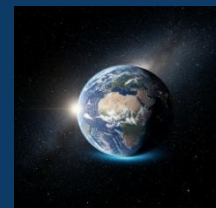




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Alternate-Day, Low-Dose Oral Iron Supplementation and Hepcidin-Guided Dosing Timing in Athletes: A Narrative Review

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Abstract

Introduction: Iron deficiency is one of the most common micronutrient deficiencies in athletes, particularly in endurance athletes and women. The effectiveness of oral iron supplementation depends not only on the dose but also on supplementation timing, dosing frequency, and hepcidin regulation.

Aim: To summarize current evidence on oral iron supplementation strategies in athletes, with particular emphasis on the role of hepcidin in optimizing iron absorption.

Material and methods: A literature search was conducted through PubMed (MEDLINE) and Google Scholar. Randomized controlled trials, stable-isotope studies, and review articles published in English up to February 2026 were analyzed.

Results: Current evidence suggests that alternate-day, low-dose oral iron supplementation improves gastrointestinal tolerance and may enhance iron absorption compared with daily dosing. Iron absorption is influenced by circadian rhythm and exercise-induced increases in hepcidin, making supplementation timing clinically important. Conventional ferrous salts remain the first-line treatment, whereas novel formulations and intravenous iron may be appropriate in selected cases.

Conclusions: Iron supplementation should be individualized according to iron status, training schedule, treatment tolerance, and clinical needs. Optimizing dosing frequency and timing represents a simple strategy to improve treatment effectiveness. Further athlete-specific studies are needed to establish evidence-based recommendations.

Keywords: iron deficiency; iron supplementation; hepcidin; athletes; alternate-day dosing; oral iron; endurance athletes

1. Introduction

Iron deficiency is one of the most common micronutrient deficiencies in athletes. It affects approximately 15-35% of female and 3-11% of male athletes, with the highest prevalence in endurance disciplines and women [1,2]. Left untreated, iron deficiency with or without anemia may impair oxygen transport, mitochondrial function, and training adaptation. Therefore, iron supplementation has become a routine part of sports medicine and sports nutrition practice [1,3]. Beyond its role in erythropoiesis, iron is a cofactor for enzymes involved in oxidative energy metabolism, and even non-anemic iron deficiency may impair endurance capacity and training tolerance in some athletic populations [4–6].

Oral iron supplementation remains the first-line treatment for most athletes. However, its efficacy is inconsistent and depends on dosing strategy and individual factors. Iron absorption depends not only on the administered dose, but also on the body's ability to absorb it. This process is regulated by hepcidin, a hormone which controls iron homeostasis.

Hepcidin is upregulated both by the ingestion of iron and in response to exercise-induced inflammation. As a result, athletes supplementing iron may experience reduced iron absorption that does not apply to sedentary individuals [7–11].

Nevertheless, for many years, oral iron supplementation in athletes has followed the same dosing schedule used in the general population, without considering hepcidin kinetics. Over the past decade, growing evidence has emerged showing that less-frequent, lower-dose regimens, timed appropriately relative to both the circadian hepcidin rhythm and training sessions, may improve tolerability and, in some contexts, absorption efficiency [12–15]. These findings are relevant for athletes, who are more likely to require iron supplementation and experience exercise-induced increases in hepcidin levels.

The aim of this review is to summarize current evidence on oral iron supplementation strategies in athletes, with particular emphasis on dosing frequency, dosing timing in relation to exercise and the circadian rhythm of hepcidin, and emerging oral iron formulations. Particular attention is also given to the role of hepcidin as a physiological link between exercise, iron supplementation and iron absorption. Based on available evidence, practical recommendations are provided for clinicians, sports physicians and sports nutritionists.

Appropriate dosing decisions are made every day in clinical practice. Athletes with low ferritin levels are often prescribed standard iron supplementation protocols, without considering the effect of exercise on hepcidin concentrations. Small, low-cost changes to dosing frequency have the potential to meaningfully improve both absorption efficiency and the tolerability that determines whether an athlete actually completes a prescribed course of supplementation. Rather than focusing on the mechanisms of hepcidin biology, this review emphasizes practical strategies that may help optimizing iron supplementation in athletes.

