Iron Supplementation for Female Athletes: Effects on Iron Status and Performance Outcomes

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Abstract

Iron is an essential micronutrient involved in oxidative metabolism and critical to exercise performance. The prevalence of iron deficiency (ID) is much higher in active women for a variety of reasons, and poor iron status has been shown to be detrimental to overall health as well as physical performance. Iron status can be assessed using a number of indicators; however clinical cut-offs for active populations remain controversial. Randomized, placebo-controlled supplementation trials of iron-depleted female athletes have shown that oral iron supplementation in doses of 100-mg $FeSO_4 \cdot d^{-1}$ (approximately 20 mg elemental iron) improves iron status and may improve measures of physical performance. It is recommended that female athletes most at risk of ID be screened at the beginning of and during the training season using hemoglobin and serum ferritin, and appropriate dietary and/or supplementation recommendations be made to those with compromised iron status.

Introduction

Iron deficiency (ID) is the most prevalent nutrient deficiency in the world. In the United States, ID with anemia (IDA) affects 3% to 5% of premenopausal women, and ID without anemia (IDNA) affects approximately 16% of premenopausal women (7). Compared to their sedentary counterparts, active women are twice as susceptible to IDNA (13,45), and changes in oxidative metabolism and physical performance have been described in humans with compromised iron (Fe) status (22). Beyond menstrual status, the increased prevalence of IDNA in active women may be due to one or a combination of the following factors: hemolysis (foot strike and impact) (37); increased Fe losses (gastrointestinal tract, hematuria, and sweat) (47); poor dietary Fe intake (18,23); or altered intestinal Fe absorption, including the effects of inflammation due to training (21). Other modifiable contributors to the prevalence of ID in this population may include routine use of nonsteroidal anti-inflammatory drugs, as well as blood donation (4).

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Data from a recent analysis of the National Health and Nutrition Examination Survey (NHANES) 2003 to 2006 show that over 50% of U.S. women were consuming dietary supplements, and 15% of supplement-consuming women aged 19 to 30 years reported taking one containing Fe (1). These data are comparable to that of female athletes showing that more than 50% use some type of supplement, and those containing Fe are among the most popular (11,24). Despite reported Fe supplement use, ID continues to be a problem and has many consequences relevant to athletes. Therefore the objective of this review is to provide a summary of the effects of oral Fe supplementation on both Fe status and performance in active women and to provide recommendations to improve Fe status in this population.

Assessment of Iron Status and Effects on Performance

Anemia is identified clinically using hemoglobin (Hgb) <12 g·dL^{-1} (women) and <13 g·dL^{-1} (men). These cut-offs, however, may be insufficient to identify the condition in female athletes, as improvement of mildly anemic Hgb status in nonanemic athletes supplemented with Fe has been reported (15,42). Low Hgb concentration leads to reduced oxygen (O_2) transport to working muscles, which is the primary mechanism for reduced performance due to anemia. Performance outcomes resulting from poor O_2 transport due to anemia include decreases in maximal O_2 consumption ($\dot{V}O_{2max}$) and aerobic power.

Serum ferritin (sFer) is the most common index of body Fe stores, reflecting Fe stored in the liver. Clinically, individuals are identified as ID with an sFer <12 μg·L^{-1}; however, many studies use sFer 12 to 20 μg·L^{-1} to define ID. Some studies have shown associations with performance outcomes, as well as improvements in Fe status with supplementation, using higher sFer cut-offs (14,39).

There are many Fe-containing cofactors involved in muscle and energy metabolism affected by Fe depletion beyond O_2 transport by Hgb (*e.g.*, cytochromes and coenzymes of

the Krebs cycle) (12). When Fe stores (sFer) have become depleted but Hgb has not yet declined to a level indicative of anemia, this is the beginning of functional or subclinical ID, which affects compounds associated with muscle metabolism (*e.g.*, tissue oxidative capacity), and may result in impaired endurance performance (*e.g.*, energetic efficiency and endurance time). At this stage, Hgb synthesis and O_2 transport (*e.g.*, $\dot{V}O_{2max}$) likely are not affected. Under conditions of severe ID, Hgb synthesis may become compromised in addition to depleted iron stores (IDA). With IDA, a range of physical performance measures are affected due to reduced O_2 transport (*e.g.*, $\dot{V}O_{2max}$), as well as reduced tissue oxidative capacity (*e.g.*, endurance capacity and energetic efficiency).

