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Iron Deficiency Without Anemia in Athletes: Pathophysiology, Diagnosis, and Modern Management Strategies

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Abstract

Background: Iron deficiency without anemia (IDNA) is a metabolic condition in which the depletion of systemic stores impairs physical performance despite normal hemoglobin concentrations. It affects up to 35% of female athletes overall, with the prevalence of latent hypoferritinemia (<50 ug/L) reaching as high as 53.9% among female collegiate athletes.

Pathophysiology & Diagnosis: At the subcellular level, iron deficiency impairs mitochondrial oxidative phosphorylation, inducing an inefficient metabolic shift toward anaerobic glycolysis and causing a 3–19% reduction in endurance capacity. The diagnosis is primarily established based on serum ferritin and transferrin saturation (TSAT) levels.

Management: Therapeutic approaches include dietary counseling and oral iron supplementation (16–100 mg of elemental iron), with alternate-day dosing regimens demonstrating high efficacy in minimizing the hepcidin blockade and improving gastrointestinal tolerance. Intravenous (IV) iron supplementation remains a second-line therapeutic option, reserved for athletes with severe malabsorption, non-responders to oral protocols, or under critical time constraints before competitions.

Conclusions: Early screening and tailored supplementation strategies are essential to mitigate performance declines and maintain biochemical homeostasis in athletic populations.

Keywords: iron deficiency without anemia, ferritin, hepcidin blockade, alternate-day dosing.

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1. Introduction

The exercise capacity of the elite athlete largely depends on maintaining biochemical homeostasis. Based on peripheral hemoglobin (Hb) concentration, standard diagnostic methods regularly miss patients with subclinical depletion of tissue reserve. Modern investigations modify this strategy toward the clinical entity of iron deficiency without anemia as an evolving physiological continuum in which the lack of this element at the tissue level induces a local energetic crisis. Sport-related impairment in this issue is so prevalent (in women, circa 35%, in men, 3–11%) that it could be viewed as endemic, and even higher values are documented in collegiate populations, reaching 53.9%.

At the subcellular level, iron is a cofactor for enzymes in the Mitochondrial Respiratory Chain (MRC) and the Tricarboxylic Acid Cycle (TCA). Its absence suppresses the production of respiratory proteins and impairs oxidative phosphorylation, leading to a compensatory, inefficient metabolic transition to anaerobic glycolysis and increased lactate production. In athletes, a negative balance of this mineral is exacerbated by mechanical hemolysis, microscopic gastrointestinal bleeding, and an increase in hepcidin levels post-exercise, which transiently inhibits its intestinal absorption. In women who are menstruating, this risk is also increased because of blood loss secondary to menses and the concomitantly related condition, Relative Energy Deficiency in Sport (RED-S).

The main challenge in diagnosis is that the symptoms of IDNA are masked by regular training fatigue, and hematological masking can lead to normal red blood cell values for a long time while the condition is in a state of depletion. When non-pharmacological measures and oral pharmacological supplementation are insufficient, treatment intensification is required. Intravenous (IV) supplementation is for patients with an absolute intolerance to the oral route of administration, in severe malabsorptive states (e.g., active phase of inflammatory bowel diseases or history of bariatric surgeries), or in situations where there is a critical time shortage before a target event. Here, we focus on the pathophysiology of IDNA, identify diagnostic challenges, and summarize current dietary and pharmacological options.

2. Pathophysiology and Mechanisms of Iron Loss

Iron-deficiency without anemia is a metabolic condition characterized by decreased iron availability for metabolic functions, leading to impaired physical performance despite normal hemoglobin levels. Conventional diagnostic schemes have consistently failed to detect IDNA. The diagnosis centers on blood-based oxygen carriage. Nevertheless, studies in exercise biochemistry and metabolomics suggest that the functional impairments may be due to a local energetic crisis in mitochondria, combined with accelerated iron loss and sex-dependent endocrine stressors.

