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The Forgotten Clinical Impact of Evolutionary Iron Resistance

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ABSTRACT

Evolution of life has developed mechanisms to regulate iron levels. Understanding the mucosal iron resistance may be the key for a better iron replacement strategy in patients with iron deficiency. This paper discusses the efficiency of the mini dose iron replacement strategies that are gaining popularity for iron deficiency with or without anemia, in the light of the current literature.

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INTRODUCTION

A recent study showed that treating iron deficiency with a lower amount of elemental iron (24mg) effectively increased hemoglobin and ferritin levels without causing substantial adverse effects (1). This approach was also found to be significantly more effective in reducing the severity of fatigue compared to the standard of care. In light of this study, let's delve into some historical aspects of iron replacement theory.

Basics of iron metabolism

Iron is the fourth most common metal comprising almost 5% of the earth's crust. Since the early days of life on earth, this redox-active metal was crucial for the evolution of life. As it serves an indispensable co-factor of many enzymes as cytochrome oxidase, peroxidase, and catalase and is a structural part of proteins like myoglobin, iron is involved in various metabolic processes required to survive (2,3). Conversely, excessive iron produces harmfull reactive oxygen species, which are toxic. Life on earth not only seeks but also refrains from iron. Starting with siderophores of primordial bacteria, evolving into specific iron transport systems in complex life forms, life has developed sophisticated mechanisms to moderate iron levels, with strictly controlled absorption, metabolism, and extraction processes.

When the body becomes saturated with iron—meaning that nearly all of the apoferritin in the storage sites is bound to iron—additional iron absorption from the intestine is significantly reduced. Conversely, when the iron stores are depleted, the absorption rate can increase dramatically, sometimes up to five times the normal rate (3). Thus, total body iron is primarily regulated by modulating the rate of intestinal

absorption. In humans, iron absorption is primarily regulated by Hepcidin (HAMP) and involves several other genes related to iron metabolism (like IREB2, TFR1, DMT1, ZIP14, IRP1/2, CYP1B1, CYP4V2 and more) making it a complex system that involves both systemic and cellular processes (3). Hepcidin inhibits iron absorption by binding to ferroportin, the protein that exports iron from intestinal cells and macrophages. When hepcidin levels are high, it leads to mucosal iron resistance that decreases iron absorption. Increased hepcidin levels are often observed in individuals with obesity or certain liver diseases. In pro-inflammatory conditions or infections, interleukin-6 stimulates hepcidin production to limit iron availability to pathogens. Treating iron deficiency increases serum iron concentration as well and causes hepcidin levels to rise as an evolutionary reflex to the excess amount of iron entry. While the absorbed iron is responsible for the desired effects, the non-absorbed iron is the reason for the side effects (4). The reduced iron absorption capacity due to mucosal iron resistance is thought to be the main cause of gastrointestinal (GI) intolerance which is a common reason for discontinuing iron replacement therapies. Discontinuation of iron replacement is a common problem. A recent study reports the adherence ratios to iron replacement treatment is as low as 23% to 55% (5).

The debate on the iron replacement schedules

For years of practice, some clinicians have observed that the current iron treatment schedules and doses are likely excessive, and the righteous dose for iron replacement is less than the classical suggestions. Methods such as every other day dosing, menstruation-week dosing, and pediatric dose syrups for adults were experimented to improve GI tolerance, but these approaches lack scientific validation.

Formulas still used today to calculate the total iron deficit tend to be unreliable in treating iron deficiency (6). These calculations depend on assumptions of 20th century knowledge, using a reasonable blood volume of 5 liters, an average iron loss rate of 1 mg per day, and a fixed intestinal iron absorption rate of 10% (7). But this theory is cracking, because recent studies demonstrated that both iron absorption and daily iron loss rates dramatically changed on the course of iron replacement and most of the absorbed iron was lost during supplementation (8). Low-dose iron treatment was already shown to be effective in elderly patients with iron-deficiency anemia (9). A recent placebo-controlled randomized clinical trial and another prospective open-label single-arm trial in young premenopausal women with non-anemic iron deficiency documented that low-dose (27 mg once daily and 6 mg twice daily respectively) iron replacement effectively maintained an improved blood-iron status without causing significant GI distress (10,11).

Despite advancements, traditional iron dosing schemes are still prevalent in medical textbooks, indicating a need for updated information to be disseminated across the medical community. Evidence has prompted changes in iron supplementation guidelines. One of the recent guidelines to offer a lower dose of iron supplementation is the “2021 British Society of Gastroenterology Guideline for the Management of Iron Deficiency Anaemia in Adults” which offered alternate day dosing as a solution to iron-related GI side effects (12). Some recent text books started concerning this evolutionary mucosal iron resistance and a lower dose of iron replacement is being offered for individuals with GI intolerance (6, 13). It turns out to be the time to re-evaluate iron replacement strategies for patients with non-anemic iron deficiency and iron deficiency anemia.

CONCLUSION

The mini-dose iron replacement strategies have been underestimated as “vitamin – mineral replacement dose” for years. With more proof for the undeniable effect of mucosal iron resistance, it is needed to be cleared if mini-doses of iron are a better alternative to the standards of care in iron replacement providing enough treatment with more GI tolerance. Initiating iron replacement in much lower doses, rather than reducing the standard 100-300 mg doses of iron replacement for GI intolerance, may improve treatment adherence too. To do so, new prospective research on the effect of different mini-dose posologies of iron in different patient groups, different anemia etiologies, and different states of iron absorption are needed.

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