2. Materials and methods

This article is a narrative review. A literature search was conducted using the PubMed (MEDLINE) and Google Scholar databases for studies published in English up to February 2026. The search included the following terms: “hepcidin”, “iron supplementation”, “alternate-day dosing”, “dosing frequency”, “split dosing”, “iron absorption”, “circadian”, “diurnal”, “Sucrosomial”, “intravenous iron”, “athletes”, “endurance exercise” and “runners”. Priority was given to randomized controlled trials and stable-isotope absorption studies directly comparing dosing regimens or timing strategies, supplemented by studies characterizing the exercise-induced and circadian hepcidin response. Reference lists of identified articles were manually screened for additional relevant articles, and recent narrative and systematic reviews on iron status in athletes were used to verify completeness of the search. Case reports, conference abstracts without peer-reviewed full texts, and non-English articles were excluded.

3. Research Results

3.1. Iron deficiency in athletes: physiological consequences

Iron deficiency in athletes results from several interacting factors. These include exercise-induced inflammation, hepcidin upregulation, mechanical hemolysis, gastrointestinal iron losses, menstrual blood losses in female athletes and inadequate dietary iron intake, particularly in athletes with low energy availability or plant-based diets [1,2,16]. The clinical consequences range from subtle reductions in training tolerance and recovery in non-anemic iron deficiency to clearly demonstrated impairments in maximal oxygen uptake and endurance performance once anemia develops [5–7]. Because endurance athletes and female athletes are at highest risk of iron deficiency and most likely to receive oral iron supplementation, optimizing dosing strategies is highly relevant in sports medicine.

3.2. Hepcidin: the physiological link between exercise, iron supplementation and iron absorption

Hepcidin is the main regulator of systemic iron homeostasis. It binds ferroportin, the only known cellular iron exporter, and promotes its internalization and degradation. As a result, intestinal iron absorption decreases and less iron is released from macrophages into the bloodstream [17]. Hepcidin synthesis is stimulated by several factors. These include increased iron stores, inflammation mediated by interleukin-6 acting through the JAK-STAT pathway, and by iron itself via the BMP-SMAD signaling pathway. Consequently, inflammation, infection or iron supplementation may all reduce iron absorption.

In athletes, hepcidin increases for two independent reasons. First, endurance exercise induces a transient inflammatory response mediated by interleukin-6, which stimulates hepatic hepcidin synthesis. Hepcidin levels typically peak 3-6 hours after exercise and may remain elevated for several hours afterward [7,9]. Second, oral iron supplementation also provokes a hepcidin response that can persist for up to 24 hours, reducing the absorption of any additional iron taken during this period [11]. In athletes training regularly and supplementing iron daily, these two mechanisms may overlap, limiting iron absorption. These interactions explain why timing and frequency of iron supplementation in athletes are important.

3.3 Circadian variation of hepcidin

Beyond its response to iron intake and exercise, hepcidin shows a circadian rhythm independent of dietary iron intake. Circulating hepcidin concentrations are lowest in the early morning, then gradually increase during the day and decline in the evening. This pattern persists even during fasting, which indicates that it is regulated by the circadian system rather than food intake [18,19].

These physiological changes have clinical implications. Because hepcidin concentrations are naturally low in the morning, conditions for iron absorption are more

favorable at this time of day. In athletes who train later in the day, supplementing oral iron in morning hours also avoids the post-exercise increase in hepcidin, which may reduce iron absorption. Therefore, both supplementation timing and training schedule should be considered when planning iron supplementation.

3.4 Effects of dosing on hepcidin and iron absorption

Studies have shown that a single oral dose of iron increases serum hepcidin concentrations within hours, and that this response reduces the absorption of a second dose given later the same day or on the following day [11,12]. These findings have challenged the long-standing assumption that more frequent dosing improves cumulative iron delivery. Instead, doses given too close together may lead to sustained elevation in hepcidin and reduced iron absorption over time.

3.5 Daily versus alternate-day dosing

One study directly compared iron absorption after oral iron supplements given on consecutive days versus alternate days in iron-depleted women. The authors measured both fractional and total iron absorption. They showed that alternate-day dosing resulted in higher absorption per dose than consecutive daily dosing. As a result, total iron absorption was similar or even better despite fewer doses administered [12]. Another study in patients with iron deficiency anemia similarly found that alternate-day dosing was associated with a more favorable absorption profile than daily dosing. Hepcidin was used as a biomarker to assess this response [13].

