

# Iron Supplementation in Athletes—First Do No Harm

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Although it generally does not improve performance, iron is often used by elite athletes. The physiologic changes induced by exercise can mimic iron deficiency and decrease hemoglobin and ferritin concentrations. Determination of serum transferrin receptor concentrations may identify true iron deficiency, which occurs particularly in young athletes. In contrast, increased iron stores in the body are a frequent finding in elite athletes who have used long-term iron supplementation. Elite runners have increased intestinal blood loss, but this usually can be compensated by enhanced absorption of dietary iron. The combination of exercise-induced hemolysis with enhanced intestinal blood loss in various endurance sports leads to severe abnormalities of routine tests, and extreme physical activity may be responsible for positive fecal occult blood determinations. Indiscriminate iron supplementation carries the risk of inducing hemochromatosis in individuals homozygous for the widespread C282Y allele of the HFE gene. This polymorphism is common and can be found in about 1% of individuals of Northern European descent; moreover, iron supplementation can modify the presentation of important underlying diseases such as celiac disease or colon carcinoma. In conclusion, iron supplements should be prescribed for athletes with iron-deficiency anemia and carefully monitored if given for prophylaxis; unless a therapeutic response occurs, investigations to establish the cause of iron deficiency should be initiated. *Nutrition* 2004;20:615–619. ©Elsevier Inc. 2004

**KEY WORDS:** iron, sports, hemochromatosis, supplementation, diet, athlete, iron deficiency

## INTRODUCTION

Iron as an emblem of strength and power originated in Greek mythology, where Hephestos was the god of fire and iron. Thus, over the centuries, iron therapy was tested in a variety of medical conditions and, at least in chlorosis (an archaic term for some causes of iron-deficiency anemia), it improved strength, power, and other manifestations of anemia.<sup>1</sup> We address the questions of whether iron is beneficial in athletes and whether there is a rationale for supplementation of diets with iron during training and for competitive events.

Improvement and maintenance of physical and mental fitness and maximal performance are the principal dietary requirements demanded by athletes. Supplementation of proteins, carbohydrates,<sup>2</sup> lipids,<sup>3</sup> vitamins,<sup>4</sup> and trace elements have been studied and reviewed for their effect on athletic performance in power and endurance sports.<sup>5–7</sup> The focus of this article is to summarize current knowledge of the adaptive changes in iron metabolism of athletes during training and to review available evidence for the effect of dietary iron supplementation on physical performance.

## ADAPTIVE CHANGES IN BLOOD INDUCED BY EXERCISE

A need for iron supplementation was proposed on the basis of observed changes in blood count and serum iron parameters during

periods of intense training. A transient decrease in blood hemoglobin concentrations occurs particularly at the start of training. This phenomenon has been described as sports anemia<sup>8</sup> and is most prominent in endurance athletes (“runner’s anemia” or “swimmer’s anemia”). However, the anemia is only temporary and long-term studies have shown that most athletes have normal hemoglobin concentrations at the completion of training or the competition season.<sup>9,10</sup> Furthermore, several studies have shown that low hemoglobin concentrations (<14 g/dL in men and <12 g/dL in women) occur in fewer than 8% of conditioned and elite athletes.<sup>11–13</sup> The adaptive changes responsible for the decreased hemoglobin concentration are complex. Training increases plasma volume and stimulates erythropoiesis, adaptive changes that are regulated by different mechanisms that show different temporal responses to the onset of physical activity.<sup>14,15</sup> The increase in plasma volume occurs more rapidly and to a greater extent than expansion of red cell mass and is mediated by osmotic and hormonal responses. The hormonal response depends on training intensity and conditioning. One study found that novice joggers will expand their plasma volume by 300 mL, whereas elite distance runners will expand their plasma volume by almost 1 L (~20%).<sup>14</sup> In contrast, the enhancement of red cell mass is less, increasing by 10% to 18%<sup>16–18</sup>; this effect is attributed principally to enhanced secretion of erythropoietin.

The combination of a rapid plasma expansion and a slow expansion of the red blood cell mass explains the transitory decrease in hematocrit, especially in the early stages of training; such changes are typical of those that occur after the midtrimester of pregnancy.<sup>19</sup> Plasma expansion decreases blood viscosity and thus improves blood flow in large vessels, whereas capillary blood flow is primarily determined by red blood cell deformability, which is greater in newly formed erythrocytes.

