

Oral iron supplementation: new formulations, old questions

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Abstract

Iron-deficiency anemia and pre-anemic iron deficiency are the most frequent pathologies. The first line of treatment involves oral iron supplementation. The simplest, least expensive, and most commonly prescribed drug is ferrous sulfate, while other ferrous salts and ferric complexes with polysaccharides or succinylated milk proteins are also widely used. In recent years, novel iron formulations have been developed, such as the lipophilic iron donor ferric maltol, or nanoparticle encapsulated sucrosomial® iron. Oral iron supplementation is usually efficacious in correcting iron-deficiency anemia and replenishing iron stores but causes gastrointestinal side effects that reduce compliance. When oral iron supplementation is contraindicated, intravenous iron therapy can rapidly achieve therapeutic targets without gastrointestinal complications. Herein, we critically review literature on relative efficacy and tolerability of currently available oral iron supplements, and summarize recent data on optimal dosage and frequency.

Introduction

Iron is essential for oxygen transport, respiration and several biochemical functions by virtue of its ability to form coordination complexes and shuttle between its ferrous (Fe^{2+}) and ferric (Fe^{3+}) forms.¹ However, redox reactivity renders iron potentially toxic and excess, unshielded iron promotes oxidative tissue damage. Thus, a balanced iron supply is important, as both iron deficiency and overload cause morbidity.

While iron is abundant, its bioavailability is low. This poses a risk of iron-deficiency anemia (IDA) or non-anemic iron deficiency (ID), which are managed by oral (and in specific cases intravenous) iron replacement therapy. During the last years, new oral iron formulations have been added to many already available, while several studies raised questions on optimal dosing and frequency. Recent advances and knowledge gaps in this emerging field are discussed herein.

Iron physiology, absorption and homeostasis

Most of the iron in the body (>70%) is present in hemoglobin and only a minor fraction (<1%) circulates in transferrin, the plasma iron carrier. The transferrin iron pool is

small (~3 mg at steady state) but highly dynamic to meet the needs of erythropoiesis (25-30 mg/day). Iron supply to transferrin is maintained primarily by splenic and hepatic macrophages, which clear aged red blood cells and recycle their iron, and to a lesser extent by duodenal enterocytes, which absorb 1-2 mg/day dietary iron. If metabolic needs are unmet, iron stores are mobilized from hepatocytes. As there is no mechanism for iron excretion, dietary iron absorption is essential to compensate for non-specific losses occurring during cell desquamation or bleeding.

It is estimated that only 14-18% of ingested iron is absorbed from mixed diets and 5-12% from vegetarian diets.² A reason for this is that Fe^{2+} is oxidized to virtually insoluble (at physiological pH) Fe^{3+} . Even though Fe^{3+} can be solubilized in the acidic milieu of the stomach, it cannot be directly transported to enterocytes.³ Thus, luminal Fe^{3+} needs to be reduced to Fe^{2+} prior to its assimilation via the apical enterocyte transporter DMT1 (Figure 1). This is accomplished enzymatically or with the aid of ascorbate (vitamin C), which is thought to enhance iron absorption. Some dietary components (phytates, polyphenols, fibers, tannins) and common pharmaceuticals (calcium supplements, antacids, proton pump inhibitors) form insoluble complexes with iron and thereby inhibit its absorption.⁴ Heme is a more efficient source of iron; however, the mechanism for heme absorption remains elusive.⁵ Inter-

nalized heme undergoes enzymatic degradation liberating its iron, which follows the fate of assimilated inorganic iron. Enterocytes release Fe^{2+} to plasma via the basolateral exporter ferroportin.⁶ Exported Fe^{2+} is re-oxidized to Fe^{3+} and captured by transferrin for delivery to tissues.

High iron levels or inflammation induce expression of the iron regulatory hormone hepcidin in the liver, which inhibits iron absorption by suppressing intestinal ferroportin.⁷ Hepcidin also prevents ferroportin-mediated iron efflux from erythrophagocytic tissue macrophages (Figure 2), acting as a negative regulator of iron entry into plasma.

Iron deficiency

IDA and non-anemic ID are the most common pathologies worldwide and remain leading contributors to global

burden of disease. They cause fatigue and in severe cases immunological, developmental, or neurocognitive defects.⁸⁻¹⁰

In 2021 anemia was the third cause of years lived with disability and had a global prevalence of 24.3% with 1.92 billion cases reported.¹¹ By far the most frequent type of anemia is IDA, which can be prevented and controlled by iron fortification of foods or iron supplementation.¹² ID, with or without anemia, is the most prevalent nutritional deficiency. ID and IDA primarily affect women of reproductive age or pregnant women, but also children and vulnerable populations in low- and middle-income countries. In most patients, ID and IDA are etiologically linked to blood loss, except in pregnant women, in whom the causes are the extraordinarily high iron need of the growing fetus, and the increase in blood volume (hemodilution).

