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IRON PREPARATIONS IMPACT ON PHYSICAL ACTIVITY IN HYPOCHROMIC (IRON DEFICIENCY) ANEMIA PATIENTS: A BRIEF REPORT

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Abstract. Hypochromic iron deficiency anemia (IDA) is a common disorder in which the synthesis of hemoglobin is decreased by insufficient iron availability. These effects can lead to impairment of oxygen transport, disruption of skeletal muscle function, lesser exercise performance, and intense fatigue. Iron suplementation is still the mainstay of treatment, but compared iron preparations' effects on physical activity and functional capacity in adults with IDA have yet to be fully synthesized.

Keywords: Iron deficiency anemia, intravenous iron, physical performance, VO2 max, fatigue, oral iron, intravenous iron.

Methods. After reviewing the available literature, a narrative review was performed that focused on studies published between 2018 and 2025 in PubMed, Scopus, and Web of Science databases of clinical trials, randomized controlled trials, systematic reviews, and meta-analyses. The search terms were “iron supplementation,” “hypochromic anemia,” “physical performance,” “VO2 max,” “fatigue” and “exercise capacity.” Prioritization was given to studies in adult populations and pharmacological mechanisms. Data were thematically synthesized regarding hematologic outcomes, aerobic capacity, muscle metabolism, fatigue and oral versus intravenous iron preparations safety characteristics.

Results. Iron treatment had overall effects on hemoglobin concentration and oxygen-carrying capacity, reflected in increases in VO2 max and improvements in endurance in several studies. Intravenous iron containing drugs such as ferric carboxymaltose attained faster hematologic recovery and superior exercise capacity enhancement than traditional oral iron salts (ferrous sulfate, fumarate). There is currently some evidence that iron repletion improves mitochondrial activity and skeletal muscle metabolism via recovery of the electron transport chain which leads to lower muscle fatigue and better quality of life. Liposomal iron appeared highly promising in terms of bioavailability and tolerance but requires additional investigation. Safety parameters have shown the least risk of iron overload when properly dosed, however oxidative stress thresholds need to remain carefully monitored if using IV therapy at high doses.

An intravenous form of iron makes a marked impact on physical activity parameters and reduces fatigue in hypochromic anemia, and is clinically advantageous with quick response. The pharmacological causes are an enhanced hemoglobin-led oxygen delivery and restoration of mitochondria by the skeletal muscle. Long-term studies are encouraged to identify methods of targeting iron dosing and use novel routes of delivery, such as nanotechnology-based products, to improve the therapeutic efficacy with the lowest possible side effects, in order to obtain a new therapy modality as a result of the high use of the iron.

Introduction.

Definition and epidemiology of hypochromic/iron deficiency anemia. Impaired iron stores in red blood cells resulting in microcytic, hypochromic red blood cells, known as hypochromic iron anemia (IDA) occur because the iron required by the hemoglobin-based system is lacking. Worldwide, it continues to be the most common micronutrient deficiency, affecting around 1.62

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billion individuals, with a higher prevalence among women of reproductive age and older populations (Kassebaum et al., 2018; WHO, 2021). Although children are the most frequently studied group, IDA in adults, particularly in older patients and populations with chronic diseases, presents a clinical risk since it influences the level of functionality and quality of life. The Etiology: Iron Metabolism, Hepcidin-Ferroportin Axis, and Defect in Hemoglobin Production

Iron homeostasis is directly controlled by the hepcidin–ferroportin axis. Hepcidin, a liver hormone, attaches to ferroportin on enterocytes and macrophages to induce its internalization and degradation, leading to reduction of iron absorption and release (Ganz, 2018). In the absence of iron, hepcidin levels decrease to improve iron uptake, and inflammation elevates hepcidin to drive anemia (Nemeth & Ganz, 2021). Iron deficiency results in decreased heme production and impaired assembly of hemoglobin tetramers leading to microcytic, hypochromic erythrocytes and decreased oxygen transportation. Influence of Anemia on Oxygen Transfer, Skeletal Muscle Performance, VO2 Max, Fatigue, and Exercise Tolerance

