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Challenges for The Future, Iron Deficiency and Anemia in Bariatric Surgery

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ABSTRACT

Iron deficiency and obesity are global epidemiological problems affecting billions of people worldwide. In the last 30 years, the prevalence of obesity in Europe has risen to 23% and continues to increase. The unequivocal molecular-level connection between obesity and iron deficiency has been demonstrated. Due to the lifestyle and diet of modern humans, obesity and iron deficiency are no longer limited to industrialized countries; developing and underdeveloped nations are also affected by these issues. The most common form of anemia is iron-deficiency anemia. Although all recommendations unanimously advocate for iron correction before and after bariatric surgery, current guidelines are at level C and need improvement. Similarly, there is a growing emphasis in the literature on administering intravenous iron to patients during the first two weeks of hospitalization after bariatric surgery, followed by oral supplements upon discharge, although the specific type of oral supplements remains unclear. According to current protocols, patients are expected to be monitored for the next twelve months for anemia correction. Yet, after bariatric surgery the majority of patients do not receive additional information and advice on nutrition and iron supplementation, leaving them more or less to their own. Considering the numerous side effects associated with non-hem iron, a significant number of patients abandon iron therapy, which can undoubtedly impact the ultimate treatment outcome. Given the much better tolerance and high efficacy, the introduction of hem iron preparations may open a completely new chapter for research in this field.

KEYWORDS*:* anemia, bariatric surgery, heme iron

ARTICLE DETAILS

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INTRODUCTION

According to the World Health Organization data, the prevalence of obesity in Europe has increased to 23% in the last 30 years and is still rising (1). Within the context of obesity, there is an accumulation of adipose tissue. Obesity leads to changes in the metabolic and endocrine functions of adipose tissue, resulting in increased release of fatty acids, hormones, and proinflammatory molecules (2). The increase in adipose tissue quantity also leads to elevated leptin production, a hormone that regulates energy intake, energy deposition, and insulin resistance. Chronic elevation of leptin due to obesity results in the development of resistance to leptin receptors in the hypothalamus, leading to additional fat deposition and insulin resistance. Adipose tissue deposition is also associated with a decrease in adiponectin levels, a hormone that under normal physiological conditions reduces hepatic gluconeogenesis and increases lipid oxidation (3, 4). At the same time, there is an increase in the production of proinflammatory cytokines, adipokines, TNF-α, IL6, nitric oxide, etc., in adipose tissue (5, 6). As a consequence of these disturbances in obese individuals, over time, there is the development of hypertension, dyslipidemia, atherosclerosis, glucose intolerance, type 2 diabetes, and an increase in the incidence of certain cancers.

In this context, the relationship between obesity and anemia is particularly interesting. Iron deficiency and obesity are global epidemiological problems affecting billions of people worldwide, while several hundred million people grapple with the challenges of anemia. The molecular-level connection between these two events has now been unequivocally demonstrated. Due to the lifestyle and diet of modern humans, obesity and iron deficiency are no longer limited to industrialized countries but also affect developing and underdeveloped nations (7). The prevalence of iron deficiency in obese individuals can reach up to 45%. However, the complexity of the relationship between obesity and anemia is manifested through a condition known as "dysmetabolic iron overload

syndrome" because despite the inaccessibility of iron to cells, its reserves are relatively large. This syndrome occurs in almost a third of individuals with non-alcoholic fatty liver or metabolic syndrome. Fortunately, true iron overload is a rare occurrence.

The goal of the paper is to underscore the importance of iron supplementation in patients undergoing bariatric surgery and to highlight new perspectives in the application of novel forms of oral iron preparations.

ANEMIA DUE TO IRON DEFICIENCY

The most common form of anemia is iron-deficiency anemia, accounting for up to 75% of cases. It is estimated that iron deficiency affects over two billion people (8). Iron is an essential element with a daily turnover of around 20-30 mg, primarily obtained from the reticuloendothelial system. After sequestration of aged and damaged erythrocytes in the spleen and liver, macrophages and hepatocytes separate iron from the rest of the hemoglobin. Depending on the body's needs, it is either released into the plasma through ferroportin or stored in the form of ferritin. Released iron binds to transferrin and is transported to most cells, where it is taken up via the transferrin receptor. The majority of iron is re-incorporated into hemoglobin in new erythrocytes, while a portion is used in mitochondrial processes and DNA molecule synthesis. Tissues with high proliferative capacity, including immature erythroid cells, express a large number of transferrin receptors due to increased iron demands (9). Approximately one milligram of iron is lost daily through tissue debris from the skin and mucous membranes, including the digestive tract mucosa (10). This amount of iron must be replenished exogenously on a daily basis.

