CHAPTER 10

Iron depletion in athletes

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10.1 Introduction

Athletes, in particular females and adolescents, are at risk of depleting iron stores. If untreated, iron depletion can ultimately develop into anaemia, which severely affects training capacity. Recent findings suggest that maintaining an optimum iron status within the cells and tissues is far more important for athletes than has previously been realised. Even a mild shortfall in tissue iron status appears not only to reduce maximum oxygen uptake and aerobic efficiency, but also reduce the body's endurance capacity. Any athlete involved in regular high intensity physical activity has a higher requirement and turnover of iron and can quickly deplete iron.

Figure 5.2 Mean group differences between actual and predicted resting metabolic rate (RMR) for 24 male (a) and 13 female (b) highly-trained endurance athletes (adapted from Thompson & Manore 1996)

* Indicates values were significantly different from actual measured RMR ($P < 0.05$). HB = Harris and Benedict equation (1919); Mifflin = Mifflin et al. equation (1990); Owen 1 = Owen et al. equation (1986) for active and non-active women; Owen 2 = Owen et al. equation (1987) for men using either body weight (WT) or lean body mass (LBM); and Cunningham = Cunningham (1980) equation. Equations are listed in Table 5.1

Although iron is widely distributed in foods, inappropriate food combinations can compromise its absorption. High-carbohydrate diets recommended for athletes may be high in compounds that inhibit iron absorption. While diet contributes to iron depletion in athletes, physiological and medical factors also play a role. Dietary strategies to help prevent iron depletion should be implemented early in the training program in high-risk individuals. Early detection of depleted iron stores and dietary intervention is warranted. Recovery from depleted or exhausted iron stores is slow and can take months to reach previous condition and training levels.

10.2 Stages of iron depletion

Several commonly used biochemical (or haematological) indicators are used to categorise iron status in the general population,. As iron stores are depleted progressively, iron-containing compounds in the body (for example ferritin, haemoglobin, transferrin, myoglobin, red blood cells) also become depleted, but not all compounds are affected at the same time. When iron stores are exhausted, the functional iron compartment then becomes affected (Suominen et al. 1998).

Although iron depletion is a continuous process, traditionally three stages of iron deficiency have been identified. An additional category specific to athletes, called dilutional pseudoanaemia (or sports anaemia), has been used to describe a unique physiological response to training in an athletic population. Table 10.1 summarises the adult population reference values for haematological indicators of iron status in each stage of iron depletion, including iron overload. Cut-off values for determining the iron status in children and adolescents are published elsewhere (Looker et al. 1997). Interpreting these indicators in athletes is described in detail in section 10.8.1.

Table 10.1 Population cut-offs for haematological indicators commonly used to evaluate iron status in clinical practice

Stage of iron deficiency	Haematological indicators	Deficiency/overload state
Stage 1		
Depleted iron stores	Stainable iron in the bone marrow	Absent
	Total iron binding capacity	> 400 µg/dL
	Serum ferritin	< 12 µg/L (> 15 years old)
Stage 2		
Early functional iron deficiency	Transferrin saturation	< 16% (> 10 years)
	Serum transferrin receptor	> 8.5 mg/L
Stage 3		
Iron deficiency anaemia (IDA)	Haemoglobin	< 130 (males, > 15 years old) < 120 (females, > 15 years old)
	Mean cell volume	< 80 fL
Iron overload*	Plasma ferritin	> 200 µg/L (males, 20–44 years)* > 150 µg/L (females, 20–44 years)*
	Plasma iron	≥ 175 µg/L
	Transferrin saturation	> 60%

Source: *Expert Scientific Working Group (1985); INACG (1985); Ferguson et al. (1992); Sauberlich (1999); Food and Nutrition Board (2000b)

Table 10.2 Components in food that affect bioavailability of iron, mainly from non-haem food sources

Iron enhancers	Iron inhibitors
• Vitamin C-rich foods (ascorbic acid) [a, b] (salad, lightly cooked green vegetables, some fruits and citrus fruit juices or vitamin C fortified fruit juices) • Some fermented foods (with a low pH) [e, f] (sauerkraut, miso, some types of soy sauce) • Peptides from partially digested muscle tissue enhance both haem and non-haem iron [k or j] (often called the 'meat enhancement factor', beef, lamb, chicken, fish, pork, liver) • Alcohol and some organic acids [f] (very low pH foods containing citric acid, tartaric acid eg citrus fruit) • Vitamin A and beta carotene [m]	• Phytate (myoinositol hexaphosphate) [n, f] (cereal grains, wheat bran, legumes, nuts, peanut butter, seeds, bran, soy products, soy protein, spinach) • Polyphenolic compounds [a, d, f] (strong tea and coffee, herb tea, cocoa, red wine, some spices (e.g. oregano)) • Calcium inhibits both haem and non-haem iron [a, b, c] (milk, cheese) • Peptides from partially digested plant proteins [g, d, i, l] (soy protein isolates, soy products)

