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NOVELTIES IN THE TREATMENT OF IRON DEFICIENCY ANEMIA IN ADULTS, TO IMPROVE SERUM IRON AND FERRITIN LEVELS

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Abstract: Iron deficiency anemia is the most common form of anemia in the world, resulting from iron deficiency, which compromises hemoglobin synthesis and red blood cell production. In view of this, the aim of this work is to develop a study on the main innovations in the treatment of iron deficiency anemia in adults, in order to improve serum iron and ferritin levels. The methodology applied is based on a literature review, in which health databases were used that contributed to the development of the research. The results showed that the treatment of iron deficiency anemia in adults is evolving towards a personalized, multimodal and evidence-based model. While oral supplementation remains the first line, innovative formulations and optimized dosage regimens reduce adverse effects and improve adherence. In conclusion, intravenous iron is expanding its indications, benefiting patients with complex comorbidities. In parallel, emerging nutritional and pharmacological strategies promise to further improve clinical outcomes. Thus, close monitoring and a multidisciplinary approach are essential to ensure effective iron replacement and the resolution of anemia.
Keywords: Iron deficiency anemia. Serum iron. Ferritin. Iron supplementation.

INTRODUCTION

Iron deficiency anemia is the most common form of anemia in the world, resulting from iron deficiency, which compromises hemoglobin synthesis and red blood cell production. In adults, the most frequent causes include chronic blood loss (such as excessive gastrointestinal or menstrual bleeding), inadequate dietary iron intake and malabsorption (Silva *et al*., 2024).

Traditional treatment involves oral iron supplementation and correction of the underlying cause. However, recent advances have provided new approaches to optimize iron replacement, improve adherence to treatment and reduce adverse effects (Boas Marinho *et al*., 2023).

Traditional ferrous salt supplements (ferrous sulfate, ferrous gluconate) are often associated with gastrointestinal adverse effects (nausea, constipation, diarrhea), which limit adherence. New formulations have been developed to improve tolerability, as Silva *et al*. (2024) explain:

- Liposomal iron: Encapsulates iron in liposomes, improving its absorption and reducing gastric irritation. Studies show greater bioavailability and fewer side effects.
- Prolonged-release iron: Formulations such as polymaltose iron (ferric carboxymaltose in oral presentations) have less gastrointestinal toxicity and can be administered in more spaced doses.

Studies such as Negreiros *et al*. (2024) suggest that alternate-day administration (rather than daily) may improve iron absorption, since hepcidin (iron-regulating hormone) increases after the initial dose, reducing subsequent absorption within 24 hours. This scheme may be as effective or more effective than daily supplementation, with fewer side effects.

In addition to supplementation, nutritional strategies are essential, such as the consumption of heme iron (red meat, liver), which has greater bioavailability, as well as avoiding absorption inhibitors (calcium, coffee, black tea) close to iron-rich meals and fortified foods (cereals, enriched vegetable milks) as adjuvants (Ar22 *et al.,* 2022).

Regarding monitoring with advanced biomarkers, Teixeira *et al*. (2024) cites that the CBC can be used together with ferritin and transferrin saturation, in which new markers can assist in management, such as the soluble transferrin receptor (STFR): Useful for differentiating pure iron deficiency anemia from anemia of chronic disease and Indices of erythropoiesis (such as reticulocyte hemoglobin content - CHr).

The treatment of iron deficiency anemia in adults is evolving with more tolerable formulations of oral iron, optimized administration protocols (such as alternating doses), expanded use of intravenous iron and innovative nutritional and pharmacological strategies. Personalization of treatment, taking into account the underlying causes and individual response, is fundamental for the effective correction of serum iron and ferritin levels (Galvão *et al.,* 2024).

In view of this, the aim of this study is to develop an overview of the main innovations in the treatment of iron deficiency anemia in adults, in order to improve serum iron and ferritin levels.

