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Original Article

Effectiveness of Oral Iron Supplementation on Hemoglobin in Non-Anemic Women with Serum Ferritin Levels of 15 to 50 Micrograms/Liter

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Abstract

Background: According to medical resources, iron deficiency anemia occurs after the depletion of iron stores when ferritin levels reach 15 micrograms per liter (µg/L) or less. However, clinical experiences show different results. This study aimed to determine the effectiveness of oral iron supplementation on hemoglobin levels in non-anemic women with serum ferritin levels of 15–50 µg/L.

Methods: Women aged 18 to 60 years with complaints of fatigue and/or anemia, hemoglobin above 12 grams per deciliter (g/dL) or above 11 g/dL with thalassemia minor characteristics, and ferritin levels of 15 to 50 µg/L were included. Participants were not pregnant and had no underlying acute or chronic disease. Those who did not take iron supplements regularly or did not attend a second appointment were excluded. Patients were treated with a daily oral ferrous sulfate iron supplement containing 50–100 milligrams (mg) of elemental iron for at least six weeks. Laboratory data were compared before and after treatment

Results: Fifty-two females with a mean age of 40.23 ± 16.31 years were included. The mean hemoglobin level before treatment was 12.40 ± 1.08 g/dL, increasing to 13.04 ± 1.04 g/dL after treatment ($P < 0.001$). The mean serum ferritin level increased from 27.51 µg/L before treatment to 51.81 µg/L after treatment ($P < 0.001$). Hemoglobin increments were also observed in two subgroups: those with ferritin levels of 15–30 µg/L ($P < 0.001$) and those with levels of 30–50 µg/L ($P = 0.001$).

Conclusion: Oral iron supplementation increases hemoglobin levels in non-anemic women with serum ferritin levels of 15–50 µg/L. It is advisable to consider ferritin levels below 50 µg/L as an indicator of depletion of iron body stores.

Keywords: Anemia, Iron Supplement, Ferritin

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Introduction

Iron deficiency anemia is the most common type of anemia worldwide and represents an important health issue among young women of reproductive age [1]. Studies conducted in Iran have reported the prevalence of iron deficiency anemia in the adult population to range between 10% and 30% on average, and among women of reproductive age between 23% and 47% [2]. This anemia occurs when the body's iron stores become so low that they no longer support normal red blood cell production [3].

Ferritin is a protein that serves as the primary intracellular storage site for excess iron in mammalian tissues [4]. Under normal physiological conditions, serum ferritin reflects the body's iron reserves [5]. However, ferritin is also an acute-phase reactant that can increase independently of iron status in the setting of inflammation, infection, liver disease, heart failure, and malignancy [4]. Iron deficiency anemia represents the final stage of a multi-stage process involving the gradual reduction of iron in the body [6].

Three stages have been described in the development of established iron deficiency anemia. The first stage is negative iron balance, meaning that the amount of iron lost or required exceeds the amount absorbed. At this stage, ferritin decreases to less than 20 micrograms per liter (µg/L), but serum iron level and transferrin saturation remain normal. When the body's iron reserves are depleted, the second stage iron-deficient erythropoiesis begins, during which serum iron decreases and transferrin's total iron-binding capacity (TIBC) increases. Ferritin is less than 15 µg/L in this stage. Gradually, the third stage, iron deficiency anemia, occurs, characterized by the production of small and pale blood cells [7, 8].

There is no universal agreement on the ferritin threshold for detecting depletion of bone marrow iron stores. While many studies use a cutoff level of 12 to 15 µg/L (99% specificity, 57% sensitivity), other studies have suggested a threshold of 30 µg/L [9, 10]. The sensitivity and specificity for the threshold of 30 µg/L are estimated to be 92% and 98%, respectively [6]. However, anemia has not yet begun at the stage of iron-deficient erythropoiesis [6, 7].

Clinical experience suggests that hemoglobin depletion and the onset of iron deficiency anemia begin at higher ferritin levels, and that iron supplements can increase hemoglobin before ferritin drops below 15 µg/L.

Based on this, the present study was conducted to determine the effectiveness of oral iron supplementation in non-anemic women with serum ferritin levels of 15 to 50 µg/L.

