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REVIEW

Iron and the endurance athlete[1]

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Abstract: Iron is a trace mineral that is highly significant to endurance athletes. Iron is critical to optimal athletic performance because of its role in energy metabolism, oxygen transport, and acid-base balance. Endurance athletes are at increased risk for suboptimal iron status, with potential negative consequences on performance, because of the combination of increased iron needs and inadequate dietary intake. This review paper summarizes the role of iron in maximal and submaximal exercise and describes the effects of iron deficiency on exercise performance. Mechanisms that explain the increased risk of iron deficiency in endurance athletes, including exercise-associated inflammation and hepcidin release on iron sequestration, are described. Information on screening athletes for iron deficiency is presented, and suggestions to increase iron intake through diet modification or supplemental iron are provided.

Key words: iron deficiency, exercise, athlete, ferritin, hepcidin.

Résumé : Le fer est un oligoélément très important chez les athlètes d'endurance. Le fer est essentiel pour une performance sportive optimale, et ce, à cause de son rôle dans le métabolisme énergétique, le transport de l'oxygène et l'équilibre acidobasique. Les athlètes d'endurance sont plus à risque d'un taux de fer suboptimal et de ses possibles conséquences négatives sur la performance physique à cause de leur plus grand besoin en fer et de leur apport alimentaire insuffisant. Cette analyse documentaire présente succinctement le rôle du fer lors d'un exercice sous-maximal et maximal et décrit les effets d'un manque de fer sur la performance physique. L'auteure énonce les mécanismes sous-jacents à l'accroissement des risques en présence d'une déficience en fer chez les athlètes : inflammation associée à l'effort, libération de l'hepcidine et séquestration du fer. L'auteure donne des renseignements pour le dépistage de la déficience en fer et suggère une augmentation de l'apport en fer par une modification du régime alimentaire ou la supplémentation en fer. [Traduit par la Rédaction]

Mots-clés : déficience en fer, exercice physique, athlète, ferritine, hepcidine.

Iron

Iron is a transition metal and, in mammalian systems, iron is present in 3 different "redox" states: the ferrous (Fe^{+2}), ferric (Fe^{+3}), and ferryl (Fe^{+4}) redox states. Because iron exists in these different redox states, it participates in electron-transfer and oxidation-reduction reactions and reversibly binds ligands (most commonly oxygen, nitrogen, and sulfur). There are 4 classes of functional iron-containing proteins that facilitate these reactions: (*i*) iron-containing nonenzymatic proteins (e.g., hemoglobin and myoglobin); (*ii*) iron-sulfur enzymes; (*iii*) heme-containing enzymes; and (*iv*) iron-containing non–iron-sulfur, nonheme enzymes (Beard 2001). Many of these functional forms of iron are essential in processes that affect athletic performance, such as oxygen transfer and energy metabolism. Iron is important to endurance athletes not only because iron-dependent metabolic pathways affect performance, but also because of the increased prevalence of iron deficiency with or without anemia among athletes (Clement et al. 1987; Rowland et al. 1987; Nachtigall et al. 1996; Constantini et al. 2000; Malczewska et al. 2001; Spodaryk 2002; Dubnov and Constantini 2004; Sinclair and Hinton 2005; Fallon 2008; Woolf et al. 2009; DellaValle and Haas 2011). Iron deficiency without anemia (i.e., nonanemic iron deficiency) is an early stage of iron deficiency and is characterized by low body iron stores and suboptimal functional tissue iron. As iron deficiency progresses to anemia, hemoglobin concentrations are also reduced (Food and Nutrition Board (FNB) 2001).

