

Iron deficiency anemia in males: a dosing dilemma?

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ABSTRACT

Introduction: Iron deficiency anemia is a major problem worldwide treated by replenishment of iron stores. The treatment is complicated by differing pharmacodynamics of administrative routes, equations with design effects, ongoing losses, additional daily requirement, plateauing of markers required for iron absorption, food–drug interactions, gender, and age. Accounting for these factors in one dosing regimen becomes difficult, specifically in males. This review aimed at analyzing multiple dosages of iron supplements in different studies and determining if there are factors that could individualize treatment in male patients.

Methods: A scoping review was performed using PubMed, Google Scholar, and ClinicalTrials.gov. We reviewed literature from 1980 to 2020. The keywords used in the review were ‘iron deficiency’, ‘dosage’, ‘males’, and ‘standardized’.

Results and conclusions: The review included 1507 male participants from 9 major studies (4 clinical trials, 1 systematic review, 2 prospective and 2 descriptive studies). In the case of males, differences in lean body weight, and factors affecting absorption of iron also need to be considered. In order to thoroughly explore the issues in treatment of iron deficiency anemia, randomized controlled trials are required to investigate the frequency of dosing, impact of vitamin C and proper counselling, and weight changes in male participants.

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1. Background

Iron deficiency anemia is a global concern and is responsible for 800,000 deaths per year worldwide [1]. Anemia is well described in certain groups such as women of child-bearing age and children; however, the risk for anemia in males is increasing. There are a few risk factors evident in males, including ethnicity. Age was found to be a greater risk factor in males as compared to females [2]. Absolute iron deficiency is caused by physiologically increased iron requirements, reduced iron intake, pathological defective absorption, or chronic blood loss [3]. Functional iron deficiency has a slightly different pathology. It is characterized by a state in which there is a failure of iron incorporation into erythroid precursors despite having adequate stores [4]. This pathophysiology explains the iron deficiency in infectious, inflammatory, and malignant diseases [5]. Therefore, there are many causes of iron deficiency anemia that have to be investigated. A few diagnostic clues include a dietary history that is low in iron and a history of pagophagia [6]. However, laboratory diagnosis remains the mainstay of confirming such a diagnosis. The first step in this

process includes clinical features suggesting anemia, with a low mean corpuscular volume ($\leq 80\mu\text{m}^3$) and low mean hemoglobin ($\leq 13.7\text{ g/dL}$). This is followed by measuring serum ferritin levels. Levels $\leq 30\text{ ng/ml}$ are diagnostic of iron deficiency anemia. In patients with indeterminate serum ferritin levels, the total iron-binding capacity, serum iron, and transferrin saturation levels are measured. In cases of iron deficiency anemia, the iron-binding capacity is increased while serum iron and transferrin saturation levels are decreased [7].

The mainstay of treatment for iron deficiency anemia is to replenish iron stores. This can be done through the administration of oral or parenteral iron supplements. There are tablets with varying dosages available for consumption in oral form as opposed to parenteral iron which is an individualized infusion. This discrepancy in dosing between the two routes requires an in-depth review of how the dosages of iron supplements can be standardized.

The objective of this review was to describe and analyze multiple dosages of iron supplements in previous studies and to determine if there are factors that could individualize treatment in male patients.

2. Methods

For the purposes of this study, a scoping review was performed. PubMed, Google Scholar, and ClinicalTrials.gov were used for the retrieval of studies required for the review. We reviewed literature from 1980 to 2020. The keywords used in the review were ‘iron deficiency’, ‘dosage’, ‘males’, and ‘standardized’.

3. Review

Iron deficiency anemia is described as diminished red blood cell production in which there is either a decrease in iron stores owing to physiologically high requirements, decreased iron consumption, blood loss, or a decrease in incorporation of iron to aid in red blood cell maturity. This issue is a cause of extreme concern because it affects more than 35% of the world’s population and more than 50% of pregnant women [8]. After diagnosis of iron deficiency anemia is made using algorithms, iron supplementation is the main management apart from counselling patients regarding their lifestyle [9]. However, standardization of the empiric regimen for an efficacious response is a question that still needs to be addressed.