On a subcellular scale, iron is an essential cofactor in the production of heme and iron sulfur (Fe-S) clusters, both of which are necessary components of the molecular machinery of cytochromes and enzymes in the mitochondrial respiratory chain (electron conduction chain) [1, 2]. The lack of this element limits the synthesis of respiratory proteins, thereby impairing oxidative phosphorylation and severely reducing the tissues' aerobic potential [1, 3, 4, 5]. Under such bioenergetic stress, metabolism shifts toward anaerobic glycolysis, leading to lactate and pyruvate accumulation and promoting the production of reactive oxygen species (ROS), which cause oxidative stress and damage mitochondrial structure [1, 2]. As a result, even at a normal hemoglobin level (IDNA status), the muscle is unable to fully utilize the oxygen supply. This “cellular bottleneck” leads to a subjective sense of early fatigue as well as suboptimal energy use during physical exertion [1, 3, 4, 5]

In top-level athletes, this energy shortfall has been shown to reduce tissue oxidative capacity and endurance performance by 3–19% [3, 4, 5, 6]. The significance of this mitochondrial-enzymatic machinery is supported by clinical findings: iron supplementation restores VO₂max, energy efficiency, and lactate kinetics rapidly and, frequently, without

raising basal hemoglobin levels [3, 4, 5, 7]. Direct functional and temporal links between subcellular pathophysiology and decreased exercise capacity are manifested through linked metabolism. Enzymatic deficiency induced by cytochrome destruction reduces respiratory chain activity and causes an immediate ATP deficiency, which drives a compensatory shift to anaerobic glycolysis. This ultimately leads to a hastened accumulation of lactate and pyruvate, which induce early metabolic acidosis and aggravate the subject's sensation of muscle "burning" during submaximal work [1, 2, 5]. At the same time, ongoing structural decay and dysfunctional biogenesis lead to an irreversible loss of total mitochondrial capacity, which, when coupled with enhanced oxidative stress (ROS overproduction), results in the devastation of cellular matrices and the maintenance of deep peripheral fatigue [1, 2].

The Endurance Athlete: The Consequence of Mechanical Trauma and Physiological Loss (Excretion). Iron depletion in endurance athletes (mainly runners and cyclists) is due to cumulative mechanical trauma and the loss of iron through body fluids. Among the mechanisms is intravascular hemolysis triggered by repeated foot strikes against the ground, with mechanical rupture of erythrocytes in capillaries and direct loss of iron [8, 9]. The post-exercise hematological profile typically consists of decreasing haptoglobin and increasing reticulocyte counts (frequently at normal hemoglobin levels) [9]. With an admixture of oxidative stress that injures erythrocyte cell membranes and mechanical strain-related factors, they can be reduced by the proper selection of footwear cushioning [8, 9].

At the same time, athletes experience gastrointestinal microbleeding due to splanchnic ischemia during strenuous or prolonged exercise. Disruption of mucosal integrity leads to occult blood loss in the intestinal lumen, which is a major contributor to absolute iron deficiency in marathoners and cyclists [8,9,10, 11]. The element's negative balance is further increased by other excretions: hematuria and hemoglobinuria caused by mechanical and metabolic stress, and the trace iron losses through heavy sweating in multi-week training blocks [8, 9, 10, 11].

Direct physical losses are intensified by an inflammation-mediated regulatory block, controlled by hepcidin. Physical activity triggers a cytokine-hormone axis signaling cascade: exhaustive exercise bouts lead to a dramatic rise in interleukin-6 (IL-6), which acts as a potent stimulator of hepcidin production. It is elevated 1.5- to 2.5-fold and peaks at approximately 3h post-exercise [1, 4, 10]. This process involves hepcidin binding to ferroportin channels, leading to their degradation and the temporary sequestration of iron within cellular repositories. This leads to a blockade of intestinal iron absorption and a decrease in iron salvage from old red blood cells [1, 4, 10].

This functional iron limitation may be additionally intensified by metabolic stressors, such as low energy availability (LEA) or carbohydrate restriction, which each stimulate post-exercise inflammation. Following that, endurance athletes who undergo prolonged periods of heavy training blocks experience accelerated direct loss, compounded because of suppressed absorption for extended periods, making these athletes most prone to run down their iron stores [1, 10, 11, 12].

