



CLINICAL RESEARCH STUDY

Are we giving too much iron? Low-dose iron therapy is effective in octogenarians

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ABSTRACT

PURPOSE: Elderly patients are vulnerable to the dose-dependent adverse effects of iron replacement therapy. Our study examines whether low-dose iron therapy can efficiently resolve iron-deficiency anemia in patients over the age of 80 years and reduce adverse effects.

SUBJECTS AND METHODS: Ninety hospitalized patients with iron-deficiency anemia were randomized to receive elemental iron in daily doses of 15 mg or 50 mg as liquid ferrous gluconate or 150 mg of ferrous calcium citrate tablets for 60 days. Thirty control patients without anemia were given 15 mg of iron for 60 days. A 2-hour iron absorption test was performed after the initial dose. Hemoglobin and ferritin levels were measured on day 1, 30, and 60 after initiating therapy. Each patient completed a weekly questionnaire regarding drug-induced adverse effects.

RESULTS: Serum iron rose significantly in the anemic patients beginning 15 minutes after the first dose but not in nonanemic patients. Two months of iron treatment significantly increased hemoglobin and ferritin concentrations similarly in all 3 groups of iron-deficiency anemia patients (for example, hemoglobin levels rose from 10.0 g/dL to 11.3 g/dL with 15 mg/d of iron therapy and from 10.2 g/dL to 11.6 g/dL with 150 mg/d). Abdominal discomfort, nausea, vomiting, changes in bowel movements, and black stools were significantly more common at higher iron doses.

CONCLUSIONS: Low-dose iron treatment is effective in elderly patients with iron-deficiency anemia. It can replace the commonly used higher doses and can significantly reduce adverse effects.

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The percentage of iron absorbed in the gastrointestinal tract can vary from less than 1% to greater than 50%.¹ A feedback mechanism allows increased absorption when the stores of iron in the body are low and decreased absorption when they are sufficient.²

The usual recommended dose for treating iron deficiency in adults is between 150 mg and 200 mg of elemental iron

daily.³ Much higher doses are recommended when iron is poorly absorbed, for example, in patients on chronic dialysis.⁴ Absorption of dietary iron in the elderly is thought to be less efficient than in young patients, partly due to hypochlorhydria caused by atrophic gastritis.⁵ Between 10% and 20% of iron-treated patients experience gastrointestinal symptoms that may be ascribed to the iron preparation and that seem to be dose dependent.^{3,6} These patients sometimes require intravenous iron therapy.⁷ Although iron is essential for life, it is a double-edged sword that has been implicated in diseases in almost all body systems. There is epidemiologic evidence of a relation between high iron stores and liver

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injury, especially hemochromatosis,⁸ coronary artery disease,⁹ noninsulin dependent diabetes mellitus,¹⁰ Parkinson disease,¹¹ and recurrent infections.¹² Chronic iron intake may increase body stores resulting in some of these potentially harmful effects.

The recommended dietary intake of iron for older persons is 10 mg per day, indicating in healthy people that this amount can be absorbed and utilized.¹³ Two studies of iron-depleted patients demonstrated efficient absorption of small doses of iron (20 mg/d).^{14,15} However, the small iron dose was studied using a single absorption test for identifying iron deficiency without a longer therapeutic follow-up. A recent study of pregnant women demonstrated the efficacy of low-dose iron therapy to raise hemoglobin levels compared with placebo, without any gastrointestinal side effects.¹⁶ The aim of our study was to determine whether low-dose iron supplementation can replace the conventional doses for treatment of iron-deficiency anemia in patients over 80 years of age.

Subjects and methods

Sample

All consecutive admissions to the Acute Geriatric Ward of Kaplan-Harzfeld Medical Center between March, 2001, and February, 2004, were examined for hemoglobin and ferritin levels. Patients were enrolled in the study if they had hemoglobin levels between 80 g/dL and 119 g/dL and ferritin levels below 40 ng/mL. Patients who were unable or unwilling to sign an informed consent, or who had vitamin B₁₂ deficiency, severe systemic illness, underlying malignancy, considerable renal failure (creatinine level above 2.5 mg/dL), or who received iron therapy or a blood transfusion less than 1 week prior to enrollment were excluded, as were patients with positive serologies for celiac disease, active known gastrointestinal blood loss, and acute infection. Patients who were hospitalized in the same department at the same time, but who did not have laboratory evidence of anemia, served as a reference group and received 15 mg of elemental iron daily for 2 months.

