Parenteral Iron Therapy: Examining Current Evidence for Use in Athletes

Authors
Nikita Fensham[1], Alannah Kelly Anne McKay[1], Marc Sim[2, 3], Peter Peeling[4, 5]

Affiliations
1 Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia
2 School of Medical and Health Sciences, Edith Cowan University, Joondalup, Australia
3 Medical School, The University of Western Australia, Perth, Australia
4 School of Sport Science, Exercise and Health, The University of Western Australia, Crawley, Australia
5 Western Australian Institute of Sport, Mt Claremont, Australia

Key words
iron supplement, intravenous iron, athlete, nutrient deficiency

accepted 13.11.2023
accepted manuscript online 14.11.2023
published online 2023

Bibliography
Int J Sports Med
DOI 10.1055/a-2211-0813
ISSN 0172-4622

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Prof. Peter Peeling
The University of Western Australia
School of Sport Science, Exercise and Health
35 Stirling Hwy
6009 Crawley
Australia
Tel.: + 61 8 6488 1383, Fax: + 61 8 6488 1039
peter.peeling@uwa.edu.au

ABSTRACT

A high prevalence of iron deficiency exists in athlete populations. Various mechanisms, including increased losses through sweat, haemolysis, haematuria, and gastrointestinal microischemia; inadequate dietary intake; and transient exercise-induced increases in the regulatory hormone, hepcidin, contribute to the increased prevalence in athletes. Indeed, hepcidin has been shown to peak around 3–6 hours post-exercise, limiting iron absorption from the gut. As the practitioner's ability to control losses is limited, the key to treatment of iron deficiency in athletes is optimal timing of dietary and oral iron supplementation around these periods of reduced gut absorption. While timing and dosing schedule strategies might be sufficient to treat iron deficiency non-anaemia, the significant lag to impact iron status is relatively long. Therefore, in iron deficiency anaemia, the use of parenteral iron has the benefit of rapid repletion of iron stores and normalisation of haemoglobin status, while bypassing the action of hepcidin at the gut. Furthermore, newer intravenous formulations can be administered as a single total dose over 15–60 min and have a similar safety profile to oral treatment. This review discusses the existing evidence for parenteral iron use in athletes and the unique context for consideration when choosing the parenteral route in this population.

Introduction

Iron deficiency is a common nutrient disorder in athletes, which left untreated, can have significant impacts on training consistency and athletic performance. Currently, there are a variety of methods that practitioners can use to address an iron deficiency [1], with the appropriate approach taken usually determined by the severity of the issue. Such approaches include dietary assessment and food modulation (lowest severity), oral iron supplementation, or parenteral iron delivery (highest severity). To determine the best approach, a standardised process for establishing the severity of the issues must be first considered.

Currently, there are numerous biological markers available to establish the iron status of an athlete [2]; however, many of these markers are acutely influenced by exercise, and a true gold stand-

ard of measuring/reporting iron status in athlete populations is yet to be clearly determined. Despite these issues, typical current practice sees iron status commonly determined via the presenting iron stores (serum ferritin; sFer), transferrin saturation (Tsat), and haemoglobin concentration (Hb). In combination, these three blood markers are then typically used to categorise the significance/severity of disrupted iron stores into three stages, as shown in ▶ **Table 1**, which provides a collective summary of several published sources as a guide to help categorise an athlete's iron status [3–6]. Of note, the interpretation of iron status from a single marker (i. e. only sFer) is not recommended [7], and the impact of exercise/training on these blood markers should be minimised using the pre-blood screening guidelines established by Sim et al. [8].

Within athlete populations, it is commonly reported that the prevalence of iron deficiency (anaemia (IDA) and non-anaemia (IDNA)) is 15–35 % in females and ~3–11 % in males [8–10]. However, specific athlete cohort studies report > 50 % of a study population can present with compromised iron stores [11, 12]. Regarding the more severe stages of iron deficiency (IDA), various studies inform a prevalence of 2–5 % in females and 1–2 % in males [13, 14]. Across both IDNA and IDA, the higher prevalence in females is generally attributed to the impact of the menstrual cycle.

Given the high prevalence of iron deficiency in athlete populations, it is important to understand the mechanisms of relevance that can collectively impact iron stores. Currently, we understand that there are several mechanisms of iron loss during exercise. These include processes such as haemolysis, sweating, haematuria, and gastrointestinal blood loss [15]. Further, it is also evident that athletes commonly battle energy deficit (through lack of time for adequate recovery nutrition or through purposeful calorie restriction in weight-sensitive sports), which can be associated with low nutrient quality and inadequate iron intake from the diet [16]. Finally, we also know that exercise results in a transient increase to the body's iron regulatory hormone, hepcidin [17], which results in a temporary reduction in the absorption of iron from the gut, especially in foods consumed 2 h post-exercise [18], where absorption seems to coincide with the peak post-exercise elevations in hepcidin levels at 3–6 h [17].