While a good indicator, sFer can be elevated falsely in an inflammatory state (*e.g.*, infection, exercise, and obesity); thus inflammatory markers such as C-reactive protein or α-1-acid glycoprotein can aid in the interpretation of sFer in the assessment of Fe status (46). The most recent advancements in the area of Fe and exercise, however, are related to hepcidin, which is a negative regulator of Fe status. Hepcidin expression is upregulated by inflammation, and increased expression can be linked to decreased Fe status. This topic has been more extensively reviewed recently by Gaffney-Stomberg and McClung (21).

Soluble transferrin receptor (sTfR) is regulated by cellular Fe status and reflects ID at the tissue level. Compared to sFer, sTfR is a more sensitive index of functional ID. In subgroup analyses of an Fe supplementation trial in women adapting to aerobic training, performance improvements were observed only in those with elevated sTfR at baseline (>8 $mg \cdot L^{-1}$), compared to those with normal tissue Fe status (<8 $mg \cdot L^{-1}$) (5,6). Furthermore sTfR is unaffected by inflammation and has been shown to have lower within-subject variability in training athletes (32). sFer and sTfR respond to Fe supplementation in opposite directions (sTfR decreases and sFer increases with repletion of Fe stores). As sTfR reflects overall erythropoiesis, athletes would be expected to have higher sTfR concentration levels than untrained individuals; thus further research is needed to determine appropriate sTfR cut-offs for athletes (2,43).

Due to the debate on sFer cut-offs to define ID in athletes, as well as the conflicting results about the effects of IDNA on physical performance, the sTfR/sFer ratio may be preferable to sFer alone to assess the need for supplementation. With the inclusion of sTfR (measure of Fe-deficient erythropoiesis), this ratio is more sensitive to a wider range of body Fe status. The log of sTfR/sFer is directly proportional to the amount of total body iron (TBI, milligram iron per kilogram body weight) (9): *iron stores* ($mg \cdot kg^{-1}$) = *[log(sTfR/sFer) − 2.8229]/0.1207*. Although TBI is driven by sFer in a population with a low prevalence of anemia, this measure of Fe status permits the detection of mild tissue ID in nonanemic individuals.

Iron Requirements: What is the Optimal Intake for Female Athletes?

To maintain sufficient Fe stores, the recommended daily allowance (RDA) of Fe for healthy premenopausal women is 18 $mg \cdot d^{-1}$. The estimated average requirement (EAR) for healthy populations (used to calculate RDA) is 8.1 $mg \cdot d^{-1}$. It has been suggested, however, that physical training may increase the EAR in female athletes by 30% to 70% (from 8 to 10–14 $mg \cdot d^{-1}$) (27). The U.S. military has set the RDA for female soldiers who are training at 22 $mg \cdot d^{-1}$ (8). Estimates of basal losses (1.7 $mg \cdot d^{-1}$) by Weaver and Rajaram (47) were used as a basis for these recommendations on Fe requirements for training military personnel, accounting for sweat losses, training duration, and workload.

If active women do require more Fe, it may most likely be for those engaged in weight-bearing activities, which result in greater losses via the gastrointestinal tract and foot-strike hemolysis. Future studies that screen active women for ID and monitor Fe status as well as dietary intake and menstrual status upon recruitment, during training, and throughout the competitive season (or military deployment) may help to substantiate the argument over increased Fe requirements for this population.

Can Increasing Dietary Iron Intake Improve Iron Status?

Increasing dietary intake of Fe or supplementation is the only way to replace Fe losses and improve body Fe status. Several studies have compared the effects of oral Fe supplementation with that of highly bioavailable dietary Fe (*e.g.*, meat intake) on body Fe status. Many of these were conducted in untrained women. One randomized controlled trial (RCT) of non-ID women during 12 wk of aerobic training showed that increasing meat intake was as effective as a low-dose oral Fe supplement (50 $mg \cdot d^{-1}$ $FeSO_4$) at maintaining sFer (30).

