# Exercise-Associated Iron Deficiency: A Review and Recommendations for Practice

Erica R. Goldstein, MS, RDN, LD/N, CSCS, CISSN
Mayo Clinic, Jacksonville, Florida

## ABSTRACT

IRON DEFICIENCY IS PREVALENT IN FEMALE ATHLETES AND CAN IMPEDE ENDURANCE PERFORMANCE (I.E., SLOWER TIME TRIAL), AND WITH ANEMIA CAN REDUCE ENDURANCE CAPACITY. LEVELS OF HEPCIDIN ARE ELEVATED AFTER EXERCISE SECOND TO INFLAMMATORY STIMULI (INTERLEUKIN-6) AND MAY CONTRIBUTE TO THE DEVELOPMENT OF IRON DEFICIENCY. HEPCIDIN ACTS TO INTERNALIZE AND DEGRADE FERROPORTIN (CELLULAR CHANNEL RESPONSIBLE FOR IRON EFFLUX). THIS RESULTS IN SEQUESTRATION OF IRON WITHIN MACROPHAGES, WHICH RECYCLE IRON FROM AGED AND DAMAGED ERYTHROCYTES. PROLONGED HIGH-INTENSITY TRAINING, ESPECIALLY A MODALITY THAT INCLUDES REPETITIVE FOOT STRIKES, CAN CAUSE HEMOLYSIS RESULTING IN UPREGULATION OF HEPCIDIN AND MAY CONTRIBUTE TO THE DEVELOPMENT OF IRON DEFICIENCY.

## INTRODUCTION

Maintenance of adequate levels of dietary iron consumption, absorption, storage, and cellular uptake (e.g., incorporation into hemoglobin and developing red blood cells [RBCs]) is critical to endurance performance. Oxygen transport is most commonly associated with endurance sports, but iron is also required for mitochondria iron-dependent oxidative enzymes that support aerobic metabolism and generation of adenosine triphosphate (ATP) through the Krebs cycle and cytochrome activity necessary for the transfer of electrons in the electron transport chain (8,18,33). Iron deficiency, inadequate body iron stores, and iron deficiency anemia, depleted iron stores with decreased hemoglobin synthesis, can impede endurance performance by dampening muscle tissue oxidative capacity and cytochrome activity (e.g., slower time trial performance) and by diminishing $\dot{V}O_2max$ or oxygen transport (reduced endurance capacity), respectively (8,18).

Inadequate total daily energy intake and dietary iron consumption in addition to menstrual blood loss in endurance-trained women increase the risk of iron deficiency, with progression to anemia, if diet is not corrected and/or supplementation is not initiated (34). Nutrition education with attention to type and combination of animal and plant sources of iron in addition to individualized needs (i.e., total daily required energy intake, recommended dietary allowance [RDA] per population) is necessary for reducing the risk of iron deficiency and for helping to reverse the occurrence (34). Supplementation as warranted (8,20,28,30) should be closely supervised and is commonly provided in the form of ferrous sulfate with 20–105 g provided as elemental iron (i.e., amount that is absorbed) (8,30).

Finally, through a series of investigations (2,32,39,40,43), scientists have begun to examine the hormone, hepcidin, which is elevated 3 hours after exercise secondary to inflammatory stimuli, namely, the cytokine interleukin-6 (IL-6). Prolonged high-intensity training, especially modalities that include repetitive foot strikes, can cause hemolysis resulting in upregulation of hepcidin and may contribute to the development of iron deficiency. It has been shown, however, that hepcidin will be downregulated in athletes who initiate training with already clinically deficient iron stores (41).

It is important that allied health professionals have an understanding of both the dietary iron needs of the athlete and how certain aspects of training (type, intensity, and duration) can contribute to physiological disturbances of

**KEY WORDS:**
iron; iron deficiency; anemia; hemolysis; inflammation; hepcidin; red blood cells

iron handling, disruption of homeostasis, and how this can ultimately impede performance, particularly in trained endurance athletes.

## REVIEW OF PHYSIOLOGY

Iron is obtained from both plant and animal sources and is largely absorbed into intestinal cells (enterocytes) at the duodenum or first portion of the small intestine (13). Ferric iron must undergo a change in oxidative state to its divalent form (ferrous, $Fe^{2+}$) to enable movement across the brush border and absorption into the intestinal cell through the divalent metal transporter (DMT1). However, once absorbed, iron can be used by the cell or stored through the protein ferritin in enterocytes, hepatocytes, and macrophages (13,47). Enterocytes have a high turnover, so iron stored in these cells will be lost to excretion approximately every 2 days (13,16,48). Iron exits the cell as ferric ($Fe^{3+}$) iron, where it binds to the protein transferrin, and is circulated to various tissues to be used, chiefly by developing RBCs (36).

Mitochondria support hemoglobin synthesis in developing RBCs, which are produced in bone marrow (13,16,26,48,49). Within the mitochondria, free iron is used to synthesize heme (36,48,49). Therefore, heme contains iron bound to it, which is then used to form the protein hemoglobin.

Other locations of iron storage are macrophages (reticuloendothelial cells) in the liver and spleen (13,36,48). After 120 days, RBCs undergo various physiological changes that essentially mark aged erythrocytes for phagocytosis, principally by macrophages of the spleen (13). Macrophages are then able to store iron from degraded hemoglobin, which can ultimately be excreted and recycled to supply demand by other cells (14). In particular to athletes, hemolysis, or the destruction of RBCs, is often induced by chronic mechanical trauma, such as high impact repetitive foot striking, generally associated with running. Hemoglobin escapes from the ruptured membrane of a RBC, is released into plasma, and is captured by macrophages (16). The iron is then either stored through ferritin or recycled in a process similar to the aging erythrocyte.

Hepcidin is a protein synthesized by the liver that has been well described as the master regulator of systemic iron homeostasis (13,14,36). Hepcidin acts as a hormone that controls iron export from macrophages, liver, and intestinal cells (13,14). Movement of iron from the cell to the bloodstream is blocked because of the action of hepcidin on ferroportin (13,14). Ferroportin has a dual purpose as it serves as the cell receptor for hepcidin and is also a transmembrane transporter responsible for the efflux of iron from the cell to plasma (13,14). Hepcidin stimulates the internalization and degradation of ferroportin, which traps iron within the cell (13,14). It seems that hepcidin is downregulated in response to elevated erythrocyte production in the bone marrow or increased use of serum and tissue iron (13,14,35).