ID and IDA are also associated with inflammatory bowel disease (IBD),¹³ chronic kidney disease (CKD)¹⁴ and bariatric

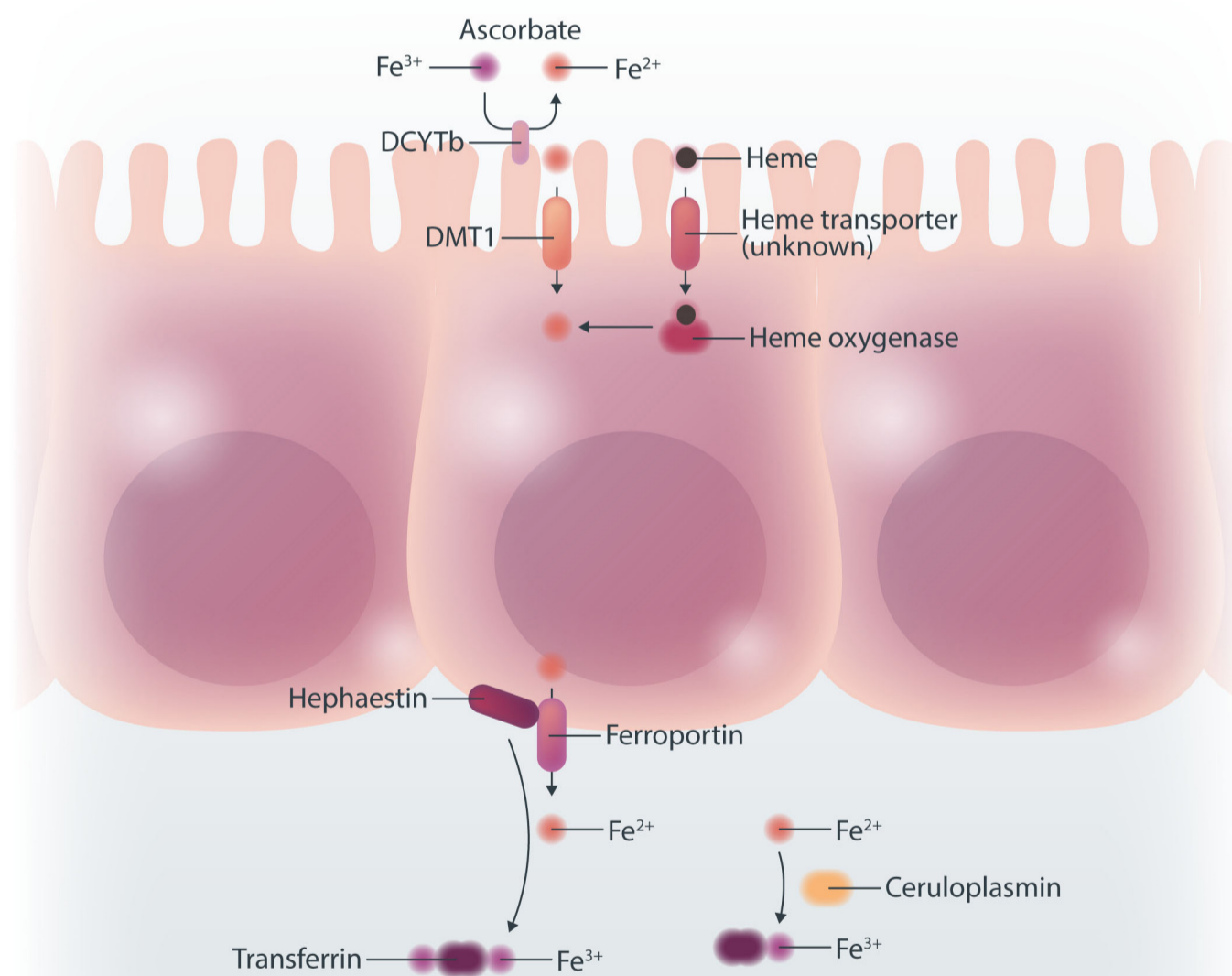


Figure 1. Mechanism of iron absorption by enterocytes. Inorganic ferric iron (Fe^{3+}) in the intestinal lumen is reduced to ferrous iron (Fe^{2+}) by the ferrireductase DCYTb (*duodenal cytochrome b*), ascorbate or other reducing agents, and then transported across the apical membrane of enterocytes via DMT1 (*divalent metal transporter 1*). Iron export of ferrous iron into the bloodstream is mediated by ferroportin and coupled by reoxidation of ferrous to ferric iron via the ferroxidases hephaestin or ceruloplasmin; ferric iron is then captured by transferrin. Heme is absorbed by an unknown mechanism and undergoes degradation within enterocytes by heme oxygenases; the released iron is exported via ferroportin.

