
# Invited Review: Iron Balance and Iron Supplementation for the Female Athlete: A Practical Approach

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**Abstract (max. 250 words)**

Maintaining a positive iron balance is essential for female athletes to avoid the effects of iron deficiency and anaemia and to maintain or improve performance. A major function of iron is in the production of the oxygen and carbon dioxide carrying molecule, haemoglobin via erythropoiesis. Iron balance is under the control of a number of factors including the peptide hormone hepcidin, dietary iron intake and absorption, environmental stressors (e.g. altitude), exercise, menstrual blood loss and genetics. Menstruating females, particularly those with heavy menstrual bleeding are at an elevated risk of iron deficiency. Haemoglobin concentration [Hb] and serum ferritin (sFer) are traditionally used to identify iron deficiency, however, in isolation these may have limited value in athletes due to: 1. the effects of fluctuations in plasma volume in response to training or the environment on [Hb], 2. the influence of inflammation on sFer and 3. the absence of sport, gender and individually specific normative data. A more detailed and longitudinal examination of haematology, menstrual cycle pattern, biochemistry, exercise physiology, environmental factors and training load can offer a superior characterisation of iron status and help to direct appropriate interventions that will avoid iron deficiency or iron overload. Supplementation is often required in iron deficiency; however, nutritional strategies to increase iron intake, rest, and descent from altitude can also be effective and will help to prevent future iron deficient episodes. In severe cases or where there is a time-critical need, such as a major championships, iron injections may be appropriate.

**Keywords**

Endurance, haemoglobin, nutrition, deficiency, anaemia, iron deficiency

## Introduction

Iron is a component of multiple cellular functions and physiological systems and is therefore essential for human health and athletic performance, yet iron deficiency is one of the most common deficiencies in sport. Athlete's iron requirements may be higher due to the increased erythropoietic drive caused by regular exercise. Furthermore, footstrike haemolysis, gastro-intestinal bleeding, exercise-induced inflammation, anti-inflammatory drug use and environmental factors such as hypoxia may all influence iron metabolism in athletes. The female athlete is at a particular risk of iron deficiency due to menstruation and screening for iron deficiency is widely recommended for all athletes (DellaValle, 2013). The effects of the female hormones on iron metabolism in athletes are largely unknown.

Iron deficiency anaemia requires medical intervention; however, increasingly sport scientists and nutritionists are measuring, monitoring and attempting to optimise iron status in athletes since it is closely connected to endurance performance (Montero et al., 2017; Pedlar et al., 2013; Peeling et al., 2007). Individuals can respond to iron treatment even when they are within a normal clinical reference range and vice-versa: athletes may ostensibly be iron deficient and yet iron treatment is ineffective (Burden, Pollock, et al., 2015; Pedlar et al., 2013; Wachsmuth, Aigner, Volzke, Zapf, & Schmidt, 2015). Those athletes with the most severe iron deficiency are most likely to respond positively to treatment (Wachsmuth et al., 2015).

Some discrepancy in the literature exists over the appropriate identification and treatment of iron deficiency in sport and there are no widely used guidelines for clinicians and dieticians to follow although there have been a number of relevant reviews (Archer & Brugnara, 2015; Clenin et al., 2015; Latunde-Dada, 2013). The present review considers research pertaining to the female athlete and provides recommendations for identifying and correcting iron deficiency. Specific scenarios where female athletes are at risk of iron deficiency are discussed.

## Iron balance and exercise performance

High performing endurance athletes are characterised by a high aerobic capacity together with a high aerobic power output or velocity. This phenotype is achieved via a number of physiological adaptations that promote the delivery of oxygen-rich blood to the musculature including: increased cardiac size and function, increased blood

volume or red cell mass, and enhanced off-loading of oxygen within the muscle tissue (Mairbaurl & Weber, 2012; Montero et al., 2017; Schmidt & Prommer, 2010).

Haemoglobin, carried in the red blood cell, is a globular protein pigment molecule containing a non-protein heme group in its centre, carrying the iron ion at the site of oxygen binding. Haemoglobin is carried in red blood cells which are produced and cleared at a rate of approximately 2 million per second (Higgins, 2015), thus total haemoglobin mass (tHbmass), a primary determinant of maximal oxygen uptake ( $\dot{V}O_2max$ ) (Schmidt & Prommer, 2010), is fundamentally reliant upon adequate iron stores. Iron is also a requisite component of cytochromes and enzymes involved in electron transport within the mitochondria. A reduction in iron stores may therefore impact upon the capacity for both oxygen transport and utilisation, lead to fatigue, or cause under-performance. Further, since iron is essential for brain development and cognitive performance (Murray-Kolb & Beard, 2007), iron deficiency could affect motivation, concentration and decision-making, also impacting upon exercise performance.