Although the iron loss from any single mechanism above might be small, it is their combined effect over multiple training sessions that may accrue and present as a burden on an athlete's iron stores over time. Clearly, these mechanisms present a case for iron loss during exercise, but equally, a period of reduced iron absorption in the post-exercise period. Impacting the mechanisms of iron loss during exercise is challenging, since there is limited ability for a practitioner, coach, or athlete to control these factors when a certain type, duration, or intensity of training is required for appropriate physical adaptation. However, our ability to impact iron provision and uptake from the diet and/or from various methods of supplementation, are very good. Therefore, a focus on timing iron intake to coincide with peak periods of absorption (or to avoid peak periods of malabsorption) from the gut becomes important, since it is the gut propensity for iron uptake that limits our ability to effectively treat iron deficiency through food and oral iron supplements.

Recent work from our group [1, 12, 19–21] and others [18], have been exploring factors that impact dietary iron absorption from the gut in relation to exercise. Collectively, this work informs us that there appears to be a peak period for iron absorption within the 30 min either side of exercise [19, 21], which is lost if the food/supplement is consumed ≥ 2 h post-exercise [18]. Further, this propensity for increased absorption appears better in the morning as compared to the afternoon [19], likely due to the natural diurnal increase in hepcidin levels that marginally negates afternoon iron absorption from a one-off meal [22]. Collectively, this work provides us with significant strategic approaches to timing iron intake for optimised iron absorption at the gut. However, if we are using these strategies to correct an iron deficiency, it should be considered that the time duration to have a significant impact is relatively long (i. e. 8–12 weeks of oral supplementation to improve iron status by 40–80 % [12, 23, 24]. Although this result is positive and appropriate for individuals who are IDNA or better, an 80 % improvement in iron stores for an IDA athlete with sFer < 10 $\mu g.L^{-1}$ and compromised Hb concentrations would likely still not shift them into the IDNA classification. Accordingly, contemporary approaches to iron replenishment in these specific IDA athlete populations are focussed on parenteral iron provision, which has the

▶ **Table 1** Classification, description, and common treatment approach to various levels of iron status based on the presenting serum ferritin (sFer), transferrin saturation (Tsat), and haemoglobin (Hb).

Classification	Serum Ferritin	Transferrin Saturation	Haemoglobin	Description	Common treatment approach
Healthy iron status	> 50 $\mu g.L^{-1}$	> 16 %	F: > 120 $g.L^{-1}$ M: > 130 $g.L^{-1}$	Iron stores and blood parameters are healthy	NA
Sub-optimal iron stores	35–50 $\mu g.L^{-1}$			Ferritin threshold of 50 $\mu g.L^{-1}$ is associated with a hepcidin threshold for increased iron absorption, signalling the onset of early ID	Nutritional assessment
Iron depletion (ID)	25–35 $\mu g.L^{-1}$			Iron stores in the bone marrow, liver, and spleen are depleted	Nutritional assessment and potential oral iron supplement
Iron deficiency non-anaemia (IDNA)	15–25 $\mu g.L^{-1}$	< 16 %		Iron supply to the erythroid marrow is reduced	Nutritional assessment and oral iron supplement
Iron deficiency anaemia (IDA)	< 15 $\mu g.L^{-1}$		F: < 120 $g.L^{-1}$ M: < 130 $g.L^{-1}$	Haemoglobin concentration and oxygen-carrying capacity is decreased	Parenteral iron

Note: F = female; M = male. Table created based on combined data and explanations from [3–6].

benefit of by-passing the gut (where our key limitations exist) and supplying iron direct to circulation. Regardless, the use case for such approaches should be well considered by the practitioner and athlete, and therefore, the remainder of this review will focus on parenteral iron delivery in athletes.

Parenteral iron approaches to treating anaemia

Parenteral treatment of iron deficiency is particularly warranted in the presence of severe IDA, or when there are ongoing and significant iron losses (e. g. heavy menstrual bleeding) [25]. Of note, thorough investigation of the underlying cause and exclusion of medical conditions such as occult gastrointestinal (GI) blood loss (e. g., from non-steroidal anti-inflammatory use, carcinoma), malabsorption (e. g. coeliac disease), and non-GI blood loss (e. g. abnormal uterine bleeding), should be considered by the treating physician [26]. Unsurprisingly, in clinical populations with chronically elevated hepcidin levels (e. g. cancer, inflammatory conditions), parenteral iron administration is recommended as it overcomes the negative effect of hepcidin on GI absorption [27]. In athletes, where repeated exercise-induced elevations of hepcidin occur daily [17, 28], the limitations to gut absorption of oral iron intake may be substantial. Interestingly, the amount of hepcidin required to block iron absorption from the gut is lower than that required to block iron recycling from macrophages, where intravenous (IV) iron is taken up [29]. Therefore, parenteral iron therapy becomes a viable treatment option for athletes presenting with IDA, or in those presenting with an inadequate response, intolerable side-effects, or poor adherence to oral iron therapy [25].

Intravenous iron: formulations and safety

Intravenous (IV) iron consists of an iron core within a carbohydrate shell [29]. The stability of the shell dictates the maximum dose that can be given in a single infusion: iron sucrose is less stable, allowing for only 200 mg to be administered per infusion [29], whereas the newer formulations of ferric carboxymaltose, ferric derisomaltose, low molecular weight iron dextran, and ferumoxytol have stable shells, permitting larger doses and fewer total infusions [25, 30]. Ferric derisomaltose and ferumoxytol, for example, are typically provided in a single infusion of up to 1000 mg over 15 min, in contrast to the multiple infusions required with iron sucrose [31]. Iron polymaltose is a cheaper preparation, which is also approved for total dose infusion, although over a longer period by slow infusion (~ 5 h) [32, 33]; more rapid infusion (~ 1 h) of iron polymaltose, however, may be safe and well-tolerated [33, 34]. The cumulative dose required is based on the individual's Hb, target Hb, and body weight [32], although some centres adopt a 'standard' 1-g dose protocol [35].