The changes observed in hematologic parameters induced by exercise are complex and cannot be attributed exclusively to

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hemodilution; in endurance athletes, alterations of erythrocyte morphology occur and may be recorded as macrocytic red indices. "Runner's macrocytosis" is a well-known hematologic phenomenon attributed to reactive reticulocytosis in response to hemolysis. Release of free hemoglobin into the circulation leads to hypohaptoglobinemia as a result of hepatic uptake of intact hemoglobin-haptoglobin complexes. The mechanisms responsible for such hemolysis in various athletes differ. The observed exercise-induced hypohaptoglobinemia in swimmers, oarsmen,<sup>20,21</sup> and weight lifters<sup>10</sup> cannot be entirely explained by "foot-strike hemolysis" as in runners, in whom peripheral trauma has been identified as the main cause for red cell fragmentation and hemolysis.<sup>22</sup> Investigation of red cell lifespan, by chromium-labeling studies, shows that erythrocyte turnover is accelerated in male but not in female runners. Chromium half-lives were  $25.4 \pm 3.6$  d compared with  $33.1 \pm 4.5$  d (mean  $\pm$  standard deviation;  $P < 0.01$ ) in male runners and sedentary control males, respectively. In females, the biological half-life of labeled red cells was calculated at  $28.3 \pm 4.6$  d in athletes compared with  $32.3 \pm 2.6$  d in sedentary women, a difference that was not statistically significant.<sup>21,23</sup>

Increased red cell production is also associated with an expansion of red bone marrow. Magnetic resonance imaging studies in athletes have shown that red marrow is expanded in marathon runners as indicated by increased T1 relaxation time. In sedentary adults, red marrow was found only in the axial skeleton; in 60% of marathon runners studied, it had expanded into the spine and was found in the distal femur following an axial-to-appendicular expansion pattern. However, T1 relaxation time did not correlate with red blood cell count, serum iron parameters, or maximum oxygen uptake ( $\dot{V}O_{2max}$ ).<sup>24,25</sup>

In summary, the hematologic changes induced by endurance exercise can be regarded as part of a series of adaptive processes that include hemodilution and stimulation of erythropoiesis. Other changes include reticulocytosis caused by hemolysis, which may be responsible for macrocytosis, associated with other changes in red cell morphology. If hemoglobin concentrations are artificially increased by induced polycythemia, i.e., transfusion of blood or administration of recombinant human erythropoietin, and improved performance has been demonstrated in endurance athletes.<sup>26,27</sup> These observations thus prompt the following questions: (1) Is iron availability the limiting factor for hemoglobin production during physical exercise? (2) Can iron supplementation improve athletic performance?

## ADAPTIVE CHANGES OF IRON METABOLISM DURING EXERCISE

The decline in hemoglobin concentrations reported during early stages of endurance training is accomplished by decreased concentrations of the serum iron parameter ferritin. Serum concentrations of ferritin serve as a surrogate marker for body iron stores, but ferritin expression and its appearance in serum are influenced by other factors. Ferritin is an acute-phase reactant and its serum concentration can be increased by liver disease, infections, and other inflammatory conditions, malignant diseases (especially Hodgkin's disease), renal failure, cardiovascular diseases, high alcohol consumption, and advancing age. Thus, serum ferritin concentrations can not invariably be equated to iron stores.<sup>28</sup> Serum ferritin concentrations decrease during training, and it has been concluded that this reflects an induction of iron deficiency after physical activity. However, iron stores in the body can more reliably be determined by measuring the amount of iron removed during repeated phlebotomies until anemia develops and then subtracting the amount of dietary iron absorbed during phlebotomy. This method is unsuitable for the repeated determination of iron stores in athletes before and after training. Alternatively, corporeal iron stores or red blood cell progenitor demand for iron

can be evaluated by measuring certain surrogate markers other than serum ferritin, namely serum transferrin receptor (sTfR), red blood cell protoporphyrin, or stainable iron in bone marrow (bone marrow hemosiderin).<sup>29</sup>