Appropriate identification and correction of iron deficiency can have a significant impact on athlete performance and wellbeing in endurance sports and team sports with a significant endurance component. Importantly, there is no evidence that supra-normal iron levels enhance performance beyond a placebo effect. On the contrary, there is evidence and concern over the negative effects of iron overload (Zoller & Vogel, 2004; Zotter et al., 2004) due to the potential for the production of damaging free radicals from free iron. Iron is a transition metal and has 5 oxidation states. Through the Haber–Weiss reactions, highly reactive OH radicals are produced, causing lipid peroxidation, and the appearance of malondialdehyde and thiobarbituric acid (TBARS) reactive substances. Although human studies are rare, in various animal studies of iron overload, elevations in TBARS have been found in the liver, kidney and plasma in response to iron administration (Zhuang, Han, & Yang, 2014). A link between iron overload and other diseases including cancer has also been reported (Mallory & Kowdley, 2001). Thus, any intervention should only be aimed at normalising iron status.

The challenge therefore is to maintain an appropriate iron status, avoiding the negative consequences of either iron toxicity or iron deficiency. Environmental

factors, exercise volume and intensity, diet and supplementation are under the control of the athlete, whereas genetics, menstrual blood losses, the rate of iron absorption and compensatory physiological mechanisms are not. The factors affecting iron balance as it pertains to athletic performance can be described with the conceptual formula in **Table 1**. With an awareness of the factors influencing iron balance, Sports Science and Sports Medicine practitioners can appropriately monitor and advise athletes. **Figure 1** provides a timeline with a number of scenarios known to affect iron balance, illustrating the importance of context at the time of assessing iron status.

*Control of iron status*

The regulation of iron absorption, storage and the regulation of erythropoiesis is under the control of iron protein regulators and hypoxia inducible factors respectively (Kuhn, 2015). Iron absorption is under the control of the peptide hormone hepcidin which was only relatively recently discovered (Nemeth et al., 2004). Briefly, hepcidin is secreted in the liver and increases in response to iron overload (Burden, Morton, Richards, Whyte, & Pedlar, 2015) or inflammation, shutting down iron absorption via ferroportin. Conversely, hepcidin decreases in anaemia, promoting iron absorption. Since exercise results in an inflammatory response, it can transiently increase hepcidin (Burden, Pollock, et al., 2015), potentially reducing the capacity to absorb iron. Therefore, heavy and frequent exercise training bouts may put the athlete at risk of iron deficiency although more studies are needed to understand the longitudinal effects of exercise upon hepcidin. Recent evidence suggests that during recovery from marathon training iron status improves (Pedlar et al., 2017), thus, rest may be an effective means of correcting iron deficiency although more studies are needed.

*Altitude training*

Altitude is known to have a profound impact upon iron status and therefore athletes travelling to altitude should consider the need for iron supplementation. The reproducible effect of a transition to altitude upon iron metabolism has been clearly demonstrated in athletes. In hypoxia, erythropoietin increased and sFer decreased while a slow increase in tHbmass occurred over 3 weeks at a simulated altitude of 3000m in male and female endurance athletes (Robertson et al., 2010). Furthermore, in an analysis of data from the Australian Institute of Sport database (n=147 athletes), iron deficient athletes provided with iron supplementation while resident in normobaric hypoxia (simulated altitude), demonstrated the greatest increase in

tHbmass (Garvican-Lewis et al. 2016). Conversely, upon return to sea level, iron status improves, causing a rise in ferritin (Robertson et al. 2010). Thus, removing the hypoxic stimulus may correct an imbalance between iron availability and erythropoietic drive. The mechanisms responsible for this shift to storage of iron may also include the destruction of new red blood cells (neocytolysis; Alfey, Rice, Udden & Driscoll, 1997), or premature clearance older cells (elevated clearance threshold; Higgins, 2015), however, both these mechanisms remain to be proven in athletes. Studies specifically investigating differences between males and females in altitude and post-altitude responses are lacking.