Procedures

Participants were randomized to receive 15 mg, 50 mg, or 150 mg of elemental iron daily, either 1 hour prior to or 2 hours after meals. The low iron doses (15 mg and 50 mg) were given as liquid ferrous gluconate mixed in simple syrup. One tablet of 500 mg ferrous calcium citrate taken 3 times daily constituted the conventional treatment of 150 mg of elemental iron for 2 months (the large amount of liquid required for the 150-mg group

forced us to replace the ferrous gluconate with ferrous calcium citrate in the form of tablets).

Patients were assigned to the 3 treatment groups by a randomization box, which contained 90 notes: 15 mg was written on 30 notes, 50 mg was written on 30, and 150 mg was written on 30. When a new patient was enrolled in the study, the physician involved took out a folded note from the box and opened it.

Iron absorption was assessed 2 hours after intake of 15 mg of iron in all patients, including controls. Serum iron was measured before the first ingestion of iron and at 15, 30, 45, 60, and 120 minutes thereafter.

A complete medical history was obtained, and a thorough physical examination was performed. Baseline hemoglobin and ferritin blood levels were measured before any iron supplement was given and at days 30 and 60 after the start of the treatment. One physician was responsible for ongoing contact with the patients and for making home calls and visits to those unable or unwilling to attend follow-up appointments. A questionnaire was sent to the patients' primary physicians asking them to investigate the cause of iron deficiency and report the results.

Hemoglobin levels (reference range, >13 g/dL for men and 12 g/dL for women) were analyzed by an automated analyzer (Technicon H*2, Technicon Instruments Corp, Tarrytown, NY). Ferritin levels (range, 24 ng/mL to 300 ng/mL for men and 15 ng/mL to 307 ng/mL for women) were measured using a chemiluminescence assay (Access, Beckman, Fullerton, Calif). Serum iron levels (range, 59 µg/dL to 158 µg/dL for men and 37 µg/dL to 145 µg/dL for women), was measured using a closed Hitachi system (Roche Diagnostics Systems, Mannheim, Germany) based on a guanidine hydrochloride/ferrozine reaction. Anemia was defined as hemoglobin concentrations below 13 g/dL for men and below 12 g/dL for women. Iron deficiency was confirmed when ferritin levels were below 40 ng/mL on two separate tests.¹⁷⁻¹⁹ A questionnaire of 5 potential side effects was completed by all patients at the beginning of the study and at 10 days, 30 days, and 60 days after initiation of iron therapy. A visual analogue scale was used to assess the darkness of the stools and was divided arbitrarily into 4 levels: brown, dark, very dark, and black. An adverse effect that persisted for at least 1 week, with or without medical treatment, was considered clinically relevant.

The study was approved by the ethics committees of Kaplan Medical Center and the Israel Ministry of Health. All subjects signed an informed consent after receiving an oral explanation of the purpose of the study and its possible risks and benefits.

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Table 1 Baseline characteristics of participants receiving 2 months of iron therapy

Characteristic	Daily iron dose per group*			
	15 mg	50 mg	150 mg	No anemia 15 mg
	Number (%) or mean \pm SD			
Mean age, years	86.1 \pm 5.4	84.4 \pm 4.1	84.9 \pm 4.4	85.9 \pm 5.7
Male sex	11 (37)	12 (40)	14 (47)	11 (37)
Chronic diseases†	3.4 \pm 1.6	3.4 \pm 1.9	3.6 \pm 1.3	3.9 \pm 2.0
Medications‡	4.5 \pm 3.3	4.4 \pm 2.9	4.6 \pm 2.4	4.7 \pm 3.2
Mean hemoglobin level (g/dL)	10.0 \pm 1.1	10.9 \pm 1.0	10.2 \pm 1.3	13.1 \pm 0.9
Mean corpuscular volume (fL)	79.2 \pm 7.1	79.7 \pm 5.9	80.0 \pm 7.4	86.6 \pm 4.4
Ferritin (ng/mL)	19.8 \pm 6.6	25.1 \pm 8.8	22.2 \pm 9.1	93.9 \pm 16.5
C-reactive protein (mg/L)	11.6 \pm 6.6	14.9 \pm 9.0	13.5 \pm 8.3	52.6 \pm 36.1

(Reference range for the following values, hemoglobin: men, >13 g/dL and women, >12 g/dL; mean corpuscular volume: 80 fL to 99 fL; ferritin: men, 24 ng/mL to 300 ng/mL and women, 15 ng/mL to 307 ng/mL, C-reactive protein: 0.01 mg/L to 8.00 mg/L.)

*Thirty patients were included in each treatment group.

†Chronic diseases are defined as those requiring active treatment.

‡Medications is defined as any drug, including over-the-counter drugs.

