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Approaches to Prevent Iron Deficiency in Athletes

Ansätze zur Prävention eines Eisenmangels bei Athleten

CLINICAL REVIEW

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Summary

› **For athletes,** iron plays an important role in improving oxygen supply, energy production, muscle function, and cognitive performance. However, iron deficiency is a common problem in athletes, especially endurance athletes, due to factors such as increased iron loss due to exercise-induced sweating, hematuria, and gastrointestinal bleeding. Exercise induces hematological adaptations due to increased demand of oxygen transport as well as inflammation, which reduces the ability to absorb iron post-exercise. Iron deficiency can lead to fatigue, reduced performance, poorer recovery and increased susceptibility to infections.

› **Iron absorption** is tightly regulated to prevent toxicity, with hepcidin playing a central role. Elevated hepcidin levels, which are influenced by exercise-induced inflammation and circadian rhythms, can significantly reduce iron absorption. In addition, the bioavailability of dietary iron varies, with heme iron from animal products being more readily absorbed than non-heme iron from plant sources. Athletes on a vegetarian or vegan diet may require increased iron intake to meet their needs.

› **Monitoring iron status** through regular blood tests, including serum ferritin and hemoglobin levels, is critical for early detection and treatment of iron deficiency. Strategies to improve iron absorption include consuming iron-rich foods with promoters such as vitamin C, while inhibitors such as phytates and calcium should be avoided. In cases of significant deficiency, supplementation under medical supervision may be necessary. Understanding these factors and using appropriate nutritional and monitoring practices can help athletes maintain optimal iron levels and overall performance.

KEY WORDS:
Iron Metabolism, Heme and Non-Heme Iron, Dietary Iron, Hepcidin, Promotors and Inhibitors of Iron Absorption, Nutrient Timing

Introduction

Iron plays a crucial role for health and performance of athletes by supporting oxygen transport and delivery, mitochondrial energy production, muscle function, immune response and cognitive function (2). Among others, iron is an essential component of hemoglobin and myoglobin, which are responsible for transporting oxygen in blood and muscles, respectively (21). Thus, iron deficiency may impair athletic performance by lack of energy and reduced work capacity, suppressed training adaptation, impaired recovery from exercise, fatigue and increased susceptibility to infections (15). In line with the importance of iron, athletes notice an iron deficiency by unspecific symptoms such as fatigue, dyspnea, lethargy and higher susceptibility to infections. Secondary symptoms include a reduction of training and competition outcomes, reduced adaptation to training load and overall work capacity (15).

Iron deficiency is one of the most common nutritional deficiencies worldwide. Athletes, particularly those involved in endurance sports, are at an even higher risk for iron deficiency with a prevalence of 15-35% of female athletes and 3-11% of male athletes compared to approximately 5% in the general population.

Risk factors for developing iron deficiency in athletes include

a) increased iron loss due to exercise-induced sweating, hematuria, and gastrointestinal bleeding,
b) exercise-induced hematological adaptations due to increased demand of oxygen transport and
c) exercise-induced inflammation, which reduces the ability to absorb iron post-exercise (20).

Regulation of Iron Absorption

Although iron is essential for health, well-being, and athletic performance it is also a highly reactive mineral that may be toxic to the human body when ingested in high dosages (26). Iron overload is discussed to be associated with different diseases such as hemochromatosis, cardiovascular diseases, cancer and type 2 diabetes mellitus (24).

Due to the toxicity of iron, its absorption is highly regulated and very limited with absorption rates ranging from only 2 to 35%. One of the key fac- ›

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Table 1

Promotors and inhibitors of iron absorption and dietary sources (adapted from Biesalski HK (3)).