[a] Hallberg 1981
[b] Hallberg et al. 1993
[c] Cook et al. 1991
[d] Hallberg & Rossander 1982b
[e] Baynes et al. 1990
[f] Gillooly et al. 1983
[g] Lynch et al. 1994
[h] Brune et al. 1992
[i] Hurrell 1997
[j] Layrisse et al. 1984
[k] Gillooly et al. 1984
[l] Hallberg & Rossander 1982a
[m] Garcia-Casal et al. 1998, 2003

10.8 Assessment of iron status of an athlete: clinical perspectives

Confirmation of a diagnosis of true iron depletion in athletes is difficult and controversial, and requires the use of a number of diagnostic criteria, including a comprehensive assessment of the physiological, medical, biochemical and dietary factors implicated in the aetiology of iron deficiency. Blood tests alone do not necessarily confirm a diagnosis.

10.8.1 *Laboratory measures of iron status and their interpretation*

The diagnosis of biochemical iron deficiency has been complicated by the absence of a clear and reliable reference method for detecting early iron depletion and the use of varying cut-offs for haematological indicators at each stage. Several key haematological indicators are used to assess iron status and define each stage in clinical practice; SF to measure depleted iron stores (Stage 1), serum transferrin receptor (sTfR) to measure functional iron deficiency (Stage 2), and haemoglobin concentration to measure of iron deficiency anaemia (Stage 3) define each stage (Skikne et al. 1990). The interpretation of these values and other haematological indicators commonly used in clinical practice is described briefly in this section. Further detail on these indicators and other less commonly used markers used in research is found elsewhere (Smith & Roberts 1994; Pyne et al. 1997).

10.8.1.1 Storage iron

Serum ferritin (SF)

Iron is stored within cells as molecular complexes called ferritin and haemosiderin, a partially degraded form of ferritin. Small amounts of SF circulate in the blood in concentrations between 15 and 300 µg/L in adults (Worwood 1991). SF is considered the best index of iron stores in healthy people and athletes (Borch-Iohnsen 1995) and is closely associated with intra-cellular ferritin, which parallels concentration of storage iron (Lipschitz et al. 1974).

The mean SF in the NHANES 101 survey of US adults (20-65 years) was 109 µg/L (range, 66–285) in 649 men and 34 µg/L (range 12–94) in 409 women (Cook et al. 2003). In a recent survey of elite athletes (age 15–31 years) training at the Australian Institute of Sport (AIS), the mean SF was 85 µg/L (range, 16–288) in 105 males and 54 µg/L (range, 8–205) in 166 females (Fallon 2004). The distribution of SF is skewed towards the lower end of the range in athletes and population surveys (Cook et al. 1974; Maes et al. 1997).

In athletes and non-athletes, SF varies with age, sex and physical activity, and is low in young children and in adolescents during the growth phase (Baynes 1996).

Often male adolescent athletes have low SF, despite high dietary iron intakes and iron supplements (Telford et al. 1993), which are probably physiologically 'normal' at this age. In population studies, a slow increase in SF and body iron occurs through adolescence followed by a substantial rise in males in late adolescence (Bothwell 1995; Bergstrom et al. 1996, p. 161; Cook et al. 2003). Females do not show a late adolescent increase. Further increases in body iron stores occur in men with ageing and in postmenopausal females, but not in younger women (Cook et al. 2003). The reasons for these differences have not been defined. SF has some day-to-day variability (Stupnicki et al. 2003) and can be distorted under different physiological conditions (see section 10.8.2).

In elite athletes, SF declines during the training season in both males and females. In 46 matched pairs of female AIS athletes, SF decreased by around 25% during training seasons, with greater declines seen in weight-bearing sports (netball and basketball) than non-weight-bearing sports (swimming and rowing) (Ashenden et al. 1998).

Diagnostic cut-offs for SF

In untrained adults, SF below 30 µg/L suggests depleted iron stores (Crosby & O'Neill 1984) and 12 µg SF/L denotes exhaustion of iron stores (Cook et al. 1974). In one large study of 422 hospital patients with disease specific anaemia, the cut-off for functional iron deficiency was diagnosed (based on several haematological indicators) at 20.8 µg SF/L (Thomas & Thomas 2002). In another study, functional iron deficiency (Stage 2) was detected at levels ≤ 15 µg SF/L, based on the absence or presence of stainable iron in the bone marrow and other markers in both male and female adolescents and women (Hallberg et al. 1993a, 1993b). Clearly cut-offs are not standardised and may differ in athletes, so interpretation of low SF values needs to be cautious.