Epidemiologic evidence demonstrates a clear sexual dimorphism in the incidence of IDNA, with 15–35% of female athletes vs. 3–11% of males being affected [13]. This disproportion results from a mixture of physiological, metabolic, and genetic factors. Due to the biological characteristics of women, associated with cyclical menstrual bleeding, a much higher iron intake (recommended 18 mg/day vs. 8 mg/day in men) is required, and female athletes with heavy menstrual bleeding are considered a clinically at-risk population [8, 13]. While 19–54% of active women experience menstrual cycle abnormalities, secondary amenorrhea should be viewed as a manifestation of RED-S pathology rather than an adaptation against iron loss [14].

Female susceptibility to IDNA is also strongly associated with low energy availability and the Relative Energy Deficiency in Sport syndrome, with diagnoses in 47–53% of endurance-sport participants [14]. LEA leads to persistent deficiencies at the micronutrient level, such as iron, calcium, and vitamin D, and in women, this is additionally worsened by an overall tendency to adopt more restrictive dietary patterns (vegetarianism, veganism) and by the removal of sources of heme iron [8, 13, 14]. Carb intake inadequacy, which is also related to echogenic eating patterns, exacerbates RED-S symptoms, and these symptoms are more common in female elites than in males [16, 17, 18]. In the end, this dimorphism is controlled by genomic factors: certain genetic variants that regulate iron homeostasis are linked to pathways that impact reproductive physiology and blood clotting phenotypes [15].

3. Diagnostic Staging, Screening Procedures, and Early Detection Hurdles

The differential diagnosis of IDNA in athletes is challenging. Routine hematologic tests based on hemoglobin (Hb) concentration are known to underestimate subclinical depletion of iron stores and may mask the extent of tissue iron deficiency. Treatment of Fe deficiency as a progression in physiological status, and the introduction of population-based surveillance programs beyond routine complete blood counts, are needed to prevent adverse consequences of this condition.

Iron deficiency is not a dichotomous, "all-or-nothing" condition but occurs progressively over a continuum at physiological levels, as characterized by relationships between serum ferritin, transferrin saturation, and hemoglobin. This sequence begins with Stage 1, or early store depletion (IDNA-1), representing the initial consumption of tissue reserves while continuing full functionality of all other metabolic compartments. In sports medicine diagnostics, this stage is officially defined as ferritin levels $<30 \mu\text{g/L}$ and TSAT $>16\%$ with normal hemoglobin ($\geq 120 \text{ g/L}$), although values of $30\text{--}40 \mu\text{g/L}$ are also considered a warning sign of depleted reserves [3, 4, 19].

A subsequent development leads to Stage 2, termed iron-deficient erythropoiesis (IDNA-2), in which iron availability for RBC production is limited, resulting in functional restriction. In female athletes, this advanced non-anemic state is characterized by ferritin $<20 \mu\text{g/L}$, TSAT $<16\%$, and Hb $\geq 120 \text{ g/L}$. Results from studies on bone marrow biopsies confirm that women who are physically active show signs of deficiency over a significantly broader ferritin range ($15\text{--}40 \mu\text{g/L}$), rendering this stage the one at which the most critical treatment is needed for clinical survival [2, 3, 4].

This progression ends in Stage 3, typical IDA, which arises when systemic stores are entirely depleted, leading to a terminal fall in circulating red blood cell (RBC) mass. This is a condition of very low ferritin with concomitant Hb $<120 \text{ g/L}$ in females and $<130 \text{ g/L}$ in males [3, 4]. Although the traditional ferritin cut-off endorsed by WHO is $<15 \mu\text{g/L}$, values safely exceeding $40\text{--}50 \mu\text{g/L}$ are considered a reflection of full adequacy of systemic resources in sport sciences, as long as TSAT and Hb-related indicators are optimal [2, 3, 4, 19].