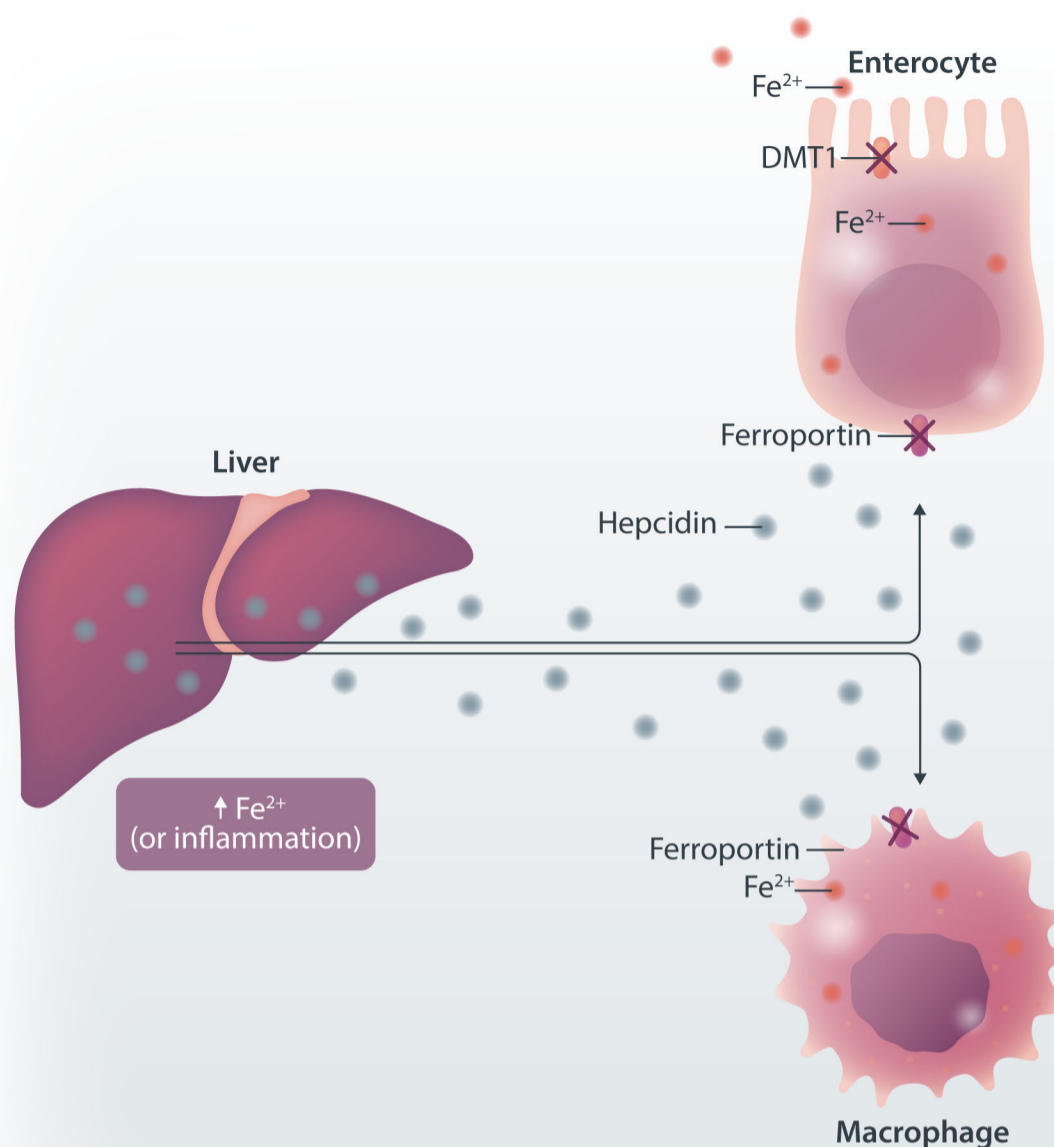


Figure 2. Hormonal regulation of systemic iron traffic by hepcidin. Hepcidin is secreted from the liver in response to high iron or inflammation. It inhibits ferroportin-mediated iron efflux into the bloodstream from duodenal enterocytes and tissue macrophages.

surgery.¹⁵ In patients with IBD or CKD, ID is often combined with “functional ID”, a condition in which significant quantities of body iron remain sequestered within tissues and cannot be efficiently utilized to support physiological erythropoiesis. This is caused by chronic inflammatory processes, including induction of hepcidin.¹⁶

Iron replacement therapy

The goal of iron replacement therapy is to correct IDA or non-anemic ID and replete iron stores. Iron can be administered in oral or intravenous formulations.^{17,18} Oral iron is usually the first line of therapy due to its convenience to use, availability over the counter and low cost of its mainstream formulations (Table 1). Effective iron repletion with oral supplements requires relatively high doses of 50–200

mg/day of elemental iron for 3–12 weeks. Only ~10–20% of it gets absorbed, resulting in accumulation of excess iron in the digestive tract, which causes gastrointestinal side effects. Excess iron may also alter the microbiota diversity and composition, shifting the balance towards pathogenic bacteria.^{19,20} These responses are tightly linked to increased susceptibility to infections, intestinal inflammation²¹ and metabolic syndrome pathologies.^{22,23}

Intravenous iron therapy is of paramount importance for the treatment of severe IDA when fast repletion of iron stores is desired (e.g., in patients awaiting surgery), or when intestinal iron absorption is impaired and oral iron is ineffective (e.g., in many patients with IBD or CKD). Candidates for intravenous iron are also iron-deficient patients with poor tolerance to oral iron, and women with heavy menstrual bleeding or in late pregnancy. Compared to oral iron, intravenous iron increases hemoglobin levels and iron

Table 1. Oral iron supplements used for iron replacement therapy.