Iron can be ingested through the digestive tract in form of inorganic or non-hem iron, and organic, hem iron**.** Whether hem or non-hem iron, the majority is absorbed in the duodenum and initial part of the jejunum, although a significant amount can also be absorbed in the cecum and proximal colon (11, 12). Hem iron, primarily derived from animal sources, is absorbed bound to the hem molecule via hem protein carrier 1 on the apical surface of enterocytes and, to a larger extent, through hem receptor-mediated endocytosis. Absorption of this form of iron is independent of natural iron chelates and the acidic environment provided by gastric juice. Non-hem iron, predominantly sourced from plant-based foods, is absorbed via divalent metal transporter 1 (DMT1) (13). Divalent metal transporter 1 is not only a transporter for iron but also for other divalent metals. Several conditions must be met for non-hem iron to be absorbed: the availability of DMT1, adequate acidity in the duodenum and jejunum for the functioning of enzymes that reduce trivalent iron to divalent, and the absence of natural chelates from food.

Ferroportin is the primary transporter of absorbed iron on the basolateral membrane of enterocytes in the duodenum and proximal jejunum. Ferroportin facilitates the export of iron (non-hem iron dominantly) from other cells, including hepatocytes and macrophages On the other hand, hem iron can pass intact through enterocytes, and at the basolateral membrane, and transported into circulation via the "feline leukemia virus C" receptor (FLVCR), where it binds to hemopexin (14, 15). The key regulator of ferroportin activity is the liver enzyme hepcidin. Under physiological conditions, iron is the primary regulator of hepcidin homeostasis. Increased plasma iron levels and iron stores stimulate hepcidin production, which subsequently blocks iron absorption and further deposition. During erythropoiesis, there is a significant iron demand requiring the release of iron from its stores, made possible by hepcidin suppression. Conversely, in conditions of inflammation or infection, hepcidin levels increase, leading to hypoferremia and anemia of chronic disease (16, 17, 18).

ANEMIA AND OBESITY

Although the increase in total mass and the number of adipocytes is the main morphological characteristic of obesity, functional changes in the entire adipose tissue are crucial for most obesity-related issues. One such characteristic is the infiltration of macrophages into adipose tissue with local production of proinflammatory cytokines IL1, IL6, and TNF-α, maintaining a low level of systemic inflammatory response. It is estimated that the adipose tissue of obese individuals may contain up to 40% macrophages (19). Similarly, mature adipocytes express a fatty acid-binding protein that activates macrophages, leading to the release of inflammatory cytokines (20, 21). This state of elevated inflammatory cytokine levels within chronic inflammation results in consistently high hepcidin values. As mentioned earlier, the liver is the primary source of hepcidin, but it is not the only one. Macrophages, pancreatic cells, and adipose tissue also serve as sources of hepcidin, with them becoming significant sources in conditions of excessive obesity. Hepcidin regulates iron homeostasis by blocking ferroportin receptors through their phosphorylation and degradation. This blockade occurs at both the enterocyte and macrophage and hepatocyte levels, preventing iron exit from these cells. Consequently, iron remains trapped in depots and is inaccessible to other cells. In the early stages of iron deficiency development, individuals may experience weakness, pallor of the skin and mucous membranes, and, over time, the manifestation of anemia includes concentration decline, drowsiness, easy fatigue, changes in nails, and alterations in heart function.

The American Society for Metabolic and Bariatric Surgery (ASMBS) and the NICE protocol recommend surgical intervention as an absolute treatment model for all individuals with a body mass index (BMI) >35 kg/m2 and for specific individuals with a BMI >30 kg/m2. For individuals of Asian descent, BMI values must be evaluated separately. Numerous studies have shown that reduction and correction of diet, physical activity, and other alternative models are not successful intervention methods for individuals with these BMI values. Traditionally, bariatric surgery is divided into restrictive, which reduces stomach size with

consequent limitation of energy intake; malabsorptive, which connects specific parts of the intestines and disrupts nutrient absorption; and combined approaches (22).

In addition to iron deficiency or anemia due to chronic inflammation and the consequent action of hepcidin occurring preoperatively, postoperative occurrences result from restrictive food intake, increased satiety with consequent reduced intake of micronutrients, poor tolerance to iron-rich foods, especially red meat, in the weeks following surgery, reduced secretion of gastric acid in the stomach, use of medications to reduce gastric acid acidity, and reduced absorptive surface in the duodenum and proximal jejunum due to surgical intervention. Secondary to these changes in the stomach and duodenum and jejunum, a large number of patients, due to gastric discomfort caused by non-hem iron use, do not have proper connections with iron supplements and are reluctant to use them, further contributing to the development of anemia in bariatric patients (23). Studies have shown that even 47-90% of patients do not receive additional information and advice regarding nutrition after bariatric surgery (24). It is essential not to overlook the fact that inflammation develops even after the surgical intervention, contributing to an increase in hepcidin and subsequent anemia of chronic disease.

