Iron-Enriched Nutritional Supplements

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Iron deficiency (ID) affects people of all ages in many countries. Due to intestinal blood loss and reduced iron absorption, ID is a threat to IBD patients, women, and children the most. Current therapies can efficiently recover normal serum transferrin saturation and hemoglobin concentration but may cause several side effects, including intestinal inflammation. ID patients may benefit from innovative nutritional supplements that may satisfy iron needs without side effects. There is a growing interest in new iron-rich superfoods, like algae and mushrooms, which combine antioxidant and anti-inflammatory properties with iron richness.

Keywords: nutrition ; iron deficiency ; algae ; superfoods ; iron

1. Introduction

Iron is an essential metal for human physiology, and it is involved in several cellular metabolic reactions including oxygen transport. Most living organisms have developed different strategies to acquire, store, and recycle iron. In humans, inorganic iron is reduced in the gut lumen and absorbed by divalent metal cation transporters expressed by epithelial cells in the duodenum. A different source of iron is represented by heme-iron, which is directly absorbed, mainly in the large intestine, through specific receptors. Once absorbed, it is transported into the bloodstream, bound to transferrin, and stored in the liver. Among these two different pathways, the main dietary iron uptake is heme-iron, derived from meat and fish; while non-heme iron is derived from plants, vegetables, fruits, and iron-fortified foods. Some nutrients can also influence iron absorption: vitamins like ascorbic acid enhance its absorption, as well as prebiotics, probiotics and symbiotics, while polyphenols like phytate reduce its bioavailability and absorption; also, calcium can inhibit iron absorption, even when it is administered as calcium salts or in dairy products.

Iron levels are tightly balanced because both iron-deficiency and iron-overload affect human health, impairing oxygen transport, inducing tissue damage particularly in the liver, and impairing inflammatory responses. The effects of iron availability on the immune cell inflammatory capabilities are less likely considered. The physiological iron concentration acts as a powerful support for inflammation while its reduced or increased concentration can hinder an effective immune response. Every day small quantities of iron are lost through enterocyte shedding and sweat, but under normal conditions, they are compensated by habitual dietary intake. Because iron is necessary for red blood cell formation, a reduced concentration in circulating and stored iron may lead to the development of anemia.

Inorganic iron is absorbed mostly in the duodenum and in the proximal ileum mainly due to the low pH, which keeps iron soluble; different pH values along the gastrointestinal tract influence iron absorption. In the duodenum and the first tract of the jejunum, pH is moderately acid, while in the distal tract of the small intestine as well as in the colon, it becomes progressively more alkaline. Of notice, inflammation can change the luminal pH and, consequently, change host iron absorption capacity.

Furthermore, inflammation induces hepcidin activity due to inflammatory cytokines release (e.g., IL-6). Hepcidin binds to ferroportin on enterocytes, thus causing its internalization and lysosomal degradation, leading to intracellular iron sequestration.

Foods rich in antioxidants (namely fruit and vegetables) can help reducing the inflammatory burden on intestine as well as on adipose tissue, but, unluckily, they might reduce iron absorption too. Although citric acid and Vitamin C, mainly found in fruits, enhance iron absorption, plant food contains various ‘anti-nutrient’ compounds including lectins, oxalates, phytates, phytoestrogens, and tannins, that are thought to restrict bioavailability of key nutrients, as iron. Nonetheless many studies concluded that these foods, also known as superfoods, have health promoting effects and provide significant reduction in chronic disease risk, attributable to the synergistic actions of these anti-inflammatory compounds.

Therefore, the correct provision of those superfoods, which combine anti-inflammatory, antioxidant, and high iron content is crucial in the treatment of chronic diseases and fight ID.

2. Nutritional Sources of Iron

Every day, approximately 25 mg of iron are needed by our body for its correct homeostasis, most of them are required for hematopoiesis. A large part of the iron requirement is sustained by the recycling process of aged red blood cells, with only less than 2 mg still needed to be provided by food. Moreover, many foods can increase or decrease inorganic- and heme-iron absorption.

Heme-iron rich foods are the best source for human daily iron needs. A rich source of heme-iron is red meat, whose consumption is widespread in Western countries. However, meat contains only 40% of heme-iron, the rest being inorganic iron, absorbed in different ways. Poultry meat and fish are also good sources of heme-iron. Besides, dietary guidelines often suggest fish portions be bigger, therefore providing great amounts of iron as well as omega-3 fatty acids that may stimulate iron metabolism. Moreover, patients with IBD are made aware that red meat may increase the risk of colon cancer, so nutritionists advise those people to shift animal meat consumptions by increasing fish consumption.