Type of supplements	Amount of elemental iron,* mg per tablet	Approximate cost,** \$ per tablet	Advantages	Disadvantages
Ferrous salts				
Ferrous sulfate	65	0.07	Low cost, high efficacy, wide availability	Poor tolerability
Ferrous fumarate	100	0.26		
Ferrous gluconate	35	0.10		
Ferrous bisglycinate	50	0.15		
Ferrous ascorbate	65	0.45		
Ferric complexes				
Ferric polysaccharide (Ferrex™ 150)	150	0.08	Possibly fair tolerability	Relatively low efficacy
Ferric polymaltose (Maltofer®)	100	0.90		
Ferric polydextrose (Feramax® 150)	150	0.85		
Iron protein succinylate (Ferretts®)	40***	3.40***	High efficacy, fair tolerability	High cost
Ferric citrate (Auryxia®)	210	7.18	Efficacy in CKD patients	
Ferric maltol (ACCRUFer®)	30	8.58	Efficacy and tolerability in IBD patients	High cost, risk of IBD flare
Sucrosomial® iron (SiderAL®)****	30	2.00		High cost, no iron stores rebuild
Liposomal iron	30	0.83		Scarce data, no iron stores rebuild
Other				
Carbonyl iron	18	0.33	Low cost, wide availability	Scarce data, no iron stores rebuild
Heme iron polypeptide (Proferrin-ES®)	12	0.60	Efficacy in CKD patients	

*Elemental iron content may vary in different products and countries. **Prices may vary among different vendors. ***In liquid form (elemental iron content and price per 15 mL). ****Not available in the USA. CKD: chronic kidney disease; IBD: inflammatory bowel disease.

stores faster. Potential side effects are the risk of infections,²⁴ hypophosphatemia,²⁵ and acute hypersensitivity reactions, which can vary from mild itching and flushing to severe anaphylaxis.²⁶ The extent of side effects depends on the type and dose of intravenous iron formulation, and the infusion time. Anaphylactic reactions are very rare but can be life-threatening. Therefore, administration of intravenous iron should always be performed in an adequately equipped medical facility with the assistance of trained health care providers. The cost of an intravenous iron infusion varies between \$400-4,000, depending on the product and the facility providing the treatment.

Types of oral iron supplements

There are various types of oral iron supplements (Table 1). The two major classes are ferrous (Fe^{2+}) salts and ferric (Fe^{3+}) complexes. Other types include carbonyl iron and heme iron polypeptide.

Ferrous salts

The most common oral iron supplements are ferrous salts with sulfate, fumarate or gluconate. Others include ferrous glycine sulfate, bisglycinate, ascorbate, carbonate, tartrate, iodine, chloride, sodium citrate, aspartate or succinate.²⁷

Ferrous salts are available as tablets or syrup. Because dissolved Fe^{2+} is readily oxidized to insoluble Fe^{3+} , a main challenge for liquid supplements is to maintain Fe^{2+} reduced; this is done with the addition of excipients such as sodium bisulfite. Slow-release (enteric-coated) ferrous salt formulations have also been designed with the aim of reducing gastrointestinal adverse effects, while preserving iron absorption.

Ferric complexes

An alternative to ferrous salts is offered by supplements containing ferric polysaccharide complexes (mixed polysaccharides, polymaltose, or polydextrose). Their digestion by gastric fluid results in release of iron and monomeric or oligomeric saccharides, which have a reducing capacity and can convert Fe^{3+} to Fe^{2+} , increasing the bioavailability of the iron.²⁸ Another type of ferric supplement is iron protein succinylate (Fe^{3+} bound to succinylated milk proteins).²⁷ During the past few years, new types of ferric supplements have been licenced in several countries: ferric citrate, ferric maltol and sucrosomial® iron. Their cost is substantially higher compared to that of conventional ferrous salts (Table 1).

A ferric citrate formulation is clinically applied to reduce hyperphosphatemia in patients with dialysis-dependent CKD, and as an iron donor to correct IDA in patients with

non-dialysis CKD.¹⁴ The coordination of citrate anions renders ferric citrate soluble. In the acidic pH of the stomach, it forms oligomeric complexes that bind and neutralize phosphate anions, giving rise to insoluble precipitates. At the higher pH of the duodenum, ferric citrate predominates in monomeric complexes, where iron is bioavailable.

Maltol (3-hydroxy-2-methyl-4-pyrone) is a naturally occurring molecule that is used as a flavor enhancer. It has structural similarities with the clinically applied chelator deferiprone (L1).²⁹ Maltol forms a lipophilic complex with Fe³⁺ at 3:1 stoichiometry. Ferric maltol can deliver iron to enterocytes and maintain the unabsorbed fraction of iron chelated in a redox-inert form. Iron gets dissociated from the maltol complex prior to absorption, while free maltol is absorbed separately, bio-transformed, and excreted in urine.

Sucrosomial[®] iron consists of ferric pyrophosphate encapsulated within a matrix of phospholipids and sucrose esters of fatty acids (sucresters).³⁰ The phospholipid bilayer of the matrix is coated and stabilized with tricalcium phosphate and starch, forming a “sucrosome”. Iron remains protected within the “sucrosome”, while sucresters function as absorption enhancers by reducing intestinal barrier resistance. As a result, sucrosomial[®] iron is efficiently absorbed as intact nanoparticles via paracellular and transcellular routes and independently of DMT1, even under conditions of inflammation. The same principle applies to commercially available liposomal iron preparations, which consist of ferric pyrophosphate encapsulated within biodegradable natural or synthetic phospholipids (liposomes).³¹ Nanotechnology has the potential for development of additional iron delivery systems utilizing alternative pathways of absorption.^{32,33}

