

Iron status and exercise¹⁻³

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ABSTRACT The prevalence of iron deficiency anemia is likely to be higher in athletic populations and groups, especially in younger female athletes, than in healthy sedentary individuals. In anemic individuals, iron deficiency often not only decreases athletic performance but also impairs immune function and leads to other physiologic dysfunction. Although it is likely that dietary choices explain much of a negative iron balance, evidence also exists for increased rates of red cell iron and whole-body iron turnover. Other explanations of decreased absorption and increased sweat or urine losses are unlikely. The young female athlete may want to consider use of low-dose iron supplements under medical and dietary supervision to prevent a decline in iron status during training. *Am J Clin Nutr* 2000;72(suppl):594S-7S.

KEY WORDS Iron deficiency, aerobic capacity, exercise endurance, anemia

INTRODUCTION

Iron deficiency is the most common single nutrient deficiency disease in the world and is a major concern for $\approx 15\%$ of the world's population (1). The commonly used definition for anemia, regardless of its cause, is a low hemoglobin concentration. If iron deficiency is an underlying etiology, then by definition an individual must have depleted iron stores, low ferritin in plasma or decreased stainable iron in bone marrow, and inadequate delivery of iron to tissues as characterized by a low transferrin saturation, a high erythrocyte protoporphyrin concentration, and an elevated transferrin receptor concentration (2, 3).

Iron deficiency can be defined as occurring when the body's iron stores become depleted and a restricted supply of iron to various tissues becomes apparent (4). The clear consequences of iron depletion are a reduction in oxygen transport capacity and a reduction in oxidative capacity at the cellular level of functioning. The process by which iron stores are depleted may occur rapidly or very slowly and depends on the balance between iron intake and iron requirements. From the evidence already published in the scientific literature, it is reasonable to conclude that iron intake is marginal or inadequate in numerous females who engage in regular physical exercise (5, 6). In many females, iron depletion is undoubtedly related to both quantities of food and the inherent density of iron in the typical American diet, as well as the decision by many persons to remove meat from their diet.

DIETARY IRON

Clearly, daily iron intake depends on the composition of food consumed and the quantity of iron therein. Several inhibitors and a small number of enhancers of iron absorption are now known to exist. Iron absorption increases in individuals who have depleted iron status, and this internal regulator of absorption may be more important than any particular constituents of the food supply (7). Basal obligatory losses in humans are ≈ 1 mg Fe/d and must be replaced by an equivalent amount of iron derived from the diet.

The typical Western diet provides an average of 6 mg of heme and nonheme iron per 4120 kJ of energy intake. The bioavailability of iron is both a function of its chemical form and the presence of food items that promote or inhibit its absorption. Ascorbic acid and meat are known as the most powerful of these enhancers of nonheme iron absorption, whereas the list of inhibitors is much longer. In contrast to heme iron absorption, many factors affect nonheme iron absorption and include bran; hemicellulose; cellulose; pectin; phytic acid, which is found in wheat and soy products; and polyphenolic compounds (8, 9).

Heme iron is an important dietary source of iron because it is more effectively absorbed than is nonheme iron; thus, vegetarians can be at a relatively greater risk for iron deficiency, especially if food restriction is part of the dietary self-control exerted by female athletes. From 5% to 35% of heme iron is absorbed from a single meal, whereas nonheme iron absorption from a single meal can range from 2% to 20%, depending on the iron status of the individual and the ratio of enhancers and promoters in the diet. Thus, although heme iron constitutes only $\approx 10\%$ of the iron found in the diet, heme iron may provide up to one-third of absorbed dietary iron (10, 11). Heme iron appears to be affected only by animal proteins, which facilitate its absorption, and calcium, which inhibits its absorption (12).

The absorption of supplemental iron depends on the type of preparation used. The amount of iron that is bioavailable from multimineral preparations, especially when calcium salts are used, is less than that absorbed during the administration of iron alone (13, 14). These preparations may provide less iron

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²Presented at the workshop Role of Dietary Supplements for Physically Active People, held in Bethesda, MD, June 3-4, 1996.