The sTfR more accurately reflects the demands of bone marrow for iron, i.e., high sTfR concentrations indicate iron-deficient erythropoiesis. Further, day-to-day variability is greater for ferritin (13% to 75%) than for sTfR (4% to 16%).<sup>30</sup> The sTfR and especially the sTfR/log(ferritin) index is less variable and may more precisely reflect the iron status of the athlete.<sup>31</sup> However, the influence of physical activity on sTfR expression has been subject to limited investigation. In accordance with previous studies, Schumacher et al. found that ferritin concentrations declined after exercise tests in 39 individuals; in contrast, sTfR was unaffected by a 45-min constant-speed running test at 70%  $\dot{V}O_{2max}$  and decreased only during incremental exercise challenges to the point of exhaustion. Taking the different extracellular fluid shifts into account (hemoconcentration during the exhaustive test and hemodilution during the aerobic test), the investigators concluded that sTfR more reliably reflects exercise-induced changes in iron metabolism than does serum ferritin, which is also influenced by factors other than iron stores.<sup>32</sup>

The hypothesis that iron availability is not limiting for red blood cell production despite reduced concentrations of serum ferritin during exercise is further supported by the observation that free erythrocyte protoporphyrin concentrations remain unchanged during intensive training.<sup>33</sup> The final step of heme biosynthesis is the insertion of ferrous iron into protoporphyrin and depends critically on the availability of iron as a substrate; the first step of heme biosynthesis, the formation of 5-aminolaevulinate, is also subject to regulation by iron. Thus, no operational limitation of heme biosynthesis by the availability of iron in the erythrocyte can be demonstrated in such athletes. Experiments conducted in vitro have suggested that expression and activity of erythroid aminolaevulinate synthetase, which catalyzes the first rate-limiting step of heme biosynthesis, can be induced by iron.<sup>34,35</sup> However, this stimulatory effect of iron cannot be observed in vivo, which is surprising because quantification of bone marrow iron stores by cytological observation has shown that bone marrow hemosiderin is less than expected in middle- and long-distance runners, even though quantitative determination did not meet diagnostic requirements for iron deficiency.<sup>36</sup>

Although serum ferritin concentrations in elite athletes are usually low, frank iron deficiency is unusual; nevertheless, obligatory daily iron losses are often increased, but this is usually compensated by enhanced absorption of dietary iron. Gastrointestinal bleeding occurs predominantly in long-distance runners and overt melena or even hematemesis has been reported.<sup>37</sup> Studies conducted in clinically asymptomatic runners showed that fecal occult bleeding occurred in up to 83% after a competition.<sup>38</sup> Quantification of intestinal iron losses using radiolabeled red cells showed that blood loss increased from the normal baseline of less than 1.5 mL/d to 4.9–6.6 mL/d during intensive training periods.<sup>39</sup> The mechanisms for occult or overt intestinal bleeding include intestinal trauma and reduced splanchnic perfusion during exercise,<sup>40</sup> which cannot be prevented by dietary supplementation of L-arginine.<sup>41</sup> Gastrointestinal bleeding is more severe in runners who have taken non-steroidal anti-inflammatory drugs.<sup>42</sup> Excess bleeding cannot be prevented by the administration of the H<sub>2</sub> blocker cimetidine, which suggests that acid does not mediate gastrointestinal injury during running.<sup>43</sup> Iron losses via the urinary tract are negligible in most endurance athletes but may result from bladder trauma; renal losses after exercise are uncommon even after traumatic intravascular hemolysis,<sup>44</sup> which is more frequent in contact sports.<sup>45,46</sup> Iron is also lost in sweat, but its quantification is difficult, and studies in which contamination of sweat by exfoliated epithelia was minimized have shown that sweat losses of iron are very small even in hot environments ( $0.08 \text{ mg} \cdot \text{m}^{-2} \cdot \text{h}^{-1}$ ).<sup>47</sup>

Non-invasive estimation of hepatic iron stores using radioactive iron isotopes showed significantly lower but normal liver iron concentrations in runners.<sup>39</sup> It was also postulated that a negative iron balance could result from increased losses and decreased intestinal absorption of non-hemoglobin iron during endurance training. In one study, mean absorption of a standard test dose of ferrous sulfate was 16.4% in eight long-distance runners as compared with 30% in eight male blood donors.<sup>48</sup> However, in 23 male runners, intestinal iron absorption was increased compared with a control population.<sup>39</sup> Such an increased absorption of iron by the intestine is plausible considering the decreased calculated body iron half-life to 1000 d in runners compared with 2100 d in control sedentary men and 1300 d in women.<sup>48</sup> The difference reached statistical significance in males only.