Therefore, the research is justified because it is relevant, given that new therapies, such as hepcidin modulators and approaches based on the intestinal microbiota, promise to further improve results, especially in patients with complex comorbidities. Adequate laboratory monitoring and a multidisciplinary approach are essential for therapeutic success.

METHODOLOGY

The paper is based on a literature review, the aim of which is to examine recent advances in the treatment of iron deficiency anemia in adults, focusing especially on therapeutic strategies to improve serum iron and ferritin levels.

The search was carried out in scientific databases such as *PubMed, Scielo, Scopus, Lilacs and Cochrane*. The search was carried out using the following key terms, combined by Boolean operators (AND, OR) using DeCS Health Sciences Descriptors (*DeCS*), for example: "iron deficiency anemia"; "iron supplementation"; "serum iron"; "intravenous therapy" and "oral supplementation".

The inclusion criteria were evaluated clinical studies, systematic reviews, meta-analyses and cohort articles that address the treatment of iron deficiency anemia in adults; recent publications from the last 5 years (2019 to 2024), to ensure the relevance and updating of data and Articles that discuss different forms of treatment for iron deficiency anemia, such as oral supplementation, intravenous iron therapy, iron transfusion, dietary strategies and new therapeutic alternatives.

The exclusion criteria were studies involving paediatric patients, since the review focuses on adults; articles that do not clearly specify the intervention methods or the results related to improving serum iron and ferritin levels; and studies with poor methodological quality or small samples that compromise the generalizability of the results.

The selection of articles was carried out in two stages: initial screening by reading the titles and abstracts to identify the most relevant studies and a complete reading of the articles to check that they met the inclusion criteria, as well as checking the methodologies, samples and results.

Therefore, the results were presented descriptively, grouping the treatments evaluated and their effects on improving serum iron and ferritin levels, through 8 selected articles.

RESULTS AND DISCUSSION

In iron deficiency anemia, ferritin levels are below the reference values, accompanied by a reduction in serum iron, low transferrin saturation and an increase in total iron binding capacity, factors that together characterize the diagnosis of this condition (De Souza, 2020).

According to Alexandre and Bonani (2023), serum iron reference values vary according to the method used, ranging from 75 to 175 µg/dL in adult men and between 65 and 165 µg/dL in women. However, its interpretation alone is limited and it is necessary to analyze it in conjunction with other parameters, such as serum ferritin and transferrin saturation.

While the reference value for serum iron varies according to the method used, it is between 75 and 175 μg/dL in adult men and between 65 and 165 μg/dL in women. However, its analysis alone is limited and it is essential to consider it in conjunction with other parameters, such as serum ferritin and transferrin saturation (Alexandre; Bonani, 2023).

In the study conducted by Lo *et al.* (2022), iron deficiency was identified as the most prevalent nutritional deficiency on a global scale. Oral iron supplementation is widely used as the first-choice treatment for both acute and chronic cases, due to its practicality and accessibility. However, there is still no consensus on the ideal formulation or dosage, nor on which patients should prioritize treatment with intravenous iron.

Management of this condition is hampered by iron regulation mediated by hepcidin and ferroportin. This mechanism is a biological adaptation designed to prevent iron overload, but at the same time it imposes a natural limitation on the gastrointestinal absorption of this mineral, compromising the effectiveness of oral supplementation. In addition, unabsorbed iron can trigger frequent side effects such as dyspepsia and constipation, especially when administered in excessive doses (Lo *et al.,* 2022).

As pointed out by Lo *et al.* (2022), protocols that explore less frequent dosing strategies - such as reduced daily doses or alternate--day administration - have been developed to overcome these physiological barriers. While this approach aims to improve absorption and minimize adverse effects, the results still reveal a low fractional absorption rate of iron.