Other

Carbonyl iron and heme iron polypeptide offer additional options for oral iron supplementation. Carbonyl iron is a form of elemental iron that is generated from vaporized iron pentacarbonyl complexes and is commonly used as a food additive. It is solubilized at a slow rate by gastric fluid, resulting in prolonged absorption.³⁴ Heme iron polypeptide is produced by enzymatic hydrolysis of bovine hemoglobin.³⁵ The rationale for its commercialization is the better absorption of heme *versus* inorganic iron. While pure heme cannot be utilized as an iron supplement because it aggregates into insoluble polymers in the gastric environment, peptides and amino acids produced during the hydrolysis of hemoglobin maintain heme soluble.⁵

Efficacy of oral iron supplements

The bioavailability of a drug is typically assessed by measuring its serum concentration. Experimental studies with anemic patients^{36,37} and non-anemic blood donors³⁸ suggested that this also applies to iron supplements, as the

response to treatment correlated with increased serum iron and transferrin saturation. On the other hand, it has been argued that the dynamic nature of the transferrin pool renders a transient increase in serum iron irrelevant to the efficacy of iron supplementation.³⁹

In any case, efficacy can be effectively monitored by assessing the fraction of iron that is absorbed and incorporated into hemoglobin, and most importantly, by measuring the hemoglobin concentration response to iron supplementation.^{37,40} An optimal response to oral iron therapy is expected to increase hemoglobin by 2 g/dL within 3–4 weeks.^{17,41} A hemoglobin increase of 1 g/dL within 4 weeks is considered reasonable. Repletion of body iron stores, reflected by serum ferritin >100 µg/L often requires longer treatment.

Ferrous salts

Ferrous sulfate is the least expensive and most frequently prescribed iron formulation in many countries; thus, it is considered as the gold standard in oral iron supplementation. Ingestion of ferrous sulfate (or other ferrous salts) is expected to promote a rapid surge in serum iron and effectively increase hemoglobinization and iron stores.^{42,43} The use of ferrous sulfate, fumarate or gluconate is recommended as a first line treatment for IDA in adults by the current British Society of Gastroenterology guidelines.⁴⁴ Slow-release ferrous salt supplements have performed poorly in several studies, possibly due to delayed liberation of encapsulated Fe²⁺ past the duodenum and upper jejunum, where iron absorption is optimal. Hence, serious concerns have been raised on their efficacy,^{45–47} and their use is not recommended.⁴⁴

Ferric complexes

Ferric complexes exhibit lower bioavailability and slower uptake kinetics compared to ferrous salts, but can likewise increase hemoglobinization and iron stores.²⁷ In the BESTIRON study, a double-blind randomized controlled trial (RCT) with 80 pediatric IDA patients, ferrous sulfate resulted in greater hemoglobinization within 12 weeks compared to ferric polysaccharide.⁴⁸ Similar results were obtained in another double-blind RCT with 80 infants and children aged 9–48 months,⁴⁸ but also in an observational study comparing the effects of ferrous glycine sulfate *versus* iron protein succinylate in women with IDA.⁴⁹ Nevertheless, a systematic review of data with 8,454 patients published over 30 years concluded that the efficacy of iron protein succinylate was similar to or higher than that of other iron treatments.⁵⁰ Along these lines, iron protein succinylate and ferrous sulfate were equally effective in correcting IDA and increasing serum iron in a rat model.⁵¹

Ferrous iron is absorbed directly, while ferric iron requires reduction. Another important consideration is that iron absorption may be affected by food interactions;⁴ thus, iron supplements are better absorbed on an empty stomach. According to the manufacturers' recommendations, some

iron formulations (ferric polysaccharide, ferric citrate, heme iron polypeptide and sucrosomial® iron) can also be taken with a meal, which suggests independence of food interactions. Nevertheless, further validation is warranted. In a phase III RCT involving patients with non-dialysis CKD and IDA, administration of ferric citrate for 16 weeks resulted in statistically significant increases in hemoglobin (>1 g/dL) and iron parameters compared to the values following administration of a placebo.⁵² The results led to licensing of the drug for this group of patients. In another RCT involving patients with non-dialysis CKD, ferric citrate increased iron stores more effectively compared to ferrous sulfate within 12 weeks, but there were no differences among the arms of the study in mean changes of hemoglobin.⁵³ Longer (52 weeks) treatments with ferric citrate were also able to increase iron stores, improve hematologic parameters, and reduce the need for therapy with intravenous iron and erythropoiesis-stimulating agents in patients with dialysis-dependent CKD.¹⁴ These data are promising and demonstrate efficacy of oral ferric citrate. However, it is debatable whether a lengthy oral treatment with ferric citrate offers advantages over intravenous iron therapy, which is the standard of care for patients with dialysis-dependent CKD.