In summary, endurance sports cause hyperferritinemia, which primarily reflects changes in plasma volume and is only partly caused by enhanced demands for iron in response to increased iron losses. There is no evidence of iron-deficient erythropoiesis or heme biosynthesis, and more specific indicators of iron-deficient erythropoiesis are largely unaltered in endurance athletes.

Apart from its important function as a constituent of hemoglobin, iron is a component of many other enzymes, e.g., mitochondrial complex III of the respiratory electron transport chain, which undergoes adaptive changes during exercise in animals.<sup>49</sup> Thus, it was postulated that iron deficiency could affect performance by mechanisms other than those that impair hemoglobin production and oxygen delivery to the tissues. Evidence indicating that tissue iron deficiency could affect performance was published by Finch et al. who showed that iron-deficient rats had markedly impaired treadmill running times, although their anemia had been corrected by transfusion.<sup>50</sup> However, these short-term experiments represent a series of non-physiologic interventions, and similar results could not be reproduced in humans. In one such study, iron deficiency was induced in healthy animals by repeated phlebotomies over 9 weeks. After correcting the anemia by retransfusion, the mean endurance running time in the iron-deficient group was 51.9 min compared with 49.1 min in the control group, suggesting no effect of tissue iron deficiency on physical performance, at least in the short term.<sup>51</sup> In contrast, long-term iron deficiency can result in decreased work performance even in non-anemic subjects. Studies conducted in developing countries have associated long-term iron deficiency with longer treadmill times. Although iron supplements ameliorate performance in most long-term iron-deficient populations, they are also associated with a higher incidence of malaria infections.<sup>52</sup>

## RISK FACTORS FOR TRUE IRON DEFICIENCY IN ATHLETES

Endurance athletes are particularly prone to iron deficiency. In the general population, young subjects, adolescents, and women are at risk.<sup>53</sup> The prevalence of iron deficiency in elite athletes is lower than in young individuals involved in intensive physical training programs.<sup>54</sup> This difference is likely biased by the current widespread and uncontrolled use of iron supplementation in such athletes.<sup>55</sup> Other risk factors for iron-deficiency anemia in young athletes are *Helicobacter pylori* infection,<sup>56</sup> vegetarian diet, and multiple pregnancies.<sup>57</sup> The prevalence of anemia in prepubertal boys undergoing training for a national swimming competition in Poland was as high as 9%, and 15% of those children who had completed training had indications of latent iron deficiency.<sup>54</sup> In another study, 3 of 23 (13%) female adolescent volleyball players had iron-deficiency anemia.<sup>58</sup> The overall prevalence of iron deficiency in young athletes is difficult to assess because interpretation of many studies is hampered by variable definitions of iron deficiency and many reports include ferritin levels, which, as discussed above, are poor indicators of iron status in athletes. Even

values of serum ferritin used to define iron deficiency have varied between 12 and 40  $\mu\text{g/L}$ .<sup>59</sup>

## IRON SUPPLEMENTATION

In light of the multifactorial effects of athletic activity on iron metabolism and its surrogate markers and the diversity of athletes as a population group for study, it is very difficult to define those athletes who will benefit from iron supplementation. In most reported studies, iron supplementation shows no beneficial effect on athletic performance. Further, low serum iron parameters immediately after competition do not correlate with performance.<sup>60-62</sup> In controlled trials in which a beneficial effect of iron supplementation was shown, only athletes with iron-deficiency anemia or untrained individuals with low serum ferritin were studied. When administered to iron-replete athletes or athletes with low serum ferritin, iron was repeatedly shown to have no objective effect on performance<sup>61-65</sup>; however, in one controlled study, it improved the subjective assessment of performance in female athletes.<sup>64</sup> In another study, 40 male elite athletes with low serum ferritin levels and normal hemoglobin concentrations showed an increase in  $\dot{V}O_{2\text{max}}$  after iron supplementation, but red blood cell volume and lactate threshold remained unchanged in the iron-treated and placebo-treated groups.<sup>66</sup> These results were confirmed in a study of 41 iron-deficient females who were not anemic (ferritin < 16  $\mu\text{g/L}$ , hemoglobin > 12 g/dL) and in whom performance and maximal oxygen uptake increased only in the group in which iron was supplemented but not in the placebo group.<sup>67</sup> In contrast, the effect of iron supplementation in 18 female iron-depleted runners without anemia was studied in a controlled trial; although serum iron parameters improved, no positive effect of iron on  $\dot{V}O_{2\text{max}}$  could be found.<sup>63</sup> Together, the published evidence restricts the indication for oral or even parenteral iron supplementation<sup>65</sup> to athletes with established iron-deficiency anemia. In conclusion, in light of the available (and limited) information, iron deficiency without anemia in athletes remains a questionable indication for therapeutic iron supplementation.