While serious adverse events and infusion reactions (e. g. anaphylaxis) were previously a concern with early IV preparations, primarily due to high molecular weight iron dextran formulations that are no longer available [36, 37], the newer formulations appear to have a similar safety profile to oral iron [31]. In fact, a meta-analysis from 2015 (n = 103 randomised controlled trials) reported no increased risk of serious adverse events (relative risk 1.04 95 %CI 0.93–1.17), compared to oral iron or placebo [38]. Milder reactions, such as headache, fever, joint pain, and urticaria, however, might be expected [25, 39]. Nevertheless, monitoring for 30 min after infusion by appropriately qualified staff is still advised [25] to monitor for and manage severe reactions (e. g. loss of consciousness, cardiac arrest, wheezing/stridor, hypotension) [39]. Iron-induced hypophosphatemia can occur following IV iron, particularly with ferric carboxymaltose, however is usually transient and frequently asymptomatic [31]. Nevertheless, phosphate measurement and replacement must be considered in individuals presenting with symptoms, such as muscle weakness and mental state changes, following parenteral iron treatment [25]. In the case of repeated administration, bone pain and fractures may also alert the clinician to possible hypophosphatemia [25] a risk that should also be considered and discussed prior to administration in athletes.

Intramuscular iron

Intramuscular (IM) iron, while effective, has shown to be no safer than intravenous (IV) iron, can be more painful, and is associated with permanent skin staining and possibly sarcomas [26, 27, 32, 33]. For athletes, this would be especially problematic as it has the potential to negatively impact training or competition in the immediate days post-treatment. Notably, current best practice guidelines from the Australian Institute of Sport (AIS) indicate a preference for IV iron infusion (preferably ferric carboxymaltose) only in athletes presenting with severe IDA, ineffective oral supplementation, or compromised Hb_{mass} in close proximity to a major sporting event [40]. Most importantly, both IV and IM iron therapy must be guided by sports physicians in-conjunction with a particular organisations policy (e. g. no needle).

Efficacy of IV formulations on haematological variables

Advantageously, newer IV formulations allow for complete, or almost complete, iron repletion to occur with a single dose (~1000 mg) administered over 15–60 min [31]. With these total dose protocols, peak ferritin concentrations are achieved in 7–9 days [41] with pharmacokinetic studies (using lower doses of 200 mg) demonstrating persistent elevations compared to baseline at 2 weeks [42]. The incremental increase in Hb varies depending on the initial Hb and the dose given [43]. Current evidence in clinical populations suggests that Hb increases by 2 $g.dL^{-1}$ per week; plateauing around 5–14 days [44, 45]. Here, the significant advantage of IV formulations is highlighted by the rapid normalisation of haematological parameters when compared to oral therapy. Indeed, in IDA pregnant women (mean sFer: 13 $\mu g.L^{-1}$, Hb 11.4 $g.dL^{-1}$), IV iron (1000 mg of ferric carboxymaltose or iron polymaltose) resulted in larger sFer and Hb increases at 4 weeks post infusion when compared to oral supplementation (325 mg daily ferrous sulphate) [46]. Similarly, a study in IDA postpartum women (sFer < 15 $\mu g.L^{-1}$, Hb < 9 $g.dL^{-1}$) also demonstrated that those treated with IV iron (iron sucrose 200 mg x 2) had more rapid increases in Hb in the first 2 weeks than those receiving oral supplementation (ferrous sulphate 200 mg twice daily) [45]. However, there was no significant difference between groups in Hb concentration at 6

weeks [45], emphasising that, where GI absorption is not impaired, similar longer-term outcomes can be achieved with oral and IV routes. Nevertheless, the rapidity of repletion and the ability to circumvent the gut is particularly attractive in certain clinical populations, including IDA athletes.

A target increase in Hb of ~ 2 g.dL^{-1} at 2–4 weeks is recommended in medical guidelines [47], with subsequent measurement of Hb at 4 weeks (or earlier if symptomatic), to evaluate treatment response and decide on subsequent doses [47]. Here, it is worth noting that, in athletes, the measurement of Hb to monitor the response to iron therapy in anaemia may be misleading. Haemoglobin concentration is dependent upon both the absolute mass of haemoglobin (i. e. Hb_{mass}) and blood volume (plasma and red cells) [48]. In athletes, Hb may be falsely low due to increased plasma volume or falsely high in the setting of dehydration. Therefore, the use of Hb_{mass} (through carbon monoxide rebreathing technique [49]) may be more precise and provide better information about oxygen carrying capacity. Nevertheless, this measurement is generally confined to research situations and is difficult for clinical practice. Accordingly, practitioners and clinicians are advised to employ current best practice standardisation protocols (e. g. well-hydrated state, morning sample, body position, rested and limited exercise in the 12 h prior to sampling) to maximise the validity and reliability of venous blood measurements [8].