Methods

Ethical considerations

The study protocol adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Babol University of Medical Sciences (Code: IR.MUBABOL.HRI.REC.1400.221). All participants received written and verbal explanations of the study aims, and confidentiality was maintained through anonymized data collection.

Study Design and Population

This was a pre- and post-test clinical trial. Women referred to the hematology clinic of Omid Special Clinic, Babol University of Medical Sciences (2021) with complaints of general weakness, early fatigability, or anemia were studied after providing informed consent. The sample size was calculated based on a previous study, [11], indicating a minimum of 52 patients. The sampling method was convenience sampling. According to the World Health Organization definition, hemoglobin levels below 12 grams per deciliter (g/dL) are considered anemia.

Inclusion criteria were as follows: women aged 18 to 60 years with no underlying acute or chronic disease affecting ferritin levels; no use of iron supplements in the past month; not pregnant; serum ferritin level of 15 to 50 µg/L; hemoglobin $\geq$ 12 g/dL, or $>$ 11 g/dL provided there was evidence of thalassemia minor (i.e., increased red blood cell count and decreased mean corpuscular volume [MCV]). Patients were excluded from the study if they did not adhere to treatment and failed to take iron supplements daily based on self-report, developed another disease, became pregnant, or did not attend the second appointment.

Procedure

After obtaining written informed consent, patients were included in the study. They were allowed to discontinue participation at any time. Demographic information, iron profile tests, and complete blood count (CBC) performed within a maximum of one month before entering the study were collected in a data checklist designed by the researchers. Patients were then treated with ferrous sulfate tablets containing 50 to 60 milligrams (mg) of elemental iron, approximately one to two times per day. After at least six weeks, the tests were repeated. For each patient, initial tests and follow-up

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tests were measured in the same laboratory. All tests were performed on venous blood samples taken after an overnight fast.

Data analysis

Data were analyzed using SPSS version 26 software. Quantitative data were described as mean and standard deviation, and qualitative variables as frequency and percentage. A paired-sample t-test was used to compare laboratory tests before and after the intervention. The significance level was set at $P < 0.05$.

Results

Fifty-seven females enrolled in the study. Five participants were excluded due to not attending the second visit or not taking the medication correctly. A total of 52 participants were analyzed. The mean age of the patients was 40.23 ± 16.31 years. Ferritin levels increased in all 52 patients after oral iron supplement consumption. The mean hemoglobin level at baseline was 12.40 ± 1.08 g/dL, which increased to 13.04 ± 1.04 g/dL after treatment with oral iron supplement for at least six weeks; this difference was statistically significant ($P < 0.001$). Additionally, based on the paired-sample t-test, MCV, mean corpuscular hemoglobin (MCH), serum iron, ferritin, and transferrin saturation percentage all increased significantly ($P < 0.001$). Serum iron and transferrin saturation were not measured in all patients (Table 1 and Figure 1). Patients were divided into two groups based on hemoglobin level: one group with hemoglobin 11 to 12 g/dL (thalassemia minor), including 22 patients (42.3%), and the other group with hemoglobin greater than 12 g/dL, including 30 patients (57.7%). The mean hemoglobin levels before treatment were 11.43 ± 0.32 g/dL and 13.11 ± 0.87 g/dL, respectively, which increased to 12.23 ± 0.69 g/dL and 13.64 ± 0.90 g/dL, respectively, after treatment in the two groups ($P < 0.001$), based on the paired-sample t-test (Table 2).

To evaluate the threshold of 30 µg/L for ferritin, which according to some sources (8,9), indicates depletion of iron stores, patients were divided into two groups based on ferritin level: one group with ferritin 15 to 30 µg/L, including 33 patients (63.5%), and the other group with ferritin 30 to 50 µg/L, including 19 patients (36.5%). The mean hemoglobin levels before treatment were 12.38 ± 1.05 g/dL and 12.38 ± 1.21 g/dL, respectively, which increased to 12.98 ± 1.06 g/dL in the first group ($P < 0.001$) and to 12.98 ± 1.19 g/dL in the second group ($P < 0.001$), based on the paired-sample t-test (Table 3).

