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Iron Absorption and its Influencing Factors to Prevent Iron Deficiency

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***ABSTRACT*:** Iron is an important nutrient, required to support tissue oxygen delivery, cell growth and differentiation regulation, and energy metabolism. Body iron levels are mainly controlled by regulation of iron absorption in duodenum and proximal jejunum, allowing absorption to be accurately matched to unregulated losses. Since iron bioavailability often reduced, dietary iron absorption is controlled by cellular and systemic factors to ensure that overall body iron levels are maintained at adequate levels. A better understanding of the mechanism for iron absorption and factors influencing its absorption and bioavailability is important to avoid iron deficiency or iron overload. There are complex regulatory frameworks managing iron absorption, transportation, storage, and recycling. It is able to provide enough iron for critical body functions and react relatively quickly as iron demands increase, but mechanisms must also be in place to restrict iron absorption once the body is overwhelmed with iron. Several factors promote and impede iron absorption, such as phytate and ascorbic acid, respectively. The danger of iron deficiency for the world's population is of great significance, it is important to introduce effective strategies to tackle this issue through nutrition programs; food iron supplements; iron medication supplements; and probiotic, prebiotic, and symbiotic approaches.

Keywords: iron, iron deficiency, iron absorption, bioavailability

INTRODUCTION

Iron is an integral part of nearly all living cells and a requirement for all human cells. Iron is required to support tissue oxygen delivery, cell growth and differentiation regulation, and energy metabolism. Iron 's role in these physiological processes revolves around metal 's ability to exist in two stable oxidation states: ferric (Fe3+) and ferrous (Fe2+). These very characteristics that make iron so valuable to living systems also mean that the metal is capable of catalyzing reactions leading to the creation of toxic oxygen radicals, particularly when excessive. To counter this dual existence of iron, individual cells and the body have developed sophisticated mechanisms to control iron flow and efflux. It is important to supply enough iron to cells to satisfy their metabolic needs, but equally important to

avoid excessive iron supply, as this could put the cell under oxidative stress. Human evolved complex regulatory mechanisms for iron absorption, transport and recycling (Abbaspour et all, 2014).

Iron, unlike other important nutrients, has no active excretory pathways in humans, although small quantities are lost by skin and gastrointestinal exfoliation, bile and urine. Thus, body iron levels are mainly controlled by regulation of iron absorption in duodenum and proximal jejunum, allowing absorption to be accurately matched to unregulated losses. Mechanisms controlling iron absorption often allow acceptable increases or decreases depending on physiological demand. Iron bioavailability is often reduced, which explains why individuals differ in iron status and iron stores. Also, various pathologies may affect the relationship between iron absorption rate and body iron levels. Therefore, dietary iron absorption by the proximal intestine is precisely controlled by cellular and systemic factors to ensure that overall body iron levels are maintained at adequate levels (Brigugoio et all, 2020).

Studying iron shortages and overload diseases was crucial to growing understanding and control of iron homeostasis. Iron deficiency is global's most widespread nutritional deficiency. According to the World Health Organization, an estimated 25% of the world's population has iron deficiency anemia. Most of this anemia is due to poor iron diet, but infectious disease and other causes of chronic inflammation can also reduce iron absorption and availability. Iron overload can also affect health. Excessive tissue iron accumulation can cause tissue damage and disease, including liver fibrosis, diabetes mellitus, arthropathy, endocrine dysfunction and cardiomyopathy (Chaparro & Suchdev, 2019).

A better understanding of the mechanism for iron absorption and factors influencing its absorption and bioavailability is important to avoid these conditions. Intestinal iron absorption is a regulated process. It must be able to provide enough iron for critical body functions and react relatively rapidly as iron demands increase (e.g. during pregnancy), but mechanisms must also be in place to reduce iron absorption until the body is overwhelmed with iron. This article also examined iron homeostasis and its factors that impede or enhance absorption and bioavailability to better understand and prevent iron deficiencies or overload.

RESEARCH METHODS

This research uses an exploratory research method with a literature analysis approach. Data were collected from various literature sources relevant to the research topic. Information on the mechanism of iron absorption, factors that affect iron absorption, and efforts to prevent iron deficiency were collected and analyzed. Data obtained from the literature were analyzed descriptively. Information on the mechanism of iron absorption and factors affecting this process will be carefully described and explained.