## RISKS OF UNCONTROLLED IRON SUPPLEMENTATION

The current practice of iron supplementation in elite athletes appears to be largely uncontrolled. Deugnier et al.<sup>55</sup> found that one-third of French elite road cyclists had hyperferritinemia. Twenty-seven probands of 198 athletes with elevated serum ferritin underwent magnetic resonance imaging or liver biopsy for quantification of hepatic iron. The correlation of serum ferritin to hepatic iron concentration was statistically significant. Eighty-eight percent of the studied athletes had been supplemented with iron, and the median cumulative dose was 25.5 g (range 1.4–336 g). Subsequent studies confirmed that elite athletes frequently have iron intakes above the recommended daily allowance.<sup>55,68,69</sup> Increased body iron stores have been discussed as an independent risk factor for liver malignoma<sup>70,71</sup> and have been associated with impaired immune effector functions.<sup>72</sup> Increased dietary iron intake is also a risk factor for developing hemochromatosis in subjects homozygous for the C282Y allele of the HFE gene. About 10% of the population of Northern European ancestry is heterozygous for this polymorphism. However, the prevalence of hereditary hemochromatosis has been estimated at 1:400, which is lower than the calculated and observed frequency of C282Y homozygosity.<sup>73</sup> HFE gene polymorphisms have incomplete penetrance, and the factors that cause hemochromatosis in genetically predisposed C282Y homozygotes include alcohol<sup>74</sup> and dietary iron intake,<sup>75</sup> although liver iron concentration in a cohort of 27 elite cyclists did not differ significantly among HFE wild-type cyclists. Athletes heterozygous for one of the HFE polymorphisms showed

a trend toward higher liver iron concentration. Further, mutations in at least one other gene appeared to determine the severity of iron overload.<sup>55</sup> The complex genetics of hemochromatosis and its clinical variants limit simple testing and identification of athletes at risk of iron overload. The high prevalence of C282Y homozygotes (1:100) in the general population has to be taken into account when iron supplementation in athletes is considered. Further, increased iron stores are a risk factor for the development of diabetes.<sup>76</sup>

However, iron deficiency is often a valuable sign of an underlying disease, and uncontrolled supplementation of iron could obscure or delay clinical presentation. Diagnosis of latent celiac disease, uterine abnormalities, or occult gastrointestinal bleeding might be overlooked when iron is supplemented without prior investigation for an underlying disorder.<sup>77,78</sup> Menstrual blood losses in women are very difficult to quantify, and iron-deficiency anemia is all too often attributed to vague estimates of perceived losses without thorough quantitative evaluation. Hallberg et al. estimated that (given an average daily iron intake  $\leq 10$  mg for most women), if blood losses exceed 40 to 60 mL each period, a negative iron balance will result.<sup>79</sup>

## RECOMMENDATIONS

There is no evidence that iron supplementation increases athletic performance, except in individuals in whom iron deficiency is established. In athletes with low serum ferritin concentrations without anemia, iron supplementation might be useful; moreover, determination of sTfR or red cell-free protoporphyrin concentrations may identify those in whom iron administration is likely to be beneficial. Serum ferritin concentrations should be monitored in conditioned athletes, and physiologic decreases in serum ferritin during the early stages of training should be taken into account when individuals are examined and before any decision to give iron is made. Exercise-induced hyperferritinemia is most prominent in endurance athletes, especially runners. Unlike in other sports, runners experience increased loss of blood from the gastrointestinal tract; this loss may amount to several milliliters and cause a negative iron balance. In the young and adolescent populations, the prevalence of iron deficiency is higher; in addition, vegetarian diet, female sex, and *H. pylori* infection are important risk factors for iron deficiency. The prevalence of iron-deficiency anemia in prepubertal athletes is up to 13%, and screening for anemia in this group of individuals is recommended. Because most studies have shown no beneficial effect of iron supplementation on performance, the uncontrolled use of iron should be avoided. It has been proposed that some athletes take iron supplements to optimize the effect of recombinant human erythropoietin, a practice that remains unethical and dangerous. Anecdotal reports that iron supplementation reduces or prevents leg cramps in cyclists cannot be taken as the basis for iron supplementation.<sup>55</sup>