Hepcidin is upregulated in response to inflammatory stimuli, namely, IL-6, and promotes sequestration of iron within the cell (31). One theory is that bacteria uses nonbound iron to thrive; therefore, the action of hepcidin is a protective mechanism from the proliferation of pathogens (14,16). Inflammation and elevated hepcidin activity will stimulate the endocytosis and degradation of the ferroportin channels of the major iron storage and exporting sites (enterocytes, hepatocytes, and macrophages) (13). This will cause a buildup of stored iron in ferritin within the cytoplasm. As the demand for iron by developing erythrocytes continues, a subsequent decrease in available circulating iron ensues, leading to iron deficiency (13,14).

Iron deficiency represents inadequate body iron stores by macrophages in the liver, spleen, and bone marrow and is clinically defined as a ferritin laboratory value $<12$ μg/L (1,8). However, there is some variance in the literature as ferritin is often reported as some value $>12$ μg/L but $<20$ μg/L, depending on the investigation (8). A continual decline of iron stores results in impaired iron transport with insufficient supply for developing RBCs (1). Iron deficiency anemia is the end result and represents depleted iron stores with decreased hemoglobin synthesis, defined as hemoglobin $<12$ g/dL (1,8,27).

Serum ferritin (SF) alone does not accurately reflect iron status because SF will increase considerably in response to inflammation (21). In fact, results of one study (34) did not find a significant relationship between ferritin level and duration of training (hours per week). Therefore, more sensitive laboratory testing beyond SF should be used to assess for iron status, including hemoglobin and soluble transferrin receptor concentration. The relationship between these indices exists such that SF represents iron storage, and hemoglobin and soluble transferrin receptor reflect iron deficiency anemia or inadequate iron supply for hemoglobin synthesis as a result of insufficient stores and absorption (4,27).

Transferrin receptors are expressed on the surface of all cells, especially developing RBCs. As previously mentioned in this article, iron circulates bound to transferrin, and when iron is transported to a cell, it is internalized and released into the cytoplasm. The soluble transferrin receptor is the end product of this process (4), which is then left to circulate in plasma. The soluble transferrin receptor is not affected by inflammation and therefore will be elevated in response to the increased demand by iron-deficient cells, specifically erythropoiesis (4,27).

In summary, there are fundamental physiological functions of iron specific to exercise that include generation of hemoglobin, important for oxygen transport to tissues throughout the body; myoglobin, an intermediate storage site for oxygen in muscle tissue; cytochromes, a series of complexes necessary for the transfer of electrons in the electron transport chain, which contributes to the generation of ATP;

and mitochondria iron-dependent oxidative enzymes that support aerobic metabolism and generation of ATP through the Krebs cycle (8,13,16,18,26,33,36,48,49).

Iron deficiency can present as lethargy, weakness, vulnerability to infection, dyspnea, and palpitations (16), and both iron deficiency and iron deficiency anemia can impede an athlete's performance. Iron deficiency can negatively affect endurance performance by dampening muscle tissue oxidative capacity and cytochrome activity, which can manifest as prolonged time to complete a competitive event, such as a slower time trial (8,18). If iron deficiency is not corrected with an improvement in energy intake and iron supplementation, progression to anemia can develop. With iron deficiency anemia, an athlete's endurance capacity is diminished as $\dot{V}O_2$max or oxygen transport is impaired, because of reduced hemoglobin synthesis. Decreased energetic efficiency and increased energy expenditure are also part of this paradigm contributing to decrements in an endurance athlete's performance within the range of iron deficiency and anemia (8,18).

## INFLAMMATION, HEPCIDIN, AND EXERCISE-ASSOCIATED IRON DEFICIENCY

Inflammation results in what is known as an acute-phase response that promotes the production and circulation of acute-phase proteins, usually as a response to injury or infection (38). Interleukin-6 is a cytokine that is both produced and released into circulation by contracting skeletal muscle during exercise (23,37). Duration and intensity of exercise seem to determine the magnitude of the IL-6 response, and running in particular seems to result in a significant production of IL-6 (10,37). Varying factors associated with endurance exercise, particularly duration and muscle glycogen content, can affect the IL-6 response. Exercise duration has been posited as having the greatest effect on the magnitude of the IL-6 response (10).

It has been suggested that IL-6 functions to regulate glucose metabolism and enhance lipolysis during exercise (11,37). Moreover, it has been proposed that IL-6 acts as an energy sensor during exercise and is markedly increased in response to low intramuscular glycogen content, especially during periods of extended duration (22,23,37). Results of one study, however, indicated that the magnitude of the IL-6 mRNA expression in response to 3 hours of exercise was significantly reduced with higher absolute work intensity, in response to 10 weeks of knee extensor endurance training (11). This study represents a training adaptation to endurance exercise in that the magnitude of the IL-6 response will decrease in response to consistent exercise (11).

Interleukin-6 has been shown to be the main mediator of hepcidin production (31,38,43). In fact, the main finding of an animal model investigation showed hepcidin levels peaked at 2 hours after exhaustive exercise in both the group treated with a pharmacological agent used to blunt plasma IL-6 levels during exercise and the control group (3). However, hepcidin mRNA levels were significantly reduced in the treatment group, which displayed 50% lower plasma IL-6 levels (3). Therefore, results of this study provide evidence that the level of hepcidin rises in response to plasma IL-6, and as such, the hepcidin expression was inhibited as a result of blunted IL-6 (3).

The relationship of carbohydrate intake during prolonged endurance exercise and subsequent IL-6 and hepcidin response has been examined. Results from a 2011 study (42) found that even though carbohydrate ingestion during endurance exercise (120 minutes followed by 5-km time trial) resulted in a significant decrease in the IL-6 response, as compared with placebo, hepcidin was still significantly increased immediately after exercise (blood samples were taken before, after, and 24 hours later), with no significant difference between trials. Furthermore, plasma iron concentrations were significantly decreased from baseline at 24 hours after exercise, and there was no significant difference between groups.

