Does Iron Supplementation Improve Performance in Iron-Deficient Nonanemic Athletes?

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Context: Supplementing iron-deficient nonanemic (IDNA) athletes with iron to improve performance is a trend in endurance sports.

Objectives: To investigate the benefits of iron on performance, identify a ferritin level cutoff in IDNA athletes, and determine which iron supplementation regimens are most effective.

Data Sources: A search of the PubMed, CINAHL, Embase, ERIC, and Cochrane databases was performed in 2014 including all articles. Citations of pertinent review articles were also searched. In 2017, the search was repeated.

Study Selection: Inclusion criteria comprised studies of level 1 to 3 evidence, written in the English language, that researched iron supplementation in nonanemic athletes and reported performance outcomes.

Study Design: Systematic review.

Level of Evidence: Level 3.

Data Extraction: The search terms used included *athletic performance, resistance training, athletes, physical endurance, iron, iron deficiency, supplement, non-anemic, low ferritin, ferritin, ferritin blood level, athletes*, and *sports*.

Results: A total of 1884 studies were identified through the initial database search, and 13 were identified through searching references of relevant review articles. A subsequent database search identified 46 studies. Following exclusions, 12 studies with a total of 283 participants were included. Supplementing IDNA athletes with iron improved performance in 6 studies (146 participants) and did not improve performance in the other 6 studies (137 participants). In the 6 studies that showed improved performance with iron supplementation, all used a ferritin level cutoff of ≤20 μg/L for treatment. Additionally, all studies that showed improved performance used oral iron as a supplement.

Conclusion: The evidence is equivocal as to whether iron supplementation in IDNA athletes improves athletic performance. Supplementing athletes with ferritin levels <20 μg/L may be more beneficial than supplementing athletes with higher baseline ferritin levels.

Keywords: medical aspects of sports; athletic training; iron supplementation; performance

Iron is an essential mineral necessary for delivering oxygen to tissue throughout the body as well as serving important roles in metabolism, respiration, and immune function. The body maintains stores of iron and carefully sustains a balance between iron lost, iron absorbed, and iron stored.[10,21-23,38]

Ferritin is the cellular storage protein for iron and is generally reflective of total body iron stores. Therefore, serum ferritin (sFer) is the measure most commonly used to predict total body iron stores. Notably, ferritin also has a role as an acute-phase reactant, and ferritin levels measured in individuals with acute or chronic illness resulting in systemic inflammation will not appropriately predict iron stores.[10,21,48]

Iron deficiency anemia (IDA) is a significant health concern worldwide and results in a host of symptoms, including weakness and fatigue. IDA represents the third, final, and most severe stage of iron deficiency.[21,38] The 2 initial stages, which are precursors to IDA, can be collectively referred to as iron deficiency nonanemia (IDNA). The first and least severe stage of

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iron deficiency (nonanemia) is marked by a fall in sFer resulting from the depletion of total body iron stores while maintaining normal levels of other iron indices and normal hemoglobin. The second stage (also nonanemia) is marked by not only low sFer but also low serum iron or decreased transferrin saturation and increased total iron binding capacity (TIBC).[21,38] Once iron stores and transport iron have been sufficiently depleted, the body can no longer keep up with the demands of hemoglobin synthesis, and the third and final stage (IDA) results.[21,23,38]

Monitoring sFer concentration has become common practice in endurance athletes at all levels, and not just athletes with a history of IDA. There is widespread belief that low ferritin, even in the context of normal hemoglobin levels (>12 g/dL), is the culprit for fatigue and poor performance.[38] Athletes with IDNA routinely use iron supplementation regimens in an effort to improve performance.[5,10,21,38,48] One significant limitation in the current body of literature concerning IDNA is a lack of standardization for what is considered a "low" ferritin level. Although many studies and most laboratories generally define low ferritin in the range of 12 to 23 µg/L,[10] the ferritin ranges used in research are not standardized, and due to the lack of clinical consensus on what constitutes "low" ferritin, published studies use a variety of different values to represent low normal levels, ranging from 12 to 40 µg/L.[4,11,19,20,27-29,35,36,39,47]