Because athletes are more likely to take medications and supplements even if the benefit is only minor or even unproven, we submit that, despite the challenging demands for performance-enhancing agents in relation to iron treatment, medical advice should remain based on the best available evidence. In the case of iron supplementation, we believe that the current evidence supports the prescription of iron administration only to individuals with unequivocal iron deficiency. Hyperferritinemia is an unusual finding in elite athletes, and we recommend that the current widespread and indiscriminate use of iron supplementation should be restricted to the accepted clinical indication of iron deficiency. Underlying causes of iron deficiency should be excluded before iron deficiency can be safely attributed to the consequences of physical activity.

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## REFERENCES

1. Beutler E. History of iron in medicine. *Blood Cells Mol Dis* 2002;29:297
2. Miller SL, et al. Metabolic response to provision of mixed protein-carbohydrate supplementation during endurance exercise. *Int J Sport Nutr Exerc Metab* 2002; 12:384
3. Clavel S, et al. Effect of endurance training and/or fish oil supplemented diet on cytoplasmic fatty acid binding protein in rat skeletal muscles and heart. *Eur J Appl Physiol* 2002;87:193
4. Dawson B, et al. Effect of Vitamin C and E supplementation on biochemical and ultrastructural indices of muscle damage after a 21 km run. *Int J Sports Med* 2002;23:10
5. Schwenk TL, Costley CD. When food becomes a drug: nonanabolic nutritional supplement use in athletes. *Am J Sports Med* 2002;30:907
6. Volek JS. Strength nutrition. *Curr Sports Med Rep* 2003;2:189
7. Lawrence ME, Kirby DF. Nutrition and sports supplements: fact or fiction. *J Clin Gastroenterol* 2002;35:299
8. Yoshimura H. Anaemia during physical training. *Nutr Rev* 1970;28:251
9. Rushall BS, Busch JD. Hematological responses to training in elite swimmers. *Can J Appl Sport Sci* 1980;5:164
10. Schobersberger W, et al. Consequences of 6 weeks of strength training on red cell O<sub>2</sub> transport and iron status. *Eur J Appl Physiol Occup Physiol* 1990;60:163
11. de Wijn JF, et al. Haemoglobin, packed cell volume, serum iron and iron binding capacity of selected athletes during training. *J Sports Med Phys Fitness* 1971; 11:42
12. Eliakim A, Nemet D, Constantini N. Screening blood tests in members of the Israeli National Olympic team. *J Sports Med Phys Fitness* 2002;42:250
13. Clement DB, et al. Iron status in Winter Olympic sports. *J Sports Sci* 1987;5:261
14. Selby GB, Eichner ER. Hematocrit, and performance, the effect of endurance training on blood volume. *Semin Hematol* 1994;31:122
15. Porter DL, Goldberg MA. Physiology of erythropoietin production. *Semin Hematol* 1994;31:112
16. Brotherhood J, Brozovic B, Pugh LG. Haematological status of middle- and long-distance runners. *Clin Sci Mol Med* 1975;48:139
17. Dill DB, Soholt LF, Morris JD, Jr. Wheel running of kangaroo rats, *Dipodomys merriami*, as related to food deprivation and body composition. *J Appl Physiol* 1978;44:17
18. Convertino VA. Blood volume: its adaptation to endurance training. *Med Sci Sports Exerc* 1991;23:1338
19. Cook JD. The effect of endurance training on iron metabolism. *Semin Hematol* 1994;31:146
20. Selby GB, Eichner ER. Endurance swimming, intravascular hemolysis, anemia, and iron depletion. New perspective on athlete's anemia. *Am J Med* 1986;81:791
21. Dufaux B, et al. Serum ferritin, transferrin, haptoglobin, and iron in middle- and long-distance runners, elite rowers, and professional racing cyclists. *Int J Sports Med* 1981;2:43
22. Telford RD, et al. Footstrike is the major cause of hemolysis during running. *J Appl Physiol* 2003;94:38
23. Weight LM, Byrne MJ, Jacobs P. Haemolytic effects of exercise. *Clin Sci (Lond)* 1991;81:147
24. Shellock FG, et al. Hematopoietic bone marrow hyperplasia: high prevalence on MR images of the knee in asymptomatic marathon runners. *AJR* 1992;158:335
25. Caldemeyer KS, et al. Hematopoietic bone marrow hyperplasia: correlation of spinal MR findings, hematologic parameters, and bone mineral density in endurance athletes. *Radiology* 1996;198:503
26. Brien AJ, Simon TL. The effects of red blood cell infusion on 10-km race time. *JAMA* 1987;257:2761
27. Adamson JW, Vapnek D. Recombinant erythropoietin to improve athletic performance. *N Engl J Med* 1991;324:698
28. Hallberg L, Hulthen L. High serum ferritin is not identical to high iron stores. *Am J Clin Nutr* 2003;78:1225
29. Cook JD. Defining optimal body iron. *Proc Nutr Soc* 1999;58:489
30. Malczewska J, et al. The assessment of frequency of iron deficiency in athletes from the transferrin receptor-ferritin index. *Int J Sport Nutr Exerc Metab* 2001; 11:42
31. Stupnicki R, et al. Day to day variability in the transferrin receptor/ferritin index in female athletes. *Br J Sports Med* 2003;37:267
32. Schumacher YO, et al. Effects of exercise on soluble transferrin receptor and other variables of the iron status. *Br J Sports Med* 2002;36:195