INHIBITORS OF NON-HEME IRON ABSORPTION	PROMOTORS OF NON-HEME IRON ABSORPTION
Phytates (in whole grain cereals, bread, legumes, nuts and seeds)	Vitamin C (in fruits and vegetables, ask your sports dietitian for support to aim for ≥50 mg in a iron-rich meal)
Polyphenolic and phenolic compounds (in herbal and non-herbal tea, coffee, red wine, chocolate)	Carotenoids (in carrots, pumpkin, apricot, green leafs, tomatoes)
Calcium (in dairy products or in multi-mineral or calcium dietary supplements)	Fermented food such as sauerkraut, kimchi or fermented mixed pickels (fermentations reduces phytates)
Other minerals (zinc, manganese)	Cooking the food (reduces presence of phytate)

tors in the regulation of iron absorption is the hormone hepcidin. Briefly, increased hepcidin levels in the blood decrease iron absorption, and hepcidin increases due to exercise-induced temporary inflammation and following a circadian rhythm with higher levels later in the day (15).

In addition, many studies have shown an increase in inflammation markers (IL-6) and hepcidin levels in athletes in a state of low energy availability (LEA), and some have observed LEA-independent yet insignificant rises in hepcidin levels following glycogen-depleting exercises or exercises with low carbohydrate availability (16) (figure 1).

Degradation of senescent red blood cells also contributes to iron loss in humans, even though the human body has the capacity to recycle 90% of the iron from degraded erythrocytes. In a state of iron homeostasis, where iron losses are minimized to 1-2 mg/d the absorption of dietary iron (0,5-2 mg) is sufficient to counterbalance the losses. However, this counterbalance may be disrupted in competitive athletes.

It must be admitted that although iron deficiency is more common in females compared to males, the paucity of studies on iron and hepcidin metabolism in athletes have been conducted in males. Due to the gender data gap little is known about iron and hepcidin metabolism in female competitive athletes (10).

Iron Availability

The availability of iron is very limited depending on the dietary source and the presence of inhibitors and promotors of iron absorption in the meal. The typical absorption rate varies between 5 to 35% for heme iron (Fe^{2+}) and 2-20% for non-heme iron (Fe^{3+}) (4).

Heme iron is found in animal products such as red meat, poultry and fish, whereas non-heme iron is derived from vegetable foods like legumes, grains, and vegetables (13). The divalent heme (Fe^{2}+) iron is easier to absorb than the oxidized non-heme iron due to its distinctive absorption pathway, resistance to dietary inhibitors, and effective transport and utilization mechanisms within the body (22). Vegetarian and vegan athletes may struggle to meet their iron needs, as their diets primarily contain non-heme iron. Vegetarian athletes might ingest approximately 10% more iron than omnivore athletes to account for the lower iron absorption.

However, the absorption of non-heme iron in vegetarian diets may be increased by adding antioxidant-rich foods to the meal which helps to reduce the oxidized Fe^{3+} into Fe^{2+}. Promotors of iron absorption are antioxidants such as Vitamin C or carotenoids and are naturally abundant in fruits and vegetables. Inhibitors of iron absorption may be found in both plant-derived and animal-derived food. For example, phytates found in whole-grain cereals, legumes, nuts and seeds or polyphenols in tea, coffee or chocolate may reduce iron absorption by 60-70%, whereas dairies may reduce iron absorption by 50-60% (table 1). It should be noted that both inhibitors, as well as promotors, modify the absorption of non-heme iron. Adding antioxidants to animal-derived food such as meat or to medical products containing divalent iron does not promote iron absorption from these sources.

Thus, athletes need to be educated about adequate iron sources considering both total amount and availability of iron in the food or complete meal (table 2).

Challenges of Adequate Iron Status in Athletes

To achieve and maintain an individually adequate iron status is often challenging for athletes as they intensively use the oxygen-transporting system. In addition to the aforementioned factors, iron losses are also increased in athletes by foot-strike hemolysis or increased blood loss in marathon runners or martial artists, which can lead to depleted iron stores (7).