Pasupathy *et al.* (2023) investigated this issue by comparing daily supplementation with alternate-day supplementation in a double--blind clinical trial involving 200 adults diagnosed with anemia iron deficiency. Participants had hemoglobin equal to or less than 10 g/dL, hypochromic microcytic anemia and/or serum ferritin below 50 ng/mL. During clinic visits, hemoglobin, serum ferritin and reticulocyte count tests were carried out, as well as reports on possible side effects.

The results showed that there were no significant differences between the two supplementation regimes with regard to increases in hemoglobin levels, serum ferritin or reticulocyte count at the pre-established follow-up times in the study. In addition, adverse effects were similar between both groups, with the exception of a higher incidence of nausea in the group that received iron every other day during the week (Pasupathy *et al*., 2023).

Another point highlighted was the potential interference of inflammation on baseline levels and subsequent variations in ferritin, which could introduce bias into the results. It was also investigated that serum ferritin levels could be momentarily elevated if the test was carried out within 1 to 3 days of taking the iron dose (Pasupathy et al., 2023).

For Pasupathy *et al.* (2023), planned clinical trials that recruited a larger number of participants and carried out supplementation over longer periods, evaluating clinically relevant stages such as variation in hemoglobin levels, may be important in determining the most effective dosing strategy.

Zhang *et al.* (2024) compared the efficacy and safety of high-dose intravenous iron with oral iron in the treatment of iron deficiency anemia, observing that both treatments resulted in improved hemoglobin (HGB) levels. However, recovery was faster in the group that received intravenous iron.

The authors examined that the group receiving intravenous iron showed a more significant improvement in iron metabolism disruptions, including serum iron, transferrin saturation, total iron binding strength [TIBC] and serum ferritin, compared to the oral group after four weeks. It was also observed

that patients in this group reported a more accelerated recovery in fatigue scores (Zhang *et al.,* 2024).

Thus, it was concluded that the administration of intravenous iron in high doses promotes a faster increase in HGB and improves early indicators of iron metabolism, as well as reducing symptoms of fatigue (Zhang *et al*., 2024).

Tarancon-Diez *et al*. (2023) investigated the safety and efficacy of intravenous treatment with generic iron (Feriv®) in 122 participants, 91% of whom were women, with a mean age of 44 years, who had absolute iron deficiency (serum ferritin < 50 ng/ml, with or without anemia). After treatment, there was a significant improvement in iron-related biomarkers such as ferritin, Hb, sideremia, transferrin, transferrin saturation index, soluble transferrin receptor (sTfR) and hepcidin.

Baseline ferritin, which was initially 13.5 ng/ml [IQR: 8-24.2], showed a progressive increase, reaching a median of 222 ng/ml at the end of the study, with 97.3% of patients reaching levels ≥ 50 ng/ml (Tarancon-Diez *et al*., 2023).

At the end of the follow-up period, the prevalence of moderate anemia dropped from 26.2% to 5%, while 34.1% of patients who did not have anemia at the start of the study had an increase of at least one point in their hemoglobin levels. The only adverse effect recorded was headache, which occurred in 2.3% of participants. In a later evaluation, carried out on a subgroup of 66 patients after a median of 27.5 weeks from the end of therapy (IQR: 22-40), it was observed that 18% of individuals had ferritin levels below 50 ng/ml (Tarancon--Diez *et al*., 2023).

A multivariate analysis revealed that low baseline ferritin levels and a high STFR ratio were independently associated with the recurrence of iron deficiency (ID). Treatment with Feriv® proved to be a safe and effective first-line option for absolute IHD, promoting significant improvement in serum ferritin and hemoglobin levels. However, the recurrence of iron deficiency was directly related to the initial degree of depletion of iron reserves, as indicated by serum ferritin and the STFR ratio (Tarancon-Diez *et al*., 2023).

Kamath *et al.* (2024) evaluated the efficacy of daily oral iron administration compared to alternate-day administration in the treatment of iron deficiency anemia, with changes in hemoglobin levels as the primary stage. The study found no significant difference in the increase in hemoglobin or iron indices, including ferritin, hepcidin, total iron binding capacity and reticulocyte count, between the two dosage regimens.