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than suspected because the bioavailability in practice is less than would be predicted if only an iron preparation was used. Additionally, multivitamin and mineral preparations are often consumed with a meal or with coffee and tea. These additional factors may further reduce the net absorption of iron. One of the frequent complaints voiced by iron supplement users about either over-the-counter iron supplements or the prescribed higher-dose iron supplements are the side effects of constipation and gastrointestinal upset (15). Because many young female athletes are told to consume iron supplements in doses of >50 mg Fe/d, noncompliance can be a significant issue. Lower-dose administration of supplements containing ≤ 125 mg ferrous sulfate (39 mg Fe) per day prevented the decrease in serum ferritin that was attributable to altered iron balance in competitive female swimmers (16). These swimmers, who had no complaints of gastrointestinal distress, were in contrast to the frequent complaints noted when therapeutic doses of iron were used (15). Reports of iron supplementation on a weekly or biweekly basis in Third World populations showed the strong possibility that less frequent use of iron supplements can still provide positive effects without gastrointestinal distress (17, 18). No known systemic studies have used this approach with athletes, although the approach holds great promise for improving long-term efficacy and improvement of iron status.

CONSEQUENCES OF POOR IRON STATUS

Many organs show morphologic, physiologic, and biochemical changes with iron deficiency in a manner related to the turnover of essential iron-containing proteins. Sometimes this occurs even before a significant decrease in hemoglobin concentration occurs (19). Iron deficiency is associated with altered metabolic processes, including mitochondrial electron transport, neurotransmitter synthesis, protein synthesis, organogenesis, and others. The overt physical manifestations of chronic iron deficiency are glossitis, angular stomatitis, koilonychia (spoon nails), blue sclera, esophageal webbing (Plummer-Vinson syndrome), and anemia. Behavioral disturbances such as pica [abnormal consumption of dirt (geophagia) and ice (pagophagia)] are often present in persons with iron deficiency, although a biologic explanation is lacking.

It is also important to delineate whether exercise itself may alter iron status and whether such alterations are detrimental to athletic performance or to the health of an athlete. Although a multitude of laboratories worldwide have contributed to a broad-based accumulation of knowledge in these areas (5, 6, 19, 20), an analysis of >2 decades of research illustrates several central points. First, it is clear that reductions in hemoglobin concentration and tissue iron content can be detrimental to exercise performance. Second, it is documented that iron status is negatively altered in many populations of chronically exercising individuals. Third, women may have an increased prevalence of exercise-related alterations in body iron because of a net negative iron balance.

The role of heme and nonheme iron in biological function and work performance has been elucidated through human and animal experiments, and several classic reviews have been published (21, 22) and updated (23). Not surprisingly, hemoglobin iron, when lacking, can profoundly alter physical work performance via a decrease in oxygen transport to exercising muscle. What is intriguing, however, is that although nonheme iron associated

with enzyme systems constitutes only 1% of total body iron, profound deficits of these cellular enzymes per se may have detrimental effects on athletic performance. Studies illustrate that maximal oxygen uptake ($\dot{V}O_{2\max}$) is determined primarily by the oxygen-carrying capacity of the blood and is thus correlated with the degree of anemia. Endurance performance at reduced exercise intensities, however, is more closely related to tissue iron concentrations because of the strong association between the ability to maintain prolonged submaximal exercise and the activity of iron-dependent oxidative enzymes.

Several of the well-known consequences of iron deficiency that occur after the depletion of iron stores are a decline in hemoglobin concentration, decreased mean corpuscular hemoglobin concentration, decreased size and volume of new red cells, reduced myoglobin, and reduced amounts of both iron-sulfur and heme iron-containing cytochromes within cells. Diffusion of dioxygen from hemoglobin into tissue becomes limited as a result of fewer erythrocytes, increased membrane diffusivity, and decreased tissue myoglobin concentration. In severe anemia, oxygen transport is clearly limiting to tissue oxidative function at anything but the resting condition (19), despite a right-shifted hemoglobin- O_2 dissociation curve and increased cardiac output. Tissue extraction of oxygen is increased by this compensation and partial oxygen pressure in mixed venous blood is significantly lower in anemic individuals. The very significant decrease in myoglobin and other iron-containing proteins in the skeletal muscle of persons with iron deficiency anemia contributes significantly to the decline in muscle aerobic capacity (19, 22).