Iron supplementation has to be implemented such that recommended dietary allowances as well as ongoing losses are accounted for. The recommended dietary allowances vary depending on both age groups and gender. In women, the recommended intake is usually 15 mg for individuals aged 14 years to 18 years and 18 mg for individuals aged 18 years to 50 years. Both groups increase to 10 mg and 27 mg during pregnancy and lactation, respectively. Compared to the same age groups, the recommended intake is lesser for men and is usually 8 to 11 mg [10–13]. Using these recommendations, it can be concluded that one factor hindering the process of standardization is gender-based physiological differences. Women generally have higher requirements for iron owing to menstrual losses in pre-menopausal females and the natural process of giving birth [14].

Despite this factor, the routine practice is to address the amount of elemental iron needed to correct the anemia. The adult dose of elemental iron is 150 to 200 mg daily for 3 months. Oral ferrous sulfate is the most commonly used formulation. The quantity of elemental iron in one 325 mg tablet is about 65 mg; therefore, the oral form is recommended for use every eight hours [15]. In that case, the total amount supplied to the body in one day would be 195 mg. However, only 2% to 13% of the supplied elemental iron is absorbed with food, and 5% to 28% is absorbed without food [16]. Even if maximal absorption rates were achieved, the additional requirement to correct anemia would still not be

met. However, it was found that when the total amount of oral ferrous sulfate prescribed in a day increased, it was associated with adverse effects such as nausea, vomiting, tarry stools, dose-related constipation, and taste changes [17]. These adverse effects can cause non-compliance in many patients.

As a result of poor absorption patterns and high non-compliance rates, studies were done to determine if there was a dosing schematic that could help change these factors. Table 1 summarizes a few findings of the studies that were reviewed.

One such study done in 2015 by Moretti et al. mainly targeted 54 iron-deficient women without anemia and provided them with various dosages of oral ferrous sulfate for 2 days while using an isotope to target the absorption. The objective was to determine the acute rise in hepcidin as hepcidin concentrations increase after iron supplementation. Being a key regulator of the metabolism of iron, high hepcidin quantities decrease iron bioavailability and ultimately, iron absorption. In this study, it was found that supplements with 60 mg of elemental iron increased hepcidin for 24 hours ($p < 0.01$), resulting in a 35% to 45% decrease in absorption ($p < 0.01$). Their recommendation was to use lower doses, 40 to 80 mg and no more than once a day, to maximize the absorption. However, the study had a few limitations, such as a small sample size ($n = 54$), a specified target population, and a short duration to measure the effect of the therapy [18]. The greatest concern is that the patients did not have anemia and there were no male participants in the study. Anemic patients usually have lower than normal hepcidin concentrations which account for the increased total iron-binding capacity [19].

Stoffel and colleagues conducted a similar study in 40 non-anemic and iron-deficient women. They were divided into two groups: group A received 60 mg of elemental iron once daily for 14 days while group B received 60 mg of elemental iron every alternate day for 28 days. It was found that alternate day regimen significantly increased iron absorption (21.8% vs 16.3%; $p < 0.01$). The total iron absorption for both groups were similar (44.3% vs 49.4%; $p > 0.05$). The serum hepcidin had significantly increased for group A ($p < 0.01$) [20]. This study had similar limitations as Moretti and colleagues, including lack of male or anemic participants. However, the time duration was longer. Additionally, the impact of clinically important labs such as ferritin were not investigated [19,20].

Another study conducted in 2020 by Kaundal et al. focused on a more clinically important outcome. This study targeted 62 patients with varying degrees of iron deficiency anemia and subjected them to either 60 mg twice daily (group BD) or 120 mg on alternate days (group AD). At 3 weeks, the endpoint of 2 g/dl

Table 1. Summary of the studies reviewed.