Diagnostic cut-offs for iron status indicators for adults cannot be applied reliably to children and adolescents because of the large variation reported during maturation (Bergstrom et al. 1996, p. 151). Different reference ranges for male and female adults are recommended (see Appendix 10). Population reference ranges for children and adolescents are available in most biochemistry or haematology textbooks and also at http://www.ironpanel.org.au/AIS/AISdocs/labcont.htm.

10.8.1.2 Transport iron

Haematological indicators involved in transferring iron in the circulation are transferrin, serum iron and haptoglobin. Serum iron and serum transferring in isolation are of limited value in determining iron status. Instead, total serum iron-binding capacity is estimated at the same time so that the percentage saturation of transferrin can be calculated. Transferrin saturation and the recently introduced sTfR measure and possibly the sTfR/log SF index are more useful to determine early-stage iron depletion than are serum iron and serum transferring.

Practice tips

VICKI DEAKIN AND FIONA PELLY

Overview

- Athletes involved in regular intensive training programs are at risk of depleting their iron stores, which can, if not detected and treated early; develop into the advanced condition of anaemia. Athletes have higher iron requirements and potentially higher iron losses than non-athletes. Suboptimal intakes of iron are evident in athletes who follow low-energy diets, very high carbohydrate diets, fad diets, vegetarian diets or who are natural food eaters. As athletes are encouraged to consume diets high in starchy carbohydrate, there is a risk that inhibitors of iron absorption (found in cereal grains, nuts and legumes) will reduce iron bioavailability. Therefore, those athletes at risk of iron depletion need practical strategies for maintaining high carbohydrate intakes without compromising iron status. Food combinations that enhance iron absorption are important to achieve this outcome.

Biochemical detection of iron deficiency

- Interpretation of biochemical indicators used to detect early iron depletion can be unreliable (see section 10.8.1.4) and can be affected by strenuous exercise just prior to testing, by inflammation, by hypohydration and even by mild infections. Despite these limitations all low iron status measures should be treated as potential iron depletion.

Medical or physiological causes of iron deficiency

- Assessing the potential contribution of any medical or physiological factor implicated in the aetiology of iron deficiency is important to target appropriate treatment or assign causation. These include:
  - increased iron requirement (such as recent pregnancy, growth spurt, sudden increase in the intensity or duration of training)
  - the habitual use of medications that decrease the acidity of the stomach, including the habitual use of antacids
  - potential blood loss (for example from frequent nose bleeds, menorrhagia, ulcers, chronic use of anti-inflammatory medications, blood donor)—signs of blood loss after competition or heavy training include discoloured urine or blood in stools
  - recent weight loss or illness
  - malabsorption of iron (for example inflammatory bowel disease, parasites such as *Helicobacter pylori*).

Dietary assessment of iron deficiency

- Dietary assessment reveals individual food choices, attitudes and habits linked to iron deficiency such as:
  - infrequent consumption of red meat, poultry or seafood
  - vegetarianism or very high CHO diets from mainly wholegrain cereals
  - irregular or erratic eating patterns
  - prolonged loss of appetite after physical activity
  - low intake of bread, breakfast cereal and iron-fortified foods
  - weight-reduction diets, some fad diets, inappropriate food combinations or limited variety of food choices
  - low intakes of vitamin C- or vitamin A-rich foods with meals
  - regular consumption of strong tea or coffee with most meals
  - poor food knowledge, limited cooking skills, reliance on takeaways.
- The new EAR for iron for Australia and New Zealand for healthy adults is 6 mg/day for men (aged > 19 years) and 8 mg/day for women (aged 19–50 years), and for adolescents males and females aged 14–18 years, 7.7 mg/day and 7.9 mg/day, respectively (Commonwealth Department of Health and Ageing, Ministry of Health, National Health and Medical Research Council 2004). These values need to be adjusted for athletes and vegetarians, but can be used as benchmarks to examine the probability that usual intake is inadequate for an individual.

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COMMENTARY

A The evolution of the Female Athlete Triad

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Introduction

The Female Athlete Triad was first described as the inter-relationship of disordered eating, amenorrhoea and osteoporosis (Yeager et al. 1993), and in its initial 1997 position stand on the Female Athlete Triad, the American College of Sports Medicine described the Triad in the same terms (Otis et al. 1997). Since then, a consensus has emerged among scientists investigating the Triad that:

- the components of the Triad should be redefined as energy availability, menstrual function and bone strength
- each of these components should be understood to span a spectrum from health to disease, with the population of female athletes distributed *and moving* along these spectrums
- an athlete's level of energy availability is the key factor causing her to move in one direction or the other along the other spectrums, and
- the apparent irreversibility of bone loss in premenopausal amenorrhoeic women warrants the earliest possible intervention to prevent further bone loss.