Newlin et al. (32) examined the acute postexercise response of both IL-6 and hepcidin in women. Female runners participated in both 60-min and 120-minute treadmill runs at 65% of $\dot{V}O_2$max. Interleukin-6 was significantly increased immediately after exercise as compared with before exercise, but not for any other time points (3, 6, 9, 24 hours), and with no significant effect between trials. Hepcidin levels peaked at 3 hours, and concentrations were significantly higher at 120 minutes than at 60 minutes. Serum iron was significantly decreased at 9 hours after exercise in both the 60- and 120-min trials (32).

Individual data from the 12 participants included in the Newlin et al. (32) investigation indicated a range in the magnitude of the hepcidin response, varying from 7 subjects with a small-to-moderate concentration (<2.4 nmol/L) to 5 with a large concentration (>5 nmol/L). Furthermore, participants with a large hepcidin response were noted to have a higher mean serum iron concentration, as compared with the subjects with both a lower mean serum and hepcidin response (32).

This observation has been reported elsewhere in the literature. More recently, Auersperger et al. (2) examined the effects of 8 weeks of endurance training in female runners. Fourteen females were recruited and divided into 2 groups: 7 defined as iron deficient (ferritin levels ≤20 μg/L) and 7 as iron normal (ferritin levels >20 μg/L). The protocol consisted of two 3-week progressive overload periods followed by 1-week tapers. Participants completed either a competitive 6-mile or 13-mile distance run in a marathon after the second taper. Blood samples were drawn at baseline, at the completion of training and after a 10-day recovery phase. Of significance, the number of females with iron deficiency increased to 10 of 14, such that 3 of the

participants originally identified as having normal iron stores advanced to iron deficiency after training. In contrast to previous studies discussed in this article (39,40,43), IL-6 plasma values were reported as undetectable at each time point, with no change in hepcidin except for a significant decrease at recovery. For both groups, the percentage of hypochromic RBCs was significantly increased at training and recovery, whereas the mean hemoglobin content of RBCs and reticulocytes (immature RBCs) was significantly decreased. Even though there was a slight increase in total iron binding capacity (TIBC) from the training to recovery time point, at recovery, TIBC still remained significantly decreased from baseline. In addition, the concentration of soluble transferrin receptor significantly increased during training and recovery, representative of iron deficiency. These results are interesting, and the authors of this study (2) posit that the hormone hepcidin is also regulated by iron demand such that in periods of low iron stores, hepcidin will not be influenced in the same manner as a state of normal iron capacity (2). In conclusion, it would seem counterproductive that hepcidin would act to restrict iron efflux in the presence of low iron stores.

Peeling et al. (41) have expanded on this theory of a suppressed hepcidin response in the presence of decreased iron stores. Data were pooled from 5 different investigations and were used to stratify athletes into 4 different groups based on levels of SF. Grouping was as follows: iron depleted, <30 μg/L; suboptimal, 30–50 μg/L; healthy, 100 μg/L; and high, >100 μg/L. Of particular interest, 13 of 16 trained females (runners, triathletes) included in this study were identified as either iron depleted or having suboptimal iron stores.

As expected, IL-6 was significantly increased after exercise as compared with baseline for all groups (41). Novel findings of this study (41) demonstrated a significantly greater hepcidin response 3 hours after exercise for high SF (>100 μg/L) participants than for all other groups. Moreover, hepcidin was significantly increased 3 hours after exercise as compared with baseline for all groups, except the iron-depleted (SF <30 μg/L) participants. These results therefore indicate a sequential increase in hepcidin 3 hours after exercise based on iron status. Of greatest concern is the fact that hepcidin was still significantly increased after exercise in the SF suboptimal group (30–50 μg/L), which makes these athletes at greatest risk for advancing to iron deficiency. Finally, the suboptimal group consisted of an $n = 8$, of which 5 were females (41).

Other training variables have been explored in relation to IL-6 and hepcidin production. For example, IL-6 was significantly elevated immediately after exercise, and hepcidin was significantly increased 3 hours after exercise (for all trials) in one study that examined the effects of exercise intensity and modality (high-intensity interval versus low-intensity continuous cycling and running) on markers of inflammation (43); Table 3. Of interest, serum iron levels (related to hemolysis) were significantly elevated in all trials of this study except low-intensity continuous cycling, which lacks the force and impact of running and associated mechanical hemolysis (43). In addition, significantly elevated IL-6 levels after high-intensity cycling demonstrate that exercise which requires high power output irrespective of impact (repetitive foot strikes) will stimulate an inflammatory response of contracting skeletal muscle (43).

It is common that athletes train twice per day and at varying intensities (e.g., conditioning, speed and agility, practice, etc.). In a study published by Peeling et al. (39), participants completed a continuous slow 10-km distance run (70% peak $\dot{V}O_2$ velocity) followed by a subsequent bout of exercise 12 hours later that consisted of 10 × 1-km interval repeats (90% peak $\dot{V}O_2$ velocity). On a different day, participants completed 1 session of the 10 × 1-km interval repeats (90% peak $\dot{V}O_2$ velocity). Results indicated that levels of IL-6 were significantly elevated after each bout of exercise but 12 hours was sufficient for this marker of inflammation to return to baseline. Results of this study (39) also demonstrated significantly increased free hemoglobin and hepcidin (3 hours post) after all exercise trials. Similar to IL-6, hepcidin returned to baseline values after a 12-hour rest period. Taken together, these results indicate elevations in hepcidin 3 hours after exercise coupled with training days that require multiple exercise bouts do not elicit an exaggerated effect but instead 12 hours is an acceptable recovery period to allow for these markers to return to baseline (39).

In a different investigation by Peeling et al. (40), the question of training intensity (continuous versus interval) and its effects on levels of inflammation and hepcidin were further investigated, as was training surface (grass versus road). Trained male athletes ($n = 10$) participated in 3 separate trials: 2 continuous 10-km runs on grass versus a bitumen road surface (75–80% peak $\dot{V}O_2$ velocity) and a 10 × 1-km interval running session on a grass surface. The interval session on grass was compared with the continuous running trial on grass. Results indicated significantly increased free hemoglobin levels for all 3 trials but no significant difference between training surfaces. Levels of IL-6 were significantly increased after exercise for all 3 trials. However, IL-6 values were significantly greater for interval than for continuous, indicating a heightened level of inflammation for training intensity. Finally, hepcidin was significantly increased 3 hours after training for all 3 trials, but there was no significant effect between trials. Therefore, although the severity of inflammation was increased after a bout of high-intensity training, the hepcidin response despite an increase from baseline was not equally exaggerated. In conclusion, this study (40) indicates that the training surface does not further induce hemolysis, but inflammation and subsequent hepcidin response

do occur with heel-strike activity regardless.