The second diagnostic problem for IDNA is that its symptoms in day-to-day life are indistinguishable from normal training stress. Two major mechanisms are assumed to contribute to this "diagnostic evasion": the non-specificity of symptoms and the hematological camouflage. The impact of deficiency on function, specifically on chronic fatigue, difficulty concentrating, and reduced exercise tolerance, in the setting of normal hemoglobin, is intrinsically multifactorial [2, 3, 4]. In the highest-performance sport, these symptoms are almost identical to those induced by high training volume, overtraining syndrome, or low energy availability [2, 17]. Because these conditions are so often entangled in athletes' lives, physicians are less likely to suspect a biochemical subtext from the interview alone and frequently delay lab work until the patient has developed full-blown anemia.

The problem is compounded by the fact that routine complete blood counts of peripheral blood are also a source of false diagnostic reassurance. In the early stages of depletion development, the body tries to maintain the volume of circulating erythrocytes, resulting in hemoglobin and red blood cell indices within normal ranges [2, 6]. Variations in parameters such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), or the proportion of hypochromic cells occur very late in the course of the disease due to the approximately 120-day lifespan of an erythrocyte [2]. Therefore, an athlete can have late-stage metabolic dysfunction in muscle yet exhibit textbook morphology. In addition, the effect of IDNA on performance may be variable: some athletes experience an abrupt decline in capacity while others continue training (and competing) seemingly without ill effects, causing conflicting conclusions in systematic reviews as to the impact of early depletion on ultimate performance [3, 4, 5, 7].

With the covert nature of IDNA, of which clinical symptoms or a drop in Hb act as indicators, the strategy of care to wait for symptoms is not suitable. Routine program-based screening for ferritin in the general population is warranted, given the magnitude of the phenomenon and the good reversibility of the induced deficits.

Large studies show that depleted iron stores constitute a common problem in collegiate and endurance sports. A meta-analysis of 17,519 athletes showed that 53.9% had subclinical hypoferritinemia ($<50 \mu\text{g/l}$) and 23.0% had absolute iron deficiency ($<20 \mu\text{g/l}$) [2]. Functionality at such minimal resources is associated with an increased risk of cardiovascular, cognitive, and muscle impairments, along with a 3–4% decline in endurance indices [2, 3, 4, 11, 12]. These figures provide a major rationale for revising international standards and introducing routine ferritin testing in young and college athletes [2, 4, 11, 12].

The main clinical rationale for proactive screening is that IDNA is highly reversible. Treatment of iron deficiency early in its course with substitution results in measurable ergogenic benefits: restoration of low ferritin levels has been reported to increase endurance capacity by 2–20% and maximal oxygen uptake ($\text{VO}_{2\text{max}}$) by 6–15% [3, 4, 11]. This is reflected in optimized metabolic efficiency, as evidenced by a dose-dependent response in lactic acid kinetics and decreased fatigue perception [3, 4, 11, 12]. A program of iron monitoring every 6 to 8 weeks during the treatment phase, then every 6 months in those at high risk, is advised to safely manage this remitting/relapsing course in female athletes [4, 11].

4. Clinical Ferritin Thresholds and Physiological Demands of Altitude Training

Diagnostic indices for iron status may not be interpreted identically even across populations. Detection limits for deficiency are greatly increased in elite sport, a change driven by the need to identify tissue deficiencies that limit performance and by unique environmental stresses (e.g., high-altitude hypoxia) that are identified and addressed before overt anemia is induced.

In general medicine, the WHO's diagnostic criteria for the non-anemic iron-deficient patient are based on a ferritin cut-off of $<15 \mu\text{g/L}$, indicating the absence of iron in the bone marrow of anemic patients [3]. In sports medicine, this threshold relates only to terminal, complete store depletion (IDA-3), making it useless for assessing earlier stages, during which physical performance and cellular energy metabolism decline first [3]. A three-stage classification system based on ferritin and transferrin saturation is used to detect these initial deficiencies. 1 (IDNA-1), the first stage (isolated depletion) can be diagnosed at a ferritin $<30 \mu\text{g/L}$ with preserved TSAT $>16\%$ and normal Hb $\geq 120 \text{ g/L}$ [3]. Feeding into the IDNA-2 (iron-deficient erythropoiesis) stage is a ferritin in the low teens, less than $20 \mu\text{g/L}$, and a falling TSAT less than 16% , along with "normal" hemoglobin indices [3]. And finally, the third stage – IDA-3 (iron deficiency anemia) is defined as a very low ferritin in combination with an obvious decrease in Hb concentration below sex-specific reference cut-offs, a condition that most often accompanies the ferritin dropping to levels of $12\text{--}15 \mu\text{g/L}$ [3].