Regarding the immune response, hepcidin levels are elevated via secretion of interleukin-6 (IL-6) and peak 3 hours after exercise remaining elevated for 3 to 6 hours after cessation of exercise. As mentioned before, elevated hepcidin levels strongly inhibit iron absorption from food or supplements (9). The background of this mechanism is the body's defense against pathogens. Iron is essential for the survival of bacteria, limiting the availability is a physiological response to "starve" the pathogens. Simultaneously, training acts as a stressor to the athletes' body and pro-inflammatory cytokines are released. The principal cellular targets of hepcidin are enterocytes, macrophages and hepatocytes. In these cells, hepcidin leads to the internalization and degradation of ferroportin, preventing the release of iron stored in liver cells, the absorption of dietary iron, and the recycling of iron in macrophages (12) (figure 2).

Altitude training poses an additional challenge to the iron metabolism. The associated acclimatization and the desired adaptation process to the reduced oxygen partial pressure stimulate erythropoiesis to increase the physiological transport capacity for oxygen. When iron availability is insufficient, adaptation on the hematological level is limited. Altitude exposure was shown to decrease hepcidin levels which in response increases iron absorption and promotes altitude-induced erythropoiesis (figure 1). Therefore, securing adequate iron availability is a key in altitude adaptation (19).

Sex also influences iron status, with female athletes being at a higher risk for iron deficiency as menstruation can lead to significant iron losses, which, when combined with the increased iron demands of physical training, places female athletes at a higher risk for iron deficiency and anemia (25). The

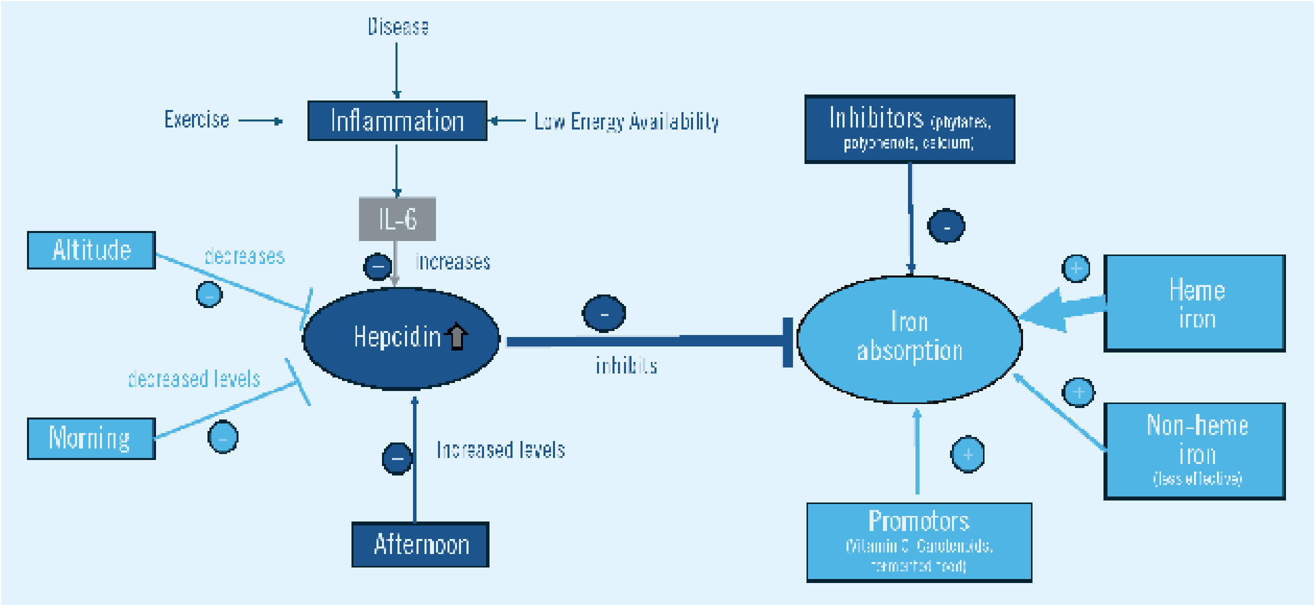

Figure 1

Regulation of iron absorption due to modifications in hepcidin levels. The figure illustrates why iron intake in the morning before or within 30 min after cessation of exercise is an evidence-based strategy to improve iron absorption. Preference of foods rich in heme-iron and promotors of iron absorption as well as avoiding co-ingestion of inhibitors such as phytates or polyphenols with iron-rich meals also supports iron absorption.