A typical repair curve for muscle iron-containing and oxidative enzymes during iron repletion experiments has been described (23). Pyruvate and malate oxidase were decreased to 35% of normal in iron-deficient muscle and improved to 85% of normal in 10 d of treatment. The 50–90% decrease in both the Fe-S enzymes and in the heme-containing mitochondrial cytochromes are consistent with many other observations over the past 2 decades (19). What seems to determine the amount of decline in activity with cellular iron deprivation is the turnover rate of iron-containing proteins.

Results of human studies focusing on the concept of a hemoglobin threshold phenomenon are in disagreement. Research by Edgerton et al (24) suggested that the decrement in work performance in subjects with iron deficiency anemia was a reflection of the degree of anemia rather than other non-hemoglobin-related biochemical changes. Their data revealed that the concentration of lactate in blood during exercise was higher in anemic subjects than in control subjects and that exercise heart rates were reduced after iron-deficiency anemic subjects were treated with iron supplements. The range of hemoglobin concentrations examined was large, from 40 g/L upward. Unlike the studies of Perkkio et al (25), these studies suggested a more linear relation between hemoglobin and work performance and thus do not necessarily support the presence of a hemoglobin threshold phenomenon. A host of detailed animal studies have identified limitations in both oxygen delivery and tissue metabolism as explanations for the deficits in exercise endurance and peak aerobic power during iron deficiency anemia (20).

Several studies conducted as early as 2 decades ago documented altered iron status in athletes but questioned whether such alterations were physiologically detrimental. That is, the investigators questioned whether exercise training itself leads to a negative iron balance with subsequent deleterious effects on exercise performance. Wijn et al (26) measured hemoglobin,

packed cell volume, serum iron, and iron-binding capacity in selected athletes and compared these with the hematologic profile of officials during the 1968 Olympic Games. These data illustrated iron deficiency anemia in 2% of male and in 2.5% of female athletes, and mild anemia without signs of iron depletion in 3% of the athletic population. Many other descriptive studies also demonstrated a significant decrease in red blood cell number and a decrease in hemoglobin and ferritin concentrations in athletes (20). In many cases, the runners were the most affected group. The authors speculated that a recurring hemoglobinuria might produce diminished iron reserves in middle- and long-distance runners. Radomski et al (27) evaluated hematologic changes in physically fit young soldiers who marched 35 km/d for 6 d at 35% of their $\dot{V}O_{2\max}$.

Subsequent investigations have supported the results of these early studies and have demonstrated a reduction in hemoglobin and hematocrit in certain athletic populations, although clear negative consequences with regard to performance are lacking. Newhouse et al (28, 29) and Newhouse and Clement (30) elucidated the implications of iron deficiency in female athletes. Others have noted an increased incidence of decreased serum ferritin in female runners (31–35). In a summary of surveys, serum ferritin concentrations in female athletes were found to be <12 mg/L in 35%, <25 mg/L in 82%, and <30 mg/L in 60%, as compared with their sedentary counterparts from the nonathletic female population (20). Although estimations of the precise prevalence rates differ, an increased incidence of reduced serum ferritin seems to be a repeatable observation among laboratories in this population. These results may be influenced by menstrual flow and perhaps dietary iron intake. The issue of menstrual flow is often overlooked in estimates of loss of body iron in female athletes. The most compelling evidence for iron depletion is the observation of altered serum ferritin concentrations, which are generally lower in female athletes.