*Menstruation*

Menstruating women lose approximately 1 $mg \cdot day^{-1}$ of iron when bleeding. This may be higher in heavy menstrual bleeding (HMB), where blood loss is estimated to be 5-6 times greater (Napolitano et al., 2014). HMB has recently been found to be prevalent in athletes at all levels, affecting 1 in 3 (Bruinvels, Burden, Brown, Richards, & Pedlar, 2016). An inflammatory process drives the majority of the normal physiological responses within the reproductive system: Cytokine expression varies through the course of the menstrual cycle, peaking during menstruation (Bertone-Johnson et al., 2014). The increased levels of inflammatory mediators have the potential to increase hepcidin release in the liver, reducing iron absorption and further increasing the risk of iron deficiency at this time. Once the bleed commences, hepcidin decreases to promote iron absorption (Angeli et al., 2016), rebounding later in the cycle. Further research is required to establish variation in hepcidin production through the menstrual cycle in athletes.

*Pregnancy*

Pregnancy is another condition in which iron intake is often insufficient due to rapid growth. The estimated worldwide prevalence of IDA in pregnancy is 15-20% (Cao & O'Brien, 2013). Enlargement of maternal erythrocyte mass, the formation of foetal tissue and the development of foetal iron stores increase maternal iron demand, elevating iron deficiency risk. Initially, in early pregnancy, the absence of menstruation means that iron status may not be compromised. However, as foetal iron demand increases as pregnancy progresses, susceptibility to iron deficiency is elevated (Cao & O'Brien, 2013). During the third trimester, daily iron requirements are 3-8 $mg \cdot d^{-1}$ (Viteri, 1994). Reliability of iron status measurement is questionable during pregnancy, particularly in the third trimester, where there is a pregnancy-induced haemodilution (Viteri, 1994). Clearly there are many other considerations for

athletes choosing to exercise during pregnancy (see Erdener & Budgett, 2016 and other recent reviews).

**The effect of iron deficiency on aerobic exercise performance**

Iron deficiency anaemia (IDA) has a profound effect on performance, depending on the severity, however, the effect of iron deficient non-anaemia (IDNA) is less clear. DellaValle and Haas (DellaValle & Haas, 2011) reported a relationship between sFer and 2 km time trial performance amongst female collegiate rowers at the beginning of a competition season, with those athletes who were IDNA reporting a 21s slower 2 km time trial times compared to those who were iron replete. Iron deficiency may also influence total training load, for example, IDNA female collegiate rowers performed significantly less weekly mileage than their iron replete counterparts (Dellavalle & Haas, 2012). Furthermore, several iron supplementation studies have shown improvement in indices of aerobic capacity following treatment in female athletes (Brownlie, Utermohlen, Hinton, & Haas, 2004; Friedmann, Weller, Mairbaurl, & Bartsch, 2001; Hinton, Giordano, Brownlie, & Haas, 2000; Hinton & Sinclair, 2007; Magazanik et al., 1991; Wachsmuth et al., 2015; Zhu & Haas, 1998), suggesting that an initial IDNA was compromising performance.

However, there are also several studies that have reported no effects of iron treatments on exercise performance in female IDNA endurance athletes (Blee, Goodman, Dawson, & Stapff, 1999; Burden, Pollock, et al., 2015; Garvican et al., 2014; Peeling et al., 2007; Radjen et al., 2011; Tsalis, Nikolaidis, & Mougios, 2004); and no direct association has been proven between sFer and performance, even when <30 $\mu g \cdot L^{-1}$

A number of variables may be responsible for these discrepancies as follows: The variation in sFer cut-off values used to identify iron deficiency; the variety of measures used to assess aerobic capacity and endurance performance; The duration of studies, which may not have provided enough time for an effect; the variation in the exercise stimulus experienced during iron therapy; the type of therapy and dosing protocol; the performance level of the participants.

**Identifying iron deficiency**

Symptoms of fatigue indicate potential iron deficiency. The gold standard for measuring iron stores is a bone marrow biopsy, but since this is not practical in athletes, and the interpretation of this test is plagued by a wide variability (Stancu et al., 2010) we recommend alternative methods based on blood testing. Serum ferritin (sFer) has been used as a biomarker of iron stores since a direct correlation between plasma ferritin and whole body iron was established in the 1970's (Jacobs & Worwood, 1975). Periodic screening sFer and [Hb] is recommended for all athletes by the International Olympic Committee (Ljungqvist et al., 2009).