RESULTS AND DISCUSSION

Human Iron Metabolism (Systemic and Cellular)

Iron metabolism in cells

Iron is integrated into many cellular proteins. Some are involved in catalytic enzyme and electron transfer, while others are involved in carrying oxygen or storing and carrying iron itself. Dietary iron comes in many ways, but is generally known as heme or non-heme iron (Stehling & Lili, 2013). Heme iron is present in the highest meat abundance in the hemoprotein hemoglobin and myoglobin. Hemoglobin and myoglobin play an important role with oxygen in cell respiration. Iron can also be present in other hemoproteins that play key roles in cellular metabolism including cytochromes. Another major class of iron-containing proteins is iron-sulfur (FeSS) clusters. These non-FeSS proteins are essential for enzymatic activity and iron storage and transportation via ferritin and transferrin (Kontoghiorges & Kontoghiorge, 2020).

Iron can be transmitted to cells in a variety of different ways, and under normal conditions, the vast majority of blood iron is bound to transferrin (Tf) and different Tf is the primary iron source for most cells. Transferrin transfers the iron to cells by binding tightly to plasma membrane protein transferrin receptor-1 (TfR1). TfR1 is a receptor between the plasma membrane and various intracellular vesicular compartments. After Tf binds to its receptor, clathrin-coated pits endocytize the complex. The iron released from Tf (now in its reduced or ferrous form) passes through the endosomal membrane and through the ferrous iron transporter divalent metal-ion transporter 1 (DMT1) into the cytoplasm. When cellular iron requirements are high, TfR1 levels decrease and the opposite is seen when cells are iron-filled (Pourelot et all, 2015).

When Tf-bound iron is delivered to the endosome lumen, the cytoplasm must also cross the endosomal membrane. This is accomplished through the divalent metal-ion 1 (DMT1) ferrous iron transporter. DMT1 is a multi-span membrane protein, widely distributed in body tissues. While it can transport ferrous iron effectively, as its name implies, it can also handle a wide variety of other divalent metal ions, including Cu2+, Zn2+, Co2 + and Cd2+. The main function of DMT1 in most cells is the distribution of Tf-derived iron from the endosome to the cytoplasm, but it also plays a special role in the transport of iron across the brush boundary membrane (Yanatori & Kishi, 2019).

Iron storage

Iron entering the cell, regardless of its source, eventually tends to join the same intracellular pool although the size and relative value of this pool may differ between cell types. Iron from this central source may be used for metabolic functions, may be stored in ferritin, or may contribute to controlling cellular iron metabolism by affecting iron regulatory proteins (IRPs) activity and other possible factors. Since iron can catalyze reactions that create toxic oxygen radicals, free iron concentrations within cells must be held at very low levels. The vast majority of intracellular iron not

needed for metabolic purposes is stored in ubiquitous protein ferritin. Where longer-term iron storage such as liver, L-ferritin subunits predominate and cells that easily turn iron, such as macrophages or cardiac myocytes, express more H subunits (Ritacco et all, 2018).

Iron release

Cell and tissue iron release is an essential component of iron homeostasis. Humans have a very small ability to excrete iron, so the iron in the body is recycled continuously. There is some mandatory body iron loss arising from physiological exfoliation of cells from epithelial surfaces like skin, genitourinary tract, and gastrointestinal tract. However, these losses are very small (almost 1 mg/day). Most of this recycling occurs via the reticuloendothelial system, where phagocytosis senescent red blood cells macrophages destroy their hemoglobin and export iron to plasma transferrin. The main plasma membrane-wide iron efflux protein is ferroportin1 (FPN) (also known as IREG1 or MTP1). Initially, FPN was known as the protein responsible for iron efflux from intestinal enterocytes, but it is expressed in most body tissues and especially high levels in cells that must export large quantities of iron. Cell iron release is usually determined by iron requirements that are systemically controlled (hepcidin erythropoiesis system) or locally (intestinal response) (Wallace, 2016).

Mechanism and Regulation of Iron Absorption in Intestinal Lumen

Iron Absorption in Intestines

Most iron absorption occurs through polarized intestinal epithelial cells or enterocytes in the upper intestine, duodenum, and proximal jejunum. These cells are distinguished by an apical side in blood contact with gut lumen and dietary contents and its basolateral side. Enterocytes arise in the intestinal crypts from dividing stem cells and migrate up the villus, with the intestinal epithelium being completely replaced every 3-4 days. Intestinal surface area and stomach pH can influence iron absorption. Differentiated duodenal enterocytes express high protein levels in dietary iron absorption. This major iron import protein is the ferrous iron transporter DMT-1 on the brush boundary. [4] Reduction of dietary ferric iron to ferrous form occurs by ferric reductase activity provided by duodenal cytochorome B (DcytB) or STEAP2 (Wallace, 2016).