What About Oral Iron Supplementation?

The increased daily Fe requirements of active and training women may not be met by dietary Fe intake alone. Supplementation may be warranted in some cases, such as in the treatment of IDA (Hgb <12 $g \cdot dL^{-1}$, sFer <12 $\mu g \cdot L^{-1}$), and for athletes with consistent suboptimal dietary intake (*e.g.*, vegetarians/vegans, weight-control sports, and the like). Individuals with normal Fe status (Hgb >12 to 13 $g \cdot dL^{-1}$, sFer >30 $\mu g \cdot L^{-1}$) likely will not benefit from supplementation, and concerns regarding unregulated doses and Fe overload should be considered. Thus Fe supplementation should not be initiated without proper determination of Fe status, as discussed previously.

Oral Fe supplements are commercially available as Fe salts and heme supplements, with the latter more bioavailable (44). Of the salts, ferrous preparations are better absorbed than ferric, with the most widely administered being sulfate, fumarate, and gluconate. All of the ferrous salts have comparable rates of absorption and incidence of gastrointestinal adverse effects (*e.g.*, constipation, nausea, vomiting, diarrhea, and darkened stools). Each type of Fe varies in the amount of *elemental Fe* (that which is available for absorption). For example, ferrous sulfate ($FeSO_4$) contains 20% elemental Fe; thus 100 mg of $FeSO_4$ is equivalent to 20 mg of elemental Fe (close to the RDA of 18 $mg \cdot d^{-1}$). In comparison, ferrous fumarate contains about 33% and ferrous gluconate 12% elemental Fe. The same factors that affect the bioavailability of dietary Fe will affect the absorption of supplemental iron. For example, the absorption of a low-moderate dose of oral supplemental iron, such as 100 mg $FeSO_4$, is most efficient when consumed daily with a source of vitamin C (*e.g.*, citrus juice) and less so when consumed with polyphenolic compounds (*e.g.*, coffee and tea).

Adverse effects may be experienced with low-moderate Fe supplementation, but generally not byall. These can be minimized by consuming a lower dose more frequently (*e.g.*, 100 mg of $FeSO_4$ taken as 50 mg twice per day) or a slow-release preparation. Additionally a lower incidence of adverse effects has been reported with heme Fe supplements compared to those containing only nonheme Fe (20). More infrequent dosing of larger amounts of Fe (*e.g.*, 60 mg of elemental iron per week for 12 wk) has also been found to be an effective treatment of IDA in nonathletic women and children (16), and some researchers have reported better compliance with this mode of supplementation compared to a daily regime (3).

Concerns About Iron Overload

"Iron overload" is a term used to describe increased total body Fe stores, with or without organ dysfunction (38). Consumption of excess Fe (via dietary or supplemental sources) is classified as secondary Fe overload, in contrast to a primary defect in the regulation of Fe balance (*e.g.*, hereditary hemochromatosis (HHC)) (38). Iron overload may be suspected when sFer is higher than the upper normal limits for an age/sex group (*e.g.*, sFer for women — 20 to 29 years: 65 $\mu g \cdot L^{-1}$; 30 to 39 years: 80 $\mu g \cdot L^{-1}$; 40 to 49 years: 100 $\mu g \cdot L^{-1}$; >50 years: 200 $\mu g \cdot L^{-1}$; sFer for men — >20 years: 350 $\mu g \cdot L^{-1}$), while sFer >1,000 $\mu g \cdot L^{-1}$ suggests liver damage in HHC (38). Those consuming large doses of Fe, especially in supplemental forms, and men as opposed to women, are at greater risk of Fe overload. Long-term consequences of Fe overload are unclear, but potential consequences include organ and cellular damage due to oxidative stress and the formation of free radicals (34).