Impact of parenteral iron approaches in athletes

Efficacy of parenteral iron on performance outcomes in non-anaemic athletes

While studies in athletes are limited, the effect of IV iron on haematological and performance indices appears to be dependent on the severity of iron deficiency pre-infusion. Burden and colleagues [50] examined the short- and medium-term effects of a 500 mg IV iron infusion in highly trained IDNA female (sFer < 30 µg.L^{-1}, Hb > 12 g.dL^{-1}) and male (sFer < 40 µg.L^{-1}, Hb > 12 g.dL^{-1}) marathon runners (Tsat 33.1 ± 12.0 %). Twenty-four hours after the infusion, mean sFer concentrations increased and remained elevated 4 weeks later. However, no differences in Hb concentrations, running economy, time to exhaustion, or VO_{2max} were reported at either 24 h or 4 weeks post-infusion. Further, a randomized controlled trial by Woods and colleagues [51] recruited 14 distance runners without iron deficiency anaemia (sFer: 30–100 µg.L^{-1}, Hb > 12.0 g.dL^{-1}), and examined the impact of three 100-mg IV iron (or placebo) treatments, each separated by 2 weeks, on performance, fatigue, and haematological indices. After 6 weeks, improvements in fatigue (Cohen's effect size –1.54, p = 0.05) and mood scores (Cohen's effect size –1.58, p = 0.02) were reported in the group receiving IV iron, in contrast to the group receiving a saline placebo injection. Unsurprisingly, no improvement in 3000-m time-trial performance was seen at week 4 nor was there any increase in Hb_{mass} at week 6 post-infusion [51], outcomes likely explained by the relatively high iron stores of the athletes (sFer > 30 µg.L^{-1}) prior to infusion.

In addition to these findings, Garvican and colleagues [24] examined the efficacy of IV ferric carboxymaltose in highly trained distance runners with low (sFer ≤ 35 µg.L^{-1} and Tsat < 20 %, or sFer ≤ 15 µg.L^{-1}) or sub-optimal iron stores (sFer < 65 µg.L^{-1}). After a series of IV injections over a 6-week period, Hbmass (4.9 %) increased only in the low iron stores group, which was accompanied by an increase in VO_{2max} (3.3 %) and run time to exhaustion (9.3 %). Conversely, no change reported in the suboptimal group, suggesting that supplementation is more effective when iron stores are compromised. Of interest, an oral iron supplement group in the same study showed no increase in Hb_{mass} or VO_{2max} after 6 weeks, regardless of initial sFer status (low or suboptimal).

To summarise, it appears that iron supplementation in non-iron-deficient athletes does not improve performance, and therefore, indiscriminate use of IV iron is not recommended. However, greater efficacy of IV iron supplementation is observed in athletes with lower sFer concentrations, suggesting the practice should be reserved for cases where iron stores are significantly compromised, such as IDA.

Efficacy of parenteral iron on performance outcomes in anaemic athletes

Few studies have investigated the effect of parenteral iron on haematological and performance variables in IDA athletes. A single case report has been published on a female athlete with IDA and represents the only 'longitudinal' (15 weeks) evidence for parenteral approaches to be used with anaemic athletes. Here, a female middle-distance runner (sFer 9.9 µg.L^{-1}, Hb 8.8 g.L^{-1}) received an IM iron injection (100 mg Fe), which was followed by 15 weeks of oral iron supplementation [52]. After 2 weeks, initial improvements in haematological variables were rapid, where the authors describe a 136 % increase in sFer (to 23.4 µg.L^{-1}), 36 % increase in Hb (to 12 g.dL^{-1}) and a 49 % increase in Hb_{mass} (389 g to 580 g). These outcomes were maintained, if not improved, at 15 weeks post-injection (sFer 27.0 µg.L^{-1}, Hb 13 g.dL^{-1} and Hbmass 710 g). Alongside the haematological improvements, the athlete ran a personal best time over 3,000 m ~70 days post-infusion. Although this case study showed a rapid and prolonged effectiveness of parental treatment in a single athlete, it should be noted that this approach was combined with oral iron supplementation, making it difficult to distinguish the sole efficacy of IM injections. Similarly, Pedlar et al., [7] showed IM iron injections given to a female Olympic Games 1500-m runner increased sFer levels more than four-fold (from 11 µg.L^{-1} to 47 µg.L^{-1}; extrapolated from Figure 1 in Pedlar et al. [7]) prior to a major event. However, these improved iron stores were back down to similar pre-IM injection levels within 6 months, despite oral iron supplements being used to support the increase. Of note, the athlete presented in the study by Pedlar and colleagues was not considered to have IDA (with Hb levels > 120 g.L^{-1}), and therefore, no study has to date examined the long-term effects of parenteral iron treatments in elite athletes with IDA, and the impact this may have on performance. Accordingly, much needed research in this space is required to better inform practitioners of the potential benefits of parenteral iron treatment.