Broadly, there are three stages of iron deficiency; firstly, a depletion of iron stores (i.e. a reduced serum ferritin) without any evidence of a haematological consequence; secondly, early signs of iron deficiency impacting upon haematological markers (for example, haemoglobin towards the lower end of the range, an elevated percentage microcytic reticulocytes and hypochromic reticulocytes), but these markers remaining within reference ranges and; finally, iron deficiency anaemia characterised by multiple markers of low iron stores and haematological variables outside of reference ranges (reviewed by Archer et al.; (Archer & Brugnara, 2015)).

Haemoglobin concentration ([Hb]) and serum ferritin (sFer) are typically used together, however, the interpretation of both measures is problematic because of the variability in individual [Hb] and sFer data such that they may not adequately reflect whole body iron stores. The clinical range provided by the laboratory may be of limited relevance to an athlete. [Hb] and sFer each have their own biological set points dependent on sex, sport, age, genes, menstrual blood loss, dietary and environmental factors (Archer & Brugnara, 2015). [Hb] can be low because of a normal plasma volume expansion caused by exercise, posture or acclimatisation (Garvican-Lewis et al., 2014). Conversely, [Hb] may reside within the normal clinical range, but tHbmass may not be optimised (Wachsmuth et al., 2015). sFer is an acute phase protein and can be artificially raised in the presence of infection or inflammation (Moore, Ormseth, & Fuchs, 2013). Finally, there is little consensus amongst clinicians or researchers on a definitive clinical cut point for sFer. A range of values for sFer have been applied in the literature to define iron deficiency ranging from 7 $\mu g \cdot L^{-1}$ (Tsalis et al., 2004) to 40 $\mu g \cdot L^{-1}$ (Burden, Pollock, et al., 2015; Garvican et al., 2014; Peeling et al., 2007), whereas a [Hb] of 12.0 $g \cdot dL^{-1}$ has been fairly consistently applied.

A closer consideration of the red blood cell morphology provides variables such as mean corpuscular haemoglobin (MCH), mean cell volume (MCV) and reticulocyte haemoglobin concentration (CHr or Ret-He) and this may have diagnostic utility for certain types of anaemia or latent anaemia. Additional biochemistry markers including serum transferrin receptor, serum iron, serum transferrin and transferrin saturation may also assist with the identification of iron deficiency (Archer & Brugnara, 2015). Assessment of total haemoglobin mass via the carbon monoxide rebreathing technique is also gaining favour as a tool for identifying iron deficiency and assessing responses to treatment in athletes (Garvican, Lobigs, Telford, Fallon, & Gore, 2011; Wachsmuth et al., 2015).

A diagnosis of IDNA can only be confirmed definitively once a positive haematological response to treatment is observed and this approach has been advocated in recent studies (Garvican et al., 2011; Wachsmuth et al., 2015).

**Correcting iron deficiency**

The most appropriate course of action depends on the data available and the severity of the iron deficiency. A review of dietary iron intake may be enough to improve iron status or to avoid IDNA and all female athletes should consider their dietary iron intake and ensure regular daily consumption of iron rich foods. Likewise, an understanding of foods that chelate iron and inhibit absorption, such as phytates and polyphenols, will help to ensure optimal dietary iron intake (see Dietary Iron section).

Where more severe iron deficiency exists and IDA is clearly present ([Hb] <12.0 $g \cdot dL^{-1}$ and tHb-mass is trending lower than would be considered normal for that individual), iron treatment should be instigated under the guidance of a medical doctor. The response to the treatment should be tracked with measurements of red cell indices and tHb-mass where possible (notwithstanding that facilities for the carbon monoxide rebreathing test are not widely available). It is reasonable to repeat tests as often as 2-week intervals to plot a positive response to treatment. If a clear improvement in tHbmass is observed, the diagnosis of iron deficiency can be accepted and regular monitoring should continue. A process for addressing iron in the context of an athlete reporting with fatigue is outlined in **Figure 2**.

*Effect of Iron Treatment on Iron Status*

Supplementing athletes with iron will increase sFer, at least transiently. Oral iron supplementation in doses ranging from 40-400 $mg \cdot day^{-1}$, for 6-24 weeks and both IM and IV injections have all resulted in significantly improved sFer values (Burden, Morton, et al., 2015). For individuals with IDA, iron treatments will increase sFer, tHb-mass and red cell indices resulting in an improved aerobic power and these indices will be maintained providing the cause for the anaemia is identified and treated. Yet when individuals identified as IDNA are treated with IV iron the initial rise in ferritin will be present for only a number of weeks, after which sFer may return to pre-treatment levels (Pedlar et al., 2013) and no change in haematological or performance indices may have occurred (Burden, Pollock, et al., 2015). Longitudinal monitoring of iron status gives the practitioner the best chance of optimising tHbmass and avoiding IDA or iron overload.