Statistical analysis

The effect of iron supplementation on iron status and on adverse effects was assessed by the repeated-measures analysis of variance. The differences in blood tests at the 2 postbaseline assessment times were analyzed by analysis of covariance with a Bonferroni adjustment. Simple linear regression was used to compare the slopes of iron absorption curves. Paired *t* tests were used for comparison of mean values. All analyses were conducted using SPSS for Windows, version 10.0 (SPSS Inc, Chicago, Ill). The sample size was calculated according to our assumption that a 0.7 g/dL or less difference in hemoglobin concentration between the treatment groups 60 days after daily iron therapy would be considered as equivalent potency of the different doses, with 80% power, $\beta = 0.05$, standard deviation = 1.2 g/dL.

Results

Of 5329 admitted patients, 548 patients over the age of 80 years were admitted with a diagnosis of anemia during the 3-year study period. Of these 548 patients, 458 were excluded from the study: 217 with ferritin levels above 40 ng/mL, 30 were unable or unwilling to sign an informed consent, 61 had iron therapy before hospitalization, 53 had vitamin B₁₂ deficiency, and 32 had received recent blood transfusions. Another 19 patients were excluded because of severe systemic illness, 17 because of an acute infectious illness, 11 with disseminated malignancy, 10 had considerable renal failure, and 8 had positive antiendometrial antibodies.

The remaining 90 patients (16.4% of the hospitalized patients with anemia), 30 patients in each dose group, were randomized to receive 15 mg, 50 mg, or 150 mg of elemental iron daily for a 2-month period (Table 1). Another 30

hospitalized patients without anemia and with ferritin levels above 40 ng/mL acted as a reference group and were given 15 mg of iron daily for 60 days.

Iron absorption test

After ingestion of 15 mg of iron, serum iron concentration rose significantly in all iron-deficiency anemia patients, beginning 15 minutes after iron intake ($P < 0.001$; Figure 1). The nonanemic patients did not have a statistically significant rise in serum iron concentration at 15 minutes ($P = 0.68$). The rate of 2-hour absorption was much faster in the iron-deficiency anemia patients than in the nonanemic group ($P = 0.029$ for comparison of the two slopes).

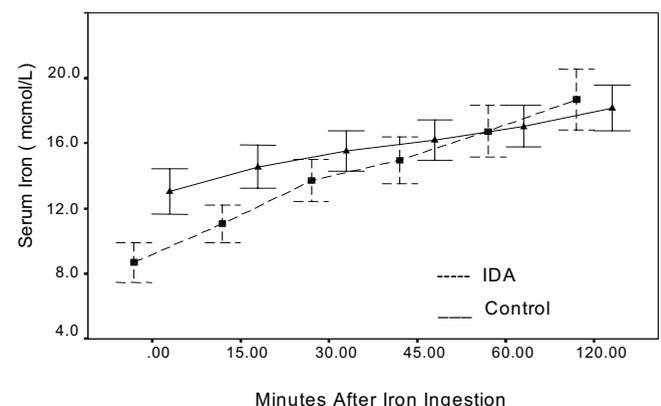


Figure 1 Low-dose iron absorption curve after a single dose of 15 mg of elemental iron to treat IDA (iron-deficiency anemia). Patients with iron-deficiency anemia were compared with patients without anemia. Data are given as mean iron levels \pm SD. $P < 0.001$ for effect and differences in slope between the two groups. Normal iron range: 59.2 μ g/dL to 159 μ g/dL.

Table 2 Changes in hemoglobin and ferritin values in study participants* during 2 months of iron therapy

Iron dose, daily	Time from first iron dose		Increase between Day 0 and Day 60 (95% confidence interval)
	Day 0	Day 60	
Hemoglobin (g/dL)	Mean \pm SD		
15 mg	10.0 \pm 1.1	11.3 \pm 0.9†	1.3 (0.7-2.0)
50 mg	10.9 \pm 1.0	12.3 \pm 0.7†	1.4 (0.8-1.9)
150 mg	10.2 \pm 1.3	11.6 \pm 0.8†	1.4 (0.9-1.8)
No anemia (15 mg)	13.1 \pm 0.9	13.2 \pm 0.9	0.2 (0.2-1.5)
Ferritin (ng/mL)			
15 mg	19.8 \pm 6.6	60.2 \pm 18.5†	40.4 (32.1-48.1)
50 mg	25.1 \pm 8.8	61.4 \pm 18.2†	36.3 (29.1-42.5)
150 mg	22.2 \pm 9.1	66.3 \pm 19.5†	44.1 (35.5-50.4)
No anemia (15 mg)	86.5 \pm 23.5	90.2 \pm 26.7	3.7 (2.1-20.4)

*Thirty participants were assigned to each dose group.