In summary, high-intensity exercise, particularly a mode that involves running or heel-strike activity, will stimulate an immediate postexercise release of IL-6 and subsequent hepcidin response. The hepcidin response has been shown to be increased with longer duration endurance exercise (32), which may have an implication for women involved in triathlon training and competition. Studies, however, have also shown that the magnitude of the inflammatory response may be reduced as a result of training adaptation. Therefore, the possibility exists that because of a training adaptation, the reduction in inflammatory stimuli during exercise, namely, IL-6, may result in a decreased hepcidin response. However, this concept, and whether it translates to a decreased prevalence of iron deficiency, is a topic that warrants further research and clarification. Moreover, it has been demonstrated that carbohydrate intake during 120 minutes of endurance exercise was sufficient to blunt the IL-6 response but not hepcidin.

The occurrence of iron deficiency does seem to be evident in women participating in endurance sport (29,34,45). It is therefore prudent that athletes (females in particular) should be monitored at all time points of a competitive season because maintenance of iron stores is crucial to endurance performance as any decrement in time to complete an event can negatively affect an athlete's competitive advantage.

## IRON LOSS AND FEMALE ATHLETES

Female athletes of reproductive age are at an increased risk of iron loss due to menstruation, with total iron loss estimated to be approximately 1.3–1.4 mg/d or 17.5 mg per cycle (16,25,48). In fact, results of one study ($n$ = 90 premenopausal women) indicated that regardless of type of diet (lacto-ovo-vegetarian versus poultry versus red meat), menstrual blood loss had the greatest influence on iron status (17). Research indicates that women who have used an oral contraceptive pill are more likely to have sufficient iron stores and associated iron markers (SF and iron) because of decreased menstrual blood loss, albeit the physiological mechanisms have yet to be elucidated (44). A comprehensive review has been published on this topic; for more details, please refer to the study by Sim et al. (44).

In addition, there is a high risk for the development of iron deficiency in females when insufficient energy intake to replace iron loss, common to the female athlete triad, is coupled with high-intensity training that includes repetitive foot striking, as discussed previously (25,34). Therefore, menstrual blood loss (especially heavy or frequent) in combination with decreased dietary iron intake likely contributes to the scenario of increased risk for the development of iron deficiency in female athletes.

Research indicates an increased incidence of iron depletion in women participating in endurance sports. Results examining iron status in male and female recreational marathon runners demonstrated iron depletion in 12 of 43 women (28%) of which 6 were anemic (29). However, only 2 of 127 men (1.6%) were iron deficient, with only one male reported as anemic (29). In a different study of iron deficiency in 121 recreationally active adults (72 females and 49 males), 36% of female participants and 6% of male participants were identified as iron deficient without anemia (45). Finally, of a sample of 165 female collegiate rowers, 30% ($n$ = 44) were identified as either iron depleted or clinically iron deficient at the start of the season, which emphasizes the need for preseason screening to identify female athletes at risk of iron deficiency and to prevent progression to iron deficiency anemia (9).

In a 2010 investigation of women undergoing basic combat training, female soldiers were provided either a fortified iron bar (2 bars daily; 55.8 mg/d ferrous sulfate) or placebo during a 9-week basic training course (20). Results indicated that supplementation was beneficial for soldiers with iron deficiency anemia but not for iron-deficient or iron-normal female military personnel (20). Specifically, hemoglobin concentration significantly increased from baseline for the iron deficiency anemia group after treatment. Moreover, soluble transferrin receptor concentration (biomarker of iron deficiency) was significantly increased after training for the iron deficiency anemia participants, who received the placebo, but not for the iron-supplemented participants within the same group (20).

In a different study (28) that examined the effects of basic combat training on iron status in female soldiers, iron supplementation in the form of 100-mg capsules (ferrous sulfate) was provided over the course of 8 weeks. Fourteen iron-deficient (≥2 of 3 indicators: SF <12 ng/mL, transferrin saturation <16%, RBC distribution width >15%) participants were identified in both the placebo and iron-supplemented groups. At the conclusion of the study (28), results indicated the number of iron-deficient participants doubled in the placebo group from 14 to 28 (100% increase), whereas the number of iron-deficient persons in the treatment group only climbed from 14 to 19 (36% increase). Results for the iron deficiency anemia group (same classification as iron deficiency plus hemoglobin concentrations <12 g/dL) indicated a significant increase in ferritin for the treatment group as compared with baseline and placebo, with a significant decrease in ferritin for the placebo group as compared with baseline. In addition, soluble transferrin receptor concentration for iron-deficient anemia participants was significantly increased from baseline for the placebo group (28).

Finally, results of a 2-mile run time test demonstrated a significantly faster mean time of 110 seconds for the iron-deficient anemia participants in the treatment group, but not for the placebo group (28). In conclusion, iron

**Table 1**
**Dietary sources of iron**

| | Milligrams of iron per 3 ounces | Milligrams per 1/2 cup | Milligrams per 1 cup |
|---|---|---|---|
| Heme | | | |
| Beef, ground, 97% lean meat | 2.46 | — | — |
| Chicken, breast | 0.38 | — | — |
| Eggs, scrambled | 1.11 | — | — |
| Fish, salmon, Atlantic, wild | 0.88 | — | — |
| Tuna fish, white, canned in water, drained solids | 0.82 | — | — |
| Nonheme | | | |
| Almonds, dry roasted | 3.17 | 2.57 | 5.15 |
| Lentils | — | 3.30 | 6.59 |
| Beans, black | — | 1.81 | 3.61 |
| Cashews, dry roasted | 5.10 | 4.11 | 8.22 |
| Raisins | — | 1.36 | 2.73 |
| Seeds, sunflower | 3.23 | 2.43 | 4.86 |
| Seeds, pumpkin and squash seeds, whole, roasted | 2.82 | 1.06 | 2.12 |
| Spinach, raw | — | 0.41 | 0.81 |
| Spinach, cooked | — | 3.21 | 6.43 |

Data obtained from the USDA National Nutrient Database for Standard Reference Release 27.

supplementation was effective for attenuating the decline in iron status in female soldiers over an 8-week period during basic combat training that involves road marching, running, and sprinting, and also periods of prolonged standing in formation, and obstacle course completion, among other activities (28).