Heme and ferritin iron absorption is less well-understood. A study showed that receptor-mediated endocytosis takes up heme, but a high-affinity receptor for enterocyte heme has yet to be identified. Heme protein-1 proton coupled folate transporter was described as an apical heme transporter, but the protein tends to play a more important role in folate absorption and has a much lower affinity to heme. There is some evidence that dietary ferritin is also taken through endocytosis into enterocytes (Wallace, 2016).

Upon enterocyte absorption of iron, it will be either retained within the endogenous ferritin or exported into the blood for transport to other tissues in the body. The absorbed heme iron is broken

down into enterocytes by heme oxygenase for the release of free ferric iron, and it has also been shown that ferritin iron is released from ferritin. Iron in many food types eventually contributes to blood being transported, and tends to join a common cell iron pool within enterocytes, but it is still poorly understood how this pool is and how iron is being trafficked within cells (Gulec et all, 2014).

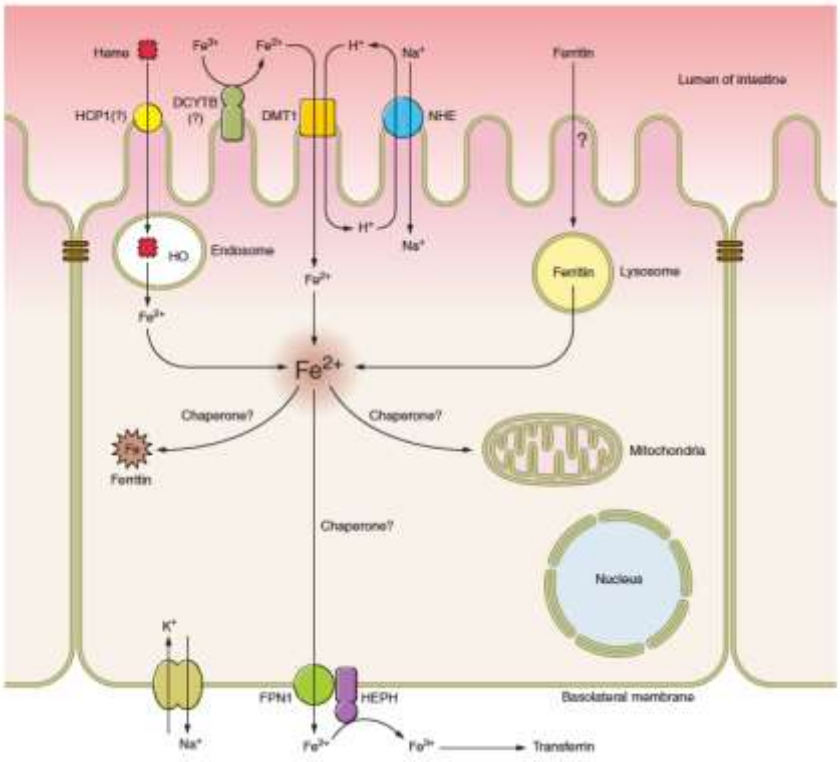

Figure 1. Mechanisms of iron absorption in the mammalian duodenum.

Source: (Gulec et all, 2014).

Iron regulation

Absorbed iron reaches a characterized cytosol pool and its fate is subjected to systemic control. When the body is iron-replete, large quantities of iron are stored and accumulated in the cytosol as ferritin, sloughed off into the gut lumen during mature enterocyte exfoliation. However, in situations of high systemic iron demand or degradation, absorbed iron is trafficked into circulation via the coordination of efflux protein ferroportin and ferroxidase, hephaestin, ceruloplasm counterpart (Backe et all, 2016).

Iron demand to promote bone marrow erythrocyte development is the best iron absorption stimulator. Iron absorption increases with low body iron stores or high erythropoietic concentrations and decreases in the reverse case. Iron absorption is improved by stimulating erythropoiesis (e.g. blood loss or acute hemolysis) because hemoglobin synthesis requires iron in developing erythrocytes. Hypoxia also increases iron absorption to hypoxia in duodenum and liver due to changes in erythropoietic intensity. Absorption also increases pregnancy and sucking. Hepcidin (HEPC) regulates systemic regulation of this absorption process. Hepcidin, formed primarily by hepatocytes in the liver,

circulates in the blood and binds to ferroportin (FPN1). Molecules that control HEPC expression, such as transferrin receptor 2 (TFR2), HFE, hemojuvelin (HJV) and matriptase-2, "sense" body iron levels allowing adequate iron absorption modulation (Gulec et all, 2014).