Most human studies have focused on ID rather than Fe overload in athletes due to the greater prevalence of ID, which may lend to overuse of Fe supplementation, or supplementation without first screening for Fe status. In a recent study of Swiss runners, while 28% of women and 2% of men were ID (defined as sFer <15 $\mu g \cdot L^{-1}$), Fe overload (defined as sFer >200 $\mu g \cdot L^{-1}$) was found in only 4.7% of women but in 15% of male athletes (35). The higher prevalence of Fe overload in men is primarily due to lower basal loss compared to women (no monthly blood loss).

The tolerable upper level (TUL) has been set at 45 $mg \cdot d^{-1}$ elemental Fe (*e.g.*, as 225 mg of $FeSO_4$), and oral supplementation greater than the TUL increases the chance for gastrointestinal and other adverse effects, including Fe overload (27). To decrease risk of Fe overload, athletes should not consume oral supplements unless indicated by a health professional after proper assessment of Fe status (Hgb and sFer).

Iron Supplementation of Active Women: Response of Body Iron Status

Many researchers have studied the effects of IDNA on performance outcomes in women. Results vary widely due to poor study design and small sample size, variable sFer cutoffs used to define IDNA at baseline, and use of indirect markers of performance. Many studies have been conducted in nonathletic women or recreational exercisers without controlling for physical activity level or training load, making translation to highly trained athletes difficult.

Table highlights a few studies examining the effects of oral Fe supplementation on Fe status and physical performance outcomes in active women. Eleven randomized, double-blind, placebo-controlled oral Fe supplementation trials studying both Fe status (Hgb and sFer) and performance outcomes in active women were selected. The majority of these female low-moderate dose of subjects studied were nonanemic (Hgb >12 $g \cdot dL^{-1}$) and Fe depleted (sFer <20 $\mu g \cdot L^{-1}$). The training status of subjects varied and included untrained women who were enrolled in aerobic training programs, recreational athletes, military recruits, and trained runners.

Although Hgb status was clinically normal at baseline, an Hgb response to Fe supplementation was observed in four of these studies, indicating mild or relative anemia in the subjects at baseline (17,29,31,42). sFer was the main index of Fe status assessed in most studies and responded well to a range of daily supplementation dose and duration (20 to 200 mg of elemental iron over 2 to 12 wk). While two studies did not report an increase in sFer in the supplementation groups, a prevention of the decline in Fe status over the course of the trials was observed compared to placebo (31,33). Overall these studies showed that even moderate doses of Fe supplementation (1 to 2× RDA) led to improvements in sFer in active individuals with mild to moderately compromised Fe status.

Regarding dosage, four of the studies summarized in Table implemented low-moderate doses (1 to 2× the RDA) of daily Fe supplementation (25,26,31,33). Five studies used 3 to 5× the RDA as a dose (17,28,29,36,42), and two studies used >10× the RDA as a daily dose (19,41). Overall 100 mg of $FeSO_4$ (approximately 20 $mg \cdot d^{-1}$) over the course of 6 to 8 wk was sufficient to improve or prevent decline in sFer in compliant, IDNA women.

Iron Supplementation of Active Individuals: Effects on Physical Performance

Performance outcomes in the studies reviewed are presented also in Table. Outcomes included those through which Fe plays a major role in oxidative metabolism, such as endurance time, blood lactate concentration, time trial (TT) time, and energetic efficiency, as mentioned previously. Results among the studies varied due to Fe dose used, performance testing protocol, as well as subject training status.

Performance outcomes in active women due to Fe supplementation are not as clear as those for Fe status. Three of the 11 studies reviewed found no effect of supplementation on performance despite improvement in sFer levels (17,28,36). The negative outcomes of these three trials may be due to poor study design, as the protocols used to test the effects of increased Fe stores (sFer) were related to O_2 transport (*e.g.*, $\dot{V}O_{2max}$ as an outcome), and not tissue oxidative capacity (*e.g.*, endurance).

The other eight studies showed that subjects supplemented with Fe had improved endurance times (*e.g.*, longer time to exhaustion), faster TT times (*e.g.*, completed a simulated race faster), and increased energetic efficiency (*e.g.*, completed same amount of work using less energy) compared to those supplemented with placebo. Supplementation leading to improved sFer would be expected to have an effect on these endurance performance outcomes. Overall these studies showed that low-moderate doses of Fe supplementation

Table.

