

Iron as an Ergogenic Aid: Ironclad Evidence?

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Iron supplementation for the iron-depleted nonanemic athlete is a controversial issue. Athletes may be iron deficient due to poor dietary intake, significant or obligatory blood loss, or deficiency via increased need secondary to intense physical activity. Athletes who are found to be anemic secondary to iron deficiency do benefit and show improved performance with appropriate iron supplementation. There is contradictory evidence for iron supplementation and improving performance in the iron-depleted nonanemic athlete. An athlete's iron status is usually monitored via serum ferritin. Currently, there is no standardized ferritin level at which supplementation is recommended, nor is there a consensus as to the appropriate maintenance of ferritin. Screening endurance athletes or female athletes in general for iron deficiency and also educating these athletes regarding the importance of a balanced diet to maximize performance would seem prudent and beneficial. Based on the literature, supplementation for the iron-depleted nonanemic athlete does not appear to be justified to solely improve performance.

Introduction

Iron status in athletes has become an increasingly popular topic, focusing discussion on whether supplementation improves performance. Protocols and justification for iron supplementation are widespread. Publications such as *Runner's World* are read by endurance athletes and coaches touting increased aerobic capacity for any athlete utilizing supplemental iron [1]. A questionnaire distributed to elite coaches and athletes at the Australian Institute of Sport elicited expectations of the athlete and coach revolving around the presentation and care of an athlete with the complaint of fatigue/tiredness. The expectation of blood tests rose

with the duration of fatigue, increasing from 5 to 7 days to 4 weeks, with iron levels indicated as the laboratory test result of prime importance in the athlete's evaluation. Expectations for blood tests also rose if athletic performance worsened [2]. Fallon [3•,4] looked at the clinical utility of blood tests in elite athletes with short-term fatigue and found that hematologic and biochemical tests were of little diagnostic use. They were more useful in excluding problems such as iron deficiency and in reassuring both the athlete and coach. In fact the primary diagnoses for short-term fatigue in the athlete were training- and infection-related, with only two of 50 athletes having serum ferritin levels below 30 ng/mL [4].

It is evident that athletes and coaches are conditioned to fear low ferritin levels. There is no debate concerning supplementation of iron in the iron-deficient anemic athlete. However, many questions arise regarding the utility of iron supplementation in the athlete that has low ferritin stores and normal hemoglobin levels, indicating a nonanemic state. Pressure to be at peak athletic performance at all times is high. In the eyes of athletes and coaches, peak iron stores may offer that small edge that distinguishes a champion competitor. The evidence is scattered but the debate on this topic continues to evolve. This article reviews some of the latest information and guidelines available concerning iron supplementation, and provides a review of iron specifics.

Iron Facts

Iron is a trace mineral that is vital to the human body, whether athletic or not. It is a component of hemoglobin that acts to transport oxygen and carbon dioxide in the blood. Iron also plays a vital role in myoglobin, which extracts oxygen from hemoglobin in muscle tissue. Iron's role as an antioxidant is well known. It is a vital component of the electron transport chain in the production of ATP, providing the energy source that provides and allows movement and performance. Iron is stored in the body as ferritin and is circulated by transferrin. In order for metabolism and oxygen transport to work properly, there must be an adequate level of iron, especially during growth and physical activity

[5,6]. When iron stores are deficient and anemia is present, these processes can be adversely affected, and in turn performance can suffer [7••,8].

Iron is obtained via dietary sources, and this in turn is the basis of iron stores. Iron is best obtained through the diet from either of two groups: heme or nonheme iron. Heme iron is found in flesh foods (meat sources) as myoglobin. Nonheme iron comes from vegetables and grains. Healthy adults absorb about 10% to 15% of dietary iron, but individual absorption is influenced by several factors, including the chemical form of iron (heme or nonheme) and the body's storage levels of iron. Storage levels have the greatest influence on iron absorption; absorption increases when body stores are low. Absorption decreases when iron stores are high, as a protective mechanism against toxic effects of iron overload. Heme iron's absorption averages between 15% to 35% compared with nonheme iron's absorption of 2% to 20% from a single meal. Men absorb an average of 6% of total dietary iron and women of child-bearing age absorb an average of 13%. Meat proteins and ascorbic acid (vitamin C) can improve the absorption of nonheme iron, whereas tannins (found in tea), calcium, polyphenols, and phytates (found in legumes and whole grains) can decrease absorption of nonheme iron. In populations that are at risk for low iron intake or absorption (adolescents, females, and vegetarians consuming nonheme sources of iron), those who have high iron losses (eg, menstruating women), or those who have high iron requirements (eg, pregnant women), it is important to include foods in the diet that will enhance nonheme iron absorption [9••]. Food sources containing both heme and nonheme iron (with daily value amounts of iron provided in a serving listed in table form) can be found at the National Institute of Health's Dietary Supplement Fact Sheet on Iron at <http://www.ods.od.nih.gov/factsheets/iron.asp> [9••].