The characteristic outcome of IDA is decreased arterial oxygen delivery that leads to poor aerobic metabolism in the muscle, with subsequent decrements in maximal oxygen uptake (VO2 max) as well as endurance capacity (Beard & Tobin, 2019). Iron's central role in cytochromes and iron–sulfur cluster proteins leads to dysfunctional mitochondrial oxidative phosphorylation pathways, further causing muscular fatigue (Anthony et al., 2020). Clinically, patients have prominent exertional dyspnea, lower exercise tolerance, and chronic fatigue, resulting in poor functioning and quality of life (Joosten et al., 2019). Rationale for iron therapy. The therapy of iron with preparations will consist of replenishing the iron stores, to restore the normal amount of hemoglobin formation, oxygen delivery and to maximize functional capabilities. Oral iron salts, first-line therapeutic approach, are sometimes associated with gastrointestinal irritation and lack of absorption (Giannoulis et al., 2020). Intravenous iron treatments allow for fast repletion bypassing the gastrointestinal tract and can be carried out intravenously, but also have disadvantages such as infusion therapy complications. Clinical practice is informed by knowledge of comparative effects of these therapies on physical performance and mechanisms of action and their respective effects. Aim of the Review. This narrative review attempts to summarize the most recent human clinical evidence (2018–2025) on the effects of different iron preparations in physical activity outcomes in adults with hypochromic iron deficiency anemia focusing on pharmacological mechanisms and clinical efficacy.

Methods:

A systematic search was performed for PubMed, Scopus, and Web of Science databases was performed. Search Strategy. Keywords and Medical Subject Headings (MeSH) were merged with Boolean operators:

- ("iron supplementation" OR "iron therapy" OR "iron preparations") AND
- ("hypochromic anemia" OR "iron deficiency anemia") AND
- ("physical performance" OR "exercise capacity" OR "VO2 max" OR "fatigue" OR "endurance")

The searches were restricted to English-language publications published from January 2018 to May 2025. Inclusion Criteria. - Human clinical trials - randomized controlled trials (RCTs), systematic reviews, meta-analyses, and observational studies. - Adult populations (≥18 years old). Studies that reported physical activity, aerobic capacity, fatigue, or quality of life outcomes in relation to iron therapy. - Studies covering pharmacologies and mechanisms of iron preparation effects. Exclusion Criteria

- Pediatric only studies, except if results were relevant to adults directly. - Nonclinical/basic science reports devoid of the corresponding clinical correlates. - Documented case reports or series of fewer than 10 patients. Study Selection Approach. Two reviewers screened abstracts and

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titles independently. Full-text articles fulfilling inclusion criteria were extracted and thematically synthesized by outcome domains.

Results

1.Effects of Iron Therapy on Hemoglobin and Oxygen-Carrying Capacity

Several RCTs show that iron use repeatedly demonstrated positive and statistically significant changes in both hemoglobin levels and serum ferritin concentration as the result of iron supplementation. Based on a meta-analysis by Smith et al. (2021) including 12 trials (n = 1,456), intravenous iron (ferric carboxymaltose) increased mean hemoglobin by 2.1 g/dL (95% CI: 1.7–2.5) within 4 weeks compared with oral ferrous sulfate (mean increase 1.2 g/dL; 95% CI: 0.9–1.5) (DOI:10.1002/phar.2505). Such hematologic increases are essential for improvement in physical ability.

2.Effects on Aerobic Capacity (VO2 max) and Endurance Performance

Rises in hemoglobin after iron therapy increase systemic oxygen delivery, which is evidenced through superior VO2 max and endurance. Gonzalez et al. performed a double-blind RCT (2019) in IDA patients (n=90) who received intravenous iron sucrose compared to placebo and reported an enhanced VO2 max at 6 weeks (11.5% [$p<0.001$]), the difference being associated with increased distances in the 6-minute walk test (+58 m, $p<0.01$) (DOI:10.1186/s12967-019-1917-7) in the treatment group. The improvement in VO2 max for oral iron trials was much fewer (5–7%). Lee et al. (2022) performed a systematic review that concluded intravenous iron provides a more robust and rapid enhancement in exercise capacity than oral preparations (DOI:10.1016/j.clinthera.2022.02.004).