Ferric maltol has been evaluated in several phase I to III RCT involving patients with IDA, mainly due to IBD or CKD.⁵⁴ In brief, compared to placebo, ferric maltol promoted statistically significant changes in hemoglobin within 12-16 weeks. Hemoglobin increased on average ≥ 2 g/dL by week 12 and the increase was sustained up to week 64. Increases in serum ferritin and transferrin saturation were also observed. In an open-label phase IIIa RCT in IBD patients, ferric maltol achieved significant increases in hemoglobin but did not show non-inferiority *versus* intravenous iron by week 12, while the long-term effects over 52 weeks were comparable.⁵⁵

The efficacy of sucrosomial® iron has likewise been evaluated in several RCT involving patients with ID or IDA of diverse etiologies (non-anemic pregnant women, oncologic patients with solid tumors, women undergoing bariatric surgery, patients with pre-operative anemia, celiac disease, IBD, CKD or congestive heart failure).⁵⁶ The overall data suggest that sucrosomial® iron improved hemoglobinization but did not always efficiently replenish iron stores. For instance, sucrosomial® iron significantly increased hemoglobin but not serum ferritin in IDA patients with IBD.⁵⁷ Likewise, liposomal iron has generally shown effectiveness in improving hemoglobinization in various populations of patients with IDA without, however, increasing serum ferritin.^{31,58,59}

Ferric maltol and sucrosomial® iron are certainly promising new oral iron formulations. Nonetheless, they have not proven to be superior to conventional ferrous salts and are considerably more costly (Table 1). While they were found to offer comparable therapeutic benefits to intravenous iron in some settings, they need to be taken over several months to replenish iron stores. Moreover, their prolonged

use is accompanied by some degree of gastrointestinal side effects (see below). For most patients, the same clinical endpoint can be reached by administration of a single dose of intravenous iron within 15-60 minutes at equivalent or lower cost, and without gastrointestinal side effects. In fact, there is no evidence that any oral iron formulation is non-inferior to intravenous iron with regard to efficacy of correcting ID and IDA.

Other

Data on the efficacy of carbonyl iron and heme iron polypeptide are relatively scarce. High doses of carbonyl iron were able to correct IDA in premenopausal women and prevent ID in female blood donors, but this treatment did not offer any significant efficacy advantage when compared with standard doses of ferrous sulfate.⁶⁰⁻⁶² Heme iron polypeptide has been mainly tested in patients with anemia due to CKD. An RCT concluded that heme iron polypeptide did not achieve non-inferiority to ferrous sulfate in correcting anemia among darbepoetin-treated patients undergoing peritoneal dialysis.⁶³ In another single-blind RCT, heme iron polypeptide had similar efficacy as intravenous iron sucrose in maintaining hemoglobin in non-dialysis patients with CKD and IDA, but was inferior in correcting serum ferritin.⁶⁴

Tolerability and adverse effects of oral iron supplements

In general, the proper use of oral iron supplements is considered safe and does not cause severe adverse effects. However, it frequently triggers gastrointestinal side effects such as constipation, diarrhea, dyspepsia, abdominal pain, nausea, vomiting and mucosal injury, which may reduce compliance.

Ferrous salts

While efficacious in repletion of iron stores, ferrous sulfate and other ferrous salts often exhibit limited tolerability due to gastrointestinal side effects. Ferrous salts may also cause teeth staining and a metallic taste in the mouth, particularly with prolonged use in liquid form or when not properly diluted before ingestion. A systematic review and meta-analysis investigated the tolerability and adverse effects of ferrous sulfate *versus* placebo or *versus* intravenous iron in 43 RCT involving 6,831 adults.⁴² The use of ferrous sulfate significantly increased the risk of gastrointestinal side effects *versus* placebo with an odds ratio of 2.32 (95% confidence interval: 1.74-3.08; $P < 0.0001$), and *versus* intravenous iron with an odds ratio of 3.05 (95% confidence interval: 2.07-4.48; $P < 0.0001$). There was no significant association between odds ratio and ferrous sulfate dose. Additionally, there was no evidence that slow-release ferrous sulfate formulations were tolerated better.

Ferric complexes

Although ferric iron supplements are generally thought to be better tolerated compared to ferrous ones, there are not many directly comparative studies. In the BESTIRON RCT⁴⁸ and the trial with infants and children aged 9–48 months,⁴⁸ there were more reported cases of diarrhea in patients receiving ferric polysaccharide than in those receiving ferrous sulfate, but there were no significant differences in combined *post hoc* gastrointestinal adverse effect profiles. Likewise, there were no differences in adverse effects between women with IDA treated with ferrous glycine sulfate or iron protein succinylate.⁴⁹ In a recent crossover, double-blind RCT in healthy women of reproductive age, microencapsulated ferric saccharate showed a better tolerability profile compared to that of ferrous sulfate regarding the incidences of symptoms, numbers of complaints/symptoms, overall intensity, and total days with symptoms.⁶⁵

A combined analysis of a phase II and III RCT with non-dialysis CKD and IDA patients showed that ferric citrate triggered more treatment-emergent adverse events (discolored feces, diarrhea, constipation, nausea) compared to placebo (75.3% versus 61.7%).⁶⁶

The tolerability of ferric maltol has been evaluated in patients with IDA due to IBD, CKD or pulmonary hypertension who received the drug for 12–16 or 52–64 weeks.⁵⁴ In a multicenter phase III RCT, the proportion of IBD patients who prematurely stopped a 12-week course of therapy due to adverse effects was 10%, as high as that of randomized patients in the placebo group.⁶⁷ Good tolerability has also been reported in the long-term studies.^{68,69} In most cases, the incidence of adverse effects (constipation, diarrhea, nasopharyngitis, abdominal pain) did not differ significantly between ferric maltol-treated patients and placebo or intravenous iron-treated patients. Nevertheless, the US Food and Drug Administration reported that “*ferric maltol can cause serious side effects including increased risk of inflammatory bowel disease flare and iron overload in the body*”.⁷⁰