The Recommended Dietary Allowance (RDA) for iron varies by age and sex of the individual, and has a wide range. The RDA for menstruating women is 18 mg/d and is increased to 33 mg/d if that woman is vegetarian. For a pregnant woman, the RDA is 27 mg/d. RDA for men is 8 mg/d and increased to 14 mg/d if that man is vegetarian [9••]; boys aged 4 to 8 years and those aged 14 to 18 years require 10 mg/d and 11 mg/d, respectively.

Iron supplements are available in two forms: ferrous iron or ferric iron. Ferrous iron salts (ferrous fumarate, ferrous sulfate, and ferrous gluconate) are better absorbed in the digestive tract but only 12% to 33% of a supplement is available for absorption into the body. This 12% to 33% is termed *elemental iron* [9••]. Average absorption of the ferrous iron salts ferrous fumarate, ferrous sulfate, and ferrous gluconate are 33%, 20%, and 12%, respectively [9••]. Supplementation above 45 mg/d of elemental iron increases the chances for gastrointestinal side effects such as nausea, vomiting, constipation, diarrhea, dark colored stools, and/or epigastric distress [9••,10].

Table 1. Iron depletion states

Iron depletion without frank anemia: prelatent iron deficiency		
Low serum ferritin levels	AND	Normal total iron-binding capacity Normal percent transferrin saturation Normal serum iron concentration Normal hemoglobin
Iron depletion with impairment of transport iron: latent iron deficiency		
Low serum ferritin levels	AND	Increased iron-binding capacity Decreased percent transferrin saturation Normal hemoglobin
	OR	
Low serum ferritin levels	AND	Decreased serum iron concentration Normal hemoglobin
Iron depletion with blocked erythropoiesis: iron deficiency anemia		
Low serum ferritin levels	AND	Increased total iron-binding capacity Decreased percent transferrin saturation Decreased serum iron concentration Low hemoglobin

Iron Deficiency

Depletion or deficiency of iron stores can lead to a wide variety of symptoms, ranging from asymptomatic decrease in body iron stores to noticeable fatigue with both depletion of iron stores and decreased hemoglobin production. There are three iron depletion states, which are addressed in Table 1 [11].

Measuring Iron Stores: Ferritin

When iron supplies are adequate and transferrin is saturated, iron is transported to reticuloendothelial cells and hepatocytes and is incorporated into ferritin. When iron is transported between cells, it is carried in ferritin (apoferritin). Apoferritin can be measured by sensitive radioimmunoassay and has been utilized as a marker of adequate iron stores [11]. Reported normal values for serum ferritin are 12 to 300 ng/mL for men and 12 to 150 ng/mL for women [9••]. Total iron stores range from 2.3 g for a 60-kg woman to 4.1 g for a 70-kg man; 70% is found in hemoglobin and myoglobin, 1% is utilized in cytochromes involved in respiration, 0.1% is bound to transferrin, and the remaining 15% to 30% is stored