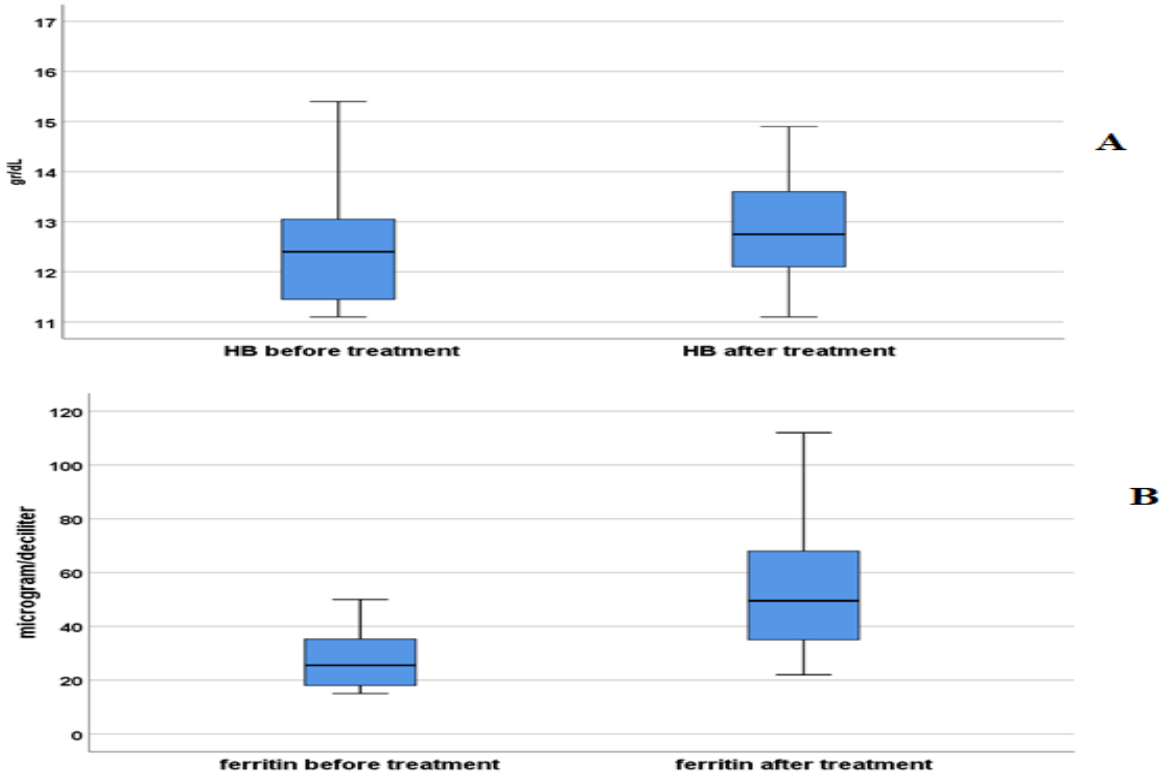

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Figure 1: Box plot-A: Hemoglobin (HB) levels of the participants before and after treatment. Box plot-B: ferritin levels of the participants before and after treatment, gr/dL: grams per deciliter

Table 1: The laboratory data of women with hemoglobin more than 11 g/dL and ferritin 15 to 50 µg/L before and after treatment

Variables	Number of patients		Min		Max		Mean ± SD		P-value
	Before	After	Before	After	Before	After	Before	After	
Hemoglobin (gr/dL)	52	52	11	11.1	15.40	16.1	12.40 ± 1.08	13.04 ± 1.04	<0.001*
MCV (fl)	52	52	55	56	93.60	93	80.27 ± 7.64	82.32 ± 7.09	<0.001
MCH (pg)	51	51	15.8	18	30.30	31.1	26.19 ± 2.83	27.47± 2.37	<0.001
Serum iron	41	36	27	41	120	147	64.43 ± 25.62	91.19 ± 31.53	<0.001
Serum ferritin (µg/L)	52	52	15	22	50	112	27.51 ± 10.77	51.87 ± 21.82	<0.001
Transferrin saturation	22	21	6	10	43	47	20.50 ± 10.07	30.19 ± 11.14	<0.001

SD: Standard deviation, *: p-value of hemoglobin 11 to 12 g/dL (paired T Test), **: p-value of hemoglobin above 12 g/dL (paired T Test), gr/dL: grams per deciliter, MCV: mean corpuscular volume, fl: Femtoliters, MCH: mean corpuscular hemoglobin, pg: Pictograms, µg/L: micrograms per liter