Iron and athletic performance

Iron is essential to oxidative metabolism and thus is especially important for the endurance athlete whose athletic performance depends on a high aerobic capacity (for reviews specific to female athletes, see McClung (2012); DellaValle (2013)). Hemoglobin and myoglobin bind oxygen by means of the porphyrin ring of heme. Hemoglobin in red blood cells (RBCs) carries oxygen from the lungs to the exercising skeletal muscles; myoglobin transfers oxygen from erythrocytes to muscle cells. The electron transport chain, which is the final step in oxidative ATP synthesis, depends on heme-containing cytochromes (a, a_3, b, b_5, c, c_1) and on nonheme iron-sulfur enzymes (NADH dehydrogenase, succinate dehydrogenase, and ubiquinone–cytochrome c reductase) (Beard and Tobin 2000). Thus, iron deficiency impairs ATP production and increases reliance on anaerobic metabolism of glucose to produce ATP, in effect reducing endurance capacity. Given the essential roles of these iron-containing proteins in both oxygen utilization and aerobic metabolism, iron status has the potential to affect both maximal and submaximal exercise capacity.

Maximal aerobic capacity

The effects of iron status on aerobic capacity have been demonstrated by comparison of iron-deficient animals (or humans) to those with normal iron status. Animals with experimentally induced iron deficiency show marked reductions (~30%–70%) in hemoglobin, myoglobin, muscle mitochondria content, and in mitochondrial iron-dependent proteins and reduced maximal

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oxygen consumption ($\dot{V}O_{2max}$) (Davies et al. 1982). In addition, animals with the most severe anemia, i.e., lowest hemoglobin concentrations, have the lowest $\dot{V}O_{2max}$ (Perkkio et al. 1985). Humans with experimentally induced anemia also exhibit reductions in $\dot{V}O_{2max}$, which are proportional to hemoglobin concentrations (Woodson et al. 1978; Celsing et al. 1986).

Additional evidence that iron status affects maximal aerobic capacity comes from supplementation trials in which anemic subjects are iron repleted (i.e., brought back up to normal iron status) by means of iron supplementation and aerobic capacity is measured before and after repletion. For example, in one of the earliest supplementation trials to examine the effects of iron deficiency on physical performance, Gardner et al. (1975) showed that iron supplementation of anemic women improved iron status and performance during a standardized, multi-stage treadmill test and reduced exercise heart rate and blood lactate concentrations (Gardner et al. 1975). It is important to note that iron supplementation of iron-deficient nonanemic subjects (i.e., normal hemoglobin) does not improve $\dot{V}O_{2max}$ (Rowland et al. 1988; Newhouse et al. 1989; Klingshirn et al. 1992; Zhu and Haas 1998*a*), as the primary determinant of $\dot{V}O_{2max}$ is oxygen delivery.

Submaximal aerobic capacity

From an athletic performance perspective, diminished submaximal exercise capacity translates into reduced endurance, which is defined as the ability to sustain a submaximal workload until exhaustion. To demonstrate the role of iron in aerobic metabolism during submaximal exercise, animals with experimentally induced anemia are transfused with RBCs to normalize hemoglobin concentrations, while other iron-containing proteins remain reduced. Normalization of hemoglobin restores $\dot{V}O_{2max}$, but endurance during submaximal aerobic exercise remains impaired (Finch et al. 1976). The results of iron supplementation studies of women who are iron-depleted, but not anemic, also suggest that iron affects aerobic metabolism during submaximal work (Rowland et al. 1988).

Accurate measurement of endurance in humans is difficult because study participants must exercise for extended periods of time to achieve exhaustion and performance is highly dependent on subject motivation. An alternative strategy for measurement of endurance capacity in human subjects is to use a time trial of sufficient distance that subjects exercise at a submaximal intensity for the majority of the test, yet are motivated by a defined end-point. Zhu and Haas (1998*a*) found that iron supplementation reduced energy expenditure and fractional utilization of peak oxygen consumption ($\dot{V}O_{2max}$) in iron-depleted, nonanemic women (Zhu and Haas 1998*a*). Likewise, Hinton et al. (2000) found that iron supplementation during 4 weeks of aerobic exercise training resulted in greater improvements in endurance compared with placebo in iron-deficient, nonanemic women (Hinton et al. 2000), and the effect of the iron supplement was greatest in subjects with the greatest potential to respond, i.e., elevated tissue iron need as defined by serum transferrin receptor (sTfR > 8.0 mg/L) at baseline (Brownlie et al. 2004). Using a progressive muscle fatigue protocol to assess submaximal work capacity, Brutsaert et al. found that iron supplementation of iron-deficient, nonanemic women attenuated onset of fatigue in maximal voluntary contractions of the right isolated quadriceps femoris muscle (Brutsaert et al. 2003). In a study of female collegiate rowers, DellaValle and Haas (2012) found iron-deficient, nonanemic athletes had slower 4-km time trial times and reduced energetic efficiency compared with iron-replete athletes (DellaValle and Haas 2012).