CURRENT RECOMMENDATIONS FOR CORRECTING ANEMIA IN BARIATRIC SURGERY

Recommendations according to the protocols of the American Society for Metabolic and Bariatric Surgery (ASMBS) and the Coordinating Agency for National Data (NICA) indicate that in all patients who develop iron deficiency or anemia preoperatively, iron should be corrected with oral supplements. According to the ASMBS protocol, 18 mg of iron per day is recommended for patients without a previous history of iron deficiency and anemia. For menstruating women, the recommendation is a minimum of 45-60 mg of iron daily, while for individuals with more severe forms of anemia, this value can go up to 300 mg daily. Intravenous iron supplementation is only recommended for individuals who cannot tolerate oral iron supplements or for whom oral supplements are ineffective in correction, and blood transfusion is not recommended. Monitoring iron deficiency and anemia is recommended for at least one year after bariatric surgery.

CHALLENGES FOR THE FUTURE

Although unanimous recommendations suggest that iron correction should be carried out after bariatric surgery, current guidelines need improvement. The recommendation level is currently in category C, indicating a relatively weak endorsement. Similarly, the literature increasingly emphasizes that patients, while in hospital conditions during the first two weeks, should receive intravenous iron, and upon hospital discharge, continue with oral preparations. The type of oral preparations is also undefined. Specifically, non-hem iron preparations require that patients already on therapies for gastric acid reduction use vitamin C to enhance absorption. Calcium-containing preparations should not be used two hours before or after the administration of non-hem iron preparations. Given the relatively high daily iron requirements and low bioavailability of non-hem iron, these preparations can cause gastric disturbances, leading to the rejection and irregular use of these preparations.

A particular issue in the literature is the dynamics of iron administration. Although ASMBS recommendations advocate for daily iron intake, research has shown that this should be revised. After bariatric surgery, inflammation decreases over time, but hepcidin levels remain high for several weeks. The reason for this paradox is presumed to be the metabolism of iron, which, under physiological conditions, serves as the primary regulator of hepcidin release. According to these studies, when the recommended iron doses exceed 60mg, fractional absorption is higher if iron is taken every 48 hours. The World Health Organization has recognized this issue and adopted the recommendation for children and menstruating women (25, 26, 27).

Hem iron preparations contain both hem and non-hem iron. Studies have shown that the bioavailability of hem preparations is higher than non-hem iron, even though the total iron content in the preparation is lower. The efficacy of modern hem preparations is almost at the level of intravenous iron under appropriate conditions. Due to their characteristics, no adverse reactions to hem iron preparations have been recorded, making the acceptability of such formulas higher than non-hem iron. The absorption rate of non-hem iron is up to 5%, while the absorption rate of iron from hem preparations is 15-45%.

One very important characteristic of hem iron is that its absorption is much less influenced by acidic conditions, specific iron transporters, and the effects of hepcidin on ferroportin.

CONCLUSION

Obesity and iron deficiency, with or without anemia, are increasingly prevalent issues worldwide. The unequivocal molecular-level connection between obesity and the development of iron deficiency and iron-deficiency anemia has been established. Bariatric surgery is a potential solution for individuals with a BMI > 35, but it brings along a set of problems, including iron deficiency. According to existing recommendations, adequate preparation of patients for bariatric surgery regarding iron deficiency and iron-deficiency anemia, as well as postoperative iron supplementation, are essential prerequisites for the successful recovery of these patients. However, numerous questions remain unanswered, from when to discontinue intravenous iron supplementation to the dynamics and quantity of oral iron supplement application.

It's crucial to note that upon discharge from the hospital, patients are left to take responsibility for continuing both dietary and iron supplement regimens. Different iron supplements often cause a range of unwanted effects, which frequently lead to inadequate iron replenishment within the first twelve months post-surgery. Considering further improvements in correcting iron deficiency and iron-deficiency anemia, new forms of iron supplements, such as hem iron, should be taken into consideration. Despite limited direct research on these supplements, experiential evidence indicates significantly better compliance and efficacy compared to non-hem iron.

CONFLICT OF INTERESTS

The author declare that there is no conflict of interest in the study.

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