average iron loss during menstruation is estimated to be 0.55 mg/day with a huge inter-individual variety (5). Cohort studies have shown that female athletes, often have lower iron stores compared to their male counterparts (6). More high-quality studies are needed to determine whether sex hormones or monthly blood loss are the cause of differences in iron metabolism parameters.

Athletes at Risk for Iron Deficiency

Considering the above-mentioned factors that either increase iron loss, reduce total iron intake or reduce iron absorption from food athletes at risk for inadequate iron stores and the development of iron deficiency include:

- athletes with monthly blood and iron loss during menstrual cycles
- athletes with high exercise load such as endurance athletes (due to increased iron loss via sweat, hematuria and gastrointestinal bleeding)
- vegetarian and vegan athletes (as these diets are typically low in heme-iron which is more likely to be absorbed than non-heme iron)
- athletes who co-ingest high amounts of grains and cereal foods together with iron-rich foods to meet their carbohydrate requirements (as grains contain phytates that are inhibitors of iron absorption)
- athletes with low energy intake (as low overall food intake is associated with low intake of several micronutrients, including iron)
- athletes suffering from Relative Energy Deficiency in sports (RED-S) (as this may increase hepcidin levels due to lowered estrogen levels and possibly due to exercise-induced transient inflammation) (4, 15, 16).

Monitoring Iron Status

Early stages are referred to as non-anemia iron deficiency and are characterized by hemoglobin levels within the respective reference range but reduced iron stores (serum ferritin; sFer range<12 to 40 µg L^{-1}). Left untreated, non-anemia iron deficiency can develop into iron deficiency anemia where iron stores and iron transport are insufficient to sustain hemoglobin production (sFer<15 µg L^{-1} and [Hb]<11.5 g dL^{-1}) (15).

Peeling et al. suggested to distinguish between three different stages of iron deficiency (table 3). Using this model of an iron deficiency spectrum may be helpful for practitioners to involve more than only one parameter to assess iron status, as early stages of iron deficiency may be detected and adequately treated to prevent a progression of severity (18).

Regular blood tests (e.g. during annual pre-participation screening or more often for athletes at risk) are essential to monitor the iron status of athletes. Any history of iron deficiency (<24 months), irregular/excessive menses or amenorrhea, high training loads and volume, unexplained loss of performance, vegetarian or vegan diet, or history of RED-S/LEA represent indications for quarterly blood tests. Blood tests twice a year should be considered in female athletes with a previous history of iron deficiency. All other athletes should be screened for iron status annually (20). A minimum clinical screening for iron deficiency should include the following parameters: serum ferritin (sFer), hemoglobin and transferrin saturation to be able to monitor the progression between the different stages of iron deficiency (table 3). As an increased iron requirement is often accompanied by a systemic immunological reaction, inflammatory changes should always be monitored. Accordingly, the combined measurement of inflammatory cytokines, such as CRP and IL-6, provide more accurate information (20). Desirable markers which are less affected by training-induced inflammatory responses, are represented by soluble transferrin receptor (sTfR) and sTfR/log ferritin ratio (sTfR index) (14).