Sucrosomial[®] iron appears to have excellent gastrointestinal tolerability.⁵⁶ In a prospective study, 96.6% of IBD patients completed sucrosomial[®] iron therapy for 12 weeks, and 80% of them took all prescribed doses; only 17% of patients reported mild gastrointestinal side effects.⁵⁷ Sucrosomial[®] iron was also well tolerated by IDA patients who were intolerant of or refractory to ferrous sulfate,⁷¹ and by women with post-partum IDA.⁷² Similar positive tolerability results were obtained with liposomal iron in studies with IBD⁵⁸ and non-dialysis CKD³¹ patients. Ongoing RCT in additional populations of IDA patients are expected to yield a more comprehensive view, yet interim analysis data seem to validate the favorable tolerability profile of sucrosomial[®] iron.⁵⁶

Other

There are only limited studies on tolerability of carbonyl iron and heme iron polypeptide. While carbonyl iron was found to be safe, it created the typical gastrointestinal side

effects observed with ferrous sulfate.^{60–62} Likewise, heme iron polypeptide did not offer any safety or tolerability benefit compared to oral or intravenous iron supplements.^{63,64}

Iron supplementation in populations exposed to infections

In malaria-endemic countries, oral (or intravenous) iron supplementation that successfully treats anemia will inevitably and transiently increase the risk of malaria and other infectious diseases in children, unless accompanied by effective infection control measures.⁷³ This is because the virulence of infectious microorganisms depends on their capacity to acquire iron, which is essential for their growth. During infection, iron sequestration is considered as a defense strategy of the host to deprive bacteria of iron, within a “nutritional immunity” program.⁷⁴ Thus, iron supplementation may pose a risk in patients with opportunistic or systemic infections. On the other hand, iron deficiency may impair adaptive immunity, as adequate iron supply is required for proliferation of T lymphocytes and neutrophils.¹⁰ These seemingly contradictory findings indicate that a delicate iron balance is crucial for the host to clear infections.

Other biological responses to oral iron supplements

There is evidence that oral ferrous sulfate promotes unfavorable biological responses besides gastrointestinal side effects, such as a transient increase in serum non-transferrin bound iron (NTBI).^{75–77} This is most likely linked to fast absorption, as relatively slower absorbed ferric polysaccharides had negligible effects on NTBI.^{75–77} Serum NTBI was undetectable in IBD patients after 12 weeks of treatment with sucrosomial[®] iron,⁵⁷ but it is unclear whether NTBI transiently emerged earlier. NTBI is redox-active and potentially toxic because it propagates reactive oxygen species, promoting oxidative stress.⁷⁸ Ferrous sulfate but not ferric polymaltose sensitized plasma lipoproteins to oxidation in iron-deficient individuals,⁷⁹ and aggravated inflammation and oxidative stress in a rat model of colitis.⁸⁰ Likewise, ferrous sulfate but not sucrosomial[®] iron induced serum inflammatory markers in mice.⁸¹ Nevertheless, oxidative stress markers did not differ significantly among children with IDA randomized to ferrous glycine sulfate or ferric polymaltose therapy.⁸²

It is important to highlight that the impact of different oral iron formulations on NTBI and oxidative stress markers is not an established or validated parameter for monitoring adverse effects. Thus, further studies would be required to clarify whether transient NTBI increases in response to iron intake are clinically relevant.

Considering that iron is an essential nutrient to almost all microorganisms, elevated luminal iron derived from oral supplements may alter the balance and composition of gut bacteria.²⁰ An open-label RCT compared the effects of oral *versus* intravenous iron on the intestinal microbiome of patients with IBD or simple ID. The study showed that oral ferrous sulfate, but not intravenous iron, promoted major unfavorable shifts in bacterial diversity, which were more pronounced in IBD patients.⁸³ Similar results were obtained in mouse models of IBD, in which intake of ferrous sulfate exacerbated inflammation.^{84,85} Nevertheless, ferrous bis-glycinate⁸⁴ or ferric maltol⁸⁵ had beneficial effects against colitis. In another study with mice, contrary to ferrous sulfate, sucrosomial[®] iron triggered rather favorable changes in the intestinal microbiome.⁸⁶ Taken together, these data suggest that different types of oral iron supplements may trigger diverse effects on intestinal bacterial communities. It is not clear yet whether these effects are related to the oxidation state of excessive luminal iron (ferrous *versus* ferric). A role of the iron ligands is also possible. For instance, experiments in mice suggested that the lipid-lowering capacity of polydextrose, a ligand of ferric supplements, may favorably affect the intestinal microbiome.⁸⁷

Optimal dosage and frequency of oral iron supplementation

The elemental iron content (actual amount of iron available for absorption) differs between commercial iron formulations (Table 1). Thus, the iron dosage needs to be adjusted. Oral supplementation typically starts with ferrous sulfate or other salts, each containing ~60–70 mg elemental iron.⁸⁸ It has traditionally been recommended to take the supplement two or three times per day on an empty stomach, to reach a daily dose of ~200 mg elemental iron. Considering that only 10–20 mg of iron gets absorbed, this amount would be required to reach the target of increasing hemoglobin by 2 g/dL within 3–4 weeks.^{17,41} However, recent studies provided new insights on optimal dosing and frequency, challenging the need for multiple dosing per day. The studies were prompted by our understanding that iron intake triggers homeostatic responses aiming to prevent iron overload. These are orchestrated by hepcidin, which is induced in an iron-dependent manner to inhibit further iron absorption⁷ (Figure 2).