In large cohorts of elite athletes, sports science raises diagnostic thresholds for subclinical deficiency. In a global meta-analysis of 17,519 collegiate athletes, latent hypoferritinemia was loosely defined as a ferritin level $<50 \mu\text{g/L}$, while the cutoff for absolute deficiency remained $<20 \mu\text{g/L}$ [2]. Epidemiological evidence produced by such stricter criteria demonstrates that subclinical iron insufficiency is a mass condition. Among respondents, student-athletes, 53.9% were classified as having latent hypoferritinemia, and 23.0% of the global population had absolute iron deficiency [2]. The researchers expressed concern about the high prevalence of these disorders, along with evidence of negative consequences for performance measures and general health, and concluded that mandatory, systemic ferritin screening in adolescent and collegiate athlete populations is warranted [2].

The need for iron is very high during high-altitude training. Hypoxia exposure is a potent biological stimulus that rapidly induces erythropoiesis to enhance the oxygen-carrying

capacity of blood, thereby greatly increasing the daily requirement for this element [4]. According to longitudinal studies on long-distance runners, the iron requirement for athletes living in the mountains is approximately 4.9 mg/day higher than that of a sedentary person living at sea level [4]. Starting training with borderline reserves prevents the adaptation training. Direct analyses show that only those with a high baseline ferritin level go on to have a significant increase in maximal oxygen uptake following a sojourn in the mountains. In contrast, athletes with low stockpiles of this resource fail to improve performance, thus iron deficiency negates the benefit of a high-altitude camp even in the face of strong hypoxic stimulus [4].

Because hypoxia imposes such a heavy metabolic burden, normal deficiency cut-offs (<15–20 ng/mL) are grossly inadequate to meet tissue demands at altitude. In the new high-performance protocols, a ferritin level of 30–99 ng/mL is considered a functional iron deficiency in hypoxia, and only levels >100 ng/mL are considered completely sufficient for unobstructed erythropoiesis [4]. To avoid risk of maladaptation, current guidelines require mandatory testing before departure and customized supplementation below stringent minima: in female athletes, supplementation is warranted at ferritin <30 µg/L, and in men, at ferritin <40 µg/L [20]. Ultimately, it is important to increase an athlete's ferritin level to near or above 50 ng/mL before introducing them to a hypoxic environment to ensure the altitude stimulus results in an increase in hemoglobin mass instead than overall exhaustion.

5. Impact on Performance Parameters

In IDNA, functional impairments are detectable, but are usually mild in relation to the effects of overt anemia. The best quantified data are for elite female athletes with hypoferritinemia (<40 µg/L), who, on average, have a reduced overall endurance capacity of 3–4% [1]. However, analysis of time trials and time-to-exhaustion tests indicates a larger deficit, ranging from 3% to 19%, compared with athletes with normal iron stores [3]. Importantly, these two separate physical deteriorations are already evident in Stages 1 and 2 (IDNA-1 and IDNA-2, the IDNA without and with preliminary multiple organ damage, respectively), and therefore have already emerged in stages when the patient's hemoglobin levels are still considered normal [3].

The extent of the functional alteration varies widely depending on the severity of the cellular deficit and the nature and duration of the exercise. High-volume, long-duration stresses manifest energy deficits associated with the early stages of depletion more clearly [3]. Scoping

reviews support an association between depleted iron stores, reduced peak oxygen consumption ($\text{VO}_{2\text{peak}}$), and increased chronic peripheral fatigue, even in the absence of anemia [3]. Despite a few reviews that offer an unbiased perspective stressing the diversity of life, the overall evidence indicates that IDNA reduces endurance performance by approximately 3–4% and, under severe conditions, by 10–20%. The most consistent diagnostic sign is not an abrupt decline in maximal oxygen uptake, but rather a clear reduction in the duration of work and in load tolerance during prolonged submaximal work [3, 4].