Importantly, one study has directly compared daily and alternate-day oral iron supplementation in athletes. In this study, endurance-trained runners with suboptimal ferritin received iron supplements daily or on alternate days for over eight weeks. The results found no statistically significant difference in the rise in serum ferritin or hemoglobin mass between the two regimens. However, the alternate-day group reported fewer and less severe gastrointestinal side effects, with six severe complaints in the daily-dosing group compared with only one in the alternate-day group [14]. This study demonstrated that the main benefit of alternate-day supplementation may be a better tolerability rather than an improvement in iron status. Nevertheless, the physiological rationale for improved iron absorption remains strong and has been confirmed in non-athlete populations.

3.6. Split versus single daily dosing

Another investigated strategy of iron supplementation is divided dosing, in which the total daily elemental iron dose is split into two administrations. Current evidence shows that splitting the daily dose does not improve absorption compared with a single morning dose. In some protocols, iron absorption was lower, because the hepcidin response to the first dose suppressed the absorption of the second dose [12]. These findings suggest that taking a single daily dose is more effective than dividing the same dose into two administrations. Therefore, split-dose regimens are not recommended in oral iron therapy.

3.7. Timing of iron supplementation in relation to training

The timing of iron supplementation in relation to a training session has direct, measurable effects on absorption. One study demonstrated that fractional iron absorption in endurance runners was greatest in the morning and when iron was consumed within 30 minutes after completing exercise, before the post-exercise hepcidin rise [15]. A related study extended this work by timing iron intake to meet with the expected 3-hour post-exercise hepcidin peak: fractional absorption fell by 36% when iron was consumed 2 hours after a prolonged run, compared with a resting control condition, alongside a 51% rise in plasma hepcidin [10]. Together, these studies indicate that the same total daily iron dose can be absorbed differently depending on dosing time - whether it is taken in a favorable window (morning, immediately post-exercise) or an unfavorable one (mid-to-late post-exercise, coinciding with the hepcidin peak).

These findings are consistent with the post-exercise hepcidin kinetics described elsewhere: hepcidin concentrations typically peak 3–6 hours after exercise in trained athletes [7,9]. In practice, this creates two appropriate dosing windows: in the morning or immediately after finishing a session (within the roughly 30-minute window before hepcidin begins to rise). If neither option is possible, supplementation should be delayed until post-exercise hepcidin concentrations have returned to baseline. These strategies may improve iron absorption without changing the dose or type of supplement.

3.8. Oral iron formulations and absorption enhancers

The formulation of oral iron, in addition to dose, frequency, and timing, affects both absorption and tolerability. Conventional ferrous salts - ferrous sulfate, ferrous fumarate, and ferrous gluconate - remain the first line treatment because they are least expensive, most widely available, and supported by clinical evidence. However, a large fraction of the ingested elemental iron is released as free ionic iron in the gastrointestinal lumen, which can directly irritate the intestinal mucosa, producing the nausea, constipation, and abdominal discomfort that reduce treatment adherence.

Chelated iron forms have been developed to improve iron absorption and gastrointestinal tolerance. One of the best studied formulations is ferrous bisglycinate chelate, in which iron is bound to two glycine molecules. A systematic review and meta-analysis found that it increased hemoglobin more effectively and caused fewer gastrointestinal adverse events than conventional iron salts, particularly in pregnant women, although its effects on ferritin were less consistent [20].

Another formulation is glycoprotein matrix-bound iron. In a study, it produced significantly higher peak and cumulative serum iron concentrations than ferrous fumarate. However, ferrous bisglycinate chelate showed similar absorption to ferrous fumarate in this study, suggesting that the delivery mechanism, rather than chelation alone, may be an important determinant of iron absorption [21]. Although this study included a recreationally active population rather than competitive athletes specifically, it suggests that newer oral iron preparations may improve treatment tolerance, and in some cases, iron absorption.

One of the most studied forms of iron is Sucrosomial® iron, a nanoparticulate formulation in which ferric pyrophosphate is encapsulated in a phospholipid and sucrose matrix. It is absorbed substantially through alternative intestinal pathways that are largely independent of the classical hepcidin-ferroportin mechanism. A recent clinical review summarizing trials across multiple iron-deficient populations found that Sucrosomial® iron achieves hematological responses comparable to intravenous iron, at substantially lower elemental iron doses (20-30 mg/day) and with fewer gastrointestinal side effects than conventional iron salts [22]. Although studies in athletes are lacking, its hepcidin-independent absorption profile makes it a candidate for further study in athletic populations who supplement during periods of high intensity training.