as ferritin [11]. Many clinicians believe that ferritin levels may serve as a correlate for health and performance in endurance athletes and utilize ferritin levels to determine the need for iron supplementation in athletes [3••,7••,11,12]. The large range of normal values for ferritin reflects the enormous variations found in individuals [11]. The level at which to initiate supplemental iron is controversial [3••]. Ferritin levels of less than or equal to 12 ng/mL correlate with lack of marrow iron stores and completely exhausted iron stores. Iron absorption studies using ^{59}Fe have defined plasma ferritin levels of 35 ng/mL as the lower limit of normal. However, up-regulated absorption rates have been found in individuals with ferritin values up to 60 ng/mL [13,14]. Various studies have looked at iron-depleted nonanemic individuals and utilized values ranging from 12 to 40 ng/mL [7••,11]. Coaches and endurance athletes often quote arbitrary ferritin values from 30 to 90 ng/mL as optimal for allowing peak performance. Other data have suggested that ferritin levels of 16 to 20 ng/mL may be an appropriate low value to initiate iron supplementation [3••,14]. *Runner's World* has published reports by David Martin, PhD (from the Laboratory for Elite Athlete Performance at Georgia State University), indicating that a ferritin level below 20 ng/mL impairs performance [15]. Also adding to the confusion is the fact that ferritin is an acute phase reactant, which can act as a generalized marker of inflammation in the body and in the presence of inflammatory conditions (illness, injury, stress), may be falsely elevated. Therefore, using ferritin to evaluate iron stores may be even more difficult [16]. The quandary arises in the context of what to do when ferritin is used to evaluate iron stores in an individual who is considered iron depleted, nonanemic, and not performing at peak capacity. What value of ferritin is considered low and in need of iron supplementation? What is considered a "normal" ferritin level allowing optimal performance without supplementation? How high of a ferritin level must be achieved with supplementation to achieve peak performance? Is this a relative value based on individual needs? Various studies have utilized ferritin values equal to 20 to 35 ng/mL as both an adequate level for ferritin maintenance and a baseline at which supplementation is suggested [3••,7••,11,14,17]. Ferritin and complete blood count (CBC) remain the most cost-effective method of screening athletes for iron deficiency and anemia [3••].

Causes of Low Iron

The RDA for iron intake is generally considered to be between 15 and 18 mg/d, and there are various adjustments based on age, sex, pregnancy status, and growth (RDAs for iron listed above for men, women, and vegetarians) [9••]. One of the main reasons for iron depletion/deficiency is iron malnutrition. Diets that are lacking in meat products generally are low in iron and utilize the

less absorbable nonheme iron. Vegetarians are therefore at an elevated risk for iron depletion/deficiency, not only for the lack of meat products with good iron sources, but also because the iron from grain and vegetable sources is not as readily absorbed [18]. There are many vegetarians who consume adequate amounts of iron, but the bioavailability is lower and therefore results in an inadequate intake [19]. Women tend to be at higher risk secondary to menstrual blood loss and poor dietary intake, whether due to lack of meat products, vegetarian status, or just decreased caloric consumption in general. Adolescent females are particularly prone to decreased iron stores [6,7••,14,20]. As mentioned above, interactions with other nutrients such as tannins, calcium, polyphenols, and phytates can decrease absorption of nonheme iron [9••]. Some evidence points to the proportion of protein, not the absolute iron intake, in the diet as the important predictor of iron status, indicating that diets high in carbohydrates and fats (as seen in many adolescents) may inhibit iron absorption [6]. Other causes of iron loss in athletes specifically related to the body's uptake and loss of this mineral include 1) gastrointestinal blood loss (1.5 mL/d up to 6–7 mL/d or 3–5 mg iron/d) [7••,14]; 2) increased loss of iron in sweat (range from $0.04 \text{ mg} \times \text{m}^{-2} \times \text{h}^{-1}$ in women and $0.12 \text{ mg} \times \text{m}^{-2} \times \text{h}^{-1}$ in men) [7••,20]; 3) increased iron loss in urine; 4) intestinal iron malabsorption; and 5) menstrual blood loss.

Foot-strike hemolysis may be another source of iron loss that may affect endurance athletes. It consists of the runner's feet striking the ground, resulting in iron loss through the hemolysis of blood from the impact of running (although the amounts actually may be trivial) [12,20]. This results in a runner's macrocytosis secondary to a reactive reticulocytosis in response to hemolysis with release of free hemoglobin leading to hypohaptoglobinemia as a result of hepatic uptake of intact hemoglobin-haptoglobin complexes [7••]. It is also postulated that iron stores in athletes can be chronically low, specifically when looking at ferritin levels [7••,12]. The need for iron can be increased by as much as 30% in individuals who participate in regular intense exercise, and this may not reflect the intensity or training protocols of higher-level athletes [9••,17]. Endurance athletes, particularly women, tend to be at higher risk for iron depletion, due not only to menstrual irregularities, but also decreased iron intake, and diminished caloric intake [6,21,22].