Iron deficiency in athletes

As discussed above, early functional iron deficiency reduces endurance capacity and energetic efficiency during submaximal exercise (Hinton et al. 2000; Spodaryk 2002; Brownlie et al. 2004; Hinton and Sinclair 2007; DellaValle and Haas 2012, 2013). Based on animal studies, this deficit is due to decreased activity of iron-containing oxidative enzymes and cytochromes (Finch et al. 1976; Davies et al. 1982; Willis et al. 1987). The hallmark symptoms of iron-deficiency anemia are fatigue, lack of energy, and apathy. Specifically, anemia impairs maximal exercise performance ($\dot{V}O_{2max}$) by reducing oxygen delivery to the body (Celsing et al. 1986).

Prevalence of iron deficiency

In the general population of adults in the United States, 3%–5% of women are anemic and 11%–13% are iron-deficient, while less than 1% of men are iron deficient (Looker et al. 1997). The reasons for the greater prevalence of iron deficiency in women compared with men are increased iron losses in menstrual blood flow and lower dietary iron intake.

The prevalence of iron deficiency, particularly nonanemic iron-depletion (i.e., normal hemoglobin and hematocrit, but low serum ferritin and (or) elevated sTfR), appears to be greater in physically active individuals and competitive athletes compared with their sedentary counterparts (Milic et al. 2011; Eliakim et al. 2002; Gropper et al. 2006; Woolf et al. 2009) (Fallon 2004). Comparison of studies that report prevalence of iron depletion is complicated by use of different cut-off values for the iron status indicators, i.e., ferritin ranging from 12–35 ng/mL has been used as the criterion for iron depletion. Nevertheless, the prevalence of iron depletion appears to be ~20%–50% in female athletes and ~4%–50% of male athletes (Clement et al. 1987; Rowland et al. 1987; Rowland and Kelleher 1989; Nachtigall et al. 1996; Constantini et al. 2000; Malczewska et al. 2001; Dubnov and Constantini 2004; Sinclair and Hinton 2005; Fallon 2008; DellaValle and Haas 2011) with higher frequency in endurance athletes, e.g., distance runners and triathletes (Nachtigall et al. 1996; Rietjens et al. 2002; Lukaski 2004; Sinclair and Hinton 2005).

Etiology of iron deficiency in endurance athletes

Maintenance of both the functional iron pool (i.e., iron-containing proteins) and adequate iron stores is determined by the balance between intestinal absorption of dietary iron, iron losses, and on the recycling of iron released from RBCs. The most common routes of iron losses are by way of sweat, skin, urine, gastrointestinal tract, and menstrual blood. The high prevalence of iron deficiency in endurance athletes can be attributed to several factors. These include inadequate dietary iron intake, exercise-associated iron losses, and reduced iron recycling.

Dietary iron requirements and intakes in endurance athletes

Comparison of studies that report the prevalence of suboptimal iron intake in athletes is complicated by the evolution of recommended nutrient intakes over time and by differences in how investigators ascertained adequacy and define adequacy. With the current dietary reference intakes (DRIs), the estimated average requirement (EAR) is the appropriate standard to evaluate nutrients intakes of groups (FNB 2000); however, the EAR for athletes may be increased by 30%–70% (FNB 2001) because of elevated iron losses. Studies that were conducted prior to the establishment of the DRIs for iron in 2001 often used two-thirds of the 1989 Recommended Daily Allowance (RDA), which was 15 mg/day for women and 10 mg/day for men (FNB 1989), as the definition of sufficient dietary iron intake.