Probiotic co-administration represents another strategy. A randomized controlled trial was conducted in non-anemic female athletes with low iron stores, comparing 20 mg of oral iron alone against the same dose combined with the probiotic strain Lactobacillus plantarum 299v, which has been shown to enhance intestinal iron absorption in meal studies. The combination resulted in a faster improvement in iron status compared with iron alone, although no conclusive effect on physical performance was observed in this exploratory study [23].

3.9. Intravenous iron as an alternative when oral iron therapy is insufficient

For athletes with more severe iron deficiency, poor tolerance of oral iron, or a need for rapid restoration of iron stores, intravenous iron may be considered. Compared with oral iron supplementation, intravenous iron bypasses the gastrointestinal tract and delivers iron directly into the circulation. Early work demonstrated that iron injections improved aerobic exercise performance in iron-depleted female athletes [24]. Another trial showed that intravenous iron effectively restored iron stores in distance runners with low or suboptimal ferritin [25], and another found that four weeks of intravenous iron supplementation reduced fatigue and mood disturbance in distance runners, even though these athletes did not have clinically defined iron deficiency; no improvement in oxygen transport capacity or performance was observed [26]. In a randomized trial in elite athletes with suboptimal iron status, intravenous iron was found to improve iron status effectively but did not produce a clear aerobic-capacity advantage over comparable oral repletion strategies [27]. Although intravenous iron is generally well tolerated, it should not be used routinely. It is more expensive, requires medical supervision, and has a risk of adverse reactions. Therefore, current evidence supports reserving it for selected athletes after a comprehensive assessment.

3.10. Special considerations in selected athlete populations

Although the general principles of iron supplementation are similar across the athletic population, some groups are at greater risk of iron deficiency and may require closer monitoring and individualized treatment strategies.

Female athletes are at increased risk of iron deficiency because of menstrual losses combined with exercise-induced hepcidin elevation and, in some cases, low energy availability associated with Relative Energy Deficiency in Sport (RED-S) [28–30].

Adolescent athletes represent a second population requiring particular attention due to rapid growth and intensive training, both of them increase iron requirement [31].

Finally, athletes following vegetarian or vegan diets are at increased risk because their diet mainly contains lower-bioavailability non-heme iron. Regular assessment of iron status is recommended, particularly in athletes with additional risk factors such as endurance training or low energy availability.

Altitude training camps are widely used by endurance athletes to increase hemoglobin mass and, potentially, aerobic performance. Athletes preparing for altitude training require special attention, because hypoxia stimulates erythropoiesis and increases iron utilization. Because of this markedly increased iron demand, athletes are typically advised to enter an altitude camp with adequate iron stores, generally cited as a serum ferritin above 30-50 µg/L [2]. However, a trial comparing intravenous iron, oral iron, and placebo in non-anemic endurance athletes during three weeks of simulated altitude found that intravenous iron did not increase the hemoglobin mass substantially [32]. For athletes preparing for altitude exposure, oral iron supplementation should be applied early enough to optimize iron stores before altitude training. Intravenous iron should be reserved for athletes who require rapid correction before altitude exposure.

3.11. Iron status monitoring

Whichever dosing strategy is chosen, treatment effectiveness should be confirmed through periodic reassessment rather than assumed. Serum ferritin remains the primary marker of iron stores, but its interpretation may be affected by inflammation [33]. Soluble transferrin receptor (sTfR) is relatively insensitive to the acute-phase response and exercise-induced inflammation, making it a useful marker when ferritin interpretation is uncertain [34]. Large screening studies in elite athletes have shown that routine monitoring for iron-related abnormalities is more effective than testing only after symptoms appear [35]. In clinical practice, ferritin, hemoglobin, and, where available, transferrin saturation should be reassessed approximately 6-8 weeks after initiating iron supplementation [2]. This allows clinicians to evaluate the response to treatment and modify the supplementation strategy if needed.