Low Iron in Athletes

The prevalence of iron deficiency anemia is similar in both the general and athletic populations, ranging from about 2.9% in women to less than 0.2% in men [3••,11]. Iron deficiency appears to be a different issue when comparing untrained individuals with trained individuals. Women appear to be more prone to iron deficiency when compared with men, with up to 37% of female athletes and 23% of untrained women having serum ferritin values under 20 ng/mL [3••,23]. The incidence of low ferritin levels in US

men appears to be less than 2%, with male athletes also appearing to display lower ferritin values when compared with sedentary men in the general population [12,20]. Physical activity can lead to decreased iron stores (low ferritin) regardless of sport, but endurance athletes (runners foremost) tend to have more frequent and pronounced decreases in iron stores [7••,11,12,20,24].

Iron Deficiency Anemia and Athletic Performance

Iron deficiency anemia occurs when iron stores are deficient and hemoglobin falls below normal values. This condition can have pronounced effects on athletic performance and work capacity. Studies have shown that iron deficiency anemia leads to decreased work capacity, decreased VO_{2max} , and decreased transportation of oxygen to the tissues for utilization secondary to decreased erythropoiesis [8]. In individuals with iron deficiency anemia, it has been shown that iron supplementation leads to improved performance. Supplementing iron in athletes who are anemic not only improves iron stores, but increases work capacity and decreases exercise heart rate and lactate concentration [7••].

Iron Depletion Without Anemia and Athletic Performance

There have been conflicting reports over the years concerning the benefit of iron supplementation in iron depleted nonanemic individuals (athletes and non-athletes). Some studies and reports have discussed improvement in VO_{2max} and/or performance [14,25–28]. Other studies and reports contradict these findings [7••,11,14,25,29]. Matter et al. [27] noted changes to serum ferritin with supplementation in the iron depleted athlete, but without any positive effect on peak oxygen uptake or lactate concentrations. Rowland et al. [28] reported improvement in treadmill time to exhaustion in iron-depleted female runners, but part of the difference resulted from an unexplained decrease in time to exhaustion in the placebo group [11,14,24,26]. Hinton et al. [25] found that iron supplementation reduced cycling time after a training regimen in a 15-km cycle ergometer test in iron-depleted nonanemic women but without effect in other objective variables (VO_{2max}) between supplemented and placebo-treated groups. It was not clear whether this result was due to training and conditioning effect in a less fit supplemented group or if it was related to improvement in relative anemia as seen in increased hemoglobin levels in the supplemented group. Friedmann et al. [26] showed that elite adolescent athletes could improve aerobic capacity based on increases in VO_{2max} and oxygen consumption during treadmill running to exhaustion with no differences noted between sexes in iron-supplemented groups. The possibility of training

effect was not excluded, nor was the subjective nature of using volitional exhaustion testing to quantify objective data. Although subjective performance may improve, the most recent research reveals that low ferritin levels do not affect VO_{2max} and objective performance measures are not statistically significant when iron supplementation is used to treat nonanemic iron depletion [7••,11,14,29]. In a meta-analysis of various studies concerning nonanemic iron-depleted subjects and iron supplementation, it was shown that supplementation can raise serum ferritin levels but did not increase endurance performance [11]. Some of the problems noted with these studies were the differing amounts of supplemental iron used, and the duration of supplemental iron treatment (8 weeks vs 3–6 months) [11]. Testing of performance also greatly differs (VO_{2max} vs exhaustion time) among studies, leading to results that may not be practical and may be a manifestation of training effect [7••,11,14,21,26–28]. Lastly, ranges of what was considered low ferritin greatly differed between studies, with ferritin deficiency being defined from 12 to 40 ng/mL [7••,11]. This discrepancy provides a confusing picture of what should be considered low or normal ferritin levels. None of the studies explained the use of their particular reference value for low ferritin.