There is evidence that adolescent and collegiate female athletes in a wide variety of sports do not consume enough dietary iron (Beals 2002; Kim et al. 2002; Papadopoulou et al. 2002; Ziegler et al. 2002; Gropper et al. 2006); although, others have reported that most female athletes consume adequate dietary iron (Steen et al. 1995; Hinton et al. 2004). The information on dietary iron intake in male athletes is limited, and, similar to female athletes, there are reports of inadequate iron intake in male athletes (Rowland and Kelleher 1989), while other studies found the diets of male athletes to be adequate in iron (Hinton et al. 2004; Lun et al. 2009).

However, as mentioned above, these discrepant results may be partially explained by differences in the value used to define adequacy, i.e., use of the RDA (18 mg/day) vs. the EAR (8 mg/day) for females.

Increased iron losses

Daily basal iron losses (0.9–1.2 mg iron/day) are small compared with total body iron content: 0.6 mg/day are lost from the gastrointestinal tract, mostly in sloughed mucosal cells; 0.08 mg/day are lost in urine; and 0.2–0.3 mg/day in skin. Menstruating women require an additional 0.6–0.9 mg/day to account for menstrual blood loss. Women with high menstrual blood flow and women who use intrauterine devices will have greater iron losses. Since oral contraceptive agents tend to reduce menstrual bleeding (FNB 2001), their use is associated with reduced iron loss.

Physical activity increases the amount of iron lost by way of the sweat, urine, and the gastrointestinal tract. Exercise-associated blood and therefore iron loss is greatest after high-intensity, prolonged, or dynamic weight-bearing activities. Thus, regular weight-bearing exercise of moderate to high intensity can increase iron losses by 30% to 70% (FNB 2001). The amount of iron lost in sweat is increased simply because athletes sweat more than their sedentary counterparts. Although sweat volume is increased during exercise in hot environments, the concentration of iron in sweat declines with heat acclimation (Chinevere et al. 2008). Exercise may cause hematuria (blood in urine). Reasons for elevated urinary blood losses are damage to the kidney because of lack of oxygen, increased renal blood pressure, increased body temperature, exercise-associated acidosis, renal or bladder trauma, and dehydration. Similarly, reduced blood flow, increased gut motility, and mechanical trauma, resulting from exercise, increase gastrointestinal blood losses. Iron losses are increased because of shortened RBC lifespan, which can be reduced significantly (e.g., 74 days in runners vs. 141 days in sedentary controls; Weight et al. 1991*a*). The increased rate of hemolysis results from general circulatory (i.e., mechanical) trauma, oxidative damage because of elevated production of superoxide, or osmotic changes that induce changes in RBC volume, increasing fragility. Exercise-induced hemolysis has been associated with swimming (Selby and Eichner 1986), cycling, rowing (Telford et al. 2003), and strength training (Schobersberger et al. 1990), and appears to be positively related to exercise intensity (McInnis et al. 1998). However, the primary determinant of hemolysis is "footstrike" (Telford et al. 2003). During activities that involve running or jumping, red blood cells in the capillaries of the bottom of the foot are destroyed by the mechanical forces experienced upon impact with the ground; hence, the term "footstrike hemolysis". These mechanisms may explain why both exercise duration and intensity are negatively associated with hemoglobin, hematocrit, and serum ferritin concentrations in highly trained athletes (Schumacher et al. 2002; Wilkinson et al. 2002).

Hepcidin-mediated iron sequestration

The amount of iron absorbed by the small intestine daily (~1–2 mg) is insufficient both to replace daily losses (~1 mg/day) and to meet the demands of erythropoiesis (~22 mg/day). Iron that is salvaged from old or damaged RBCs by the macrophages in the liver and spleen amounts to ~22 mg/day, thus supplying most of the iron taken up by the bone marrow each day for the production of RBCs (Anderson et al. 2007).