Long-term impacts and decay

In a retrospective examination of a highly trained female athlete cohort with IDNA, McKay et al. [53] modelled the rate of decay in sFer following an IV infusion. These authors reported that sFer takes

499 days [range: 212–776 days] and 647 days [361–925 days] post-infusion to fall to 50 µg.L^{-1}and 35 µg.L^{-1}, respectively. Importantly, each individual athlete responded differently, with a random intercept for "subject" accounting for the majority of model variance, and factors such as the athletes' sport, age, or pre-infusion ferritin concentrations deemed less important. Noteworthily, potential confounding factors such as training load, menstrual cycle status, and dietary intake were not considered and may significantly contribute to the rate of sFer decay. Nevertheless, current recommendations suggest that athletes undergoing an IV iron infusion should assess iron status 1 month post-infusion to determine treatment efficacy, with a repeat assessment at 6 months post-infusion to determine iron retention [53]. If further follow-up treatment is required, this should be developed on an individual basis and may include a combination of dietary, oral, and parenteral strategies; although, as noted above, sFer levels still decayed to baseline by 6 months post-IM injection in the case study presented by Pedlar et al., [7] despite being supported with oral iron supplements during this period, which further highlights the individual response to treatment. Accordingly, future research should examine the rate of decay in sFer and Hb prospectively, considering differences between IDA and IDNA athletes, as well as the potential influence of individual factors which may affect the rate of decay.

Special considerations of parenteral iron use in athletes

World Anti-Doping Code Considerations

For athletes engaging in international competition, consideration must be given to the regulations governing the use of IV infusions. The World Anti-Doping Agency (WADA) defines an IV infusion as 'the supply of fluid and/or prescribed medication by drip or push directly into a vein' and states that they are 'prohibited both in-competition and out-of-competition if the volume delivered exceeds 100 ml within a 12-h period' [54]. However, if the infusion is received in the course of hospital treatment, a surgical procedure, or clinical diagnostic investigations, a therapeutic use exemption (TUE) may be necessary [54]. Although formulations vary in how they are administered (injection versus infusion, volume of solution), iron polymaltose, given as a slow infusion, typically exceeds this volume, and therefore, preference may be given to formulations such as ferric carboxymaltose. As such, consideration must be given to the need for IV therapy, the formulation used, and in some cases, potential application for a TUE prior to administration of IV iron in athlete populations.

Altitude

Unique to athletes is the need to consider iron supplementation prospectively to defend against the anticipated increased iron demand for physiological adaptation. Altitude training is frequently utilized by endurance athletes with the aim of inducing hypoxia-mediated adaptations to erythropoiesis. Supplementary iron is recommended when sFer is less than 35 µg.L^{-1} at 4–6 weeks prior, or < 130 µg.L^{-1} at 2 weeks prior to altitude, in an attempt to optimize increases in Hb_{mass} [55]. Unless sFer is less than 15 µg.L^{-1}, oral iron is preferred to align with the "no needle" policies of many sporting organizations [55]. Indeed, a study in non-anaemic endurance-trained athletes (Hb ~ 14 g.dL^{-1}; mean sFer ~ 71.2–88.1 µg.L^{-1} with 4 of 34 subjects with sFer < 20 ug.L^{-1}), demonstrated a similar increase in Hb_{mass} after 21 days of simulated altitude exposure in both oral (3.7 %) and IV (3.2 %) iron-supplemented groups, in contrast to a lack of Hb_{mass} response in the placebo group (0.1 %) [56]. This was associated with a larger increase in sFer in the 2 weeks prior to altitude exposure in the IV group, compared to the oral and placebo groups (IV 47 % and 92 % larger, respectively), and an increase in VO_{2peak} after altitude in the IV supplemented group only. Of note, a decrease in VO_{2peak} was seen in individuals across all groups, leading the authors to postulate that the results may have been confounded by residual fatigue after altitude training [56]. This study, combined with the guidelines presented above, suggest that iron supplementation might be necessary for hypoxia-mediated erythropoietic adaptation even in non-iron deficient athletes. Further, IV supplementation does not provide additional benefit to Hb_{mass} over oral therapy in non-iron deficient athletes [56]. However, considering the time required for IV iron to impact ferritin and Hb over oral iron supplementation in the short term (1–4 weeks), IV iron may be necessary in an IDA or IDNA athlete where a rapid rate of increase is required due to a limited lead-up time to altitude exposure.

Pregnancy

Pregnant women are a special population requiring consideration, with the increased numbers of athletes continuing sport throughout pregnancy. Indeed, IDA affects ~37 % of pregnant women (aged 15–49 years) worldwide [57], and when considering the increased iron requirements needed to simultaneously support both foetal development and high training loads, it is unsurprising that pregnant athletes are an extremely high risk group for iron deficiency. Pregnant athletes are a severely under-researched population, and so, current guidance is limited. Iron deficiency in pregnancy is known to have potential adverse maternal and foetal outcomes, such as premature birth, low birth weight, maternal infections, and increased maternal mortality [57]. Where treatment is required, oral iron is the first line approach, with IV iron indicated only if the response to oral therapy is inadequate and only in the second and third trimesters [31, 58]. However, given the adverse GI side-effects from oral therapy, there is increased interest in newer IV preparations. Indeed, a recent meta-analysis suggested an increased rate of target Hb achievement (OR = 2.66), increased Hb after 4 weeks (WMD = 0.84 g.dL^{-1}), and decreased adverse reactions (OR = 0.35) in pregnant women receiving IV compared to oral iron supplementation [59]. Additionally, ferric carboxymaltose may have fewer side-effects while also being more convenient and less costly than iron sucrose [60]. In pregnant athletes, where the risk of iron deficiency may be amplified, the use of IV iron could be preferable; however, further research, particularly on long-term outcomes, is warranted.