Randomized, double-blind, placebo-controlled trials investigating the effects of oral iron supplementation on iron status and performance in active women.

Authors (date)	Location	Subjects	Initial Iron Status	Intervention	Iron Status Results	Performance Results
Schoene *et al.* (42)	US	F athletes, ID and Normal iron status	Hgb: >12 $g \cdot dL^{-1}$; sFer (ID): <20 $\mu g \cdot L^{-1}$	300 mg/d of $FeSO_4$, 2 wk	Tx ↑ sFer, Hgb in ID subjects; Tx ↑ Hgb in normals	NS effects on $\dot{V}O_{2max}$; Tx ↓ max lactate in ID subjects but not normals
Rowland *et al.* (41)	US	F runners	Hgb: >12 $g \cdot dL^{-1}$; sFer: <20 $\mu g \cdot L^{-1}$	975 mg/d of $FeSO_4$, 4 wk	Tx ↑ sFer	Tx ↑ endurance time; P ↓ endurance time
Newhouse *et al.* (36)	Canada	F runners	Hgb: 13 $g \cdot dL^{-1}$; sFer: 12 $\mu g \cdot L^{-1}$	320 mg/d of $FeSO_4$, 8 wk	Tx ↑ sFer	NS effects on $\dot{V}O_{2max}$, anaerobic power
Magazanik *et al.* (31)	Israel	Untrained F at baseline, enrolled in 7-wk training program	No inclusion criteria. Tx BL means: Hgb: 12.4 $g \cdot dL^{-1}$; sFer: 24.0 $\mu g \cdot L^{-1}$	160 mg/d of $FeSO_4$, 7 wk	Tx ↑ Hgb; P ↓ sFer	Tx ↑ $\dot{V}O_{2max}$
Fogelholm *et al.* (17)	Finland	F athletes	Hgb: >12 $g \cdot dL^{-1}$; sFer: <25 $\mu g \cdot L^{-1}$	500 mg/d of $FeSO_4$, 8 wk	Tx ↑ sFer and Hgb	NS effects on $\dot{V}O_{2max}$, blood lactate
Klingshirn *et al.* (28)	US	F runners	Hgb: >12 $g \cdot dL^{-1}$; sFer: <20 $\mu g \cdot L^{-1}$	320 mg/d of $FeSO_4$, 8 wk	Tx ↑ sFer	NS effects on $\dot{V}O_{2max}$, endurance, RER, lactate
LaManca and Haymes (29)	US	F athletes	sFer: <20 $\mu g \cdot L^{-1}$	318 mg/d of $FeSO_4$, 8 wk	Tx ↑ sFer and Hgb	Tx ↑ $\dot{V}O_{2max}$ and ↓postexercise lactate
Hinton *et al.* (25)	US	Untrained F at baseline, enrolled in 4-wk training program	Hgb: >12 $g \cdot dL^{-1}$; sFer: <20 $\mu g \cdot L^{-1}$	100 mg/d of $FeSO_4$, 6 wk	Tx ↑ sFer, ↓ sTfR	Tx and P ↓ TT time, RER; Tx ↓ TT time greater versus P; Tx ↓ %$\dot{V}O_{2max}$ during TT
Friedmann *et al.* (19)	Germany	M/F athletes	Hgb: >11.7 $g \cdot dL^{-1}$; sFer: <20 $\mu g \cdot L^{-1}$	1136 mg/d of $FeSO_4$, 12 wk	Tx ↑ sFer, P ↓ sFer	Tx ↑ $\dot{V}O_{2max}$, endurance time
Hinton and Sinclair (26)	US	M/F recreational athletes	Hgb: >12 $g \cdot dL^{-1}$; sFer: <16 $\mu g \cdot L^{-1}$; sTfR: >8 $mg \cdot L^{-1}$; sTfR/log sFer index: >4.5	100 mg/d of $FeSO_4$, 6 wk	Tx ↑ sFer	P ↓ VT after trial; Tx ↑ post-trial energetic efficiency
McClung *et al.* (33)	US	F army recruits enrolled in BCT	No inclusion criteria. Tx BL means: Hgb: 12.3 ± 1.3 $g \cdot dL^{-1}$; sFer: 37.0 ± 29.4 $\mu g \cdot L^{-1}$	100 mg/d of $FeSO_4$, 8 wk	P ↓ sFer and ↑ sTfR	Tx ↓ 2-mi run time