There is mixed evidence regarding the potential negative impact of IDNA on endurance performance in athletes. There are no known negative effects of IDNA on the oxygen-carrying capacity of athletes.[5] The hypothesized mechanism for potentially decreased endurance in IDNA athletes is decreased extraction and utilization of oxygen bound to hemoglobin due to the inactivity of iron-dependent oxidative enzymes and respiratory proteins.[5,10] Thus, supplementation with iron could theoretically correct this deficit and improve performance. The 2015 meta-analysis by Burden et al[5] supported this hypothesis and concluded that iron supplementation does indeed improve the aerobic capacity of IDNA athletes, measured by maximal VO_2.[5]

Although that meta-analysis[5] found that iron supplementation can improve aerobic capacity, there is no consensus on the optimal effective route, dose, or frequency of iron supplementation in athletes. Burden et al[5] included studies with intramuscular and oral iron supplementation as well as dosing regimens, which varied from 1 to 3 times per day at doses ranging from 10 to 209 mg.[5] In addition, the meta-analysis did not distinguish between the 2 stages of IDNA.[5]

The purpose of this study was to conduct a systematic review of iron supplementation in IDNA athletes.

METHODS

Literature Search

The PubMed, CINAHL, Embase, ERIC, and Cochrane databases were systematically searched using the following search terms: *athletic performance, resistance training, athletes, physical endurance, iron, iron dietary, ferritin, supplement, non-anemic, low ferritin*, and *iron storage*. Our preliminary search eliminated animal studies and studies in languages other than English. Additional studies were identified on reviewing references of pertinent review articles. Prior to publication, we performed an additional search to determine whether there had been published studies focusing on a ferritin cutoff of ≤20 µg/L for supplementation. We searched Embase and PubMed using the following terms: *ferritin, ferritin blood level, athletes*, and *sports*.

Inclusion and Exclusion Criteria

Studies were further screened according to predefined inclusion and exclusion criteria. Inclusion criteria consisted of: (1) randomized controlled trials; (2) athlete participants (recreational, club, high school, college, amateur, or professional athletes); (3) participants defined by the study authors as having IDNA or low ferritin without anemia; (4) at least 2 study groups, 1 of which received iron supplementation (dietary, intravenous, intramuscular, or pill form) as an intervention; and (5) outcomes comprising at least 1 measure of performance. Exclusion criteria included: (1) studies in which performance was measured subjectively; (2) studies including participants both with and without iron deficiency; (3) participants who could not be confirmed as athletes, for example, military recruits in basic combat training; and (4) studies that did not use a placebo as control. Three reviewers participated in screening and thoroughly reviewing each eligible study. Disagreements were resolved by consensus (Figure 1).

RESULTS

Overall, 12 total studies were included in our systematic review. In these 12 studies, there were a total of 283 participants (age range, 13-41 years; 257 females, 26 males). A summary of these studies is presented in Table A1 in the Appendix (available in the online version of this article).

Performance Measures

The studies included in this review used a wide variety of performance measures. Treating IDNA athletes with iron supplementation improved performance in 6 studies (146 participants); however, the other 6 studies (137 participants) did not show any improvement (Table A2 in the Appendix).

Ferritin Parameters

There was inconsistency across studies regarding a ferritin level diagnostic for IDNA. The studies included used ferritin cutoffs >20 or <20 µg/L (see Figure 2 and Table A3 in the Appendix).

Iron Supplementation Protocols

Of the 6 studies that found improved performance after iron supplementation, a variety of iron treatment protocols with differing preparations, doses, frequency, and lengths of treatment were used (see Figure 3 and Tables A4 and A5 in the Appendix).[11,20,27,29,39,47]