Pseudonemia/Sports Anemia

During intense physical training there are adaptive changes in the blood that are induced by the training response of an exercise regimen. These changes are referred to as *sports anemia*. Sports anemia is a transient phenomenon in which a decrease in blood hemoglobin occurs at the start of a training program and resolves at completion of the training or the competitive season [7••,12]. It is more common in endurance athletes and its changes are similar to those that occur during pregnancy after the second trimester [7••]. The changes include an increase in plasma volume and stimulation of erythropoiesis. The plasma volume reaches its apex at an accelerated pace in comparison with the enhancement of hemoglobin production, which lags behind. This difference allows for a pseudonemia. This condition is temporary and will normalize at the completion of training, not requiring iron supplementation to correct iron depletion [7••].

Current Practices of Iron Supplementation as an Ergogenic Aid

Current practice guidelines for iron supplementation in the iron-depleted athlete vary. Most reports state that the nonanemic athlete does not improve objective performance with supplemental iron [7••,11,14]. Garza et al. [11], in their meta-analysis, showed that the objective finding of increased work capacity or improved VO_{2max} is not altered beneficially in the nonanemic iron-depleted

athlete receiving iron supplementation [11]. There is a subset of athletes who are found to be nonanemic (based on normal laboratory values for hemoglobin) but iron depleted who may have a relative anemia indicated only when their indices improve with supplemental iron. This would be an indication for iron supplementation, especially in light of clinical symptoms such as fatigue or subjective complaints of decreased physical performance. Another problem seen in studies is how performance improvement is measured. Some investigators measured via $\text{VO}_{2\text{max}}$, which is mostly objective, whereas others measured by test-to-exhaustion, which can be subjective and influenced by training effect [11].

It would seem prudent to treat iron-depleted individuals with iron supplementation, but at what level of ferritin should supplementation be started? Should an arbitrary number be used or should the number be coupled with symptoms of poor performance or fatigue? At what ferritin levels should the athlete be maintained for peak performance? Are parameters for initiating supplementation based on specific ferritin levels, and are maintenance levels sport- and sex-specific?

In reviewing the literature, many reports used a ferritin level of 30 to 35 ng/mL as the common denominator for considering ferritin low and thus initiating iron supplementation [3••,11,14]. However, research has shown ferritin values as low as 12 ng/mL in the nonanemic iron-depleted athlete do not alter performance [7••,11,14]. Objective evidence exists for a ferritin value of 35 ng/mL as the lower limit of normal based on ^{59}Fe absorption studies [13,14]. Mast et al. [30] provide evidence that the sensitivity and specificity of ferritin could be improved to 92% and 98%, respectively, for diagnosing iron deficiency by using a diagnostic cutoff value of less than 30 ng/mL, resulting in a positive predictive value of 92%.

What level of ferritin correlates with iron sufficiency in an athlete? Should we strive to keep the athlete above 30 to 35 ng/mL or higher? As mentioned above, up-regulated absorption rates have been found in individuals with ferritin values up to 60 ng/mL [13,14]. Is this the appropriate maintenance level or should it be higher?

What doses of iron are needed to treat iron deficiency in athletes? Hematology references cite treating iron deficiency anemia with 150 to 200 mg of elemental iron daily (in divided doses) until the anemia has been fully corrected. Oral iron should then be continued to replace storage iron, either empirically for an additional 4 to 6 months or until the plasma ferritin concentration exceeds approximately 50 ng/mL [31]. Is this appropriate for treating iron depletion in athletes? Studies utilizing 18 mg/d elemental iron produced no effect on changing iron status. Elemental iron doses equaling or exceeding 50 mg/d have been shown to produce improvements in iron stores in iron depleted nonanemic athletes [14,24].