6. Modern Management and Therapeutic Methods

Non-drug interventions to improve iron status underpin clinical care and enable a dramatic increase in its bioavailability. The first axis: Increase heme iron intake (lean red meat, seafood), which has by far greater absorption rates than the plant fraction [21]. Here, the key is to leverage the so-called “meat factor”: adding small amounts of animal muscle to vegetarian dishes significantly increases the amount of iron and zinc absorbed [22]. Whole-grain cereal products, legumes, and green leafy vegetables (special millet) should constitute the base diet that can be enhanced nutritionally by sprouting or fermenting [21, 23, 24].

The second important component is the addition of ascorbic acid (vitamin C). Vitamin C converts iron ions into a soluble form, making them easier to absorb across the cell walls of enterocytes. For full effectiveness, a 2:1 molar ratio of ascorbate to iron is needed [21]. In contrast, citric and malic acids, along with certain peptides released during meat digestion, have inhibitory effects [21, 25]. Reviews conclude that long-term clinical benefit requires both high iron intake and plentiful vitamin C, including for females [21, 26, 27].

The third is the rigorous limitation of inhibitors during the peri-meal windows. The phytate barrier in grains and legumes can be neutralized by soaking and fermenting — dephytinization of food enhances absorption in more than 80% of cases [21, 23, 28]. The good is also threatened by polyphenols and tannins (coffee, tea, cocoa), which significantly decrease the absorption of the non-heme portion, and thus a time gap between their intake and a meal is needed [24, 25, 29, 30]. A comparable inhibitory mechanism concerns calcium, which interferes with heme and non-heme transport, and which is the reason why high calcium doses should be separated from iron-containing meals [21, 29].

The current pharmaceutical dose and the appropriate timing of therapy needed to restore ferritin stores are not in dispute by the accumulated science. In athlete groups, taking 16–100 mg of elemental iron per day for 6–8 wk results in a significant increase in ferritin

concentration, whereas shorter regimens are ineffective for tissue repartition [31]. The benefit is greatest in those with a baseline ferritin value $\leq 12 \mu\text{g/L}$; in sportspersons with higher baseline ferritin values, therapeutic gains are much less [31]. In adults with IDNA, daily or alternate-day doses of 60–200 mg for at least 8 weeks result in a clear hematological response [32, 33]. Alternate schemes (alternate-day dosing) are the means to achieve the same increase in ferritin with vastly superior gastrointestinal tolerability and substantially lower rates of side effects [32, 33].

Enhancements in maximal oxygen uptake (6–15%) and a phenomenal endurance gain (2–20%) following a course of iron therapy are reported almost exclusively in sportsmen with grossly depleted systemic iron reserves. This is just the cell biology version of the deeper-is-better principle, for how much you can restore. The largest ergogenic responses have been observed in top-level female athletes with ferritin concentrations $< 16 \mu\text{g/L}$ who received 16–100 mg of iron for 36–126 days, and meta-analyses also support the expectation that the most significant increases in ferritin are expected only when the baseline value is $\leq 12 \mu\text{g/L}$ [3, 31]. Ferritin threshold analyses show a pronounced dependency, as at a threshold of $\leq 12 \mu\text{g/L}$ the ferritin level increases markedly with a maximal increase in physical performance, while in the area of 13 up to $30 \mu\text{g/L}$ laboratory gains are much more moderate and improvements in athletic performance are inconsistent [3, 4, 8, 11, 31]. Conversely, crossing the $> 30 \mu\text{g/L}$ threshold results in vanishing effects on $\text{VO}_{2\text{max}}$ (or total work rate), even when supplementation is continued [3, 4, 31].