Haemoglobin concentration (<120 $g \cdot L^{-1}$) is consistently used to differentiate between anaemic and non-anaemic states but as a concentration measurement it is influenced by changes in plasma volume (PV), meaning the pre-analytics of the sample are crucial to the validity and reliability of the measure. A measurement of tHb-mass is independent of changes to PV and a more stable measurement than [Hb] (Schmidt & Prommer, 2010). A mean increase in tHbmass of 11% was demonstrated in IDA athletes following 12 weeks of oral supplementation (Wachsmuth et al., 2015). Furthermore, 2.7% and 1.9% improvements in tHb-mass have been reported 6 and 8 weeks following IV iron treatment without a change in [Hb] (Garvican et al., 2014). Therefore, tHb-mass appears to be a more sensitive and effective measure than [Hb]. However, caution should be taken as the typical measurement error associated with the CO rebreathing technique is 2.2% (Gore, Hopkins, & Burge, 2005) and annual oscillations in tHb-mass of 4.6% have been observed in athletes (Schmidt & Prommer, 2010). Therefore, interpretations of small increases in tHb-mass following iron treatment, such as those observed in IDNA athletes should be made cautiously and it is recommended that multiple tHb-mass measurements are used.

*Effect of Iron Treatment on Performance in IDNA athletes*

A number of studies have shown aerobic power to be unchanged following iron treatment in IDNA athletes (Blee et al., 1999; Burden et al., 2015; Peeling et al., 2007; Radjen et al., 2011; Tsalis et al., 2004), yet one of the few studies to investigate IV treatments for endurance athletes, did find a likely significant improvement in $\dot{V}O_{2max}$ from 59.0 ± 10.8 $ml \cdot kg^{-1} \cdot min^{-1}$ to 61.7 ± 6.8 $ml \cdot kg^{-1} \cdot min^{-1}$

following IV iron but not oral iron supplementation (Garvican et al., 2014). This study implies that iron treatments are effective for IDNA athletes and that IV treatments are more effective than oral supplements but the findings are limited by the lack of a control group. A randomised control trial examining the efficacy of a single 500 mg IV treatment showed no pre-to-post treatment changes in $\dot{V}O_{2max}$, $v\dot{V}O_{2max}$, running economy, speeds at 2 and 4 $mmol \cdot L^{-1}$ blood lactate, or time to exhaustion, suggesting that IDNA had no effect on aerobic power or other laboratory measures that are commonly used to evaluate endurance athletes (Burden, Pollock, et al., 2015). It is possible these athletes were not iron deficient in the first place, particularly given that there were also no changes in red cell indices or tHb-mass. Nevertheless, sports science and medicine practitioners should be mindful that the effects of iron treatments are not be limited to a haematological response. Increased $\dot{V}O_{2max}$ following iron treatment despite normal [Hb] has been reported (DellaValle & Haas, 2014; Friedmann et al., 2001; Hinton et al., 2000; Hinton & Sinclair, 2007; Magazanik et al., 1991; Zhu & Haas, 1998), which might be explained by a non-haem effect, influencing oxygen utilisation rather than oxygen transport. Finch *et al.* (Finch et al., 1976) proposed that iron deficiency produces a mitochondrial abnormality resulting in impairment in oxidative phosphorylation and electron transport, following investigations into the influence of iron status and [Hb] in exercising rats. Unfortunately, there have been very few studies investigating the effects of IDNA on mitochondrial function in human subjects, particularly in athletes, probably because a muscle biopsy is required.

***Dietary iron***

Cross sectional studies show an association between poor dietary iron intake and iron deficiency (Malczewska, Raczynski, & Stupnicki, 2000). Iron is contained in a variety of food sources that can be classified into 'heme' and 'non-heme'. The most readily absorbed form of iron is heme iron derived from animal meat, especially red meat. Poultry and seafood also contain reasonable amounts of heme iron. Therefore, vegetarians are at risk of iron deficiency (Venderley & Campbell, 2006) in addition to a host of other nutrient deficiencies. Athletes with Celiac disease may have compromised iron absorption (Mancini, Trojian, & Mancini, 2011). Risk of iron overload from the diet is extremely low. Rate of iron absorption from the gut measured using radioiron tracers was found to be proportional to serum ferritin at levels below $60 mg \cdot L^{-1}$ in healthy men consuming an iron rich diet (Hallberg, Hultén, &

Gramatkovski, 1997). Above 60mg·L$^{-1}$, iron absorption was negligible, suggesting that it is difficult to achieve iron overload from excessive dietary iron intake.