Export of iron from macrophages, enterocytes, and hepatocytes by means of the iron transport protein ferroportin 1 is highly regulated, as iron released from these cells controls iron availability to the rest of the body (Anderson et al. 2007). The primary regulator of iron export is the peptide hormone hepcidin, which is produced by hepatocytes. Hepcidin lowers iron efflux by reducing the amount of ferroportin 1 available for iron export. Hepcidin production is regulated by hepatic iron status, erythropoiesis, hypoxia, and inflammation (Leong and Lonnerdal 2004). The increase in hepcidin in response to inflammatory proteins, e.g., interleukin-6 (IL-6), is thought to serve an anti-microbial function by reducing iron available to bacteria.

Recently, exercise-induced inflammation has been implicated as a possible cause of iron deficiency in athletes (Peeling et al. 2008). Anemia associated with chronic inflammation is due to sequestration of iron as a result of increased hepcidin (Nemeth et al. 2003). Roecker et al. (2005) was the first to report that hepicidin is increased following exercise, noting that urinary hepcidin was increased 24 h after a marathon in 8 of the 14 female runners studied (Roecker et al. 2005). More recently, Peeling et al. (2009*a*, 2009*b*) found that IL-6, free hemoglobin, and hepcidin were increased by high-intensity running in highly trained male runners (Peeling et al. 2009*a*; Peeling et al. 2009*b*). Although exercise stimulates IL-6 release from exercising skeletal muscle (Toft et al. 2011) in a mode-, intensity-, and duration-dependent manner (Fischer 2006), exercise duration is the strongest determinant of IL-6 release (Fischer 2006). For example, relative to pre-exercise concentrations, IL-6 is increased 16-fold after 2 h, 100-fold after 6 h, and 10 000-fold after a 36-h ultra-endurance footrace (Margeli et al. 2005; Fischer 2006). Exercise-associated IL-6 release is also increased when skeletal muscle glycogen is depleted (Steensberg et al. 2001) and following exercise in hot environments (Fischer 2006). Although more data are needed to establish a causal role for chronic inflammation and hepcidin in the iron-deficiency associated with sports-participation, particularly endurance sports, hepcidin is likely to play a role.

Additional groups at risk for iron deficiency

In addition to suboptimal iron intakes and increased physical activity-associated losses, athletes who are frequent blood donors are also at increased risk for iron deficiency (Choe et al. 2001), as 200–250 mg of iron are lost per 0.5 L of blood. *Helicobacter pylori* and gastrointestinal parasitic infections also increase blood losses through the gastrointestinal tract. In addition, multiparous women also are at greater risk for iron deficiency because of pregnancy-associated depletion of iron stores. Women with heavy menstrual bleeding or who use an intra-uterine device for contraception are at greater risk for iron deficiency because of increased blood losses. In addition, athletes who regularly use nonsteroidal anti-inflammatories are likely to have increased gastrointestinal blood losses (Rudzki et al. 1995), increasing their risk of iron deficiency. Vegetarian or vegan athletes are at higher risk for iron deficiency because of the reduced iron bioavailability in a plant-based diet. Recent data suggest that iron status may be determined, in part, by genetics (Tanaka et al. 2010).

Iron supplementation of endurance athletes

Few studies have assessed the effects of iron supplementation on endurance performance in endurance athletes. McClung et al. reported that iron supplementation prevented the decline in iron stores following 8 weeks of basic combat training and enhanced training adaptations as assessed by 2-mile run times in female soldiers. Moreover, the benefits of iron supplementation were greatest in subjects with iron-deficiency anemia (McClung et al. 2009). Similarly, Hinton and Sinclair (2007) found that iron supplementation positively affected ventilatory threshold (V_T) and gross energetic efficiency during a steady-state submaximal test in iron-deficient, nonanemic, chronically trained (≥60 min/day; ≥3 days/week; ≥6 month) subjects (17 women; 3 men) versus placebo. The effects of iron supplementation on V_T were greatest in participants with the greatest potential to respond, (i.e., lowest presupplementation ferritin). Moreover, increases in serum ferritin were associated with reductions in respiratory exchange ratio (increased fatty acid vs. glucose oxidation) and V_T (% $\dot{V}O_{2peak}$) during steady-state submaximal (60% $\dot{V}O_{2peak}$) exercise. Similarly, supplementation of iron-deficient, nonanemic collegiate rowers