Summary and conclusions

The high prevalence of iron deficiency in athletes is attributed to a combination of increased losses, inadequate dietary intake, and exercise-induced increases in hepcidin. While oral iron supplemen-

tation is considered first-line treatment, the significant adverse GI side effects and the need to optimally time consumption around exercise pose potential challenges in the adherence and absorption of iron orally administered in athletes. On the other hand, parenteral iron, specifically IV, offers the advantage of circumventing hepcidin inhibition in the GI tract, while achieving more rapid increases in sFer and Hb. Of note, newer IV formulations allow for single total dose administration within an hour with a similar safety profile to that of oral iron. Current evidence suggests notable improvements with IV iron therapy in haematological and performance variables in IDA, and in IDNA where sFer is < 15 $\mu g.L^{-1}$. However, it is understandable that various sporting organisations have a cautious approach to the use of needles for treating nutrient deficiencies, confining IV iron therapy to IDA, ineffective long-term oral supplementation, or compromised haematological status in close proximity to a major sporting event [40]. In addition, parenteral iron should only be administered in consultation with a sports medicine physician, where consideration must be given to the need for a TUE in accordance with WADA regulations. Finally, future studies investigating parenteral iron approaches in athletes are warranted to assess the longer-term impacts on haematological and performance variables, in addition to exploring the individual factors (e. g. training load, dietary intake, menstrual cycle status) that affect the rate of decay.

Acknowledgement

The salary of MS is supported by a Royal Perth Hospital Research Foundation Fellowship (RPHRF CAF 00/21) and an Emerging Leader Fellowship from the Western Australian Future Health Research and Innovation Fund.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] McCormick R, Sim M, Dawson B et al. Refining treatment strategies for iron deficient athletes. Sports Med 2020; 50: 2111–2123

[2] Clénin G, Cordes M, Huber A et al. Iron deficiency in sports – definition, influence on performance and therapy. Swiss Med Wkly 2015; 145: w14196. DOI: 10.4414/smw.2015.14196

[3] World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity (2011). Available from. https://www.who.int/publications/i/item/WHO-NMH-NHD-MNM-11.1. Accessed: 10 November 2023

[4] Peeling P, Blee T, Goodman C et al. Effect of iron injections on aerobic-exercise performance of iron-depleted female athletes. Int J Sport Nutr Exerc Metab 2007; 17: 221–231. DOI: 10.1123/ijsnem.17.3.221

[5] Galetti V, Stoffel NU, Sieber C et al. Threshold ferritin and hepcidin concentrations indicating early iron deficiency in young women based on upregulation of iron absorption. eClin Med 2021; 39: 101052. DOI: 10.1016/j.eclinm.2021.101052

[6] World Health Organization. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations (2020). Available from https://www.who.int/publications/i/item/9789240000124. Accessed: 10 November 2023

[7] Pedlar CR, Whyte GP, Burden R et al. A case study of an iron-deficient female Olympic 1500-m runner. Int J Sports Physiol Perform 2013; 8: 695–698. DOI: 10.1123/ijspp.8.6.695

[8] Sim M, Garvican-Lewis LA, Cox GR et al. Iron considerations for the athlete: a narrative review. Eur J Appl Physiol 2019; 119: 1463–1478. DOI: 10.1007/s00421-019-04157-y

[9] Sims ST, Mackay K, Leabeater A et al. High prevalence of iron deficiency exhibited in internationally competitive, non-professional female endurance athletes–a case study. Int J Environ Res Public Health 2022; 19: DOI: 10.3390/ijerph192416606

[10] Sim M, Garvican-Lewis LA, Cox GR et al. Iron considerations for the athlete: a narrative review. Eur J Appl Physiol 2019; 119: 1463–1478

[11] Tan D, Dawson B, Peeling P. Hemolytic effects of a football-specific training session in elite female players. Int J Sports Physiol Perform 2012; 7: 271–276. DOI: 10.1123/ijspp.7.3.271

[12] Attwell C, McKay A, Sim M et al. Timing is everything, but does it really matter? Impact of 8-weeks morning versus evening iron supplementation in ballet and contemporary dancers. Eur J Sport Sci 2023; 23: 2275–2282. DOI: 10.1080/17461391.2023.2224285

[13] Parks RB, Hetzel SJ, Brooks MA. Iron deficiency and anemia among collegiate athletes: a retrospective chart review. Med Sci Sports Exerc 2017; 49: 1711–1715. DOI: 10.1249/MSS.0000000000001259

[14] Nicotra D, Arieli R, Redlich N et al. Iron deficiency and anemia in male and female adolescent athletes who engage in ball games. J Clin Med 2023; 12: 970. DOI: 10.3390/jcm12030970

[15] 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: 381–391. DOI: 10.1007/s00421-008-0726-6

