Iron Deficiency Anemia

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INTRODUCTION

Questions continue to arise on iron deficiency — with or without anemia — and its impact on sports performance. Recent articles have stirred the pot. An article on treating chronic heart failure with iron defines iron deficiency in a strange new way and has a puzzling result on iron therapy and performance (1). Another article (8) — on “athletic-induced iron deficiency” — led to this question: Do hard-training triathletes need parenteral iron? And a third article renews an old debate by concluding that tissue iron deficiency without anemia impairs aerobic training (2).

To be sure, iron deficiency anemia in female athletes is a common problem. The prevalence of iron deficiency anemia is estimated to be 3%—5% in women in the United States, and iron deficiency without anemia is estimated to affect 12%—16% of premenopausal adult women (11). Some studies suggest that iron deficiency anemia is more common in athletes (11), but this is controversial (3). This article addresses questions and controversies. But first, a pearl about the presenting symptom of mild anemia.

PEARL: FATIGUE HAS MANY FACES

Just as we can feel different moods, fatigue can have different faces. Depressed patients feel fatigued on arising to face the day. Athletes recovering from infectious mononucleosis or viral hepatitis feel strong in the morning but tire later in the day and need a nap. Patients with fibromyalgia or chronic fatigue syndrome are tired all day or feel exhausted from minimal exercise.

The fatigue of anemia has its own face. Athletes with mild or moderate anemia feel normal at rest and fatigue only with top exertion. In fact, exercise helps distinguish causes of fatigue. Especially with mild anemia, strenuous exercise can be the only unmasker, as in three student-athletes — all diagnostic problems initially — who lost stamina because of iron deficiency anemia (4).

Along with loss of stamina at top exertion, another clue to the presence of iron deficiency anemia can be the call of the magpie.

PEARL: THE CALL OF THE MAGPIE

Pica, the compulsive ingestion of nonnutritive substances, can be a clue to iron deficiency anemia. The word pica comes from Latin for magpie (genus Pica), a bird that picks up and packs away diverse objects. Pica may occur in up to half of iron deficient patients. The range of pica is wide, from clay, dirt, or starch to crunchy foods like pickles, celery, carrots, or pretzels, to toothpicks, match boxes, or cigarette ash. One article lists 68 forms of pica (6).

Pagophagia or ice chewing, however, is the most common pica from iron deficiency anemia. Especially in female athletes who may be losing stamina, ask tactfully about ice chewing. They tend to prefer shaved or chipped ice, but some eat ice cubes. When the underlying iron deficiency anemia is treated, the ice craving stops. One woman ate 80 ice cubes a day for 5 yr, but stopped after taking iron pills for only 2 wk.

The biologic mechanism for pagophagia remains unclear, but a mutant Drosophila fly exhibits pica-like behavior — thought to be from a brain abnormality — and is cured by iron (7). This raises haunting questions about iron and the human brain — and about evolution.

TREATING HEART FAILURE WITH IRON: STRANGE NEW WORLD

A recent clinical trial explored intravenous iron therapy for patients with iron deficiency and chronic heart failure from left ventricular dysfunction (1). The definition of iron deficiency was strange: serum ferritin <100 ugL⁻¹ or between 100 and 299 ugL⁻¹ when transferrin saturation was <20%. Mean ferritin was 53 ugL⁻¹ in the iron group and 60 ugL⁻¹ in the placebo group. If this is iron deficiency, I'll
eat my hat. In any case, the authors found that intravenous iron improved quality of life and submaximal exercise capacity (distance walked in 6 min). But improvements beyond placebo were small, and why anemic patients did not improve more than those without anemia is puzzling. This study mainly serves to reflect the quest for novel therapy for heart failure and to renew the age-old debate as to whether iron deficiency without anemia impairs aerobic or athletic performance.

PEARL: ANEMIA CAN BE RELATIVE

The debate on whether nonanemic iron deficiency impairs athletic performance has been well reviewed (9). Recent articles continue the debate by finding that iron therapy — in the face of iron deficiency without anemia — enhances aerobic training (as gauged by a 15-km time trial) and improves energetic efficiency during submaximal exercise (2,5). But the problem with these studies, as with earlier studies like them, is that the iron-treated group ends up with a slightly higher hemoglobin level than the placebo group. So what is being studied is not “nonanemia” but relative anemia. No magic cutoff defines anemia — for example, a female athlete with a normal hemoglobin level of 14 g dL⁻¹ is anemic at 13 g dL⁻¹ and will feel that her stamina is sapped (3).

THE HEPcidIN HYPOTHESIS

Finally, hepcidin, an iron-regulatory protein, is a new player. In a pilot study, urine hepcidin levels rose for a day or so in 8 of 14 females after a marathon (10). It was hypothesized that elevated hepcidin levels in endurance athletes can cause iron deficiency (8,10). This seems to be a tempest in a teapot. Hepcidin is released from the liver in the acute-phase response that can follow hard training or inflammation. Hepcidin decreases serum iron level by inhibiting the exit of iron from duodenal enterocytes and from macrophages. So hepcidin modulates the low serum iron of the anemia of chronic disease. But a blip in hepcidin after a hard training bout or a long race would imply only a fleeting and minor block to entry of iron into the bloodstream — not a cause of iron deficiency in athletes. This novel area needs more research, but endurance athletes should not be given parenteral iron based on the hepcidin hypothesis.

References
1. Anker SD, Colet JC, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N. Engl. J. Med. 2009; 361:2436–48.
2. Brownlie T, Utermohlen V, Hinton PS, Haas JD. Tissue iron deficiency without anemia impairs adaptation in endurance capacity after aerobic training in previously untrained women. Am. J. Clin. Nutr. 2004; 79: 437–43.
3. Eichner ER. Sports medicine pearls and pitfalls: anemia in athletes. Curr. Sports Med. Rep. 2007; 6:2–3.
4. Eichner ER, Scott WA. Exercise as a disease detector. Phys. Sportsmed. 1998; 26:41–52.
5. Hinton PS, Sinclair LM. Iron supplementation maintains ventilatory threshold and improves energetic efficiency in iron-deficient nonanemic athletes. Eur. J. Clin. Nutr. 2007; 61:30–9.
6. Moore DF, Sears DA. Pica, iron deficiency, and the medical history. Am. J. Med. 1994; 97:390–3.
7. Orgad S, Nelson H, Segal D, Nelson N. Metal ions suppress the abnormal taste behavior of the Drosophila mutant malvolio. J. Exp. Biol. 1998; 201:115–20.
8. Peeling P, Dawson B, Goodman C, et al. Athletic induced iron deficiency: new insights into the role of inflammation, cytokines and hormones. Eur. J. Appl. Physiol. 2008; 103:381–91.
9. Rodenberg RE, Gustafson S. Iron as an ergogenic aid: ironclad evidence? Curr. Sports Med. Rep. 2007; 6:258–64.
10. Roecker L, Meier-Buttermilch R, Brechtel L, et al. Iron-regulatory protein hepcidin is increased in female athletes after a marathon. Eur. J. Appl. Physiol. 2005; 95:569–71.
11. Sinclair LM, Hinton PS. Prevalence of iron deficiency with and without anaemia in recreationally active men and women. J. Am. Diet. Assoc. 2005; 105:975–8.