Thus, the effects of hepcidin on oral iron supplementation were first examined in an elegant pilot study with non-anemic iron-deficient young women.⁸⁹ They were treated with various doses of ferrous sulfate in different schedules (twice per day, daily, or every second day). Ferrous sulfate was provided in three different iron isotopes, so that each participant served as her own control. The results showed that ingestion of ferrous sulfate at doses of 60 mg elemental iron or higher triggered induction of

hepcidin for up to 24 h, which decreased fractional iron absorption from a subsequent dose the following day. Hepcidin levels returned to baseline after 48 h, restoring efficient iron absorption. These early data seem to disqualify the split dosing of ferrous sulfate two or three times per day, and even favor intermittent intake every second day *versus* daily dosing, to bypass the hepcidin blockade and increase fractional iron absorption.

In two prospective, open-label RCT with non-anemic, iron-deficient, premenopausal women, the participants received ferrous sulfate containing three different iron isotopes.⁹⁰ The first study examined the differences between intake of 60 mg elemental iron on consecutive *versus* alternate days, while the second study assessed the impact of split dosing of 120 mg elemental iron (in two doses of 60 mg each per day) *versus* single daily dosing. In line with the pilot data,⁸⁹ split dosing twice per day, as well as single daily dosing of 120 mg iron induced hepcidin, which diminished iron absorption the next day.⁹⁰

Using the same methodology, a cross-over study involving premenopausal women with IDA compared iron absorption from ferrous sulfate at doses of 100 mg and 200 mg elemental iron administered either on two consecutive days or on alternate days. Total iron absorption from a single dose of 200 mg given on alternate days was almost twice that from 100 mg given on consecutive days.⁹¹

In a RCT with IDA patients, the primary endpoint of a 2 g/dL rise in hemoglobin at 3 and 6 weeks was reached by significantly more patients taking 60 mg elemental iron twice daily *versus* 120 mg on alternate days.⁹² However, the median hemoglobin rise in the “alternate day” arm at 6 weeks was not significantly different from that in the “twice daily” arm at 3 weeks, while the treatment was better tolerated in the “alternate day” group. Similar results were obtained by other studies involving IDA patients.^{93–95} Current evidence supports the concept that intermittent iron supplementation every other day may be as effective as daily supplementation in controlling IDA, but with fewer adverse effects, at least in women of reproductive age.⁹⁶ Nevertheless, this view is based on a small number of studies, some of them with methodological limitations. Thus, validation in more robust and adequately powered RCT with IDA patients of various etiologies is warranted. In any case, the new findings are reflected in the British Society of Gastroenterology guidelines,⁴⁴ which recommend an initial treatment of IDA with “*one tablet per day of ferrous sulfate, fumarate, or gluconate. If not tolerated, a reduced dose of one tablet every other day, alternative oral preparations or parenteral iron should be considered*”. It should be noted that all data favoring oral iron supplementation every other day were obtained using ferrous sulfate. Therefore, the recommendation for intermittent iron intake is restricted to ferrous salts.⁴⁴ Whether this also applies to other iron supplements remains to be examined. There is evidence that ferric maltol induces hepcidin

similarly to ferrous sulfate in IBD patients,⁹⁷ while ferric citrate promoted a stronger increase in hepcidin compared to ferrous sulfate in non-dialysis CKD patients.⁵³ On the other hand, administration of iron protein succinylate⁵¹ or sucrosomial® iron⁸¹ did not affect hepcidin in rats and mice, respectively. Interestingly, ferric citrate⁹⁸ or sucrosomial® iron⁹⁹ effectively increased hemoglobinization in mouse models of hepcidin overexpression. These findings may be relevant to anemic patients who respond poorly to conventional oral iron supplements and require intravenous iron. This occurs in a subset of IBD or CKD patients who exhibit restricted iron availability for erythropoiesis due to inflammatory hepcidin induction (and impaired renal clearance of hepcidin in CKD), combined with IDA or not.^{13,14} The same considerations apply to patients with iron-refractory iron deficiency anemia (IRIDA), a genetic disorder caused by inactivation of the hepcidin suppressor *TMPRSS6*.¹⁰⁰

Conclusions

Ferrous sulfate and other ferrous salts remain the mainstay of oral iron supplementation. Their high efficacy is offset by

poor tolerability and reduced compliance, which sparked the development of alternative oral iron supplements. Recent studies with ferrous sulfate provided new insights on optimal dosage and frequency. Additional adequately powered RCT are required to address open questions on efficacy, side effects, optimal dosage and frequency of different types of oral iron supplements for selected groups of patients. As none of the old or new oral iron formulations has shown non-inferiority *versus* intravenous iron, comparisons against the gold standard (ferrous sulfate) would be more informative. The effects of oral iron supplements on hepcidin should also be investigated in animal models and clinical studies. Based on current knowledge, the choice between iron formulations should depend on the individual's iron status, tolerance, absorption capacity, and specific therapeutic goals.

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