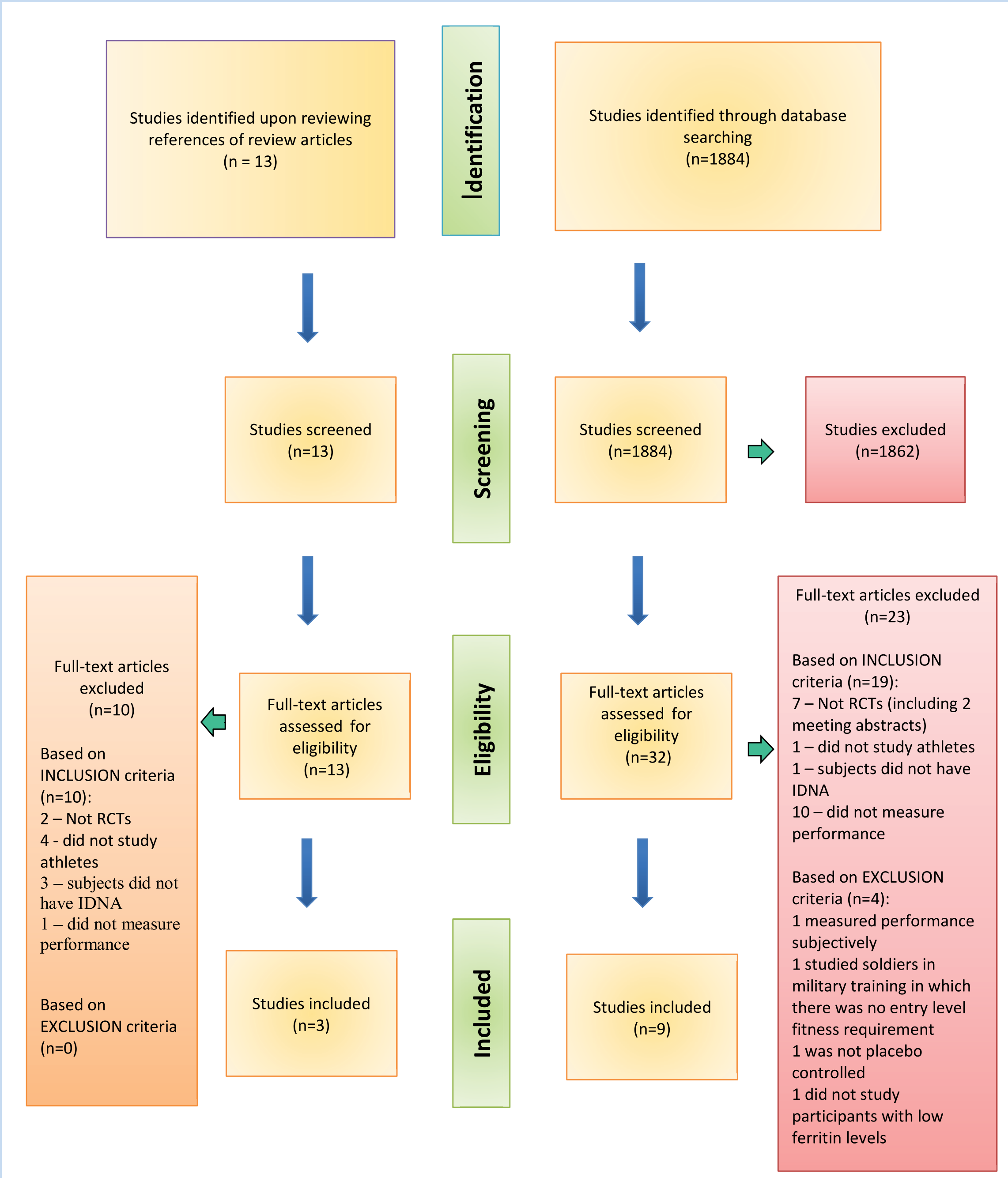

Figure 1. Flow diagram of literature selection on the effects of iron supplementation in iron-deficient nonanameic (IDNA) athletes. RCT, randomized controlled trial.

DISCUSSION

Performance Improvement

The results of our review are equivocal and do not support the conclusion that iron supplementation *consistently* improves performance in endurance IDNA athletes. Studies included in this review used a variety of clinically applicable measures of performance, such as a shuttle run time, 3000-m race pace, anaerobic speed test, maximal treadmill velocity, and treadmill endurance times.[4,33,47] Given that each sport has its own physical demands, it is logical that optimal performance will be measured differently between sports. For example, although VO_{2max} is an excellent indicator of cardiorespiratory endurance, Garza et al[21] theorized in 1997 that time to exhaustion "simulated field experience most closely."