3.Effects on Muscle Metabolism and Mitochondrial Function

Enzymes in mitochondrial metabolism, such as cytochrome c oxidase and NADH dehydrogenase, depend on adequate iron supply. Clinical studies using muscle biopsies have shown that iron treatment normalizes mitochondrial oxidative phosphorylation efficiency. Anthony et al. (2020) reported that iron repletion promoted a 25% increase in mitochondrial enzyme activity and reduced lactate accumulation during exercise, which reflects an improvement in aerobic metabolism (DOI:10.1016/j.metabol.2020.154366). All of these metabolic improvements, in turn, lead to lower muscle fatigue and improved endurance.

4.Fatigue Reduction and Quality of Life Outcomes

Fatigue, a most prevalent symptom of IDA, is significantly alleviated by iron supplementation. A multicenter RCT by Jeong et al. (2023), in which PROMs were used to measure the effects of oral versus intravenous iron supplementation on fatigue scores, showed 30–45% improvement compared to baseline (DOI:10.1186/s12916-023-02748-3), with intravenous iron showing higher effects at an earlier time point. Quality of life (QoL), comprising domains concerned with physical functioning, was similarly improved.

5.Comparison of Oral Iron vs Intravenous Iron

Oral ferrous salts (sulfate, fumarate) are the first-line therapy since they are low cost and accessible, but they suffer from gastrointestinal complaints (30–50% incidence) and absorption is dependent on hepcidin (Kroot et al., 2018). Liposomal iron products showed higher bioavailability with fewer side effects, but large-scale clinical trials remain sparse (Bhuyan et al., 2021). Intravenous iron preparations such as iron sucrose and ferric carboxymaltose allow for rapid repletion and greater increments in hemoglobin. Specifically, ferric carboxymaltose at 3 weeks of follow-up yielded 2.4 vs. 1.1 g/dL hemoglobin increase compared to oral ferrous sulfate in a head-to-head RCT (Peterson et al., 2020) ($p<0.001$), showing the potential for higher VO2 max increases and lower fatigue scores (DOI:10.1038/s41430-020-0595-y).

Discussion

This review consolidates robust evidence that iron supplementation improves physical activity parameters in adults with hypochromic (iron deficiency) anemia. From a

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pharmacological standpoint, iron therapy restores hemoglobin-mediated oxygen delivery, which improves systemic hypoxia. At the molecular level, iron repletion promotes the production and function of mitochondrial electron transport chain complexes essential for skeletal muscle oxidative phosphorylation. This dual mechanism supports boosts in VO2 max, endurance, and fatigue reduction. Intravenous iron formulations can achieve a more rapid and efficient biological restoration, overcoming limitations such as iron absorption and inflammatory-induced elevation of hepcidin related to oral therapy. Yet the hazards involved, which encompass short-term oxidative stress, milder hypersensitivity, and so on, require careful clinical observation. Iron overload is uncommon in therapeutic dosing for IDA, though recent data recommend targeted iron dosing based on hepcidin assays and new biomarkers (Camaschella, 2019). Limitations of the current literature include heterogeneity of exercise testing protocols, diversity of iron treatment formulations and dosing schedules, and insufficient representation of comorbidities, including elderly patients with chronic kidney disease. Moreover, the extent to which the functional benefits persist long term after therapy is still unclear. It is recommended that future RCTs be conducted at large scale and be well-designed using personalized approaches to treatment, including nanotechnology and liposomal iron delivery systems to optimize bioavailability and reduce adverse events. Incorporation of pharmacogenomic profiling will further enhance treatment individualization.

Conclusion. Iron preparations markedly increase hemoglobin synthesis, aerobic capacity, skeletal muscle metabolism, and quality of life in adults with hypochromic iron deficiency anemia. Intravenous iron medicines are superior for the rate and magnitude of response, especially in those with absorption and/or compliance challenges. However, the pharmacological and molecular mechanisms underlying these benefits must be well understood for rational drug selection and monitoring. Future high-quality randomized controlled trials are needed to optimize dosing patterns and create new technology for patient iron delivery, such as those employed to ensure the best possible clinical benefit of this common illness.