Heme-iron is absorbed in the intestine by the enterocyte carrier HCP1 (heme carrier protein 1) and subsequently dissociated from the porphyrinic ring by the HMOX1 (Heme oxygenase 1) protein, then it is stored into ferritin or transported into the bloodstream via the FLVCR1 (Feline leukemia virus subgroup C receptor 1) transporter, where it binds to transferrin. Heme-iron, although easier to absorb, is subjected to saturation in a dose-dependent manner. Heme-iron ingested barely under 20 mg can saturate its receptor on the enterocytes and drastically reduce its absorption rate, compared to inorganic iron, which gets absorbed without any issue way over 20 mg of ingested $FeSO_4$ (Ferrous sulfate).

Non-heme iron, by contrast, is found in plant-based foods and its absorption rate is very low, ranging from 2 to 20% of total iron content. The reasons behind the low absorption rate are the short portion of the intestine with an ideal acid environment for iron solubility and consequent absorption, as well as iron uptake inhibition mediated by plant dietary compounds, like phytates and tannins [1]. Nevertheless, a vegetarian dietary pattern offers great amounts of inorganic iron, commonly present in ferric (Fe^{3+}) form that needs to be reduced to ferrous (Fe^{2+}) ions, to be transported into the duodenal enterocytes via DMT1 (Divalent Metal Transporter 1) and then stored into ferritin or exported through ferroportin. Vitamin C is crucial for this reduction step as it transfers an electron to the luminal Fe^{3+} via cytochrome b (Dcytb) to obtain ferrous ions. Furthermore, vegetables and fruits are rich in iron-chelating molecules that reduce iron bioavailability but can also increase iron uptake by mucosal cells.

3. Superfoods as Nutritional Strategies for Iron Level Replenishment

Newly discovered nutritional strategies employ foods or additives that derive from the so-called “superfoods”, which do not have any scientifically based or regulated definitionbut generally are considered so when they provide high levels of desirable nutrients,proven to be promising in the prevention of a disease, or believed to offer health benefits. The term appeared in the early part of the 20th Century as a strategy to market bananas. Bananas consumption used to be promoted as a daily source of cheap, easily digestible nutritious food. With the increasing popularity of this fruit, its moniker began to circulatein the public; physicians endorsed bananas to treat lots of ailments, including celiac disease, electrolyte imbalances, etc. Nowadays, foods that possess high concentrations of nutrients, limited caloric contentand show antioxidant and anti-inflammatory properties are often called superfoods by nutritionists and media; nevertheless, they are often overlooked on food stores shelves. The potential benefits of superfoods have great margins of employment in the treatment of chronic inflammation or as supplements in healthy dietary patterns. Among them, some superfoods contain significant amounts of iron, thus being useful as supplements for people with ID.

Staple foods like meat, legumes, and grain products need iron fortification, correct processing, or the right supplementation to provide the right amounts of iron needed by people. ID patients or people living in underdeveloped countries, despite all these available nutritional strategies, still need way larger amounts of iron to recover from their condition.Thus, research is focused on formulating food supplements that allow a reduction of unabsorbed intestinal iron and its consequent deleterious effects on the mucosa; moreover, recent studies investigated formulations able to enhance non-heme iron absorption. New approaches to cure ID employ probiotics, polysaccharide-iron complexes, and liposomal iron. Besides, superfoods like algae and iron-enriched grains are vastly studied in low-income countries. Among the plethora of so-called superfoods only few of them combine high iron content and anti-inflammatory properties. It is important, indeed, to consider the anti-inflammatory potential of those foods to compensate for possible deleterious effects of high amounts of inorganic iron on the intestinal tract. Thus, the advantage of administrating balanced supplements releasing iron to the proximal part of the small intestine and, at the same time, provide anti-inflammatory and protective compounds.

In many studies, Lactobacillus plantarum has proved to be a successful probiotic strain in enhancing dietary iron absorption; during iron sulfate therapy its freeze-dried for-mulation also performed better and had increased stability and vitality over time.Another mixture of freeze-dried probiotic bacteria (Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, Lactobacillus casei W56, Lactobacillus salivarius W24, Lactococcuslactis W19, and Lactococcus lactis W58) has been used to study the absorption rates of iron and other metals from rat standard diet; liver iron accumulation increased significantly as well as hemoglobin parameters, indicating a positive effect on rat iron status.In conclusion, probiotics can increase iron absorption by approximately 50% as seen with a fruit drink already enriched with iron; moreover, they can reduce colonic inflammationin murine models of IL-10 knockout by decreasing mucosal IL-12, IFN-γ and IgG2a levels. Importantly, IL-10 knockout mice can mimic a population of IBD patients that fail to respond to pharmacological therapies, thus considered even more fragile.