Iron absorption is also regulated locally by cellular iron and hypoxia levels in intestinal enterocytes. One of the main players in this regulation is the IRE/iron regulatory protein (IRP) system. IRE/IRP system operates by influencing post-transcription regulation of iron metabolism proteins. Enterocyte ferritin can also play a role in this local regulation of iron absorption under normal, but undetermined, physiological conditions (Santos et all, 2016). Local regulation of iron absorption is also regulated by hypoxia at transcriptional level by the state of iron and oxygen. Hypoxia-inducible factor-2 (HIF-2) (is essential to induce transcription of iron metabolism genes containing HIF responsive elements (HREs) including DMT1, DcytB and FPN1. Increased expression of HIF2(in the intestines of genetically modified mice leads to increased DMT1 and DcytB expression and increased iron absorption, although intestinal knockout of HIF2 (leads to low levels of DMT1, DcytB and Fpn1 and systemic iron deficiency despite low levels of hepcidin (Wallace, 2016).

While there has been progress in identifying dietary, systemic, and local mechanisms that mediate and control iron absorption, much remains to be learned. Information of hepcidin-regulating signaling pathways are still evolving and potential for new theurapeutic action. Iron absorption remains a significant and productive field for many years to come.

Dietary Factor that Influence Iron Absorption and Bioavailability

Iron bioavailability ranging from 5-12 % in vegetarian diets to 14-18 % in mixed diets. Iron in food occurs mainly as heme, nonheme (or inorganic) iron. Heme iron comes primarily from meat hemoglobin and myoglobin. Heme-iron absorption is efficient and largely uninfluenced by other dietary components. Heme iron is estimated to contribute 10–15% of total iron intake in meat-eating populations but contributes 40 % of total absorbed iron due to its higher and more uniform absorption (estimated at 15–35%). Nonheme (and largely ferric) iron, present in both meat and plant foods, is extremely insoluble, typically much less well absorbed than heme iron (2-20%). In certain meals, the amount of nonheme iron in the diet is several times that of heme-iron. Thus, considering its poor bioavailability, nonheme iron contributes more to iron nutrition than heme-iron. All nonheme food iron that reaches the common iron pool in the digestive tract is absorbed to the same degree, depending on the balance between the absorption inhibitors and enhancers and the individual iron status (Piskin et all, 2022).

Factors inhibiting iron absorption

Although animal tissues improve the absorption of nonheme iron, animal proteins such as milk proteins, eggs, and albumin have been shown to inhibit iron absorption. The two main bovine protein

fractions, casein and whey, and egg white were shown to inhibit human iron absorption. Soybean proteins also decrease iron absorption, phytate was shown to be the main inhibitor in soy protein isolates. Phytate is the major inhibitor of iron absorption in plant-based diets. Phytate's negative effect on iron absorption has been shown to be dose-dependent, beginning at very low concentrations of 2-10 mg/meal (Abbaspour et all, 2014).

Polyphenols exist in varying quantities in plant foods and beverages, including tomatoes, fruit, certain cereals and legumes, tea, coffee, and wine. Black tea and herb teas demonstrated the inhibiting effect of polyphenols on iron absorption. At comparable levels, black tea polyphenols were shown to be more inhibitory than herbal tea and wine polyphenols. In cereals and legumes, polyphenols add to phytate's inhibitory effect, as seen in a study comparing high and low polyphenol sorghum (Brglez et all, 2016).

Calcium has been shown to have detrimental effects on nonheme and heme iron absorption, making it distinct from other inhibitors that only influence nonheme iron absorption. Dose-dependent inhibitory effects were shown in bread rolls at doses of 75-300 mg and 165 mg of calcium from milk products. It is suggested that single-meal studies indicate negative effects of calcium on iron absorption, while multiple-meal studies, with a wide range of foods and varying concentrations of other inhibitors and enhancers, indicate that calcium has minimal effects on iron absorption (Abbaspour et all, 2014).