However, adverse effects such as nausea, a metallic taste in the mouth and changes in intestinal transit were less frequent with alternate-day administration. Despite the absence of significant differences in hemoglobin levels between the two methods, iron absorption can have an impact in the first few days of treatment (Kamath *et al*., 2024).

It was also identified that the recurrence of absolute iron deficiency was associated with the initial degree of depletion of iron stores, as indicated by serum ferritin levels and the sTfR/hepcidin ratio before the start of intravenous treatment. This finding underscores the importance of early diagnosis and intervention in iron deficiency, even in the absence of anemia (Kamath *et al*., 2024).

Loganathan *et al*. (2023) investigated the efficacy of vitamin C or ascorbate supplementation as an adjunct to iron treatment for anemia. The results showed that the combined estimate of the standardized mean difference (SMD) for hemoglobin (g/dL) and serum ferritin (mcg/L) in the group that received ferrous ascorbate as an intervention was 0.44 and 0.03, respectively, with no statistical significance.

In the group that received oral iron combined with vitamin C, the combined MDS estimate for hemoglobin (g/dL) was 0.11 (95% CI: -0.05 to 0.28) and for serum ferritin (mcg/L) was -0.90 (95% CI: -1.09 to -0.72), also without statistical significance.

Thus, the authors concluded that the difference in hemoglobin and serum ferritin levels between the intervention groups did not declare a significant benefit for the use of ferrous ascorbate or oral iron with vitamin C. In addition, the methodological quality of the evidence was considered very low (Loganathan *et al*., 2023).

It is therefore essential to investigate the efficacy of treatment with oral vitamin C (ascorbate) in combination with oral iron for patients with anemia, considering future clinical trials (Loganathan et al., 2023).

Saini *et al*. (2024) analyzed the most recent advances in the treatment of iron deficiency anemia. As a result, there is growing interest in developing new drug delivery systems that can increase the efficiency of iron therapy and improve clinical outcomes.

Various strategies have been studied, such as nanoparticles, microparticles, liposomes and hydrogels, due to their potential to optimize iron bioavailability, minimize side effects and maximize therapeutic benefits. The authors describe the relevance of innovative approaches to the future management of iron deficiency anemia, including advanced technologies such as targeted drug delivery systems, controlled release mechanisms and combination therapies (Saini *et al.,* 2024).

The incorporation of these new systems, combined with advances in diagnostics, personalized medicine and patient-centered care, has great potential to transform the treatment of iron deficiency anemia, contributing to a significant improvement in the quality of life of affected individuals (Saini *et al*., 2024).

Therefore, it can be seen that iron deficiency anemia persists as a global health challenge, especially in adults with conditions such as chronic bleeding, malabsorption or inflammatory diseases.

CONCLUSION

Iron deficiency anemia continues to be one of the most prevalent conditions in the world, with significant implications for public health, particularly in adults. The treatment of this condition traditionally involves iron replacement, either orally or intravenously, with the aim of restoring normal serum iron and ferritin levels, which are essential for the proper functioning of biological systems. However, in recent decades, new therapeutic approaches have been explored and improved, providing more effective and less uncomfortable alternatives for patients.

Throughout the work, it was observed that the treatment of iron deficiency anemia in adults is evolving towards a personalized, multimodal and evidence-based model. While oral supplementation remains the first line, innovative formulations and optimized dosage regimens reduce adverse effects and improve adherence.

At the same time, emerging nutritional and pharmacological strategies promise to further improve clinical outcomes. Thus, close monitoring and a multidisciplinary approach are essential to ensure effective iron replacement and the resolution of anemia.

Therefore, future studies on the treatment of iron deficiency anemia in adults, especially with regard to improving serum iron and ferritin levels, are extremely important in order to deepen our understanding of this condition and improve the available therapeutic strategies

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