4. Practical recommendations

Studies have demonstrated that a reasonable starting point for most non-anemic athletes with confirmed iron deficiency is a trial of oral ferrous iron at a reduced dose (approximately 40-80 mg elemental iron), taken on alternate days rather than daily, preferably in the morning or immediately after a training session. Athletes who tolerate this regimen poorly, who have more severe deficiency (particularly iron deficiency anemia), or who are approaching a time-sensitive event such as a competition or altitude training camp may require a different approach. In these cases, a novel oral formulation may be considered or where oral strategies are insufficient, intravenous iron under appropriate medical supervision. Regardless of the supplementation strategy, the main goal is to minimize the unnecessary increases in hepcidin (repeated iron doses, exercise), while still delivering enough elemental

iron to correct the deficit. Based on the evidence reviewed above, the following practical recommendations may be applied in athletes with iron deficiency:

- Prefer alternate-day dosing over consecutive daily dosing. Although studies in athletes have not consistently shown greater improvement in ferritin levels, alternate-day supplementation meaningfully reduces gastrointestinal side effects and may improve treatment adherence [12–14].
- Use lower elemental iron doses (approximately 40-80 mg) rather than higher single doses, which do not proportionally improve absorption and are more likely to increase gastrointestinal side effects [12].
- Avoid split (twice-daily) dosing, as it offers no absorption advantage over a single dose, because the hepcidin response after the first dose reduces absorption of the second dose [12].
- Take oral iron in the morning or within 30 minutes after finishing a training session, before hepcidin levels increase. Avoid supplementation in the 2-6 hour post-exercise window, when iron absorption is reduced [10,15,18].
- For athletes with poor tolerance of conventional iron salts, consider alternative oral formulations (e.g., ferrous bisglycinate, glycoprotein matrix-bound iron) as an intermediate step, or a more heavily engineered formulation such as Sucrosomial® iron, alongside adjuncts such as probiotic co-administration [20–23].
- Reserve intravenous iron for athletes with more severe deficiency, oral intolerance, or when rapid correction of iron stores is required before competition or altitude training [24–27].
- Reassess iron status by measuring ferritin, hemoglobin, and, when available, transferrin saturation, 6–8 weeks after initiating any regimen to confirm response and adjust the treatment if necessary [3,34,36].

5. Limitations and future research directions

This review has several limitations. As a narrative review, it does not include a formal risk-of-bias assessment or meta-analysis. In addition, although the literature search strategy was broad, it was not conducted in the manner of a systematic review. Current evidence on iron supplementation in athletes is still limited. Several key studies supporting alternate-day, low-dose supplementation were conducted in iron-depleted, non-athlete women rather than in competitive athletes [11–13]. In addition, athlete-specific studies are generally small, include athletes from different sports and training loads, and often focus on short-term outcomes such as iron absorption rather than on long-term changes in iron status or athletic performance [10,14,15]. Athlete-specific data on novel formulations such as Sucrosomial® iron remain scarce [22].

Future research should focus on well-designed randomized controlled trials conducted in athletic populations. These studies should compare alternate-day and daily dosing with hematological and performance endpoints measured over a full season [14]. Longer-term studies should also evaluate different timing strategies in relation to training and the hepcidin response [10,15]. Future studies should also evaluate novel formulations and adjuncts such as Sucrosomial® iron and probiotic co-administration, compared with conventional alternate-

day dosing [22,23]. In addition, athletic-specific studies are also needed to determine how factors such as sex and menstrual cycle influence the hepcidin responses and effectiveness of iron supplementation [28,29].

6. Conclusions

Hepcidin is the physiological link between exercise, dosing frequency, supplementation timing, and iron absorption in athletes. Training itself, the circadian rhythm, and iron supplementation independently increase hepcidin concentrations and suppress iron absorption. Current evidence, together with the athlete-specific literature, supports alternate-day, low-dose oral iron supplementation administered in the morning or shortly after exercise, while avoiding the 2-6 hour post-exercise hepcidin peak. This approach is considered as the most effective strategy for balancing iron tolerability and absorption efficiency. Conventional iron salts remain the first-line treatment, while novel oral iron formulations may be considered when tolerability or absorption efficiency is a limiting factor. Intravenous iron should be reserved for selected cases, when oral iron supplementation is ineffective, poorly tolerated, or rapid correction of iron stores is required.

Overall, the available evidence supports an individualized approach to iron supplementation based on the athlete's iron status, training schedule, treatment tolerance, and clinical needs. Clinicians and practitioners should reassess iron status regularly and adjust the supplementation strategy accordingly. Although understanding of hepcidin physiology has improved, further studies are needed to determine the optimal supplementation strategies for the athletic population and to evaluate long-term effects on hematological outcomes and athletic performance.

Disclosure

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