Author	Study design	Criteria	Aim	Patient population	Conclusions
Kaundal et al. [21].	Randomized controlled trial	Inclusion criteria: both genders, age >15 years, and proven iron deficiency anemia. Exclusion criteria: Patients with borderline anemia (Hb \geq 11.5 g/dl), very severe anemia (Hb < 6 g/dl), cardiac failure, pregnancy, and clinical or laboratory evidence of other causes of anemia. Systematic review	To determine the efficacy and safety of alternate-day versus twice-daily oral iron in all severity of iron deficiency anemia	62 participants; 8 male and 54 female participants	After 3 weeks, the twice daily group had a rise of 2 g/dl hemoglobin ($p < 0.0001$) but median rise was not significant. Twice daily group had more complaints of nausea ($p < 0.05$).
Fernández-Gaxiola et al. [23].	Gaxiola et al. [23].	Systematic review	Inclusion criteria: Randomised controlled trials (RCTs) and quasi-RCTs with either individual or cluster randomization on menstruating women and intervention was the use of iron supplements intermittently compared with placebo, no intervention, or the same supplements provided on a daily basis.	To assess the effects of intermittent oral iron	supplementation, alone or in combination with other nutrients, on anaemia, compared with no intervention, a placebo, or daily supplementation.
10,996 women, no male	participants	Intermittent iron supplementation reduced the risk of having anemia and improved the concentration of hemoglobin, thus reducing risk of iron deficiency. Women receiving iron supplements intermittently were less likely to have less adverse side effects.			
Stoffel et al. [20].	Randomized Controlled Trial	Inclusion criteria: Iron-depleted (serum ferritin ≤ 25 μ g/L) women aged 18–40 years recruited from ETH Zurich and the University of Zurich, Switzerland	To compare iron absorption from oral iron supplements given on consecutive versus alternate days and given as single morning doses versus twice-daily split dosing.	40 iron-deficient women, no male participants	Alternate regimen increased iron absorption ($p < 0.01$) but total amount of absorption was same. The serum hepcidin had risen for patients with daily regimen ($p < 0.01$)
Moretti et al. [18].	Randomized Controlled Trial	Inclusion criteria: Healthy females aged between 18 and 45 years, with plasma ferritin <20 mg/L but Hb > 11.7 g/L; no chronic medication (except OCPs); no reported chronic disease; no pregnancy or lactation; no blood donation within the previous 4 months; nonsmoking; no intake of mineral, vitamin, or herbal supplements within 2 weeks of study start and during the entire duration of the study; body mass index between 18 and 25 kg/m ² ; and body weight 68 kg. Exclusion criteria: CRP > 0.5 mg/L at screening. interventional study	To determine the acute rise in hepcidin in response to various doses of iron supplements over 2 days	54 iron-deficient women, no male participants	Supplements with 60 mg of elemental iron increased hepcidin for 24 hours ($p < 0.01$) causing decrease in absorption by 35 to 45% ($p < 0.01$)
Schümann et al. [24].	Prospective,		Inclusion criteria: 8 healthy Guatemalan males, aged between 23 and 54 years. None had a history of chronic or acute disease or reported consumption of nutritional supplements during the previous 6 months.	To determine the aggravating role of non-transferrin-bound iron (NTBI) after oral	supplementations
Cohort of 8 male	participants, no female participants.		Circulating levels of serum iron and NTBI increased in a graded fashion in response to oral iron, but post iron NTBI was higher in patients with normal ferritin.		

(Continued)

Table 1. (Continued).