† $P < 0.001$ compared with day 0.

Follow-up iron status

A rise in the reticulocyte count, from 0.6% to 2.1%, occurred 30 days after initiation of treatment in the anemic group taking 15 mg of iron (range, 0.8% to 2.1%). A smaller but still significant rise was also found in the nonanemic group, from 0.8% to 1.3% at 30 days.

During the 2-month treatment period, serum hemoglobin and ferritin concentrations increased significantly in all iron-deficiency anemia patients, without statistically significant differences among the 3 doses. By comparison, no significant change was noted in the control group ($P < 0.001$; Table 2). The rise in ferritin levels was steeper in the first compared with the second month (Figure 2). The lower the baseline hemoglobin level, the more it increased with therapy (Figure 3).

Causes of iron deficiency

For the 90 patients, 51 primary care physicians (57%) responded to the questionnaire regarding the causes of iron

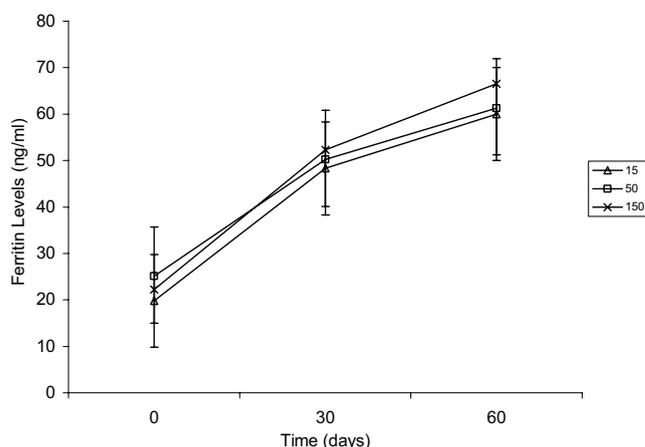


Figure 2 Effects of different doses of iron intake on serum ferritin levels. Normal ferritin range: 24 ng/mL to 300 ng/mL.

deficiency. Responses included colon cancer or polyps >1 cm in 6 patients and upper gastrointestinal malignancies and peptic disease or severe esophagitis in 8 patients. The patients with malignancy (1 with gastric cancer and 2 with colon cancer) had almost no increase in hemoglobin and in ferritin during the 2-month iron therapy. The results of the other 11 patients were similar to all other patients.

Adverse effects of iron therapy

The most prominent dose-dependent adverse effects during the study were “melena-like” black stools (Table 3) that were reported only in the higher iron doses. Withdrawal from the study due to the adverse effects of iron therapy was also dose dependent and was usually due to abdominal discomfort, nausea, or vomiting. Only 1 patient stopped taking the medications less than a week after the initiation

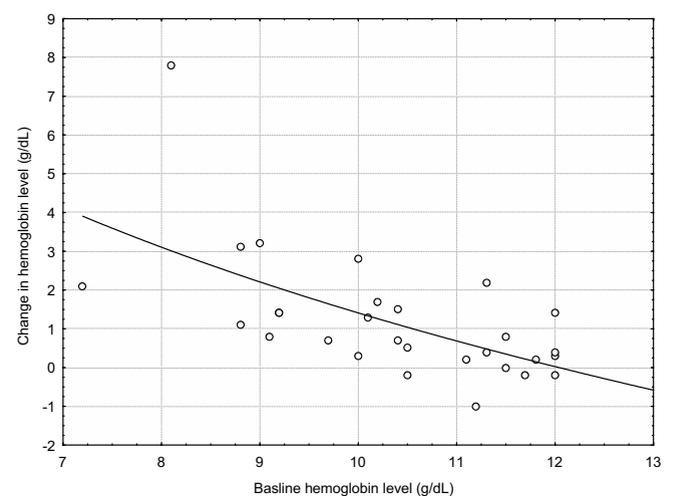


Figure 3 Increase in hemoglobin levels after 2 months of 15 mg of daily elemental iron therapy as a function of the baseline hemoglobin level. $P < 0.01$ for the relation of baseline hemoglobin level to the 2-month increase in hemoglobin.

