whole body radioactivity detector with liquid organic scintillator [7]. Serum ferritin was estimated with an immunoradiometric assay using a modification [8] of the two-site or sandwich solid phase system [6]. According to their individual diagnostic $^{59}Fe^{2+}$-absorption, serum iron, total iron binding capacity and haemoglobin concentration the subjects were subdivided into 4 groups with *normal iron stores* (diagnostic $^{59}Fe^{2+}$-absorption normal: $10-53\%$; all other parameters normal), *prelatent iron deficiency* (diagnostic $^{59}Fe^{2+}$-absorption increased to $52-100\%$, $\overline{X}_g = 76\%$; all other parameters within the normal range), *latent iron deficiency* (in addition to increased diagnostic $^{59}Fe^{2+}$-absorption serum iron reduced below 60 μg/100 ml and the total iron binding capacity increased above 400 μg/100 ml; transferrin-Fe-saturation $<20\%$) and *manifest iron deficiency* (haemoglobin concentration <12 g/100 ml, Hb_E <27 pg/erythrocyte, transferrin-Fe-saturation $<15\%$).

The inverse relationship between the diagnostic $^{59}Fe^{2+}$-absorption $A_{\%}$ and the serum ferritin concentration C is described by the regression line $\ln C = \ln 227.5 - 0.0346 \cdot A_{\%}$ (Fig. 1). A high correlation coefficient $r = -0.832$ ($P_{r \neq 0} < 0.0001$) was estimated for this inverse relationship if the data of all the 158 patients were considered. This value is very close to the correlation of $r = -0.88$

as described earlier for the inverse relationship between the diagnostic $^{59}Fe^{2+}$-absorption and the diffuse cytoplasmatic storage iron in the bone marrow RE-cells [3,4]. The negative correlation between the diagnostic ^{59}Fe-absorption and the serum ferritin concentration was also still significant for the group of 67 subjects with *normal* iron stores ($r = -0.356$; $0.01 > P_{r \neq 0} > 0.001$) and the group of 31 subjects with *prelatent* iron deficiency ($r = -0.452$, $0.01 > P_{r \neq 0} > 0.001$). No significant correlation, however, was observed within the group of 15 subjects with *latent* iron deficiency ($r = -0.188$, $P_{r \neq 0} > 0.3$) and within the group of 45 subjects with *manifest* iron deficiency ($r = -0.035$, $P_{r \neq 0} > 0.5$).

Lower correlation coefficients of -0.58 [9] and -0.398 [10] have been described for the inverse relationship between serum ferritin and ^{59}Fe-absorption from larger amounts of $2-3$ mg iron which were added to a test meal and administered to normal subjects with non-defined iron stores. Because of the existing dose relationship of intestinal iron absorption in relation to iron stores smaller doses of ^{59}Fe (*e.g.* 0.56 mg Fe^{2+}) are more suitable for a non-overlapping separation between subjects with normal and depleted iron stores than larger doses of several mg Fe [11]. Many food components do furthermore interfere with the diagnostic reliability of intestinal $^{59}Fe^{2+}$-absorption so that a higher and more reliable correlation has to be expected between serum ferritin and the absorption from a small diagnostic dose of only 0.56 mg Fe^{2+} in starved subjects.

It seems that an increase of the diagnostic $^{59}Fe^{2+}$-absorption is an earlier and more sensitive indicator of iron stores depletion and that the serum ferritin levels decrease somewhat later. This explains that more than half of the serum ferritin levels in subjects with prelatent iron deficiency (total range 7.8 $-$ 64; $\overline{X}_g = 27$ ng/ml, $C_{S.D.} = 1.77$, Table I) are still within the lower normal range of $27-64$ ng/ml whereas the other half is below the lower normal border line of 27 ng/ml and within the range of 7.8 and 27 ng/ml (Fig. 1 and Table I). The depleted iron stores in prelatent iron deficiency which are characterized by the high negative correlation ($r = -0.88$) between the increase of diagnostic ^{59}Fe-absorption and the diminution of the diffuse cytoplasmatic storage iron in bone marrow RE-cells [2–4] therefore cannot be diagnosed only on the basis of reduced serum ferritin concentrations. Serum ferritin levels between 27 and 64 ng/ml are only suspect of being caused by depleted iron stores whereas serum ferritin levels below 27 ng/ml do definitely indicate the consumption of storage iron in subjects with prelatent, latent or manifest iron deficiency. If a serum ferritin rise due to increased release in infection or inflammation can be excluded by the simultaneous estimation of normal erythrocyte sedimentation rate, leucocyte count and body temperature serum ferritin levels above 64 ng/ml do exclude exhausted iron stores or prelatent iron deficiency.

Supported in part by research grants of "Deutsche Forschungsgemeinschaft".

1 H. C. Heinrich, Therapiewoche **17,** 2099 [1967].
2 H. C. Heinrich and H. Bartels, Klin. Wochenschr. **45,** 553 [1967].
3 K. Hausmann, R. Kuse, O. W. Sonnenberg, H. Bartels, and H. C. Heinrich, Acta Haematol. **42,** 193 [1969].
4 H. C. Heinrich, Iron Deficiency, pp. 213–294, Academic Press, London-New York 1970.
5 G. M. Addison, M. B. Beamish, C. N. Hales, M. Hodgkins, A. Jacobs, and P. Llewellin, J. Clin. Pathol. **25,** 326 [1972].
6 L. E. M. Miles, D. A. Lipschitz, C. P. Bieber, and J. D. Cook, Anal. Biochem. **61,** 209 [1974].
7 H. C. Heinrich, E. E. Gabbe, B. Meineke, and D. H. Whang, Klin. Wochenschr. **44,** 827 [1966].
8 Hoechst Pharmaceutical Research Laboratories, Behring Institute, 1977.
9 J. D. Cook, D. A. Lipschitz, L. E. M. Miles, and C. A. Finch, Amer. J. Clin. Nutrit. **27,** 681 [1974].
10 G. O. Walters, A. Jacobs, M. Worwood, D. Trevett, and W. Thomson, Gut **16,** 188 [1975].
11 H. C. Heinrich, E. E. Gabbe, and D. H. Whang, Z. Naturforsch. **24 b,** 1301 [1969].