To reliably evaluate and interpret the results of blood testing for iron deficiency standardization prior to the measurements is crucial. The sports physician should obtain blood samples: ›

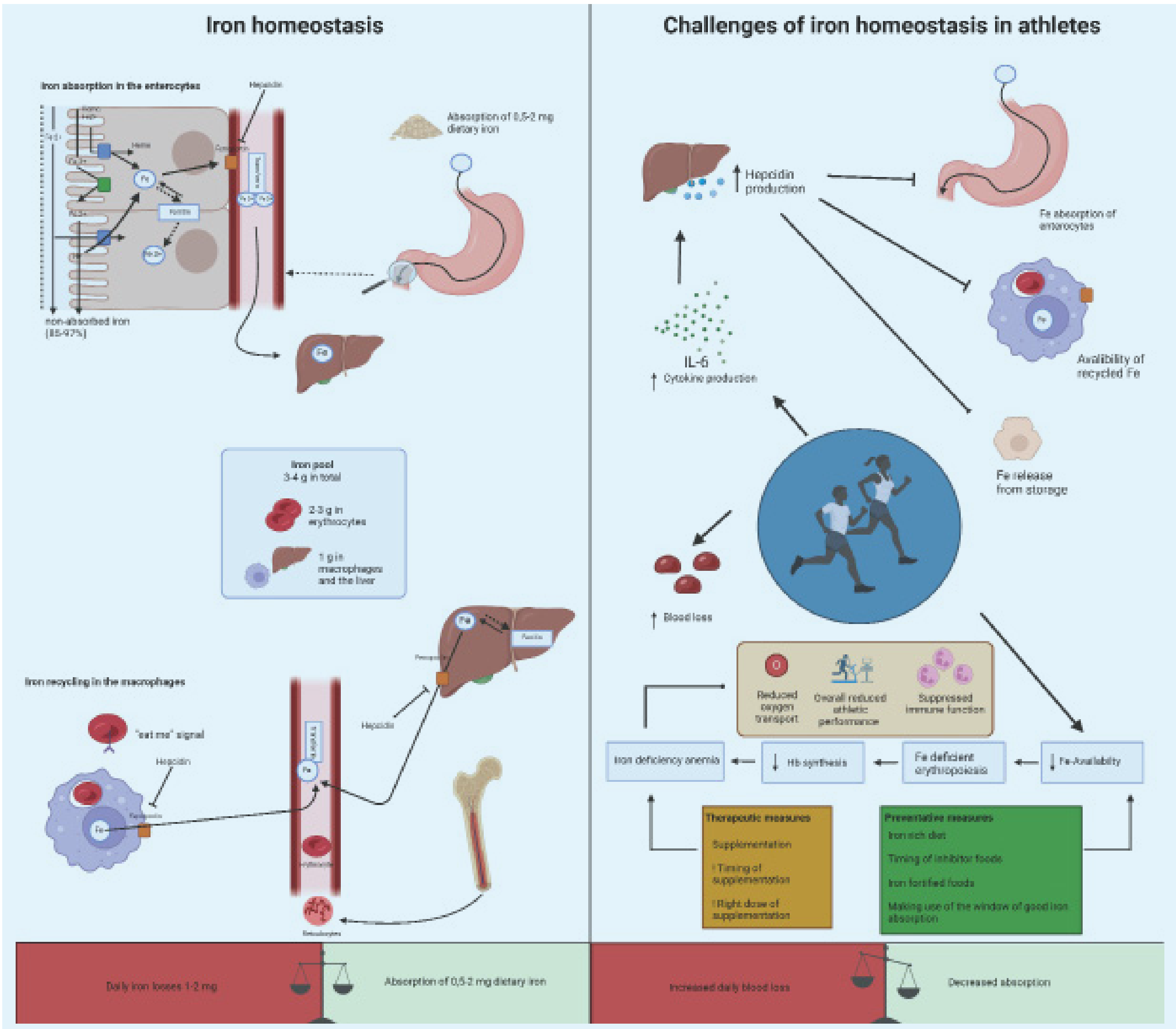

Figure 2

Regulation of iron (Fe) status and challenges of adequate iron status in athletes. The left side illustrates the regulation of iron homeostasis, showing how iron is absorbed in the intestine and recycled by macrophages. It highlights the complexity of iron balance with the focus on iron absorption, iron recycling and iron losses. The right side outlines the challenges athletes face in maintaining iron homeostasis. It indicates that factors such as increased hepcidin production and blood loss through gastrointestinal bleeding, hemolysis, and sweating can lead to reduced iron absorption and availability. This can result in impaired hemoglobin (Hb) synthesis, reduced oxygen transport, and overall decreased athletic performance and suppressed immune function. Created with BioRender.com.