[16] Peeling P, Sim M, McKay AKA. Considerations for the consumption of vitamin and mineral supplements in athlete populations. Sports Med 2023; DOI: 10.1007/s40279-023-01875-4

[17] Peeling P, Dawson B, Goodman C et al. Effects of exercise on hepcidin response and iron metabolism during recovery. Int J Sport Nutr Exerc Metab 2009; 19: 583–597. DOI: 10.1123/ijsnem.19.6.583

[18] Barney DE, Ippolito JR, Berryman CE et al. A prolonged bout of running increases hepcidin and decreases dietary iron absorption in trained female and male runners. J Nutr 2022; 152: 2039–2047. DOI: 10.1093/jn/nxac129

[19] McCormick R, Moretti D, McKay AKA et al. The Impact of morning versus afternoon exercise on iron absorption in athletes. Med Sci Sports Exerc 2019; 51: 2147–2155. DOI: 10.1249/MSS.0000000000002026

[20] McCormick R, Dreyer A, Dawson B et al. The effectiveness of daily and alternate day oral iron supplementation in athletes with suboptimal iron status (Part 2). Int J Sport Nutr Exerc Metab 2020; 30: 191–196. DOI: 10.1123/ijsnem.2019-0310

[21] McKay AKA, Anderson B, Peeling P et al. Iron absorption in highly-trained runners: Does it matter when and where you eat your iron? Med Sci Sports Exerc 2023; 55: 916–916

[22] Schaap CC, Hendriks JC, Kortman GA et al. Diurnal rhythm rather than dietary iron mediates daily hepcidin variations. Clin Chem 2013; 59: 527–535. DOI: 10.1373/clinchem.2012.194977

[23] Dawson B, Goodman C, Blee T et al. Iron supplementation: oral tablets versus intramuscular injection. Int J Sport Nutr Exerc Metab 2006; 16: 180–186. DOI: 10.1123/ijsnem.16.2.180

[24] Garvican LA, Saunders PU, Cardoso T et al. Intravenous iron supplementation in distance runners with low or suboptimal ferritin. Med Sci Sports Exerc 2014; 46: 376–385. DOI: 10.1249/MSS.0b013e3182a53594

[25] Pasricha SR, Tye-Din J, Muckenthaler MU et al. Iron deficiency. Lancet 2021; 397: 233–248. DOI: 10.1016/s0140-6736(20)32594-0

[26] Snook J, Bhala N, Beales ILP et al. British Society of Gastroenterology guidelines for the management of iron deficiency anaemia in adults. Gut 2021; 70: 2030–2051. DOI: 10.1136/gutjnl-2021-325210

[27] Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. Lancet 2007; 369: 1502–1504

[28] Fensham NC, McKay AKA, Tee N et al. Sequential submaximal training in elite male rowers does not result in amplified increases in interleukin-6 or hepcidin. Int J Sport Nutr Exerc Metab 2022; 32: 177–185. DOI: 10.1123/ijsnem.2021-0263

[29] Girelli D, Ugolini S, Busti F et al. Modern iron replacement therapy: clinical and pathophysiological insights. Int J Hematol 2018; 107: 16–30. DOI: 10.1007/s12185-017-2373-3

[30] Nikravesh N, Borchard G, Hofmann H et al. Factors influencing safety and efficacy of intravenous iron-carbohydrate nanomedicines: from production to clinical practice. Nanomedicine: NBM 2020; 26: 102178. DOI: 10.1016/j.nano.2020.102178

[31] Auerbach M, Gafter-Gvili A, Macdougall I. Intravenous iron: a framework for changing the management of iron deficiency. Lancet Haematol 2020; 7: e342–e350. DOI: 10.1016/S2352-3026(19)30264-9

[32] National Blood Authority Australia. Iron product choice and dose calculation for adults (2016); Available from: https://blood.gov.au/iron-product-choice-and-dose-calculation-guide-adults. Accessed: 10 November 2023

[33] Garg M, Morrison G, Friedman A et al. A rapid infusion protocol is safe for total dose iron polymaltose: time for change. Int Med J 2011; 41: 548–554. DOI: 10.1111/j.1445-5994.2010.02356.x

[34] Newnham E, Ahmad I, Thornton A et al. Safety of iron polymaltose given as a total dose iron infusion. Int Med J 2006; 36: 672–674. DOI: 10.1111/j.1445-5994.2006.01156.x

[35] Karim S, Butler JM, Barclay ML. A 1 g dose of intravenous iron is sufficient to treat iron deficiency anaemia. Int Med J 2020; 50: 1563–1566. DOI: 10.1111/imj.15110

[36] Wang C, Graham DJ, Kane RC et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. JAMA 2015; 314: 2062–2068

[37] Bannow BS. In older adults, iron dextran and ferumoxytol each had higher anaphylaxis risk at ≤ 1 d than iron sucrose. Annals Internal Med 2022; 175: JC95

[38] Avni T, Bieber A, Grossman A et al. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc 2015; 90: 12–23. DOI: 10.1016/j.mayocp.2014.10.007

[39] DeLoughery TG. Safety of oral and intravenous iron. Acta Haematol 2019; 142: 8–12