What these investigations do not demonstrate, however, is a clinically subnormal or reduced serum ferritin concentration concurrent with a demonstrated functional consequence in the absence of overt anemia. That is, the drop in ferritin is not detrimental to the physical performance of the athlete. Studies determined that simple dietary changes can prevent the decrease in ferritin during very modest exercise (36). The daily consumption of a single meat-containing meal was sufficient to maintain ferritin during a prolonged study when aerobic dance was used as the exercise modality. Moderate doses of over-the-counter doses of ferrous sulfate, 39 mg elemental Fe, or 125 mg FeSO_4 , are sufficient to prevent the drop in ferritin in highly trained college swimmers (16). This is in contrast to much higher doses administered by others to prevent training-induced declines in iron status (29, 30).

Several investigators have proposed mechanisms by which iron balance could be affected by intense physical exercise (20, 37–39). Explanations include increased gastrointestinal blood loss after running and hematuria as a result of erythrocyte rupture within the foot during running. The possibility of increased red cell turnover in athletes is supported by the ferrokinetic measurements conducted by Ehn et al (40). They demonstrated that the whole-body loss of radioactive iron occurred $\approx 20\%$ faster in female athletes than in nonathletes, and both were faster than that in adult men. When the rate of loss of iron from the red cell mass is examined in highly controlled animal studies, the same relation appears (41), ie, trained animals with low iron sta-

tus had a higher red cell iron turnover (decreased lifetime) than did the non-exercise-trained animals.

RECOMMENDATIONS


Recommended dietary allowances are designed for the maintenance of good nutrition in nearly all healthy people. They define intakes of iron for infants, children, and adult men and women and also consider additional iron needs during pregnancy and lactation. Given the data available and presented in this review, 3 groups appear to be at greatest risk for developing altered body iron: female athletes, distance runners, and vegetarian athletes. These groups are advised to pay particular attention to maintaining an adequate consumption of iron in their diets.

For all 3 groups, consumption of the recommended dietary allowance for iron, monitoring of dietary intake, and good nutritional counseling may preclude a negative iron balance and should be the first line of action in the prevention of iron deficiency. Indiscriminant pharmacologic intervention should be viewed as an undesirable means of achieving adequate iron intake because, at the least, it marginalizes the importance of promoting good nutritional habits in the athletic population. Among people who might be members of more than one at-risk group, female athletes who consume a vegetarian diet are likely to be at the greatest risk for a negative iron balance.

The use of iron supplements must be a judicious choice based not on the likelihood of anemia but, ideally, on hematologic evaluation. The use of complex preparations may provide less iron than anticipated and warrant a careful re-examination with regard to efficacy. Clinically utilized oral iron preparations contain ferrous sulfate, (hydrated) ferrous gluconate, or ferrous fumarate (42). These preparations contain 37–106 mg elemental Fe. Supplementation is not without consequence, however; the use of high doses of supplemental iron is often associated with gastrointestinal distress and constipation and a subsequent decline in patient compliance. In persons who are genetically predisposed to iron imbalance, hemochromatosis may develop after iron supplementation. Iron toxicity may develop even in persons who are not genetically predisposed to iron deficiency who ingest doses of ≥ 75 mg supplemental Fe. Other data illustrate the potential oxidative damage that can result from “free iron” released during exercise (43). Thus, minimal doses of supplemental iron are recommended to avoid possible accumulation of an iron burden (44).

In summary, it is clear that decreased hematocrit and hemoglobin impair the delivery of oxygen to tissues and lead to a reduced $\dot{V}O_{2\max}$. Supplementation of individuals to a normal hematocrit has verified the effects of hemoglobin iron on $\dot{V}O_{2\max}$. However, the effects of iron supplementation on the athletic performance of those with clinically low serum ferritin is less clear, although limited evidence seems to suggest improved endurance performance and a decreased reliance on glucose as an oxidative substrate. Whether such adaptations are beneficial for persons who have a subclinical but reduced serum ferritin concentration has not been established.

Future research is needed to clarify the relationship between marginal iron status and physical activity as many people throughout the world have both coexisting conditions. The issue of increased iron losses during exercise, especially in younger individuals, needs immediate attention because a negative iron balance could easily be generated. Finally, new observations of

increased oxidative damage with exercise and perhaps high doses of iron supplements warrant new investigations. 

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