1. At standardized time of the day (morning is to be preferred)
2. Prior to exercise (12-24 hours rest from exercise prior to the blood sample)
3. Considering hydration status (urinary specific gravity<1.025 to not influence concentrations of the iron status marker)
4. Avoiding blood sampling in ill or injured athletes or athletes reporting for muscle damage (e.g. following eccentric exercises), as ferritin is an acute phase protein that increases in response to stress and inflammation (validated by history, clinical exam and extended blood analysis)
5. During standardized time of the menstrual cycle in females (as during menstruation both hepcidin as well as ferritin may be modulated significantly)
6. Use of at least two markers of iron deficiency (e.g. hemoglobin and serum ferritin) to be able to diagnose the stage of iron absorption (1, 15, 20).

Key Approaches to Increase Iron Intake and Maximize Iron Absorption

To reduce the individual risk of becoming iron-deficient, athletes should endeavor to optimize iron absorption in their habitual diet. This includes adequate energy intake, as restricted food intake correlates with a lower intake of micronutrients such as iron. Athletes should at least aim for the recommended intake values for the general population, which have currently been elevated to 11 mg/day for males and 16 mg/day for adult females before menopause (8). As low energy availability and presumably glycogen-depletion may promote a hepcidin-mediated decrease in iron absorption, conditions of low energy availability should be avoided. Athletes at risk for LEA and RED-S require interdisciplinary support and treatment as quickly as possible and according to the IOC RED-S clinical assessment tool (17).