M/F, male/female; BCT, basic combat training; ID, iron deficient; $FeSO_4$, ferrous sulfate; Tx, treatment group; P, placebo group; EE, energy expenditure; $\dot{V}O_{2max}$, maximal oxygen consumption; NS, nonsignificant; RER, respiratory exchange ratio; VT, ventilatory threshold.

(1 to 2× RDA) led to improved performance outcomes in active women. However it is difficult to compare studies due to methodological differences (*e.g.*, exercise protocols, dose of Fe).

Improving Iron Status of Active Women: Controversy Surrounding Recommendations

Major disagreement exists among experts in the field about who should be supplemented with how much Fe. Given the current body of evidence surrounding Fe's role in overall health and physical performance, there is no debate that athletes with clinical ID and IDA should be identified and treated appropriately. Whether subclinical IDNA, however, leads to decreased physical performance in all athletes and should be treated with Fe supplementation remains controversial.

As described previously, studies are difficult to compare due to methodological differences in protocols used to test physical performance, training status of subjects, Fe status cut-offs used to identify replete versus deplete, and so on. Those arguing that insufficient evidence exists to support the effects of IDNA on performance would feel that routine screening of athletes' Fe status is not necessary. Such screening would entail several logistical and institutional concerns. These would include who to screen, when and how often to screen, which biomarkers and cut-offs to use to identify those at risk or in need of supplementation, as well as the cost of (and who would financially support) screening programs.

Active women are more vulnerable to IDNA, and maintaining optimal body Fe status via increased dietary Fe intake and/or supplementation is recommended for this population. There are currently no standards for the evaluation of Fe status of female college athletes; however the Academy of Nutrition and Dietetics and the American College of Sports Medicine have suggested that female athletes' Fe status should be screened periodically (40). Prior to that recommendation, a survey of NCAA Division I schools found that not only was Fe status screening not a routine practice but there was also much variability in diagnostic and treatment criteria used between schools (10). More research is needed to clarify cut-offs for Fe status indicators used to screen athletes, as well as to optimize the screening process itself in order to most efficiently identify and treat those at risk of ID.

Given the roles that Fe plays in exercise, accurately determining Fe status in female athletes is critical. Based on the current body of evidence, female athletes most at risk of ID (*e.g.*, prior history of ID/IDA, recent blood loss, vegetarian, recent decrement in sports performance, and increased fatigue) should be screened using Hgb and sFer cut-offs of 12 $g \cdot dL^{-1}$ and 20 $\mu g \cdot L^{-1}$, respectively, to identify IDNA before it leads to anemia, thus reducing the adverse effects that ID may have on their training and performance (14). After identification, anemic and IDNA athletes should be provided with appropriate treatment (*e.g.*, low-moderate dose of supplemental Fe, 100 mg of $FeSO_4 \cdot d^{-1}$) and/or nutrition counseling (*e.g.*, increase dietary intake and bioavailability of dietary Fe) as necessary. Iron status as well as dietary and supplement compliance of anemic and IDNA athletes should be serially monitored throughout the training season to ensure sufficient dietary intakes and prevent further decrements in Fe status with training.

Conclusions

Despite the wide use of Fe supplements, ID remains an issue facing athletes. Maintaining Fe balance through diet and/or supplementation is essential to overall health and physical performance. Female athletes most at risk of ID should be screened using Hgb and sFer. In addition to serial monitoring of Fe status, Fe treatment and counseling regarding supplementation and food choices should be provided as necessary to ensure sufficient dietary intakes and prevent further decrements in Fe status with training. Further research should focus on clarification of optimal cut-offs for Fe status indicators for athletes as well as optimal Fe requirements to treat and/or prevent clinical and subclinical Fe deficiency in this population.

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