33. Spodaryk K. Haematological and iron-related parameters of male endurance and strength trained athletes. *Eur J Appl Physiol Occup Physiol* 1993;67:66
34. Smith SJ, Cox TM. Translational control of erythroid delta-aminolevulinic synthase in immature human erythroid cells by heme. *Cell Mol Biol (Noisy-le-grand)* 1997;43:103
35. Zoller H, Decristoforo C, Weiss G. Erythroid 5-aminolevulinic synthase, ferrochelatase and DMT1 expression in erythroid progenitors: differential pathways for erythropoietin and iron-dependent regulation. *Br J Haematol* 2002;118:619
36. Magnusson B, et al. Iron metabolism and "sports anemia." II. A hematological comparison of elite runners and control subjects. *Acta Med Scand* 1984;216:157
37. Scobie BA. Recurrent gut bleeding in five long-distance runners. *N Z Med J* 1985;98(790):966
38. Stewart JG, et al. Gastrointestinal blood loss and anemia in runners. *Ann Intern Med* 1984;100:843
39. Nachtigall D, et al. Iron deficiency in distance runners. A reinvestigation using Fe-labelling and non-invasive liver iron quantification. *Int J Sports Med* 1996;17:473
40. Kehl O, et al. [Mesenteric anemia as a cause of jogging anemia?] *Schweiz Med Wochenschr* 1986;116:974
41. Buchman AL, et al. The effect of arginine or glycine supplementation on gastrointestinal function, muscle injury, serum amino acid concentrations and performance during a marathon run. *Int J Sports Med* 1999;20:315
42. Rudzki SJ, Hazard H, Collinson D. Gastrointestinal blood loss in triathletes: its etiology and relationship to sports anaemia. *Aust J Sci Med Sport* 1995;27:3
43. Moses FM, et al. Effect of cimetidine on marathon-associated gastrointestinal symptoms and bleeding. *Dig Dis Sci* 1991;36:1390
44. McCance RA, Widdowson EM. Absorption and excretion of iron. *Lancet* 1937;ii:680
45. Biancotti PP, et al. Hematological status in a group of male athletes of different sports. *J Sports Med Phys Fitness* 1992;32:70
46. Babic Z, et al. Occult gastrointestinal bleeding in rugby player. *J Sports Med Phys Fitness* 2001;41:399
47. Waller MF, Haymes EM. The effects of heat and exercise on sweat iron loss. *Med Sci Sports Exerc* 1996;28:197
48. Ehn L, Carlmark B, Hoglund S. Iron status in athletes involved in intense physical activity. *Med Sci Sports Exerc* 1980;12:61
49. Hood DA, Kelton R, Nishio ML. Mitochondrial adaptations to chronic muscle use: effect of iron deficiency. *Comp Biochem Physiol Comp Physiol* 1992;101:597
50. Finch CA, et al. Iron deficiency in the rat. Physiological and biochemical studies of muscle dysfunction. *J Clin Invest* 1976;58:447
51. Celsing F, et al. Effect of long-term anemia and retransfusion on central circulation during exercise. *J Appl Physiol* 1986;61:1358
52. Bates CJ, Powers HJ, Thurnham DI. Vitamins, iron, and physical work. *Lancet* 1989;2(8658):313
53. Beard J, Tobin B. Iron status and exercise. *Am J Clin Nutr* 2000;72(suppl):594S
54. Spodaryk K. Iron metabolism in boys involved in intensive physical training. *Physiol Behav* 2002;75:201
55. Deugnier Y, et al. Increased body iron stores in elite road cyclists. *Med Sci Sports Exerc* 2002;34:876
56. Choe YH, et al. Helicobacter pylori-associated iron-deficiency anemia in adolescent female athletes. *J Pediatr* 2001;139:100