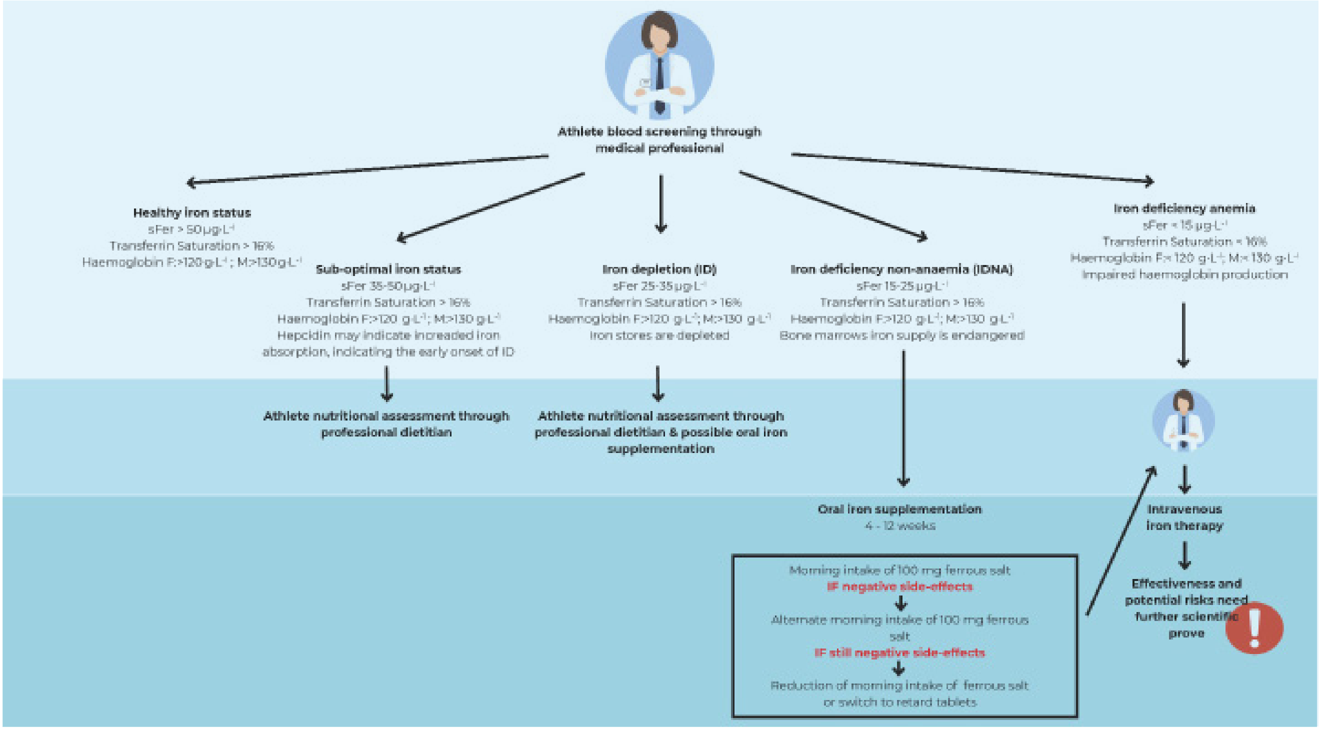

Figure 3

Flowchart to assist practitioners in the selection of optimal treatment protocols for iron-deficient athletes (F=female, M=male), diagnosed via hematological indices (serum ferritin (sFer, transferrin saturation, hemoglobin). This flowchart outlines the recommended steps for managing iron status in athletes, starting with an initial blood screening by a medical professional. If an athlete is identified with insufficient iron levels or iron deficiency, different interventions are proposed based on the severity of their condition.

Athletes at risk for iron deficiency might be encouraged to include animal sources of readily absorbable heme-iron into their weekly meal plan, where a maximum of 300 g of meat per week should not be exceeded due to its carcinogenic potential and sustainability aspects. However, combining small amounts of heme-iron with non-heme iron relevantly increases iron absorption from plant foods. Vegan athletes should be educated by sports nutritionists on how to prepare nutrient-dense foods containing high amounts of iron with promotors of iron absorption, for example combining whole-grain cereals with orange juice, wholegrain pasta with tomato sauce rich in carotenoids or steamed chickpea salad with a lime dressing. To maximize iron absorption, food and meals rich in iron should preferably be ingested in the morning rather than in the afternoon and before exercising or at least up to 30 minutes after cessation of exercise to avoid iron intake during the post-exercise hepcidin peak. Co-ingesting foods or drinks known to effectively inhibit iron absorption along with iron-rich foods should be avoided. Thus, coffee, tea or chocolate rich in polyphenols, milk and milk products rich in calcium or nuts and seeds rich in phytates should not be part of an iron-rich main meal. If preferred, those foods might be consumed as an evening post-exercise snack when iron absorption is reduced anyway.

Medical Treatment of Iron Deficiency

In cases where an adequate iron intake cannot be guaranteed through diet alone, a medical treatment using pharmacological iron may be necessary (figure 4). The dosage and duration of oral therapeutic iron administration should be taken under medical supervision and based on individual blood values to avoid overdosing and possible side effects. Recent research indicates that alternate-day oral iron supplementation is an effective strategy to replenish iron stores, enhance iron absorption, minimize gastric irritation, and increase hemoglobin levels similarly to daily supplementation (15).

Parenteral iron preparations delivered intramuscularly or intravenously (IV) offer another therapeutic solution for addressing an iron deficiency. An evident advantage of IV therapy lies in its rapid and substantial response, free from gastrointestinal discomfort, unlike oral administration. This advantage likely stems from these administration routes bypassing the gut, where absorption issues commonly occur (20). However, potential adverse events such as anaphylaxis need to be taken into consideration (11). Risks that could impair immune function (23) need further scientific proof and a parenteral preparation should be wisely considered. Current anti-doping regulations limit the amount of infusions to less than 100ml IV infusion in 12 hours, otherwise an anti-doping violation will result. With Iron(III) carboxymaltose or Iron(III) gluconat preparations lower volumes can be adminstered, otherwise a TUE (Therapeutic Use Exemption) has to be granted before treatment or the infusion is performed in a hospital setting.