Table 3 Reported adverse effects of different doses during daily iron therapy for 2 months

Adverse effect	Daily iron dose per group*		
	15 mg	50 mg	150 mg
Abdominal discomfort	6 (20)	18 (60)†	21 (70)†
Nausea/vomiting	4 (13)	11 (36)	20 (67)†‡
Diarrhea	4 (13)	16 (53)†	21 (70)†
Constipation	0	3 (10)†	7 (23)†
Darkened stools	13 (44)	20 (67)†	27 (91)†
Black stools	0	9 (30)†	20 (67)†‡
Dropout	2 (7)	5 (17)	8 (27)†

*Thirty patients were included in each treatment group. Adverse effects were assessed by a questionnaire at days 10, 30, and 60.

† $P < 0.05$ between this group and the 15-mg group.

‡ $P < 0.05$ between this group and the 50-mg group.

of the study (vomiting in a patient on 150 mg of iron per day).

Discussion

This study demonstrates that a low iron dose is an effective therapeutic option in elderly patients with iron-deficiency anemia. The lowest dose of elemental iron used was 15 mg, which is considerably lower than the 150 mg found in one tablet of ferrous fumarate, the 65 mg found in one 200-mg tablet of ferrous sulphate, or even the 35 mg found in one 300-mg tablet of ferrous gluconate. Even in elderly patients who have iron deficiency, iron absorption was very fast and efficient. By comparison, the nonanemic patients had very little absorption of this small dose of iron. However, in 5 nonanemic patients, the iron absorption rate was similar to that of the patients with iron-deficiency anemia, suggesting either iron deficiency without anemia, which was not identified by routine laboratory studies, or possible abnormalities in over-absorption of iron despite normal iron stores.

Low doses of iron can be used not only as a test for iron absorption but also for chronic treatment that gradually restores the body's iron stores. The average rise in hemoglobin concentration during the 2 months of low-dose treatment was 1.3 g/dL (ie, slightly more than the effect of one unit of packed cells blood transfusion), and this rise was greater in patients with more severe anemia (Figure 3). This increment in hemoglobin level did not lead to normal levels but was probably sufficient to reverse the negative influence of anemia on elderly patients with mild anemia. Interestingly, most of the effect of iron therapy occurred during the first month; studies of longer duration will be needed to clarify whether treatment with a low dose of iron can return iron stores to the normal range.

The adverse effects of iron therapy in this study were clearly dose dependent (Table 3). Although one study has suggested that the toxicity of 105 mg of iron given daily in 3 divided doses could not be distinguished from placebo,²⁰ several more recent studies that used conventional doses of iron therapy revealed that gastrointestinal adverse effects, including constipation, nausea, vomiting, abdominal pain, and diarrhea, were common.²¹⁻²³ The incidence of adverse effects was higher in the present study than had been previously reported, perhaps due to the older age of the participants.

In the elderly, the adverse effects of iron therapy could lead to considerable morbidity and impaired compliance. Abdominal pain, nausea, and vomiting can cause a decrease in food intake. Changes in bowel habits can worsen existing problems and lead to unnecessary gastrointestinal examinations due to suspicion of malignancy. Darkened stools are unpleasant for older patients and could be mistaken for melena. Therefore, by decreasing adverse effects, low iron doses could have substantial influence on health in this age group.

The number of patients in this study was small because we selected patients with clear iron deficiency.²⁴ Many patients were excluded because they had been taking chronic iron therapy or had received blood transfusions. The reason for these strict exclusion criteria was to confine our study sample to patients with truly low iron stores. Therefore, only 16.4% of the patients with anemia who were admitted to our department were included in the study. Ferritin levels are considered the best markers of iron status also in the elderly. However, ferritin is an acute phase reactant and its level is often high in old age due to inflammatory diseases. Choosing the cutoff value of ferritin at lower than 40 ng/mL rather than at the 15 ng/mL used in younger patients gives an optimal specificity (100%) but a low sensitivity, which means we included many iron deficiency patients who otherwise would have been excluded.¹⁹

The results of the present study may not apply to patients with iron deficiency due to malabsorption (eg, celiac disease), combined iron deficiency and anemia of chronic disease, or untreated *Helicobacter pylori* infection. Achlorhydria does not seem to impair the absorption of medical iron preparations, because they usually contain ferrous iron (Fe^{+2}) that does not need acid for absorption. Young iron-deficient patients probably absorb medical iron at least as efficiently as those over the age of 80 years. Moreover, a recent study demonstrated the efficacy of 20 mg of elemental iron in pregnant anemic women.¹⁶ Therefore, young iron-deficient patients also could probably be treated with low-dose iron therapy.

This study demonstrates that small iron doses, one tenth of what is generally recommended, efficiently raise hemoglobin and iron stores in elderly patients without producing substantial adverse effects. Future studies will be needed to determine the optimal dose of iron that can restore iron

status as fast as possible, with minimal adverse effects and drug interactions.

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