during 6 weeks of training resulted in increased ferritin and greater improvements in energetic efficiency and energy expenditure in a 4-km time trial versus placebo (DellaValle and Haas 2014). Thus, it appears that even marginal repletion of iron stores in iron-depleted athletes positively affects aerobic function (Hinton and Sinclair 2007).

It is important to note that the classification of athletes as "anemic" or "iron-deficient" based on hemoglobin and ferritin concentrations, respectively, is somewhat arbitrary (Eichner 2012). For example, a female athlete whose hemoglobin is greater than 12 g/dL and ferritin is less than 30 ng/mL may experience an increase in both hemoglobin and ferritin with iron supplementation and, consequently, exhibit improvements in both maximal and submaximal aerobic capacity.

Assessment of iron status

Anemia and nonanemic iron depletion

Blood tests are needed to diagnose the stage of iron deficiency, including the most severe stage — iron-deficiency anemia (FNB 2001). The concentration of hemoglobin in blood is one the primary criteria for diagnosis of anemia. Hematocrit, the proportion of blood volume that is RBCs, is reduced during anemia. The threshold hemoglobin and hematocrit values used to define anemia are decreased in African Americans, and increased in cigarette smokers and individuals who live at altitude. Iron is transported in the blood bound to a protein called transferrin. The percent of transferrin that is carrying iron, that is, transferrin saturation, is decreased with iron deficiency.

Anemia caused by iron deficiency can be distinguished from other nutritional anemias based on the appearance of the RBCs. Iron deficiency results in insufficient hemoglobin production. The body attempts to make up for the decreased oxygen-carrying capacity by producing new RBCs at a rapid rate. Under the microscope, these RBCs appear small (because they are immature) and very pale (because of lack of hemoglobin). This type of anemia is called hypochromic microcytic anemia.

Depletion of iron stores is assessed by determination of serum ferritin concentrations. Because the ferritin concentration in blood is proportional to ferritin stored in the liver (1 μg ferritin/L is equivalent to ~10 mg of stored iron), serum ferritin is used as an indicator of iron stores (Cook and Finch 1979). However, ferritin is an acute phase protein, so its production in the liver is elevated during illness or inflammation, independent of iron stores. Therefore, ferritin should not be measured during illness or after an exhaustive exercise bout to avoid masking depleted iron stores. The concentration of sTfRs in blood is used as an indicator of tissue iron status (Punnonen et al. 1997) because cellular expression of sTfR increases with iron need (Skikne et al. 1990). When tissues such as skeletal muscle or bone marrow need iron, the number of transferrin receptors on the cell surface increases to increase iron uptake. The use of sTfR to evaluate iron status in athletes has been advocated because sTfR is not an acute phase protein and, therefore, is not likely to be acutely affected by exercise. The ratio of [sTfr]/log[ferritin] also has been used to evaluate bone marrow iron depletion (Punnonen et al. 1997) with higher ratios indicating more severe iron depletion (Suominen et al. 1998). For example, a ratio >1.8 is indicative of depleted iron stores, while a ratio >2.2 suggests iron-deficient erythropoiesis. The ratio is particularly useful for evaluation of iron status in athletes whose ferritin stores are depleted, i.e., <12 ng/mL (Punnonen et al. 1997). However, because of the large day-to-day variability in the ratio for athletic populations who are actively training, only changes ≥0.4 should be considered significant (Stupnicki et al. 2003). Serum ferritin, sTfR, and [sTfr]/log[ferritin] respond to 8 weeks of iron supplementation in nonanemic, iron-depleted women (Zhu and Haas 1998*b*).