## RECOMMENDATIONS FOR PRACTICE

### *DIETARY SOURCES OF IRON*

Athletes participating in high-intensity sports that involve repetitive foot strikes are particularly susceptible to the development of iron deficiency. Female athletes in particular may pose a higher risk because of varying scenarios of menstrual blood loss and inadequate energy intake. Monitoring these athletes requires the work of a multidisciplinary team including sports medicine physicians, athletic trainers, strength and conditioning coaches, and sports dietitians.

As discussed in this article (39–41), exercise-induced inflammation will likely stimulate a subsequent elevation in hepcidin for at least a 3-hour period. Therefore, consuming iron-rich foods during this period may not contribute to recovery of iron stores. Athletes should be educated to understand the type and combination of foods to support recovery and maintenance of iron status.

For example, nonheme iron obtained from plant sources is less bioavailable because it presents in the ferric form. A duodenal redox enzyme at the surface of the enterocyte fronting the intestinal lumen enables the absorption of nonheme iron. Vitamin C plays an essential role in this process of reducing ferric iron to ferrous (24,36,48). Many compounds in food such as phytates (black beans, lentils, chickpeas), polyphenols (coffee, tea), and oxalates (spinach, swiss chard, chocolate) bind nonheme iron and can prevent its absorption (16,46).

Conversely, heme iron, in the form of hemoglobin and myoglobin, is obtained from animal sources (meat, fish, poultry) and is exceedingly bioavailable, although how it enters the cell is less understood (48). It seems that heme iron enters the cell intact and is subsequently catabolized (36). Regardless, absorption of nonheme iron (plant based) is improved by the presence of heme iron. Therefore, it is advisable to consume meat, fish, or poultry with plant sources of iron to enhance absorption of nonheme containing foods.

Athletes should be cautioned against drinking tea with iron-rich meals as

the former can interfere with the absorption of the latter. Moreover, although green leafy vegetables such as chard and spinach are a rich source of iron, they have a high tannin and phytate content, respectively (46), which can bind with iron and inhibit absorption. Phytate is heat stable and cooking is not effective in decreasing the phytate content of spinach or the tannin content of chard, which greatly reduces the bioavailability (46). That being said consuming a plant-based dietary source of iron in combination with other foods rich in vitamin C and/or animal protein will help reduce inhibitory effects and act to enhance overall absorption (1).

Training tables in a university or similar athletic setting should provide foods that readily combine iron-rich plant sources with meat, fish, or poultry. Chili is an excellent example of this because it combines beans with lean red meat or lentil soup with chicken; a breakfast option is an iron-fortified cereal that can be combined with raisins or strawberries. Moreover, a review article found iron-fortified foods (e.g., ferrous sulfate or fumarate) to be an effective strategy for improving iron status (15). Table 1 provides a list of both heme and nonheme dietary sources, and Table 2 provides a list of foods rich in vitamin C.

Vegetarian athletes can meet daily iron needs through a plant-based diet. However, the daily RDA is higher. Vegetarians require 1.8 times the daily iron requirement or 33 mg because of the reduced bioavailability of nonheme dietary sources, which is 10% as compared with 18% for consumption of combined heme (animal) and nonheme (plants) foods (19). The RDA for adults aged 19–50 years who consume a mixed diet (heme and nonheme) is 8 mg per day for males and 18 mg per day for females (19).

Finally, female athletes will benefit from nutrition education related to both total energy intake and dietary sources of iron. This is especially true for vegetarian athletes because their daily dietary iron needs are higher because of reduced absorption, so insufficient total daily calorie intake can put these athletes at particular risk. Female athletes who have already progressed to iron deficiency or iron deficiency anemia may benefit from supplementation as warranted, in addition to nutrition education.

**Table 2**
**Dietary sources of vitamin C**

| | Serving size | Milligrams |
|---|---|---|
| Fruit | | |
| Cantaloupe | 1 cup, cubes | 0.34 |
| Mango | 1 cup, pieces | 0.26 |
| Oranges, navels | 1 medium | 0.18 |
| Raisins | 1/2 cup | 1.7 |
| Tangerines | 1 medium | 0.13 |
| Strawberries | 1 cup, whole | 0.59 |
| Vegetables | | |
| Broccoli | 1 cup, chopped | 0.66 |
| Brussels sprouts | 1 cup | 1.87 |
| Peppers, sweet, green | 1 cup, sliced | 0.31 |
| Peppers, sweet, red | 1 cup, sliced | 0.40 |
| Tomatoes, red, ripe | 1 cup, cherry tomatoes | 0.40 |
| Tomatoes, canned sauce | 1 cup | 2.35 |

Data obtained from the USDA National Nutrient Database for Standard Reference Release 27.

## IRON SUPPLEMENTATION

There is no distinct physiological mechanism for iron excretion, especially in the case of overload. Therefore, the body must regulate iron homeostasis through absorption, and the hormone hepcidin acts as the master regulator. The major concern for iron supplementation in any population is iron overload, which is toxic and can cause cellular damage because of iron's ability to generate reactive oxygen species. Moreover, individuals with a hereditary predisposition for developing hemochromatosis are at an increased risk, because this disorder is associated with a high efficiency for dietary iron absorption and storage in the heart, liver, and pancreas, which can lead to organ damage (6,16,50). Conversely, unwarranted iron supplementation can mask iron deficiency or iron deficiency anemia, which in a clinical setting can serve as a valuable indicator for a more significant underlying condition, such as celiac disease or occult gastrointestinal bleeding, among others (5,12).