Iron Supplementation Risks

Iron supplementation is not without risks. The best way to obtain iron is via dietary sources and improving one's diet, but there are times when iron supplementation is required. It is important to monitor iron when utilized as a supplement due to the risks of iron overload. These risks are greatest for men and postmenopausal women [9••]. Women of menstruating age are at lower risk for iron overload due to the loss of iron associated with blood loss during menstruation. Iron overload is a condition in which excess iron in the blood is stored in organs of the body. Hemochromatosis, which affects approximately one in 250 individuals of Northern European descent, is a genetic condition in which individuals absorb iron very efficiently, resulting in a build up of excess iron that can cause organ damage such as cirrhosis of the liver and heart failure [7••,9••,17]. Hemochromatosis often is not diagnosed until excessive iron stores have already damaged an organ. Iron supplementation may accelerate the effects of hemochromatosis. Studies done recently on Tour de France cyclists have shown greatly elevated ferritin levels (median 332–504 ng/mL), likely due to oversupplementation. This places the athlete at undue risk for iron overload, and much of this supplementation is done without any control or monitoring [32,33]. Also, individuals who have blood disorders that require multiple transfusions are also at risk for iron overload if they supplement iron inappropriately [9••]. Lastly, it is a concern that use of iron supplements may mask other medical conditions (celiac disease, occult gastrointestinal bleeding, uterine abnormalities) and delay presentation and/or treatment [17].

Conclusions

Iron is obviously an important nutrient and involved in many biologic processes, many of which are vital to athletic performance. When an athlete who may be at risk for iron depletion or iron deficiency presents with fatigue a thorough history and examination must be completed to narrow the differential diagnosis [4]. However, athletes and coaches have certain perceptions surrounding poor performance and fatigue; the importance of ferritin testing increases as symptoms continue past 7 days [2]. In terms of testing, although there are newer methods such as soluble transferrin receptor concentration (STFR), a CBC and a measurement of serum ferritin levels should suffice, and are considered most cost-effective screening [34]. STFR has not been found to be as sensitive as ferritin levels in screening for iron depletion, and it may not be as reliable in the diagnosis of absent iron stores [35]. STFR may be useful as an adjunct in the evaluation of anemic patients whose ferritin values may be increased as the result of an acute-phase reaction [30].

It does appear reasonable to screen for iron deficiency and anemia in athletes with persistent fatigue using ferritin values and a CBC [4]. Based on evidence it would also appear reasonable to screen high-risk athletic populations such as male endurance athletes and female athletes in general [7••,14]. If an athlete is deemed iron deficient, care should be taken to rule out potentially serious medical conditions based on history, physical examination, or more specialized testing. This is particularly true of male athletes.

Additionally, female athletes should be counseled not only on screening, but also preventative measures, such as improving dietary iron intake or use of an oral contraceptive pill for menstrual irregularities [3••,36]. Vegetarian athletes should be treated with a similar approach; screening and education about dietary iron intake and the special needs regarding iron bioavailability and the vegan diet should be made available [19]. The question of dietary versus supplemental iron should also be addressed with athletes. The importance of an adequate, well-balanced diet for athletic participants is well defined, and the need for supplementation should be nullified if the athlete's diet is providing the appropriate nutrients [18]. If supplementation is needed, care should be taken to use appropriate doses with periodic ferritin monitoring, considering excessive amounts of supplemental iron can have adverse side effects. Keep in mind that iron is best absorbed under the following forms and circumstances [37]: 1) in the ferrous form (without enteric coating); 2) in a mildly acidic medium (250 mg ascorbic acid tablet at the time of iron administration enhances the degree of iron absorption); 3) between meals (to decrease binding by phosphates, phytates, and tannins, which decrease absorption); and 4) given 2 hours before or 4 hours after ingestion of antacids.

Athletes who do not tolerate iron may have better tolerance using lower doses, using an enteric-coated form or iron solution, using ferrous gluconate, or by taking the iron with meals. All of these options decrease the absorption of iron, however [37].

Finally, the questions regarding appropriate levels of ferritin at which to begin supplementation and appropriate levels of ferritin to maintain need to be answered. Are those ferritin levels 30 to 35 ng/mL and 60 ng/mL, respectively [3••,14,30]? Within this context, how then are these ferritin levels to be enhanced correctly (diet with or without supplementation) and how long should supplementation be continued? Further research should continue to help our understanding of the intricacies of iron depletion and the most appropriate treatment protocols to pursue in treatment of nonanemic iron-depleted athletes. For now the decision to initiate iron supplementation is best made on an individual basis between the athlete and physician once all risks and benefits are discussed.

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