Two discoveries since the publication of the ACSM position stand have most strongly influenced our current understanding of the Triad. First, the cause of athletic amenorrhoea has been identified as low energy availability. Amenorrhoeic and eumenorrhoeic athletes span a common range of body size and composition (Redman & Loucks in press). Furthermore, exercise has been found to have no suppressive effect on reproductive function apart from the impact of its energy cost on energy availability (Loucks et al. 1998, Williams et al. 2001b), and even severe stresses involved in military training have been found to have no

additional effect (Friedl et al. 2000). Second, low energy availability has been shown to uncouple bone turnover, which can cause irreversible bone loss in bone remodelling units (Compston 2001). In addition to increasing the rate of bone resorption by suppressing oestrogen, low energy availability also suppresses the metabolic hormones that promote bone formation (Ihle & Loucks 2004; Zanker & Swaine 1998). While oral contraceptives may prevent further bone loss (Hergenroeder et al. 1997), clinical trials in premenopausal, amenorrhoeic women with low energy availability have found that lost bone is not fully replaced by either oestrogen replacement (Cumming 1996; Warren et al. 2003), the return of menstrual cycles (Drinkwater et al. 1986; Keen & Drinkwater 1997; Warren et al. 2002; Warren et al. 2003), or weight gain (Soyka et al. 2002). Because bone mass in young adulthood is a major determinant of postmenopausal fractures, prevention is better than any treatment for the Triad, and intervention is better earlier than later. Treatment should be initiated immediately upon the detection of amenorrhoea and should not be deferred until athletes satisfy WHO diagnostic criteria for postmenopausal osteoporosis.

Justification for the Female Athlete Triad

Critics of the Triad have objected to apparently healthy female athletes being singled out as a focus of medical attention. They have argued that the physiological mechanisms involved in the Triad operate in men as well as women, and that publicity about the Triad may discourage girls and women from being more physically active at a time when obesity is a major public health problem. On the contrary, it is appropriate to single out females, because the mammalian dependence of reproductive function on energy availability operates principally in females (Bronson 1985). In addition, it is appropriate to single out athletes, because even though severe dietary restriction alone is sufficient to disrupt reproductive function, the more physically active a woman is, the less dietary restriction is required, and, if she expends enough energy in exercise, her reproductive function will be disrupted even though she does not restrict her diet at all (Loucks et al. 1998). Therefore, neither clinical eating disorders nor disordered eating behaviours are necessary to disrupt menstrual function in athletes who expend large quantities of energy in exercise. It is to be emphasised, however, that exercise has no suppressive effect on reproductive function apart from the impact of its energy cost on energy availability, and that the disruption of reproductive function can be prevented and restored by increasing dietary energy intake without any moderation of the exercise regimen (Loucks et al. 1998; Williams et al. 2001a, 2001b). Finally, it is appropriate for apparently healthy female athletes to be the subject of medical attention, because the imperceptible and apparently irreversible bone loss caused by low energy availability predisposes amenorrhoeic athletes to stress fractures in the near term and to the premature onset of osteoporosis later in life.

Others have questioned how low energy availability can be harmful to women's health, when they have heard so much about how caloric restriction has improved health and longevity in experimental animals. The answer is that it is a matter of degree. The human female reproductive system is not energetically fragile, but there is a limit to the degree of energy deficiency that a woman's body can tolerate before it starts shutting down energy-consuming physiological processes to recover energy balance. Health and longevity have been improved in animal experiments by dietary restrictions of 30% (Kemnitz et al. 1994; Lane et al. 1997; Mattison et al. 2003). In exercising women, reproductive function and bone formation begin to be suppressed when energy availability is reduced by more than 30% (Ihle & Loucks 2004; Loucks & Thuma 2003). Amenorrhoeic athletes have been reported to practise diet and exercise regimens that reduce energy availability by 65% (Thong et al. 2000)!

The concept of energy availability

Since energy availability is the key component of the Triad, it warrants discussion in some detail. In general, the term 'energy availability' refers to the amount of metabolic fuel in the form of carbohydrates and fats that is available for tissues to oxidise as a source of energy for life-sustaining physiological processes. In mammals, dietary energy is utilised for thermoregulation, cellular maintenance, immunity, growth, reproduction and locomotion. When dietary energy is inadequate for all of these processes, its allocation is prioritised to those that are essential for immediate survival of the individual and away from reproduction, which is essential for survival of the species. In effect, reproduction is deferred until more energy becomes available. Thus, the status of the reproductive system is the 'canary in the mine shaft' that indicates the adequacy of energy supplies.

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