Physically active men, as compared with women, seem to have a decreased incidence of iron deficiency and seem to be more at risk of iron overload because of the absence of menstrual blood loss (8,29,45). In a 2010 study of recreational runners participating in a Switzerland-based marathon, 15% (19 of 127) of men were identified to have iron overload, as compared with 4.7% (2 of 43) of women (29). These results (29) should be interpreted with caution because runners in this study did not provide data through a questionnaire related to supplement use or iron intake. However, excessively high SF levels (>300 ng/mL) have

**Table 3**
**Comparison of exercise protocols, IL-6, hepcidin, and iron response**

| Study | Subjects | Baseline iron status | Protocol | Findings |
|---|---|---|---|---|
| Auersperger et al. (2) | 14, F, moderately physically active | $n = 7$, ferritin $>20$ μg/L; $n = 7$, ferritin $<20$ μg/L | 3-wk progressive overload periods followed by 1-wk tapers; completed either competitive 6- or 13-mile distance run in a marathon after second taper; labs assessed at baseline, completion of training, and after 10-d recovery phase | IL-6: undetectable at all time points; HEP: SIG ↓ at recovery; ↑ in females with ID (10 → 14) after training |
| Sim et al. (43) | 10, M, well-trained triathletes | $n = 10$, ferritin, 67.1 ± 10.8 μg/L | High-intensity (85% velocity and power output $\dot{V}O_2$peak) INT versus low-intensity (85% velocity and power output $\dot{V}O_2$peak) CONT cycling and running | IL-6: SIG ↑ immediately after exercise, all trials; HEP: SIG ↑ 3 h after exercise, all trials; sFe: SIG ↑ all trials except low-intensity cycling |
| Peeling et al. (39) | 10, M, highly trained triathletes, endurance runners | $n = 10$, ferritin, 82.8 μg/L (average); range, 37.3–173.1 μg/L | CONT slow 10-km distance run (70% peak $\dot{V}O_2$ velocity) → 10 × 1-km INT repeats (90% peak $\dot{V}O_2$ velocity) 12 h later; different day: 1 session of 10 × 1-km INT repeats (90% peak $\dot{V}O_2$ velocity) | IL-6: SIG ↑ immediately after exercise × each bout of exercise, ↓ to baseline 12 h later; HEP: SIG ↑ 3 h after exercise, all trials, ↓ to baseline 12 h later; free HGB: SIG ↑ 3 h after exercise, all trials |
| Peeling et al. (40) | 10, M, highly trained endurance athletes | $n = 10$, ferritin $>60$ μg/L | 3 separate trials: 2 CONT 10-km runs —grass versus bitumen road surface (75–80% peak $\dot{V}O_2$ velocity); 10 × 1-km INT running session on grass; INT session on grass compared with CONT running on grass | IL-6: SIG ↑ immediately after exercise, all trials, SIG ↑ interval versus continuous; HEP: SIG ↑ 3 h after exercise, all trials, not between trials; free HGB: SIG ↑ all trials, no SIG trial effect between training surfaces |
| Newlin et al. (32) | 12, F, active runners | NR | 60- and 120-min treadmill run, 65% $\dot{V}O_2$max, blood samples before, immediately after, 3, 6, 9, 24 h | IL-6: SIG ↑ immediately after exercise, all trials but no other time points, no SIG between trials; HEP: SIG ↑ 3 h after exercise and for 120-min trial; sFe: SIG ↓ 9 h after exercise |
| Robson-Ansley et al. (42) | 9, M, runners, 40 ± 18 km weekly | NR | 120-min treadmill run, 60% velocity $\dot{V}O_2$max followed by 5-km time trial; blood samples baseline, immediately after, 24 h; Tx group = 8% CHO solution at 20-min intervals | IL-6: SIG ↑ immediately after exercise, all trials, SIG ↓ for CHO compared with placebo; HEP: SIG ↑ after exercise, all trials, not between trials; sFe: SIG ↓ 24 h after exercise, no SIG between trials |

F = female; M = male; NR = not reported; ID = iron deficiency; IL-6 = interleukin-6; HEP = hepcidin; SIG = significant; HGB = hemoglobin; CONT = continuous; INT = interval; sFe = serum iron; CHO = carbohydrate; Tx = treatment.

been documented in elite male cyclists, in addition to reported use of iron supplementation through repeated intravenous administration (51). It should therefore be underscored that uncontrolled or unnecessary iron supplementation in the absence of clinical biomarkers of iron deficiency with or without anemia does not enhance performance and so the risk does not outweigh the benefit (7).

Supplementation guidelines are still being developed within the literature in terms of screening, when to initiate supplementation, and adequate dose and form. Ferrous sulfate ($FeSO_4$) is a common oral iron supplement and because it is prepared in the ferrous form, absorption is enhanced, as compared with ferric (8). One hundred milligrams of ferrous sulfate provides 20 mg or 20%

elemental iron or the amount that can be absorbed (8). Supplemental forms vary in the level of elemental iron because ferrous fumarate contains 33% and ferrous gluconate 12% (8). The same guidelines provided to improve dietary iron absorption also apply to supplementation such that vitamin C will enhance absorption and polyphenols in coffee and tea will exert an inhibitory effect (8,18).

As previously discussed in this article, 100 mg of ferrous sulfate both as a food supplement and in capsule form was effective for improving various clinical markers related to poor iron status in female soldiers participating in basic combat training (20,28). This level of supplementation (100 mg of ferrous sulfate) has been suggested to be effective for both improving and preventing a decline in iron status (8); however, whether supplementation in an iron-deficient or anemic athlete (especially female) translates to positive performance outcomes, such as improved endurance times, has continued to be a focus in the literature (8,28).

In the investigation of McClung et al. (28), supplementation was associated with a significantly faster run time for females with iron deficiency anemia. An earlier investigation (18) examined the effect of 100-mg ferrous sulfate and the ability to complete a 15-km time trial in a group of iron-depleted nonanemic (SF $<16$ μg/L) females participating in an endurance training protocol. Results demonstrated a significantly faster time to completion for the iron treatment group, as compared with placebo, specifically in the second and third 5-km segments, which represents an increase in endurance capacity. Moreover, increases in hemoglobin were associated with improvements in energetic efficiency and decreased energy expenditure, and increased work rate (18).

Although the primary focus in the literature has been iron status and endurance athletes, a recent 2015 publication (30) examined the effects of 11 weeks of oral iron supplementation on elite female volleyball players during a competitive season, and the results warrant discussion. Initial iron status in both the control and treatment groups ranged from ferritin $<30$ to $>100$ μg/L. Athletes ($n = 22$) received either 325-mg ferrous sulfate, through a product that provided the equivalent of 105-mg elemental iron, or placebo. Average weekly training consisted of morning and afternoon sessions comprised of jogging, strength training, sport-specific drills, power and speed drills, and interval sessions. All athletes were coached by trained dietitians on how to track their dietary intake, and results indicated that both the control and treatment groups met the RDA for iron intake (30).