Special considerations for iron-status assessment in athletic populations

The International Olympic Committee (2009) recommends that assessment of iron status, including anemia and iron stores, be part of periodic health evaluations of athletes because of the increased prevalence of iron deficiency in athletic populations. In 1 survey, only 43% of D-IA NCAA athletic programs performed routine screening for iron deficiency (Cowell et al. 2003). Although screening large numbers of athletes makes it difficult to standardize measurement conditions, it is important to recognize that factors such as time of day, interval since last training bout, illness, or injury might impact the results and validity of the tests. Acute changes in plasma volume can mask true changes in indicators of iron status. Endurance training can cause expansion of plasma volume that might exceed or precede the adaptive increase in RBC number, which can result in an apparently low hematocrit or hemoglobin (Weight et al. 1991*b*). This phenomenon has been termed "dilutional anemia" or "sports anemia", but does not adversely affect performance. In addition to indicators of anemia, iron stores and tissue iron status, reduced serum haptoglobin, hematuria, and hemoglobinuria are evidence of elevated hemolysis.

Prevention and treatment of iron deficiency

Consumption of an iron-adequate diet

Primary prevention of iron deficiency among endurance athletes should focus on dietary strategies to increase consumption of iron-rich foods and foods that enhance iron absorption. Because the amount of iron in the American food supply is ~6 mg per 1000 calories, achieving the recommended intake of iron (18 mg/day) through diet alone is difficult for most women. Indeed, a woman would have to consume ~3000 calories to get 18 mg of iron, and this energy intake exceeds the needs and (or) actual intakes of many female athletes. Thus, consumption of iron-rich foods, such as meat, iron-fortified grains and breakfast cereals, dried fruit, nuts, and soy nuts, is particularly important. Some "energy bars" also are fortified with iron and may be significant contributors to total iron intake. Athletes should be provided information on selection of foods that have high iron bioavailability. Because plant-based iron (nonheme iron) has significantly lower bioavailability than animal-based iron, which is both heme and nonheme iron, vegetarian athletes need to be especially careful to consume enough iron.

Iron supplements

Iron supplementation is warranted in athletes with diagnosed iron-deficiency anemia or serum ferritin < 20 ng/mL (Pitsis et al. 2004). Studies in male (Nachtigall et al. 1996) and female (Hinton and Sinclair 2007; DellaValle and Haas 2014) athletes with nonanemic iron deficiency have demonstrated that ingestion of 20–100 mg of elemental iron per day for 6–12 weeks effectively increases serum ferritin concentrations. For treatment of iron-deficiency anemia, the Center for Disease Control (CDC 1998) recommends an oral dose of 60–120 mg elemental iron per day as two 50- to 60-mg doses. Many over-the-counter iron-only supplements contain this level of iron per dose. For example, a 325-mg ferrous sulfate pill provides 65 mg of elemental iron. The upper intake level (UL) for iron is set at 45 mg/day based on gastrointestinal symptoms associated with supplemental iron ingestion (FNB 2001). The UL applies to people with normal iron status and, consistent with the CDC recommendation, physicians often prescribe iron at doses >45 mg iron per day to treat anemia.

Individuals being treated with supplemental iron should be retested after 4 weeks of supplementation, and if hemoglobin responds to treatment, supplementation should be continued for an additional 2–3 months to replete iron stores. Individuals of African, Mediterranean, or Southeast Asian descent who do not