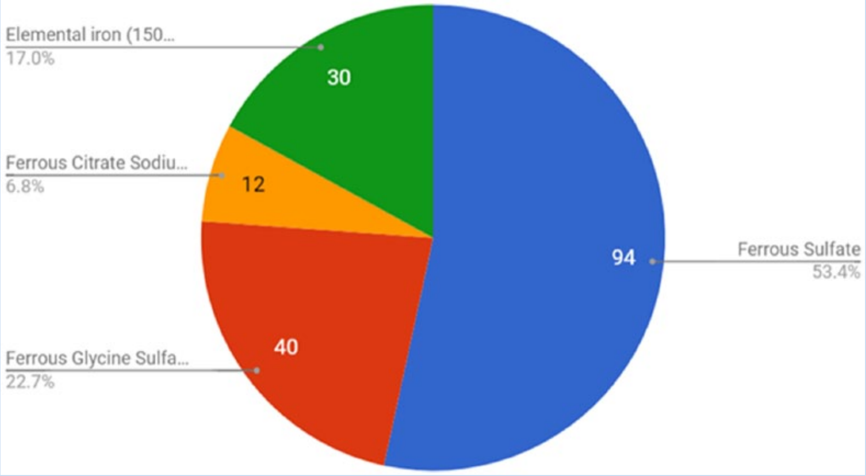

Figure 2. Iron formulations—performance improvement.

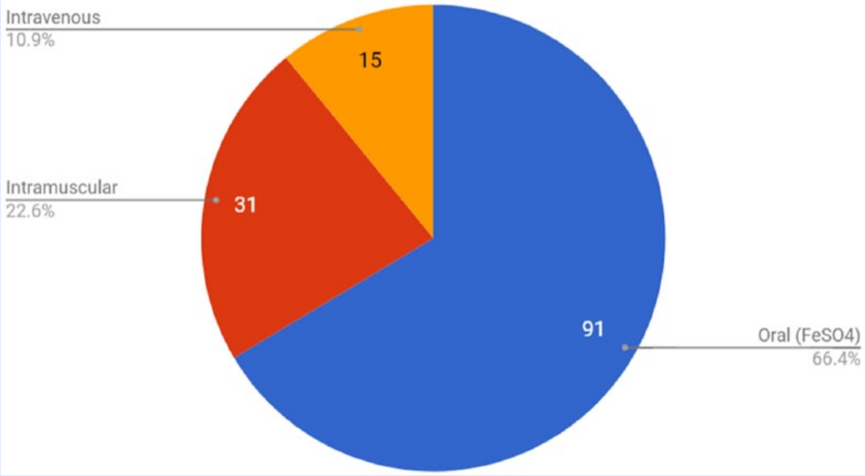

Figure 3. Iron formulations—no performance improvement.

Our conclusion that iron supplementation does not consistently improve performance in IDNA athletes differs from that of Burden et al,[5] who concluded that iron supplementation improves aerobic capacity (measured by maximal VO_2) in IDNA athletes. However, that meta-analysis only included studies that used VO_{2max} as the performance measure. On the other hand, we included all studies with quantitative performance measures. Importantly, we excluded participants who were not involved in organized sports teams or participating individually in an endurance sport. Burden et al[5] found that those studies showing the largest effect on VO_{2max} included participants with lower baseline VO_{2max} values[5]; many of these studies were excluded from our review because we could not verify that their participants were involved in organized or endurance sports prior to starting the study.[26,30]

Ferritin

There is a lack of standardization as to what constitutes a normal ferritin range in the current body of literature.[11,19,20,27-29,35,36,39,47] To make accurate and fair comparisons, we investigated whether there is a clinically applicable low ferritin cutoff that would support supplementation. A normal physiologic ferritin level varies between laboratories. However, levels less than 12 to 23 μg/L are generally recognized as iron deficient, given a near absence of bone marrow iron stores.[10] The sFer level at which investigators chose to start iron supplementation varied across the 12 studies examined in this review.[4,11,19,20,27-29,35,36,39,47]