There are several other major findings of this study (30). First was a significant decline in iron status over an 11-week training period in the control group, as compared with treatment. In terms of performance outcomes, there was a significantly greater increase in the percent change for strength for the treatment group for the clean and jerk, power clean, and total mean strength, as compared with placebo. In addition, changes in hemoglobin were significantly associated with the aforementioned increases in strength, for the treatment group (30).

Finally, of concern is the fact that these female athletes met the RDA for dietary iron intake and the women in the control group still developed a decline in iron status over an 11-week training period (25 hours training weekly), which warrants further consideration for the development of conclusive supplementation guidelines. Finally, it seems that the development of iron deficiency in female athletes is prevalent in both endurance and anaerobic sports (18,28,30). In fact, prevalence of iron depletion in a group of 84 female professional endurance and team sport athletes has been previously reported (34). Iron depletion (ferritin $<30$ μg/L) and iron deficiency with anemia were found to be more frequent in female distance runners as compared with team sport athletes; however, no statistical difference was found between groups of athletes for prevalence of iron depletion, iron deficiency, and iron-deficiency anemia (34).

In conclusion, recommendations for practice include nutrition education related to individual total daily energy needs, daily RDA for iron intake, dietary sources of iron, and approaches for enhancing absorption. Furthermore, iron absorption may be temporarily inhibited for approximately 3 hours after training because of exercise-stimulated inflammation and subsequent hepcidin response. Athletes should therefore be encouraged to consume dietary sources of iron regularly throughout the day, with all meals, to ensure adequate intake and absorption. In addition to nutrition education, iron supplementation (e.g., ferrous sulfate), mostly likely in the range of 20–105 mg/d (elemental iron), may be necessary in both endurance and team sport female athletes (18,20,28,30), and this should be clinically established and appropriately monitored through a multidisciplinary approach.

*Conflicts of Interest and Source of Funding: The author reports no conflicts of interest and no source of funding.*

**Erica R. Goldstein** *is a clinical dietitian at Mayo Clinic in Jacksonville, Florida.*

## REFERENCES

1. Alaunyte I, Stojceska V, and Plunkett A. Iron and the female athlete: A review of dietary treatment methods for improving iron status and exercise performance. *J Int Soc Sports Nutr* 12: 1–7, 2015.
2. Auersperger I, Skof B, Leskosek B, Knap B, Jerin A, and Lainscak M. Exercise-induced changes in iron status and hepcidin response in female runners. *PLoS One* 8: 1–7, 2013.
3. Banzet S, Sanchez H, Chapot R, Bigard X, Vaulont S, and Koulmann N. Interleukin-6 contributes to hepcidin mRNA increase in

response to exercise. *Cytokine* 58: 158–161, 2012.