Enhancer of iron absorption

Researchers demonstrated the dose-dependent enhancing effect of native or added ascorbic acid on iron absorption. The enhancing effect is due largely to its ability to reduce ferric to ferrous iron, but also to its chelate iron potential. Ascorbic acid can resolve the detrimental impact of all inhibitors on iron absorption, including phytate, polyphenols, and calcium and proteins in milk products, and improve absorption of both native and fortification iron. In fruit and vegetables, ascorbic acid's stimulating role is frequently canceled out by polyphenols' inhibiting effect. Ascorbic acid is the only absorption enhancer in vegetarian diets, and by using vegetable-containing ascorbic acid, iron absorption from vegetarian and vegan meals can be improved. Cooking, industrial processing and storage degrade ascorbic acid and remove its enhanced iron absorption effect (Chaparro & Suchdev, 2019).. [12] Single-meal radioisotope studies have consistently shown an enhanced effect of meat, fish, or poultry on vegetarian meal iron absorption, and 30 g of muscle tissue is considered equal to 25 mg ascorbic acid. There is strong evidence to support the enhancing effect of cysteine-containing peptides, which are rich in myofibrillar protein digests and, like ascorbic acid, can reduce iron and chelate iron (Abbaspour et all, 2014).

Vitamin C's effect (ascorbic acid) depends on dosage. Previous study showed that increasing ascorbic acid from 25 to 1000 mg in liquid formula meal containing 4.1 mg nonheme iron resulted in

iron absorption increase from 0.8% to 7.1%. However, this study only shows that ascorbic acid has a pronounced enhancing effect on the absorption of nonheme iron by feeding single meals to fasting subjects. One research found that the effect of dietary ascorbic acid on iron absorption is significantly less than suggested with single-meal measurements. Some dietary inhibitors (like phytate) in a full diet at least partially offset this effect. Therefore, the use of long-term vitamin C supplementation to improve iron absorption requires more details (Nair et all, 2013).

When theoretically feasible, ascorbic acid should be added to all complementary iron-reinforced foods to enhance bioavailability, especially in infants, to enhance growth and development. There is some evidence that the molar ratio is significant. The absolute amount of ascorbic acid in the meal and the ratio of ascorbic acid concentration to important inhibitors, especially phytates, may be more important. Base quantitative guidelines for ascorbic acid based on the molar ratio of ascorbic acid to iron between 2:1 and 4:1 (70-140 mg/d in complementary foods intended to provide adequate iron to meet the estimated average breast-fed infants requirements). Lower concentrations are appropriate in powdered cow's milk and cow's milk-based foods and cereal-based foods that either have a low native phytate content or are subject to phytate removal. A molar ratio of 4:1 ascorbic acid to iron should be used in cereal foods with high phytate concentrations, cereal foods containing polyphenols or weaning foods with large quantities of soybean flour or soybean protein products (Rusu et all, 2020).

Subject factors

Individual iron status primarily affects nonheme iron absorption, whereas heme iron absorption is usually less affected. There is an inverse association between iron status and iron absorption and using ferritin as an iron status indicator will mathematically explain the relationship. A research in young women found that controlling ferritin iron absorption was less pronounced when iron was added as a water-insoluble compound (micronized dispersible ferric pyrophosphate) relative to ferrous sulfate (Seyid et all, 2023).

Chronic inflammation and obesity increase hepcidin expression. The peptide hepcidin developed in the liver and adipose tissue was described as a key iron homeostasis regulator. The two groups' iron intake and bioavailability were not substantially different, indicating a hepcidin-mediated reduced iron absorption or increased iron sequestration in overweight children. Other factors, including vitamin A and riboflavin, also affect iron metabolism and absorption (Abbaspour et all, 2014).

Intervention Strategy to Enhance Iron Bioavailability

Food diversification

Dietary changes to prevent iron deficiency include increased intake of iron-rich foods, especially flesh foods, increased consumption of ascorbic acid-rich fruits and vegetables to enhance nonheme iron absorption, and reduced intake of tea and coffee inhibiting nonheme iron absorption. Iron

bioavailability can be enhanced by techniques such as germination and fermentation that facilitate enzymatic hydrolysis of phytic acid in whole grain cereals and legumes by enhancing endogenous or exogenous phytase enzymes. Even the use of nonenzymatic methods like thermal processing, soaking, and milling to minimize phytic acid content in plant-based staples has been effective in improving iron (and zinc) bioavailability (Moretti et all, 2015).