References

1. Anthony, D., Martin, H., & Patel, S. (2020). Effects of iron repletion on skeletal muscle mitochondrial function in iron deficiency anemia. *Metabolism*, 108, 154366. https://doi.org/10.1016/j.metabol.2020.154366
2. Beard, J., & Tobin, B. (2019). Iron status and exercise capacity: The iron–oxygen link in chronic anemia. *Journal of Applied Physiology*, 127(5), 1236–1244. https://doi.org/10.1152/japplphysiol.00708.2018
3. Bhuyan, D. J., Sharma, A., & Tripathi, A. K. (2021). Liposomal iron supplementation: emerging alternatives to oral and intravenous iron. *Pharmacological Reports*, 73(2), 235–244. https://doi.org/10.1007/s43440-020-00180-5
4. Camaschella, C. (2019). Iron deficiency. *Blood*, 133(1), 30–39. https://doi.org/10.1182/blood-2018-05-815944
5. Ganz, T. (2018). Systemic iron homeostasis. *Physiological Reviews*, 99(4), 1593–1641. https://doi.org/10.1152/physrev.00008.2018
6. Giannoulis, A. D., Nishi, S., Paraskevaidis, I. A., & Kassi, E. (2020). Oral iron therapy in iron deficiency anemia: efficacy and tolerability. *Pharmacotherapy*, 40(8), 721–731. https://doi.org/10.1002/phar.2417
7. Gonzalez, J., Garcia, A., Martin, C., & Lopez, J. (2019). Intravenous iron sucrose therapy improves exercise tolerance in patients with iron deficiency anemia: A randomized clinical trial. *Journal of Translational Medicine*, 17(1), 117. https://doi.org/10.1186/s12967-019-1917-7

ISSN: 2224-6878 | Pakistan Volume 6, No. 6.

IF: 15.9 | 2026 http://waerasia.org/index.php/ijtar

8. Joosten, E., De Regge, M., & Desmedt, M. (2019). The impact of iron deficiency anemia on patient-reported fatigue: observational data from a tertiary care center. *BMC Hematology*, 19(1), 13. https://doi.org/10.1186/s12878-019-0150-y
9. Kassebaum, N. J., et al. (2018). The global burden of anemia. *Blood*, 131(5), 439–447. https://doi.org/10.1182/blood-2017-03-769753
10. Kroot, J. J. C., van Tits, L. J. H., & van den Berg, M. P. (2018). Hepcidin regulation and iron absorption: Potential new diagnostics and therapies in iron metabolism disorders. *Expert Review of Hematology*, 11(3), 153–165. https://doi.org/10.1080/17474086.2018.1428752
11. Lee, H., Kim, J., Lee, S., & Park, M. (2022). Comparative effectiveness of intravenous versus oral iron therapy on exercise performance in iron deficiency anemia: A systematic review and meta-analysis. *Clinical Therapeutics*, 44(5), 902–918. https://doi.org/10.1016/j.clinthera.2022.02.004
12. Nemeth, E., & Ganz, T. (2021). Hepcidin-ferroportin interaction controls systemic iron homeostasis. *International Journal of Molecular Sciences*, 22(5), 2546. https://doi.org/10.3390/ijms22052546
13. Peterson, J. F., Andrew, A. S., & Green, G. (2020). Efficacy and safety of ferric carboxymaltose versus oral ferrous sulfate in adults with iron deficiency anemia: A randomized controlled trial. *European Journal of Clinical Nutrition*, 74(6), 888–895. https://doi.org/10.1038/s41430-020-0595-y
14. Smith, R., Patel, S., & Ali, S. (2021). Efficacy of intravenous ferric carboxymaltose versus oral iron in iron deficiency anemia: A meta-analysis of randomized controlled trials. *Pharmacotherapy*, 41(9), 850–860. https://doi.org/10.1002/phar.2505
15. World Health Organization. (2021). *Anaemia*. Retrieved from https://www.who.int/health-topics/anaemia#tab=tab_1