[40] Australian Institute of Sport. Iron deficiency best practice guidelines (2022). Available from: https://www.ais.gov.au/__data/assets/pdf_file/0014/1000490/Sport-supplement-fact-sheets-Iron-v4.pdf. Accessed: 10 November 2023

[41] Blunden RW, Lloyd JV, Rudzki Z et al. Changes in serum ferritin levels after intravenous iron. Ann Clin Biochem 1981; 18: 215–217. DOI: 10.1177/000456328101800405

[42] Garbowski MW, Bansal S, Porter JB et al. Intravenous iron preparations transiently generate non-transferrin-bound iron from two proposed pathways. Haematologica 2021; 106: 2885–2896. DOI: 10.3324/haematol.2020.250803

[43] Neef V, Baumgarten P, Noone S et al. The impact of timing of intravenous iron supplementation on preoperative haemoglobin in patients scheduled for major surgery. Blood Transfus 2022; 20: 188–197. DOI: 10.2450/2021.0058-21

[44] Klein AA, Chau M, Yeates JA et al. Preoperative intravenous iron before cardiac surgery: a prospective multicentre feasibility study. Br J Anaesth 2020; 124: 243–250. DOI: 10.1016/j.bja.2019.11.023

[45] Bhandal N, Russell R. Intravenous versus oral iron therapy for postpartum anaemia. BJOG 2006; 113: 1248–1252. DOI: 10.1111/j.1471-0528.2006.01062.x

[46] Khalafallah AA, Hyppa A, Chuang A et al. A prospective randomised controlled trial of a single intravenous infusion of ferric carboxymaltose vs single intravenous iron polymaltose or daily oral ferrous sulphate in the treatment of iron deficiency anaemia in pregnancy. Semin Hematol 2018; 55: 223–234. DOI: 10.1053/j.seminhematol.2018.04.006

[47] Gasche C, Berstad A, Befrits R et al. Guidelines on the diagnosis and management of iron deficiency and anemia in. inflammatory bowel diseases. Inflam Bowel Dis 2007; 13: 1545–1553. DOI: 10.1002/ibd.20285

[48] Otto JM, Montgomery HE, Richards T. Haemoglobin concentration and mass as determinants of exercise performance and of surgical outcome. Extrem Physiol Med 2013; 2: 33. DOI: 10.1186/2046-7648-2-33

[49] Schmidt W, Prommer N. The optimised CO-rebreathing method: a new tool to determine total haemoglobin mass routinely. Eur J Appl Physiol 2005; 95: 486–495. DOI: 10.1007/s00421-005-0050-3

[50] Burden RJ, Pollock N, Whyte GP et al. Effect of intravenous iron on aerobic capacity and iron metabolism in elite athletes. Med Sci Sports Exerc 2015; 47: 1399–1407. DOI: 10.1249/MSS.0000000000000568

[51] Woods A, Garvican-Lewis LA, Saunders PU et al. Four weeks of IV iron supplementation reduces perceived fatigue and mood disturbance in distance runners. PLoS One 2014; 9: e108042. DOI: 10.1371/journal.pone.0108042

[52] Garvican LA, Lobigs L, Telford R et al. Haemoglobin mass in an anaemic female endurance runner before and after iron supplementation. Int J Sports Physiol Perform 2011; 6: 137–140. DOI: 10.1123/ijspp.6.1.137

[53] McKay AKA, Goods PSR, Binnie MJ et al. Examining the decay in serum ferritin following intravenous iron infusion: a retrospective cohort analysis of Olympic sport female athletes. Appl Physiol Nutr Metab 2020; 45: 1174–1177. DOI: 10.1139/apnm-2020-0132

[54] World Anti-Doping Agency. Intravenous infusions and/or injections (2023). Available from: https://www.wada-ama.org/sites/default/files/2023-10/tue_physician_guidelines_iv_infusion_october_2023.pdf. Accessed: 10 November 2023

[55] Stellingwerff T, Peeling P, Garvican-Lewis LA et al. Nutrition and altitude: strategies to enhance adaptation, improve performance and maintain health: a narrative review. Sports Med 2019; 49: 169–184. DOI: 10.1007/s40279-019-01159-w

[56] Garvican-Lewis LA, Vuong VL, Govus AD et al. Intravenous iron does not augment the hemoglobin mass response to simulated hypoxia. Med Sci Sports Exerc 2018; 50: 1669–1678. DOI: 10.1249/mss.0000000000001608

[57] World Health Organization. Anaemia (2023); Available from: https://www.who.int/health-topics/anaemia#tab=tab_1. Accessed: 10 November 2023

[58] Tran K, McCormack S. Screening and treatment of obstetric anemia: a review of clinical effectiveness, cost-effectiveness, and guidelines. In: Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019

[59] Govindappagari S, Burwick RM. Treatment of iron deficiency anemia in pregnancy with intravenous versus oral iron: systematic review and meta-analysis. Am J Perinatol 2019; 36: 366–376. DOI: 10.1055/s-0038-1668555

[60] Christoph P, Schuller C, Studer H et al. Intravenous iron treatment in pregnancy: comparison of high-dose ferric carboxymaltose vs. iron sucrose. J Perinat Med 2012; 40: 469–474. DOI: 10.1515/jpm-2011-0231