Table 2: Comparisons of the results of laboratory data in women with hemoglobin levels of 11 to 12 g/dL and above 12 g/dL before and after taking iron supplements

Variables	**Hemoglobin 11 to 12 g/dL (Mean ± SD)**			Hemoglobin above **12 g/dL (Mean ± SD)**		
	Before	After	P-value*	Before	After	P-value**
Hemoglobin (gr/dl)	11.43 ± 0.32	12.23 ± 0.69	<0.001	13.11 ± 0.87	13.64 ± 0.9	<0.001
MCV (fL)	76.37 ± 8.23	80.23 ± 8.13	<0.001	83.13 ± 5.79	83.86 ± 5.89	<0.052
MCH (Pg)	24.70 ± 3.01	26.84 ± 2.55	<0.001	27.23 ± 2.20	27.92 ± 2.17	<0.004
Serum iron	54.09 ± 18.82	66.45 ± 17.49	<0.008	69.72 ± 27.88	102.08 ± 30.3	<0.001
Serum ferritin (µg/L)	27.71 ± 11	48.45 ± 21.05	<0.001	27.37 ± 10.79	54.37 ± 22.38	<0.001
Transferrin saturation	17.40 ± 14.04	21.80 ± 15.18	<0.029	21.5 ± 8.85	32.81 ± 8.56	<0.001

SD: Standard deviation, *: p-value of hemoglobin 11 to 12 g/dL (paired T Test), **: p-value of hemoglobin above 12 g/dL (paired T Test), gr/dl: grams per deciliter, MCV: mean corpuscular volume, fl: Femtoliters, MCH: mean corpuscular hemoglobin, pg: Pictograms, µg/L: micrograms per liter

Table 3: Comparisons of the results of laboratory data in women with ferritin 15 to 30 µg/Land with ferritin ≥ 30 µg/L before and after taking iron supplements

Variables	**Ferritin 15 to 30 µg/L (Mean ± SD)**			**Ferritin ≥ 30 µg/L Up to 50 µg/L (Mean ± SD) P-value****		
	Before	After	P-value*	Before	After	P-value*
Hemoglobin (gr/dl)	13.11 ± 0.87	13.64 ± 0.9	<0.001	12.38 ± 1.05	12.98 ± 1.06	0.001
MCV (fL)	83.13 ± 5.79	83.86 ± 5.89	<0.005	79.95 ± 8.61	81.77 ± 8.06	0.012
MCH (Pg)	27.23 ± 2.20	27.92 ± 2.17	<0.009	25.88 ± 3.20	27.01 ± 2.1	0.003
Serum iron	69.72 ± 27.88	102.08 ± 30.3	<0.001	59.48 ± 28.88	84.52 ± 32.3	<0.001
Serum ferritin (µg/L)	27.37 ± 10.79	54.37 ± 22.38	<0.001	20.37 ± 4.79	44.37 ± 17.38	<0.001
Transferrin saturation	21.5 ± 8.85	32.81 ± 8.56	<0.001	19.5 ± 12.85	29.81 ± 13.56	0.002

SD: Standard deviation, *: p-value of hemoglobin 11 to 12 g/dL (paired T Test), **: p-value of hemoglobin above 12 g/dL (paired T Test), gr/dL: grams per deciliter, MCV: mean corpuscular volume, fl: Femtoliters, MCH: mean corpuscular hemoglobin, pg: Pictograms, µg/L: micrograms per liter

Discussion

Determining the cutoff point for ferritin level is important for appropriately treating patients with iron deficiency anemia. A study that investigated the laboratory signs of iron deficiency anemia concluded that when ferritin is 50 µg/L, the probability of iron deficiency in bone marrow samples is 50% [12]. In the present study, we showed that after six weeks of treatment with oral iron supplementation, the mean hemoglobin, MCV, MCH, serum iron, ferritin, and transferrin saturation percentage in women with normal hemoglobin or mild thalassemia minor (hemoglobin > 11 g/dL) and ferritin between 15 and

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50 µg/L improved statistically significantly. These improvements were also observed in both subgroups (ferritin 15–30 µg/L and 30–50 µg/L), a finding that emphasizes the importance of 50 µg/L as a cutoff point for depletion of body iron reserves. Furthermore, the increase in hemoglobin among patients with thalassemia minor criteria and hemoglobin between 11 and 12 g/dL indicates that these individuals should be treated similarly to those with completely normal hemoglobin.