Although few studies exist that test iron repletion strategies using food alone (i.e. no supplements or injections), it is widely accepted that assessing dietary iron intake from non-heme and particularly heme sources is the first step in prevention of, and correction of iron deficiency and also forms a long term strategy for prevention of future iron deficient episodes. However, dietary iron is also poorly absorbed which, may be a consequence of the up-regulation of hepcidin following the post exercise inflammatory response, blocking gastrointestinal iron absorption (Nemeth et al., 2004). The result is a potential repletion period of between 3-6 months, which constitutes a large portion of an athlete's training year and would be unwelcome given that iron deficiency may prevent athletes from coping with the required training load (Dellavalle & Haas, 2012).

A number of factors are known to facilitate iron absorption in the gut including vitamin C (Reddy, Hurrell, & Cook, 2000), alpha and beta-carotene (García-Casal et al., 1998) whereas phytic acid, certain polyphenols, phosphorous and calcium may all inhibit iron absorption (Reddy et al., 2000). Calcium supplementation may also reduce iron absorption (Minihane & Fairweather-Tait, 1998). However none of these have been specifically studied in athletes. Additionally, a number of other foods and drugs may compromise iron absorption (see Armah, Carriquiry, Sullivan, Cook, & Reddy (2013) and Clenin et al. (2015) for comprehensive reviews): Bran and other wheat products contain phytates (organic polyphosphates) which bind iron and reduce its absorption; Antacid therapy increased gastric pH and reduces iron absorption; Non-steroidal anti-inflammatory drug use may promote intestinal iron loss via microscopic bleedings.

***Oral Iron supplementation***

Recent data suggests that up to 79% of elite athletes use iron supplements (Bruinvels et al., 2016). Supplementation is recommended where iron deficiency is suspected, with ongoing monitoring to avoid unnecessary supplementation. Although iron supplementation is considered safe, the effect of long-term iron supplement use is not known. However, increased intake of dietary iron is a primary risk factor in those with genetic abnormalities that predispose them to iron overload, for example, in those with haemochromatosis. Most cases of haemochromatosis are

caused by a HFE (high iron) mutant genotype. In those who have homozygous or heterozygous mutations of the C282Y or H63D alleles (approximately 0.4% Caucasians carry a homozygous C282Y mutation, and 6% a heterozygous C282Y mutation), risk of clinically significant iron overload is increased, therefore caution should be applied with supplementation (Hollerer, Bachmann, & Muckenthaler, 2017). In one study, HFE gene mutations were present in over 80% (37 of 46) of international gold medalists in endurance sports (Hermine et al., 2015) suggesting some performance advantage associated with this gene mutation.

Since certain nutrients can facilitate or inhibit iron absorption (see above), it is generally recommended to take iron supplements away from meals and in combination with vitamin C (Reddy et al., 2000). Absorption from oral supplements can be slow and the supplements often cause side effects such as constipation, and abdominal discomfort/cramps. It has recently been shown that supplementing with Vitamin D3 significantly reduced hepcidin concentration in Vitamin D deficient but otherwise healthy adults (Smith et al., 2017), indicating the potential for a downstream effect on iron status. Such indirect means of addressing iron deficiency, without the aforementioned side effects, is an important area of future research.

***Parenteral Iron***

In clinical settings under the guidance of a physician, intravenous iron injections are used where a more rapid repletion of iron stores is required, for example when IDA is diagnosed prior to a major competition (Pedlar et al., 2013). Injections have proven successful across a variety of patient groups at improving iron status, haematological indices and subjective fatigue (Krayenbuehl et al. 2011). To date, investigations utilising iron injections as interventions for iron deficient athletes in randomised control trial designs are sparse (Blee et al., 1999; Burden et al., 2015; Peeling et al., 2007) and therefore the understanding of the acute and chronic effects of injection in athletes is limited. However, the use of injection interventions, rather than oral treatment, for IDNA athletes is supported by investigations comparing oral vs. injection treatments in highly trained male and female distance runners (Garvican et al., 2014) and other endurance sports (Peeling et al., 2007). Both studies showed iron injections to be more effective than oral supplementation at rapidly improving iron status.