57. Snyder AC, Dvorak LL, Roepke JB. Influence of dietary iron source on measures of iron status among female runners. *Med Sci Sports Exerc* 1989;21:7
58. Beals KA. Eating behaviors, nutritional status, and menstrual function in elite female adolescent volleyball players. *J Am Diet Assoc* 2002;102:1293
59. Newhouse IJ, Clement DB. Iron status in athletes. An update. *Sports Med* 1988;5:337
60. Rogers G, et al. The response of runners to arduous triathlon competition. *Eur J Appl Physiol Occup Physiol* 1986;55:405
61. Powell PD, Tucker A. Iron supplementation and running performance in female cross-country runners. *Int J Sports Med* 1991;12:462
62. Matter M, et al. The effect of iron and folate therapy on maximal exercise performance in female marathon runners with iron and folate deficiency. *Clin Sci (Lond)* 1987;72:415
63. Klingshirn LA, et al. Effect of iron supplementation on endurance capacity in iron-depleted female runners. *Med Sci Sports Exerc* 1992;24:819
64. Risser WL, et al. Iron deficiency in female athletes: its prevalence and impact on performance. *Med Sci Sports Exerc* 1988;20:116
65. Blee T, et al. The effect of intramuscular iron injections on serum ferritin levels and physical performance in elite netballers. *J Sci Med Sport* 1999;2:311
66. Friedmann B, et al. Effects of iron repletion on blood volume and performance capacity in young athletes. *Med Sci Sports Exerc* 2001;33:741
67. Hinton PS, et al. Iron supplementation improves endurance after training in iron-depleted, nonanemic women. *J Appl Physiol* 2000;88:1103
68. Leblanc J, et al. Nutritional intake of French soccer players at the Clairefontaine training center. *Int J Sport Nutr Exerc Metab* 2002;12:268
69. Kujala UM, Sarna S, Kaprio J. Use of medications and dietary supplements in later years among male former top-level athletes. *Arch Intern Med* 2003;163:1064
70. Grando-Lemaire V, et al. Hepatocellular carcinoma without cirrhosis in the West: epidemiological factors and histopathology of the non-tumorous liver. *Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. J Hepatol* 1999;31:508
71. Stevens RG, et al. Body iron stores and the risk of cancer. *N Engl J Med* 1988;319:1047
72. Weiss G, et al. Immune response and iron metabolism. *Br J Anaesth* 1998;81(suppl 1):6
73. Asberg A, et al. Screening for hemochromatosis: high prevalence and low morbidity in an unselected population of 65,238 persons. *Scand J Gastroenterol* 2001;36:1108
74. Fletcher LM, Powell LW. Hemochromatosis and alcoholic liver disease. *Alcohol* 2003;30:131
75. Rossi E, et al. Effect of hemochromatosis genotype and lifestyle factors on iron and red cell indices in a community population. *Clin Chem* 2001;47:202
76. Lee DH, Folsom AR, Jacobs DR Jr. Dietary iron intake and type 2 diabetes incidence in postmenopausal women: the Iowa Women's Health Study. *Diabetologia* 2004(in press)
77. Sanders DS, et al. Changing face of adult coeliac disease: experience of a single university hospital in South Yorkshire. *Postgrad Med J* 2002;78:31
78. Acher PL, et al. Iron-deficiency anaemia and delay in the diagnosis of colorectal cancer. *Colorectal Dis* 2003;5:145
79. Hallberg L, et al. Menstrual blood loss and iron deficiency. *Acta Med Scand* 1966;180:639