Although consumption of one or two iron supplement pills can affect the extent of ferritin increase, ferritin levels increased after treatment in all patients; this variation in iron consumption did not affect the results of the statistical analysis. The primary aim of this study was to determine whether increasing ferritin (i.e., iron stores) in women with ferritin levels between 15 and 50 µg/L would increase hemoglobin. Therefore, the discussion focused not on the amount of iron consumed, but rather on increasing ferritin as the main goal. Nevertheless, it would have been more appropriate if patients' hemoglobin had been measured when ferritin reached above 50 µg/L.

According to available resources, during the stages of iron deficiency anemia development, the body's iron reserves are first depleted, characterized by a decrease in serum ferritin; subsequently, serum iron decreases and anemia begins [6, 7]. Thus, the increase in ferritin and hemoglobin following iron-containing supplement consumption in the present study indicates that ferritin levels were in a state of iron depletion before treatment initiation. Therefore, we indirectly conclude that a ferritin level below 50 µg/L indicates depletion of body iron stores.

In clinical trials conducted by Vaucher et al. [13] and Krafft et al. [14] in women with iron deficiency without anemia, daily treatment with 80 mg of oral iron for 6 to 12 weeks significantly increased serum ferritin levels, transferrin saturation, and hemoglobin in the iron-receiving group compared to the placebo group. In another clinical trial by Verdon et al. [12] involving 144 non-anemic women presenting with unexplained weakness, similar laboratory results were observed, along with significant improvement in weakness among women with lower ferritin levels, which occurred in individuals with ferritin below 50 µg/L. Cancado et al. explained the relationship between ferritin and the body's responses to iron deficiency in physiological terms and concluded that a ferritin level below 50 µg/L is a more appropriate cutoff for diagnosing iron deficiency [15].

A systematic review reported that the increase in hemoglobin in non-anemic women over 18 years of age after iron supplementation was 0.401 g/dL (95% CI: 1.22 to 6.81), accompanied by improvement in fatigue without a significant increase in physical activity capacity [16]. Conversely, another systematic review in athletes showed no increase in performance after iron supplementation in those with ferritin ≥ 20 µg/L; however, most participants in that study were male, which contrasts with the present study [17].

As seen in the studies mentioned above, results similar to ours were obtained. However, in the present study, we did not investigate the reduction of fatigue or improvement in participant performance, which is a limitation. Additionally, because it is unethical to withhold treatment from patients who need it (those with ferritin levels between 15 and 50 µg/L), this study was conducted without a control group. Consequently, confounding factors cannot be fully controlled, and the net effect of iron cannot be accurately assessed.

Iron deficiency and iron deficiency anemia decrease quality of life by causing early fatigability and reduced concentration. Therefore, timely and complete treatment plays an important role in the quality of life of women in society. Based on the results of our research and the studies mentioned above, it is preferable to consider a ferritin level below 50 µg/L as the cutoff point for depletion of iron reserves and the beginning of iron deficiency anemia. The statement that "depletion of iron reserves occurs when ferritin is below 15 µg/L" should be revised in medical resources. We suggest that further studies, including individuals with ferritin levels above 50 µg/L, be conducted to reject or confirm the 50 µg/L cutoff point for detecting iron store depletion and the onset of iron deficiency anemia.

Conclusion

Hemoglobin levels in non-anemic women with ferritin levels of 15 to 50 µg/L increase with oral iron supplementation. It is advisable to consider that depletion of iron stores and the onset of iron deficiency anemia begin at a ferritin level below 50 µg/L.

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Data availability

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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author's contribution

S.K. and M.VS. contributed to conceptualization. M.S. and H.GH. contributed to methodology. M.M. contributed to sampling. H.GHA. and M.S. contributed to statistical analysis and investigation. M.VS. contributed to writing – original draft preparation. M.VS., M.N., and M.M. contributed to writing – review and editing.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Ethical Statement

The ethics committee of Babol University of Medical Sciences, Iran (Approval number: IR.MUBABOL.HRI.REC.1400.221), approved the study.

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