**Recommendations**

Causes of fatigue including an underlying illness or pathological condition, sleep irregularities, non-sport factors i.e. work, education, family, social commitments and the crucial balance between exercise workload and recovery should be considered and excluded alongside haematological screening for iron deficiency. This screening should include measures of red cell number and health, iron status and tHb-mass. Best practice requires a longitudinal approach, where serial measures of iron and red cell indices are monitored to provide a trajectory for each system.

If IDA is indicated (sFer < 15 $\mu g \cdot L^{-1}$; [Hb] <120 $g \cdot L^{-1}$ and/or tHb-mass is trending lower than would be considered normal for that individual), then treatment is recommended and the athlete should seek medical advice as to the dose and protocol.

If IDNA is suspected i.e. sFer < 35 $\mu g \cdot L^{-1}$ but all other haematology is normal, then a review of the athlete's historical haematological and iron status data should be made to help understand what is normal for that individual in the context of factors affecting iron balance (**Figure 1**; **Table 1**).

In all cases, the athlete should seek a nutrition consult to review and develop dietary practices. If a change in dietary practice has been in place this should be followed up with repeat haematology screens. Monitoring the athlete with exercise physiology and tHbmass tests in addition to the haematology provides a comprehensive understanding of the ongoing efficacy of the intervention.

If fatigue persists and the potential contributing factors mentioned above have been explored then treatment could be considered with medical advice sought for the appropriate protocol and dose. Longitudinal tracking of the athlete's haematology, iron status and exercise physiology should continue.

Controlled studies assessing the efficacy of dietary iron intake in female athletes taking into account female hormones, menstrual blood losses, training volume/intensity and environmental factors are needed.

## Conclusions

Many factors can impact the iron balance in female athletes, including training, dietary intake, altitude training, menstruation and pregnancy. Understanding how

these influence iron status is essential. Iron deficiency anaemia will reduce endurance performance via impaired oxygen transport and should be clinically treated. Intravenous injections and oral supplementation are effective treatments for IDA. Questions remain over the impact of IDNA and whether or not iron treatment is appropriate for this condition. Longitudinal monitoring of an athlete's haematology and iron status during periods of treatment and non-treatment will help to clarify the efficacy of supplementation for the female athlete.

Table titles:

**Table 1**: A conceptual formula describing factors influencing iron balance as it pertains to endurance performance.

Figure titles:

**Figure 1.** The effect or predicted effect of various scenarios upon iron status, total haemoglobin mass and hepcidin, demonstrating the importance of context when interpreting athlete data. *Hepcidin responses are largely theoretical since few data have been published in athletes.

**Figure 2.** A process for identifying and correcting iron deficiency in fatigued female athletes.

**Table 1**: A conceptual formula describing factors influencing iron balance as it pertains to endurance performance.

| **Diet (A) + Absorption (Ḃ) + Exercise Stimulus (C) + Genes (D) + Environment (E) + Iron loss (Ḟ) = Hb mass (G) + Non Hb iron → Endurance Performance Phenotype (H)** | | |
|---|---|---|
| Where: | Influenced by: | In athlete's control? |
| A = Diet | ± Dietary intake vol. and freq. (heme and non-heme sources)<br>+ Absorption enhancers (Vit C, Vit A, β-carotene)<br>− Transport inhibitors (Phenolic acids (tannins); certain polyphenols; Phytates; antacid therapy) | Yes<br>*'What you consume and when'* |
| Ḃ = Rate of iron absorption | ± Absorption rate of dietary iron in the gut | No |
| C = Duration and frequency of exercise | + Stimulates erythropoiesis<br>− Inflammation*<br>− Reduced visceral blood flow<br>− Sweating | Yes<br>*'What you do'* |
| D = Genes controlling related physiology | + HFE gene mutation<br>+ HIF1α<br>+ EPO<br>+ Iron<br>− Menstrual blood loss<br>− Sweat rate<br>− Hepcidin*<br>Compensatory mechanisms:<br>+ Population dynamics (lowering Vc)<br>+ Plasma volume expansion<br>+ oxygen dissociation curves, P50, 2,3,DPG | No<br>*'What you are'* |
| E = Environment | + Hypoxia (Acclimatisation)<br>− Haemolysis (surface & sport modality)<br>− Sweating | Yes<br>*'Where you are'* |
| Ḟ = Rate of iron loss | ± Red cell clearance threshold (Vc)<br>− Excretion<br>− Sweating<br>± Neocytolysis | No |
| G = Hbmass | Total capacity for gas exchange | |
| H = Endurance Performance | G + Central (e.g. cardiac output) + Peripheral (e.g. mitochondrial density) | |
| Where: | + = increases or improves<br>− = decreases or compromises<br>± = increases or decreases<br>→ = leads to, or results in | |