Author	Study design	Criteria	Aim	Patient population	Conclusions
Johnson-	Wimbley et al. [25].	N/A		To determine the possible use of intravenous iron	supplementation in patients with severe iron deficiency anemia who have failed oral iron supplementation.
Participants not applicable, discussed studies.		In terms of lean body weight, For men: lean body weight = 50 kg + 2.3 kg for each inch in height over 60 inches For women: lean body weight = 45.5 kg + 2.3 kg for each inch in height over 60 inches			

rise in hemoglobin was significantly met in group BD with twice daily dosing ($p < 0.0001$). However, the median hemoglobin rise was not significant for group BD. Similarly, this group had more complaints of nausea ($p < 0.05$). The main limitation of this study was the small number of male participants ($n = 8, 12.9\%$). [21] Similar findings had been reported for pregnant women in a study done in Nigeria which addressed the limitations of previous studies but the study also had a small sample size ($n = 182$) [22].

A 2019 systematic review revealed that intermittent iron supplementation reduced the risk of having anemia (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.49–0.87) and improved the concentrations of hemoglobin (mean difference (MD) 5.19 g/L, CI 3.07–7.32) and ferritin (MD 7.46 $\mu\text{g/L}$, CI 5.02–9.90). Women receiving iron supplements intermittently were also less likely to have less adverse side effects (RR 0.41, CI 0.21–0.82) [23]. Again, the main limitation of this study was that the review primarily targeted women and could not be generalized to men.

The data regarding dosages are further limited in men. A study focusing entirely on male participants had described a rise in serum iron and non-transferrin bound iron after they had been given an oral iron challenge. The increment in non-transferrin bound iron was still greater than normal ferritin levels in this study population [24]. The lean body weight also plays a role in the dosing by affecting the total elemental iron. The constant for lean body weight used in calculation is 50 kg in males and 45.5 kg in females. This factor further makes standardization difficult, particularly for males [25].

The data for treatment of iron deficiency anemia in males, considering the various factors that need to be accounted for in men, is severely lacking. Furthermore, it is also difficult to assess if fixed doses of supplements, a large oral dose or a combination therapy would be effective in males because many studies do not target the specific group. Emphasis has been laid on underlying factors responsible for anemia instead of the regimen used. According to Artz et al. in a recent trial, testosterone deficiency led to unexplained or even iron-deficiency anemia in older males. Replacement significantly improved hemoglobin levels in both the groups of patients but hepcidin suppression only occurred in males without iron deficiency anemia ($P < 0.001$) [26]. Another study had focused on the use of riboflavin and ferrous sulphate that proved to be beneficial in males with poor hematological status secondary to iron deficiency anemia [27]. Surprisingly, it was noted in a study that males who frequently donated blood had lower ferritin levels; a trend consistent throughout all age groups whereas males who did not donate blood experienced the decrease at an older age range (60 years).

Table 2. Summary of the studies with male participants.