None of the studies in this review that used a ferritin level greater than 20 μg/L as their cutoff demonstrated a significant improvement in performance following iron supplementation, whereas 6 of the 8 studies that used a cutoff level of 20 μg/L or less[11,20,27,28,29,35,39,47] demonstrated an improvement in performance following iron supplementation.[11,20,27,29,39,47] Therefore, it is reasonable to conclude that iron supplementation does not improve performance in athletes with sFer levels greater than 20 µg/L but that supplementation may play a role in improving performance in IDNA athletes with baseline sFer levels less than or equal to 20 µg/L.

Though many of the included studies measured other iron indices, only 1 study characterized athletes by stage 1 versus stage 2 iron deficiency.[35] Newhouse et al[35] made this distinction and indicated that 5 of the 19 participants in the iron treatment group had stage 2 iron deficiency. Notably, iron treatment did not improve performance (work capacity) even when participants with stage 2 iron deficiency were analyzed separately. Although this study did not demonstrate any significant difference in the performance of participants with stage 1 and stage 2 iron deficiency following iron supplementation, the hypothesis that athletes with more severe iron deficiency could benefit more from iron supplementation than those with less severe iron deficiency is plausible. Given the small sample size of the study by Newhouse et al,[35] future investigation into iron supplementation that distinguishes between the results of supplementation in stage 2 relative to stage 1 IDNA athletes is warranted.

Iron Supplementation Protocols

There is no consensus recommendation to guide the dosage, frequency, or delivery method and duration of iron supplementation in IDNA athletes. All of these parameters varied significantly among the review studies. Ferrous sulfate (20% elemental iron [the percentage absorbed by the gastrointestinal tract]) was the most common iron supplement employed in the studies reviewed. A typical recommended treatment for patients with IDA is 375 mg of ferrous sulfate taken twice daily; this is a total of 150 mg of elemental iron.[23] For reference, the recommended daily allowance of elemental iron for women (age 19-50 years) is 18 mg per day; the recommendation is only 8 mg per day for men.[22,38] Based on the results of this review, there is no evidence to suggest that supplementation at or above the usually recommended daily allowance of iron improves performance in IDNA athletes. With regard to route of administration, none of the studies that used intramuscular or intravenous administration demonstrated improved performance.[4,6,36] It is difficult to make any conclusive statements about the appropriate duration of iron supplementation for IDNA athletes. Of the studies that showed improved performance, the duration of treatment was highly variable with a very small sample size for each treatment duration; the studies that did not show improved performance had slightly more consistency, with 3 studies following participants for 8 weeks of treatment.

Limitations

The findings of this review are limited by the overall sample size as well as the demographics of participants. Although data from 12 studies were used, only 283 participants were included. In addition, these studies included mainly young female participants, making it difficult to generalize results to all athletes.

CONCLUSION

Iron supplementation in IDNA athletes is a complex issue. The body of literature addressing whether iron supplementation improves performance in IDNA athletes is limited by small sample sizes, large discrepancies in performance measurement protocols, IDNA diagnostic protocols, and iron supplementation treatment protocols. The results of this review are equivocal and do not support the conclusion that iron supplementation *consistently* improves performance in endurance IDNA athletes. However, the studies that demonstrated performance benefits with iron supplementation in IDNA all used a ferritin supplementation threshold at or below 20 µg/L. There is no evidence to support the practice of iron supplementation to improve performance in IDNA athletes with sFer levels greater than 20 µg/L. Although the results of this review are equivocal regarding performance benefits following iron supplementation in IDNA athletes with ferritin levels less than or equal to 20 µg/L, we can conclude that iron supplementation in athletes with ferritin levels greater than 20 µg/L will not improve performance. This conclusion is significant in that a threshold of 20 µg/L can provide clinicians, athletes, and coaches with an evidence-based, clinically applicable threshold for iron supplementation in endurance athletes. Additionally, this review was not able to determine the optimal route or duration of treatment, since the reviewed studies used such a wide variety of supplementation regimens.

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