4. Beguin Y. Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. *Clin Chim Acta* 329: 9–22, 2003.
5. Bull-Henry K and Al-Kawas FH. Evaluation of occult gastrointestinal bleeding. *Am Fam Physician* 87: 430–436, 2013.
6. Casu C and Rivella S. Iron age: Novel targets for iron overload. *Hematol Am Soc Hematol Educ Program* 1: 216–221, 2014.
7. Deldicque L and Francaux M. Recommendations for healthy nutrition in female endurance runners: An update. *Front Nutr* 2: 1–7, 2015.
8. DellaValle DM. Iron supplementation for female athletes: Effects on iron status and performance outcomes. *Curr Sports Med Rep* 12: 234–239, 2013.
9. DellaValle DM and Haas JD. Impact of iron depletion without anemia on performance in trained endurance athletes at the beginning of a training season: A study of female collegiate rowers. *Int J Sport Nutr Exerc Metab* 21: 501–506, 2011.
10. Fischer CP. Interleukin-6 in acute exercise and training: What is the biological relevance? *Exerc Immunol Rev* 12: 6–33, 2006.
11. Fischer CP, Plomgaard P, Hansen AK, Pilegaard H, Saltin B, and Pedersen BK. Endurance training reduce the contraction-induced interleukin-6 mRNA expression in human skeletal muscle. *Am J Physiol Endocrinol Metab* 287: E1189–E1194, 2004.
12. Freeman HJ. Iron deficiency anemia in celiac disease. *World J Gastroenterol* 21: 9233–9238, 2015.
13. Ganz T. Molecular control of iron transport. *J Am Soc Nephrol* 18: 394–400, 2007.
14. Ganz T and Nemeth E. Iron metabolism: Interactions with normal and disordered erythropoiesis. *Cold Spring Harb Perspect Med* 2: 1–13, 2012.
15. Gera T, Sachdev HS, and Boy E. Effect of iron-fortified foods on hematologic and biological outcomes: Systematic review of randomized controlled trials. *Am J Clin Nutr* 96: 309–324.
16. Gropper SS, Smith JL, and Groff JL. Microminerals. In: *Advanced Nutrition and Human Metabolism* (5th ed). Belmont, CA: Wadsworth, Cengage Learning, 2009. pp. 469–487.
17. Harvey LJ, Armah CN, Dainty JR, Foxall RJ, Lewis DJ, Langford NJ, and Fairweather-Tait SJ. Impact of menstrual blood loss and diet on iron deficiency among women in the UK. *Br J Nutr* 94: 557–564, 2005.
18. Hinton PS, Giordano C, Brownlie T, and Haas JD. Iron supplementation improves endurance after training in iron-depleted, nonanemic women. *J Appl Physiol (1985)* 88: 1103–1111, 2000.
19. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Vitamin A, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zince*. Washington, DC: National Academies Press, 2001. pp. 351.
20. Karl JP, Lieberman HR, Cable SJ, Williams KW, Young AJ, and McClung JP. Randomized, double-blind, placebo-controlled trial of an iron-fortified food product in female soldiers during military training: Relations between iron status, serum hepcidin, and inflammation. *Am J Clin Nutr* 92: 93–100, 2010.
21. Kell D and Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. *Metallomics* 6: 748–773, 2014.
22. Keller C, Steensberg A, Hansen AK, Fischer CP, Plomgaard P, and Pedersen BK. Effect of exercise, training, and glycogen availability on IL-6 receptor expression in human skeletal muscle. *J Appl Physiol (1985)* 99: 2075–2079, 2005.
23. Keller C, Steensberg A, Pilegaard H, Osada T, Saltin B, Pedersen BK, and Neufer PD. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: Influence of muscle glycogen content. *FASEB J* 15: 2748–2750, 2001.
24. Lane DJR, Bae DH, Merlot AM, Sahni S, and Richardson DR. Duodenal cytochrome *b* (DCYTB) in iron metabolism: An update on function and regulation. *Nutrients* 7: 2274–2296, 2015.
25. Latunde-Dada GO. Iron-metabolism in athletes–Achieving a gold standard. *Eur J Haematol* 90: 10–15, 2013.
26. Levi S and Rovida E. The role of iron in mitochondrial function. *Biochim Biophys Acta* 1790: 629–636, 2009.
27. Lynch S. The rationale for selecting and standardizing iron status indicators. In: *World Health Organization. Report: Priorities in the Assessment of Vitamin a and Iron Status in Populations*. Panama, Geneva: World Health Organization, 2012.
28. McClung JP, Karl JP, Cable SJ, Williams KW, Nindl BC, Young AJ, and Lieberman HR. Randomized, double-blind, placebo-controlled trial of iron supplementation in female soldiers during military training: Effects on iron status, physical performance, and mood. *Am J Clin Nutr* 90: 124–131, 2009.
29. Mettler S and Zimmerman MB. Iron excess in recreational marathon runners. *Eur J Clin Nutr* 64: 490–494, 2010.
30. Mielgo-Ayuso J, Zourdos MC, Calleja-González J, Urdampilleta A, and Ostojic S. Iron supplementation prevents a decline in iron stores and enhances strength performance in elite female volleyball players during the competitive season. *Appl Physiol Nutr Metab* 40: 615–622, 2015.
31. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, and Ganz T. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest* 113: 1271–1276, 2004.
32. Newlin MK, Williams S, McNamara T, Tjalsma H, Swinkels DW, and Haymes EM. The effects of acute exercise bouts on hepcidin in women. *Int J Sport Nutr Exerc Metab* 22: 79–88, 2012.
33. Oexle H, Gnaiger E, and Weiss G. Iron-dependent changes in cellular energy metabolism: Influence on citric acid cycle and oxidative phosphorylation. *Biochim Biophys Acta* 1413: 99–107, 1999.
34. Ostojic SM and Ahmetovic Z. Weekly training volume and hematological status in female top-level athletes of different sports. *J Sports Med Phys Fitness* 48: 398–403, 2008.
35. Pak M, Lopez MA, Gabayan V, Ganz T, and Rivera S. Suppression of hepcidin during anemia requires erythropoietic activity. *Blood* 108: 3730–3735.
36. Pantopoulos K, Porwal SK, Tartakoff A, and Devireddy L. Mechanisms of mammalian iron homeostasis. *Biochemistry* 51: 5705–5724, 2012.
37. Pedersen BK. Muscular interleukin-6 and its role as an energy sensor. *Med Sci Sports Exerc* 44: 392–396, 2012.
38. Pedersen BK, Steensberg A, and Schjerling P. Exercise and interleukin-6. *Curr Opin Hematol* 8: 137–141, 2001.
39. Peeling P, Dawson B, Goodman C, Landers G, Wiegerinck ET, Swinkels DW, and Trinder D. Cumulative effects of consecutive running sessions on hemolysis, inflammation and hepcidin activity. *Eur J Appl Physiol* 106: 51–59, 2009.

40. Peeling P, Dawson B, Goodman C, Landers G, Wiegerinck ET, Swinkels DW, and Trinder D. Training surface and intensity: Inflammation, hemolysis, and hepcidin expression. *Med Sci Sports Exerc* 41: 1138–1145, 2009.
41. Peeling P, Sim M, Badenhorst CE, Dawson B, Govus AD, Abbiss CR, Swinkels DW, and Trinder D. Iron status and the acute post-exercise hepcidin response in athletes. *PLoS One* 9: 1–6, 2014.
42. Robson-Ansley P, Walshe I, and Ward D. The effect of carbohydrate ingestion on plasma interleukin-6, hepcidin and iron concentrations following prolonged exercise. *Cytokine* 53: 196–200, 2011.
43. Sim M, Dawson B, Landers G, Swinkels DW, Tjalsma H, Trinder D, and Peeling P. Effect of exercise modality and intensity on postexercise interleukin-6 and hepcidin levels. *Int J Sport Nutr Exerc Metab* 23: 178–186, 2013.
44. Sim M, Dawson B, Landers G, Trinder D, and Peeling P. Iron regulation in athletes: Exploring the menstrual cycle and effects of different exercise modalities on hepcidin production. *Int J Sport Nutr Exerc Metab* 24: 177–187, 2014.
45. Sinclair LM and Hinton PS. Prevalence of iron deficiency with and without anemia in recreationally active men and women. *J Am Diet Assoc* 105: 975–978, 2005.
46. Sotelo A, Gonzalez-Osnaya L, Sanchez-Chinchillas A, and Trejo A. Role of oxalate, phytate, tannins and cooking on iron bioavailability from foods commonly consumed in mexico. *Int J Food Sci Nutr* 61: 29–39, 2010.
47. Takami T and Sakaida I. Iron regulation by hepatocytes and free radicals. *J Clin Biochem Nutr* 48: 103–106, 2011.
48. Tandara L and Salamunic I. Iron metabolism: Current facts and future directions. *Biochem Med (Zagreb)* 22: 311–328, 2012.
49. Xu W, Barrientos T, and Andrews NC. Iron and copper in mitochondrial diseases. *Cell Metab* 17: 31–328, 2013.
50. Zoller H and Vogel W. Iron supplementation in athletes–first do no harm. *Nutrition* 20: 615–619, 2004.
51. Zotter H, Robinson N, Zorzoli M, Schattenberg L, Saugy M, and Mangin P. Abnormally high serum ferritin levels among professional road cyclists. *Br J Sports Med* 38: 704–708, 2004.