Author	Study design	Criteria	Aim	Patient population	Conclusions
Kaundal et al. [21].	Randomized controlled trial	Inclusion criteria: both genders, age >15 years, and proven iron deficiency anemia. Exclusion criteria: Patients with borderline anemia (Hb \geq 11.5 g/dl), very severe anemia (Hb < 6 g/dl), cardiac failure, pregnancy, and clinical or laboratory evidence of other causes of anemia. Inclusion criteria: CRP-0.5 mg/L at screening. Inclusion criteria: Men who were 65 years and older with two early morning serum testosterone levels <275 ng/mL.	To determine the efficacy and safety of alternate-day versus twice-daily oral iron in all severity of iron deficiency anemia	62 participants; 8 male and 54 female participants	After 3 weeks, the twice daily group had a rise of 2 g/dl hemoglobin ($p < 0.0001$) but median rise was not significant. Twice daily group had more complaints of nausea ($p < 0.05$).
Artz et al. [26].	Randomized Controlled Trial	Inclusion criteria: CRP-0.5 mg/L at screening. Inclusion criteria: Men who were 65 years and older with two early morning serum testosterone levels <275 ng/mL.	To investigate possible mechanisms by which testosterone stimulates erythropoiesis in hypogonadal older men with unexplained or iron-deficiency anemia. Inclusion criteria: 8 healthy Guatemalan males, aged between 23 and 54 years. None had a history of chronic or acute disease or reported consumption of nutritional supplements during the previous 6 months.	95 male participants; no female participants	Testosterone replacement significantly ($P < 0.001$) increased hemoglobin in men with unexplained anemia and increased hemoglobin in men with iron deficiency anemia. Testosterone replacement did not suppress hepcidin in cases of iron deficiency supplementations
Schümann et al. [24].	Prospective, interventional study			To determine the aggravating role of non-transferrin-bound iron (NTBI) after oral	
Cohort of 8 male		participants, no female participants.	Circulating levels of serum iron and NTBI increased in a graded fashion in response to oral iron, but post iron NTBI was higher in patients with normal ferritin.		
Milman et al. [28].	Prospective, observational study		Inclusion criteria: Danish population. Increasing age cohort groups by 10 years using a survey conducted by World Health Organization	To update iron status in Danish men, especially iron overload or iron deficiency anemia after abolition of food fortification.	1332 male participants, no female participants
Blood donors in all age-groups had		comparatively lower serum ferritin ($p \sim 0.0001$). Serum ferritin levels decreased for nonblood donors from age group 40 to 60 years. In nondonors, serum ferritin levels were not significantly different compared with men taking ferrous-based multivitamins ($p = 0.5$). Vitamin supplements had no impact on iron studies.			
Powers et al. [27].	Descriptive study	Inclusion criteria: Adult males and children (age 8 to 12 years); poor hematological status	To determine the efficacy of riboflavin, ferrous sulphate and combination therapy in patients with iron deficiency anemia	80 male participants; 80 children	Over 6 weeks, there was a general improvement in haematological status; riboflavin enhanced recovery, particularly in those individuals with strikingly low levels of haemoglobin.

Multivitamins, including ferrous-sulphate-based vitamins, did not significantly improve the overall status of males [28]. Apart from these studies, questions about appropriate dosing regimens, combinations and routes for age groups in males remain unanswered (refer to Table 2)

In addition to limited data for daily dosing, there are some factors that completely change the response to the therapy. Firstly, the consumption of iron supplements should not be recommended with food or products containing calcium due to risk of chelation. This is difficult for patients because the supplements produce an element of gastric upset, necessitating the need to take iron with food. Furthermore, iron is highly absorbed from the duodenum because of the acidic pH. This is problematic for patients using antacids because the amount of acid produced is less. Therefore, it is important that these patients take iron either 2 hours before or 4 hours after antacids.

The absorption of iron might increase with the use of vitamin C. There was a 48% increase in iron absorption with 500 mg of ascorbic acid for 30 mg of elemental iron, but no increase was seen for vitamin C doses less than 100 mg. The absorption was also increased by consumption of an excess of 200 mg of vitamin C per 30 mg of elemental iron [29]. Additionally, there is the possibility of other drugs interacting with iron. A study investigated the effect of ferrous sulphate on the bioavailability of oral gemifloxacin. Twenty-seven healthy male volunteers received 320 mg of oral gemifloxacin either three hours after or two hours before taking 325 mg of oral ferrous sulphate. It was found that neither routine reduced the bioavailability of gemifloxacin [30].

4. Conclusion

Based on the studies reviewed, it becomes difficult to limit treatment to daily dosing, especially during an era when individualized treatment using pharmacogenomics is being widely explored. The problem does not end with the frequency of dosing. In the case of males, there are factors such as limited data, differences in lean body weight, and factors affecting absorption of iron that also need to be considered. In order to thoroughly explore the issues outlined above concerning the treatment of iron deficiency anemia, randomized controlled trials are required to investigate the frequency of dosing, impact of vitamin C and proper counselling, and weight changes in male participants. Additionally, cohort studies should be conducted comparing males and females of similar age groups to determine the response to dosing regimens by assessing iron absorption.

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