Abbreviations: vol. = volume; freq. = frequency; Vit C = vitamin C; Vit A = vitamin A; HFE = high iron; HIF1α = hypoxia inducible factor 1 alpha; EPO = erythropoietin; Vc = red blood cell clearance threshold; P50 = the affinity of haemoglobin for oxygen, specifically the pressure of oxygen at which the haemoglobin is 50% saturated; 2,3DPG = 2,3-Bisphosphoglyceric acid;

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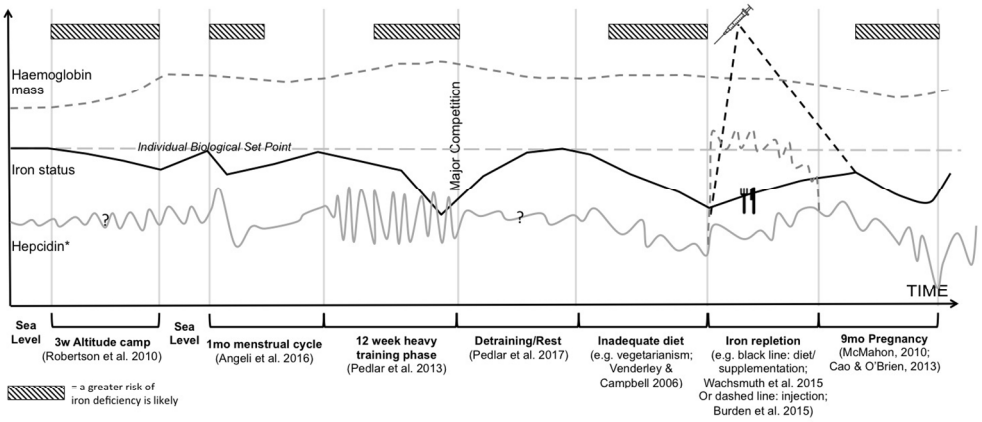


Figure 1. The effect or predicted effect of various scenarios upon iron status, total haemoglobin mass and hepcidin, demonstrating the importance of context when interpreting athlete data. *Hepcidin responses are largely theoretical since few data have been published in athletes.

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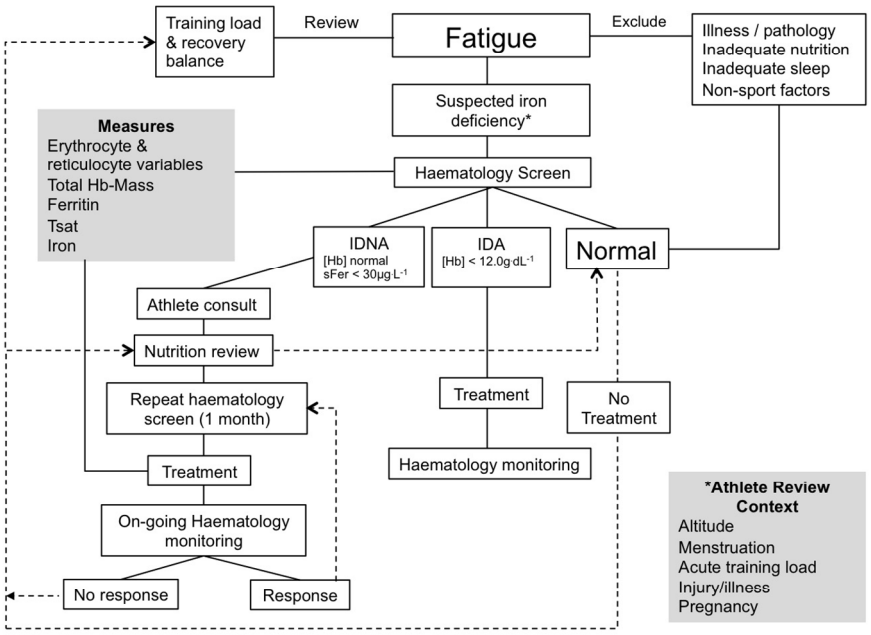


Figure 2. A process for identifying and correcting iron deficiency in fatigued female athletes.

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