Key Messages for Athletes and Practitioners

1. The main risk factors for iron deficiency in athletes are iron loss due to exercise-induced sweating, hematuria, and gastrointestinal bleeding, exercise-induced modifications in iron absorption and recycling, menstrual blood loss, low energy availability and vegetarian/vegan diets.
2. Standardized monitoring and documentation (e.g. during annual pre-participation screening) with at least serum ferritin, hemoglobin and inflammation marker (CRP), desirable sTfR and sTfR index following standardized protocols are recommended.

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Table 2

Total iron content in typical foods and the amount available iron per serving (adapted from (12)). *Bioavailability with 500mg iron stores: Heme iron (mg)*23% + Non-heme iron (mg)*5%. The average bioavailable iron content of 55% was used for lamb and beef, 35% for seafood, fish and chicken.

TYPICAL FOOD AND SERVING SIZE	PREDOMINANT IRON FORM	IRON CONTENT (mg)	
		TOTAL	BIOAVAILABLE (ESTIMATED)*
85g Chicken liver	Heme	7.20	0.81
85g Beef liver	Heme	5.34	0.60
85g Beef roast	Heme	3.22	0.48
85g Tuna fish	Heme	2.72	0.31
85g Shrimp	Heme	2.63	0.30
1 tbsp Blackstrap molasses	Non-Heme	5.05	0.25
1/2 cup Breakfast cereals	Non-Heme	4.50	0.23
1/2 cup Potato	Non-Heme	2.75	0.14
1/2 cup Kidney beans	Non-Heme	2.58	0.13
80g Tofu	Non-Heme	2.30	0.12

Table 3

Stages of iron deficiency and suggested diagnostic cut-off values (20).

STAGE OF IRON DEFICIENCY	SERUM FERRITIN (µg/l)	HEMOGLOBIN CONCENTRATION (g/L)	TRANSFERRIN SATURATION (%)
I Iron deficiency	<35	>115	>16
II Iron-deficient non-anemia	<20	>115	<16
III Iron-deficient anemia	<12	<115	<16

3. Adequate iron intake considering total amounts of iron and its availability is most important in the prevention of iron deficiency. Consuming iron-rich foods in the morning before exercise and reducing coffee and tea promotes iron absorption. Seek support from a certified (sports) nutritionist.
4. If medically indicated (i.e. diagnosed iron deficiency), a medical iron therapy according to figure 3 should be approached. Finding a dosage and timing of iron administration that works for the individual and reduces the risk of adverse events is necessary to achieve improved iron availability.
5. The intake of dietary supplements (i.e. no medical iron products as mentioned in point 4) containing iron is strongly discouraged, especially for males and young athletes. Due to the toxicity of iron overload, the Federal Institute for Risk Assessment recommends a maximum dose of 6 mg/day and a warning on iron supplements that they are unsuitable for men and postmenopausal women. The food first approach (see key point 3) should be preferred as it seems safe with respect to risk of overdosage and doping aspects.

Conflict of Interest

The authors have no conflict of interest.

Summary Box

Iron deficiency is a common problem in athletes, especially endurance athletes, due to factors such as increased iron loss due to exercise-induced sweating, hematuria, and gastrointestinal bleeding. Monitoring iron status through regular blood tests, including serum ferritin and hemoglobin levels, is critical for early detection and treatment of iron deficiency.

Strategies to improve iron absorption include consuming iron-rich foods with promoters such as vitamin C, while inhibitors such as phytates and calcium should be avoided. In cases of significant deficiency, supplementation under medical supervision may be necessary.

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