Supplementation

Ferrous iron salts (ferrous sulfate and ferrous gluconate) are favored for oral iron supplementation due to low cost and high bioavailability. While iron absorption is higher when iron supplements are given on empty stomach, nausea and epigastric pain can develop due to higher iron doses (usually 60 mg Fe/day). If such side effects occur, lowering doses between meals could be considered, or iron should be supplied with meals, since food decreases the absorption of medicinal iron by about two-thirds. Iron supplementation during pregnancy is recommended in developing countries, where women often enter pregnancy in low-iron stores (Girelli et all, 2019). A study found that fractional absorption in iron-depleted women is highest at low iron doses (40-80 mg), and that acute, consecutive-day dosage results in lower bioavailability of iron. Twice daily iron supplementation seems to have minimal additional impact compared to daily administration (Stoffel et all, 2020).

Fortification

Food fortification with iron is tougher than nutrient fortification such as zinc in rice, salt iodine and cooking oil vitamin A. Bioavailability of fortification iron varies greatly with the iron compound used, and color- and flavor-sensitive foods are typically reinforced with low bioavailability water-insoluble iron compounds. WHO's recommended iron compounds for food fortification include ferrous sulfate, ferrous fumarate, ferric pyrophosphate and electrolyte iron powder (Vonderheid et all, 2019). Wheat flour is the most popular iron-fortified food and is normally fortified by elemental iron powders not recommended by WHO. Hurrell and Egli (2010) reported only eight of the 78 national wheat flour programs are expected to boost iron status. These programs used iron compounds at recommended levels. Some countries used non-recommended compounds or lower iron levels compared to flour intake (Abbaspour et all, 2014).

Commercial infant foods, such as formulas and cereals, are typically iron-fortified. The amount of fortification iron added to complementary foods should be adequate to ensure the infant diet (human milk plus complementary food) meets the existing dietary reference intake (DRI) values for iron. Experimental evidence suggests that absorption values of 10% for cow's milk and low phytate or dephytinized cereal foods can be required if ascorbic acid and ferrous sulfate are added to the ascorbic acid-iron molar ratio of 2:1. As mentioned above, a molar ratio of 4:1 would be needed if more inhibitory foods, such as soybeans with a native phytate material, were used (Rusu et all, 2020).

Probiotic, prebiotic, and synbiotic approach for iron supplementation

Probiotics approach in iron deficiency care revealed in a systematic analysis showing how Lactobacillus plantarum 299v helps prevent iron deficiency anemia (IDA). This probiotic increases dietary non-heme iron absorption in active Caucasian Europeans (Rosen et all, 2019). One research also uses L. plantarum 299v to treat iron deficiency in pediatric patients, but with no favorable iron absorption findings. Low-dose ferrous sulfate (1–3 mg/kg/day) was given to children with or without probiotic. Researchers found no substantial difference in serum ferritin levels in subjects taking probiotic L. plantarum 299v relative to controls. There was no correlation with ferritin level and probiotic use (Rosen et all, 2019).

Several studies associated prebiotic and/or synbiotic intake with increased iron availability, often by converting Fe3+ to Fe2+ due to decreased ferric activity and encouraging enterocyte iron uptake. Several studies conducted suggest that fructans such as inulin have beneficial effects on body colon functions, even enhancing the absorption of minerals. There are two forms of physiological effects: direct effects in the large intestine and on the intestinal microbiota, and indirect systemic effects that affect metabolism and minimize disease risks (Moretti et all, 2015).

CONCLUSION

In summary, this analysis outlined complex regulatory frameworks managing iron absorption, transportation, storage, and recycling. Intestinal iron absorption is a regulated process. It must be able to provide enough iron for critical body functions and react relatively quickly as iron demands increase, but mechanisms must also be in place to restrict iron absorption once the body is overwhelmed with iron. While there has been progress in identifying dietary, systemic, and local mechanisms that mediate and control iron absorption, much remains to be learned. Several factors promote and impede iron absorption, such as phytate and ascorbic acid, respectively. Iron in food occurs mainly as heme, nonheme (or inorganic) iron. Iron bioavailability in various food sources, varying from 5-12% in vegetarian diets to 14-18% in mixed diets, which is why iron deficiency remains the most prevalent anemia etiology. The danger of iron deficiency for the world's population is of great significance, it is important to introduce effective strategies to tackle this issue through nutrition programs; food iron supplements; iron medication supplements; and probiotic, prebiotic, and symbiotic approaches.

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