The mechanism behind such a prompt reaction at very low iron-value deficiency levels is the restoration of homeostasis in disturbed oxidative metabolism in muscle mitochondria, accompanied by an immediate qualitative jump in tissue function [3, 11, 12]. An additional contributing factor is the diminishing returns phenomenon after saturating the stores, which explains why numerous studies of athletes with ferritin levels of 20– $30 \mu\text{g/L}$ failed to find any functional improvements associated with higher intakes of the element [3, 4, 31]. It is noteworthy that, even with massive supplementation, ferritin levels in many studies remained $< 35 \mu\text{g/L}$, implying only an incomplete biological correction and a severe constriction of the ergogenic space once the zone of deepest deficit is exited [31]. Hence, the choice of the sample greatly influences the ultimate outcomes — the greatest improvements were found in the most depleted subjects ($\leq 16\text{--}20 \mu\text{g/L}$), i.e., the maximum potential treatment effect of iron is demonstrated by recruiting only those with the deepest deficiency, while involving subjects of various status completely washes away the average ergogenic benefit [3, 6, 31].

Intravenous supplementation is reserved for those patients in whom the oral route was either ineffective, poorly tolerated, or when a block of absorption in the gastrointestinal tract was suspected. Application of this type of therapy in standard practice is hindered by peri-infusion reactions, the unique toxicity of the drugs, and demanding logistics. Expert recommendations suggest switching to the intravenous route if ferritin levels do not improve after adequate oral supplementation or if conditions prevent intestinal absorption [34].

Clinical conditions for which the IV route becomes the preferred choice are a history of bariatric surgeries that exclude the duodenum [34, 35], the active stage of inflammatory bowel diseases (IBD) [34, 35, 36], as well as chronic kidney disease (CKD) and tumors. These are situations characterized by a strong, hepcidin-driven absorptive block or by a requirement for immediate modification of red blood cell parameters [36, 37]. The major indications for intensified treatment are: GI intolerance, proven absence of ferritin and hemoglobin response, anatomical malabsorption syndromes, heart failure with iron deficiency and time constraints [34, 35, 38]. Owing to the need for medical supervision, the risk of adverse events, and the expense, intravenous iron delivery is not considered a routine first-line treatment for patients with mild to moderate uncomplicated deficiency [34, 35].

7. Conclusions

Iron deficiency without anemia impairs mitochondrial function in muscle, directly reducing the body's oxidative capacity and, in turn, leading to a well-established 3% to 19% decline in endurance measures. Classic diagnostics based solely on hemoglobin concentration can provide false clinical reassurance, as red blood cell indices (MCV, MCH) remain normal for a long time during storage depletion. Since more than half of the collegiate athletes' population is affected by latent hypoferritinemia, it is necessary to mandate ferritin testing every six to eight weeks during treatment and annually in high-risk groups of females.

Stricter limits are applied in the case of high-altitude hypoxia, which causes erythropoiesis to be greatly accelerated and that of elemental iron to rise at a daily rate corresponding approximately to 4.9 mg. At altitude, a venturing grows requiring a ferritin level of at least 50 µg/L (more than 100 µg/L is best) for a baseline, and starting altitude training with low stores wipes out the ergogenic gain from the hypoxic signal. Prior to departure for the high-altitude camp, supplement administration is mandatory if ferritin is below 30 µg/L in females and 40 µg/L in males.

Non-pharmacological iron status optimization needs to be multifactorial and based on maximizing the heme fraction, taking advantage of the “meat factor” phenomenon, adding ascorbic acid, and removing inhibitors of absorption during peri-prandial periods. Pharmacologic treatment: the best results are obtained with elemental iron for 6-8 weeks at a dose of 16-100 mg/d. The application of an alternate-day treatment regimen produces ferritin levels similar to those associated with daily supplementation, with improved gastrointestinal tolerability and without regulatory inhibition in response to post-exercise hepcidin spikes.

Nevertheless, improvements in physical parameters are only observed in those starting from a severe deficiency status ($<12\text{--}16\text{ }\mu\text{g/L}$). Once this $25\text{--}30\text{ }\mu\text{g/L}$ level is surpassed, additional supplementation invokes the law of diminishing returns and provides no effective advantages, which must be considered when selecting the research sample and when caring for the athlete in clinical care [3, 4]. Intravenous (IV) supplementation is still a second-line treatment that can be hampered by costs and the risk of adverse events, but it poses absolute indications for anatomic and inflammatory malabsorption syndromes, for a non-response to oral therapy, or for a critical time deficit before a target competition.

Disclosure

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