respond to supplemental iron should be tested for thalassemia or sickle cell trait. Anemia that does not respond to iron treatment might be due to either a vitamin B_{12} or folate deficiency. Supplemental ferrous iron is available in a variety of physical and chemical forms. The most common chemical form of iron supplement is ferrous iron complexed with sulfate, succinate, citrate, lactate, fumarate, or gluconate. These preparations typically contain 35–100 mg of elemental iron (Beard and Tobin 2000). In addition to pills, iron is available in chewable, enteric coated, extended release, and liquid forms. Although, the enteric coated and extended release forms have fewer side effects, their absorption is poor. Consequently, these forms should be avoided if possible. Supplemental iron should be taken with ascorbic acid to enhance absorption. The bioavailability of iron from multi-mineral supplements, in particular those that contain calcium, is less than that of iron salts (Hallberg et al. 1992). Likewise, milk, coffee, tea, phosphate-containing soft drinks, and some medications, e.g., tetracycline, antacids, and acid-blockers, reduce iron absorption and should not be consumed with the iron supplement. Gastrointestinal side effects, such as nausea, diarrhea, constipation, and cramps, are common with iron supplementation, and athletes should be counseled on the benefits of treatment despite the potential side effects to increase compliance. Gradually increasing the dose of supplemental iron or taking the iron supplement with food might reduce the severity of the side effects. In addition, the supplement can be taken less than daily, i.e., every 2–3 days, to minimize side effects without negatively impacting treatment.

Under extremely rare circumstances, iron (e.g., iron hydroxide sucrose or iron carboxymaltose) can be administered parenterally, i.e., intravenously, by a physician. A recent study compared the efficacy of 6 weeks of either oral iron supplementation (i.e., 305 ferrous sulfate daily) or intravenous ferric carboxymaltose as 2–4 injections in highly trained male and female distance runners with ferritin ≤ 65 ng/mL and hemoglobin ≥ 12 g/dL (Garvican et al. 2014). Serum ferritin was significantly increased following either oral or intravenous iron supplementation; however, the increase was greater in the athletes who received iron injections from weeks 1–6 of the study. In athletes whose ferritin at baseline was ≤35 ng/mL, intravenous iron increased hemoglobin mass, $\dot{V}O_{2max}$, and run time to exhaustion during an incremental treadmill test, while oral iron did not. Thus, supplemental iron administered intravenously rapidly improves iron status and may be a better treatment option in athletes with severely comprised iron status.

Iron overload

The UL for iron, which applies to individuals of normal iron status, is 45 mg/day (FNB 2001). Iron overload (serum ferritin > 200 ng/mL) is a real risk associated with unnecessary or unmonitored iron supplementation. Mettler and Zimmermann reported that 15% of male and 5% of female marathon runners suffered from iron overload (Mettler and Zimmermann 2010). When body iron exceeds the storage and transport capacity of ferritin and transferrin, respectively, the excess iron remains unbound to proteins. This free iron causes lipid peroxidation and free radical production, processes that damage the cardiovascular system, kidneys, liver, and central nervous system. Moreover, genetic disorders that affect iron metabolism can increase risk of iron overload. Individuals with hereditary hemochromatosis, an autosomal recessive disorder, suffer from excessive iron absorption and impaired storage, which cause extensive organ damage. Thalassemia or sideroblastic anemia also increase risk for iron overload because of increased iron absorption, secondary to elevated erythropoiesis.

Because of the potential for iron overload, iron supplementation to correct a deficiency should be under the supervision of a healthcare professional. Athletes who experience symptoms that are consistent with iron deficiency (unusual fatigue or decrements in performance, cold intolerance, frequent illnesses) should have their iron status assessed before beginning a supplemental regimen. Once iron deficiency is identified and supplementation is initiated (e.g., 65 mg elemental iron/day), the athlete should have his or her iron status monitored at regular intervals (e.g., every 4–6 weeks).

Summary

Endurance athletes are at increased risk for iron deficiency for a number of reasons, including inadequate intake, poor bioavailability, and increased losses. The high prevalence of clinical and subclinical iron deficiency among endurance athletes, particularly female athletes, is concerning, because of the significant impact this can have on both health and performance. Moreover, with education and proper nutritional intervention, iron deficiency in endurance athletes could be fairly readily prevented and (or) treated. Diet modification, rather than use of supplements, is the preferred strategy for ensuring adequate intake among athletes because high doses of iron have the potential to be dangerously toxic. Thus, the use of supplemental iron to correct a deficiency should only be undertaken with supervision by a healthcare professional to monitor treatment efficacy and safety.

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