Several algae have been studied for their potential beneficial effects as iron sources,thus they are considered superfoods. Among them, the Mankai alga (also known as duckweed) was investigated as a potential iron supplement source in a rat model of anemia. After six months of Mankai enriched diet, the physiological levels of hemoglobin and normal blood parameters were restored. Of note, iron content in several species of algae is cyclical. Macroalgae belonging to the genera of Ulva, Sargassum, and Porphyria, possess the highest iron contents during spring (even exceeding human daily requirements) and reduced levels of algae are harvested during different seasons. Nevertheless, iron can be better assimilated if compared to other sources of inorganic iron, likely due to high vitamin content.Ulva polysaccharides conjugated with iron ions can effectively rescue mice from artificially induced anemia. Moreover, Ulva polysaccharides-iron molecules raised B and T cell levels to a number comparable to control animals. Microalgae like Tetraselmis sp. CPT4, Spirulina, and Chlorella were tested for their nutritional components and proved to be rich in iron and antioxidant molecules as well as vitamins and other micronutrients that are essential to humans. Tetraselmis sp. CPT4 has recently been produced in large-scale bioreactors and its nutritional profile resulted in biomass richer in iron and many other components (amino acids, vitamins, fibers, and antioxidants)when compared to other microalgae like Arthrospira sp. and Chlorella sp.; its alcoholic extracts showed good ferric reducing and radical scavenging potential. Microbiological and toxicological analyses did not show any potential threat for the employ of this microalga in nutrition. Similarly, algae belonging to the genus Gracilaria were analyzed and proved to contain great amounts of bioactive components and inorganic iron; its extracts were able to reduce inflammatory cytokine production and cancer cell growth in vitro. Moreover, algae can fight inflammation as they are rich in many bioactive compounds that can decrease immune cell activity in vitro and in vivo.

Many mushrooms contain polysaccharides that can be easily chelated with iron ions. Naturally, these polysaccharides showed interesting anti-inflammatory and antioxidant properties as well as immune-modulating effects; in combination with iron particles, they can bypass all the oral iron therapy-related side effects on the gastrointestinal system. A Grifola frondosa iron conjugate showed important immune-modulating activity while increasing lymphocyte proliferation rates; moreover, it could release high amounts of iron when exposed to artificial gastric juices, mimicking the duodenal environment where iron is physiologically absorbed. Similarly, Auricularia auricularia complexes induced anti-inflammatory and antioxidant effects while improving blood parameters in a rat model of anemia.

There are other vegetable sources of iron that are currently being investigated, all of them combine their great iron content with good beneficial antioxidant abilities. Amaranth,Colocasia esculenta, and cowpea leaves were recently rediscovered as potential iron-rich and antioxidant foods that can provide great benefits to patients, such as IBD patients,with low iron levels and high inflammatory status in their intestine.On the same note as soymilk, soybean leaves contain large amounts of iron that resulted in increasing red blood cell iron content in borderline ID women when compared to ferrous sulfate. Soybean leaves were prepared as muffins or soups, to reduce phytate content and free the micronutrients bond to it.Breed selection and GM-crops are also revolutionizing the concept of superfoods. Cereals are commonly rich of iron poorly absorbable due to their polyphenol content. New cereal varieties, bred into iron-fortified crops, are characterized by increased iron absorption rates. Wheat and rice are among the most engineered crops, but their phytate content reduces drastically iron bioavailability of the unprocessed grains; thus, the low employ for these GM crops in third world countries. Cowpea leaves have high iron content; however, it has been fortified to increase amounts of iron in the beans too. Tubers like cassava and potatoes have been iron-fortified too; potatoes, indeed, showed a 2-fold increase in the level of bioavailable iron. GM iron fortified crops are an emerging frontier in the fight against ID in many parts of the world, there is increasing interest in endemic crops that can be fortified with iron and other micronutrients to help increase products value and people health. Remarkably, all these aforementioned foods are not yet available in food and general stores all over the world as their studies are still ongoing. Nevertheless, most of them are diffuse in some regions of the world (mainly Asian countries) where they are consumed in traditional dishes.

References

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