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REVIEW

Oral iron therapy: Current concepts and future prospects for improving efficacy and outcomes

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Summary
Iron deficiency (ID) and iron-deficiency anaemia (IDA) are global public health concerns, most commonly afflicting children, pregnant women and women of childbearing age. Pathological outcomes of ID include delayed cognitive development in children, adverse pregnancy outcomes and decreased work capacity in adults. IDA is usually treated by oral iron supplementation, typically using iron salts (e.g. $FeSO_4$); however, dosing at several-fold above the RDA may be required due to less efficient absorption. Excess enteral iron causes adverse gastrointestinal side effects, thus reducing compliance, and negatively impacts the gut microbiome. Recent research has sought to identify new iron formulations with better absorption so that lower effective dosing can be utilized. This article outlines emerging research on oral iron supplementation and focuses on molecular mechanisms by which different supplemental forms of iron are transported across the intestinal epithelium and whether these transport pathways are subject to regulation by the iron-regulatory hormone hepcidin.

KEYWORDS
anaemia, DMT1, FPN, hepcidin, intestinal iron absorption, iron supplementation

INTRODUCTION

Iron deficiency (ID) and iron-deficiency anaemia (IDA) afflict over a billion individuals worldwide, most commonly occurring in resource-poor settings.[1] Infants and preschool children are more likely to be iron deficient due to their rapid growth, which increases iron requirements. Also, women of reproductive age (due to iron losses via menstruation) and pregnant women (due to increased iron requirements) are at increased risk for ID and IDA.[2–4] Low food iron bioavailability, malnutrition, intestinal and systemic inflammation, bacterial and parasitic infections, vegetarianism and regular/frequent blood donation also increase the likelihood of iron depletion.[2,5] Absolute ID is typified by the depletion of body iron stores, while functional ID is characterized by the inability to utilize iron despite sufficient stores. Manifestations of ID occur sequentially, with IDA being the most severe.[3] Depletion of storage iron is the first stage. Next, transport (i.e. circulating) iron levels fall, and finally, iron delivery to the erythroid marrow is diminished, leading to iron-restricted erythropoiesis and anaemia. The WHO defines anaemia as haemoglobin (Hb) <13 g/dL in males, <12 g/dL in females and <11 g/dL in pregnancy.[6] ID is the most frequent cause of anaemia globally, affecting 40% of children aged 6–59 months and 36% of pregnant women.[7] Overall, an estimated 2 billion individuals worldwide may be iron deficient.[3,4] This is a major public health threat, since ID impairs immune function, increases the risk of respiratory infections, delays cognitive development in infants, lowers school performance in children and reduces work capacity in adults. During pregnancy, ID negatively impacts the mother and offspring,

increasing the risk for preterm delivery, low birth weight, and infant and maternal mortality.[2,8,9]

Oral iron supplements are the logical first choice to treat ID and IDA since they are inexpensive, safe and have proven effectiveness.[10,11] Iron salts, such as $FeSO_4$, have historically been the mainstay treatment utilized in populations with prevalent ID and anaemia; however, the less efficient absorption of iron from these compounds dictates that doses several times above the recommended dietary allowance for iron may be required.[12,13] High dosing and ineffective absorption increase enteral iron content, frequently resulting in adverse GI outcomes such as nausea, vomiting, constipation and diarrhoea, and ultimately, poor compliance.[3,10,14] Excess unabsorbed iron has also been shown to have negative impacts on the composition of the gut microbiome.[15,16] Given these notable limitations of iron salts, alternative iron supplementation formulations have been recently developed, including: iron–polysaccharide complexes (IPCs),[17] haem–iron polypeptides (HIPs),[18,19] amino acid (AA) iron complexes and chelates,[20–22] liposomal/nanoparticle (NP) encapsulated iron,[23–25] iron complexed with milk proteins (iron protein succinylate [IPS])[26,27] and lipophilic iron chelates.[28] The timing of iron dosing has also emerged as an important issue, with implications related to the effectiveness of absorption and emergence of untoward, negative side effects.[29–31] This review, which is summarized in Video S1, outlines emerging oral iron therapy strategies, which are collectively intended to increase efficacy, in comparison to iron salts, by enhancing absorption and minimizing GI side effects. Since many novel iron supplements are not normal dietary constituents, but rather, created in the laboratory, possible mechanisms and regulation of absorption will also be considered herein.

MECHANISMS OF INTESTINAL IRON TRANSPORT

Haem iron (HI) and non-haem iron (NHI) are the predominant forms of iron in the human diet. HI is more bioavailable than NHI.[32] Iron absorption occurs mainly in the duodenum and upper jejunum.[33,34] Iron is released from the food matrix by gastric and pancreatic proteases,[8] and then HI and NHI are absorbed by distinct, but possibly overlapping, pathways.[9] Mechanistic details of HI absorption remain largely elusive. Haem is probably taken up by enterocytes via receptor-mediated endocytosis and then transported out of endosomes into the cytosol. The identity of the haem receptor/importer remains unknown, but haem-responsive gene 1 (HRG1) is one possible candidate.[35] Cytosolic haem may be catabolized by haem oxygenase 1 (HO1) in the endoplasmic reticulum, which liberates iron from the protoporphyrin ring. Alternatively, intact haem may be exported across the enterocyte basolateral membrane (BLM), possibly via the feline leukaemia virus C receptor (FLVCR)[9] and then catabolized in the liver.

The mechanisms of NHI absorption are understood in greater detail. Dietary ferric NHI (Fe^{3+}) must first be reduced to ferrous (Fe^{2+}) iron, possibly by a brush–border membrane (BBM)-bound ferrireductase, duodenal cytochrome b (DCYTB),[36] which utilizes intracellular ascorbate to facilitate electron transfer.[37,38] Dietary and endogenous factors, such as ascorbic acid and gastric acid, also promote the reduction and solubilization of dietary ferric iron. Fe^{2+} is subsequently transported across the BBM via divalent metal-ion transporter 1 (DMT1), which couples iron import to inward proton fluxes.[39] DMT1 may also transport other divalent cations, such as Mn and Co.[39,40] Within enterocytes, Fe^{2+} is probably bound by chaperones, such as poly(RC) binding protein 1 (PCBP1),[41–43] and distributed to various cellular locations (e.g. mitochondria), where it can be utilized for metabolic processes or sequestered in the iron-storage protein complex ferritin. When body iron demand increases, Fe^{2+} is transported across the BLM by ferroportin (FPN)[44] and oxidized by a membrane-bound ferroxidase, hephaestin (HEPH). Fe^{3+} then binds to transferrin in the interstitial fluids of the lamina propria for distribution to the liver in the portal blood circulation.[40]

REGULATION OF INTESTINAL IRON ABSORPTION

Iron metabolism in enterocytes is regulated by cellular and systemic factors.[34] Cellular iron homeostasis involves the iron-regulatory protein (IRP)—iron-responsive element (IRE) system and a hypoxia-responsive *trans*-acting factor, HIF2α. IRPs are intracellular iron-sensing proteins that interact with stem-loop structures called IREs located in the untranslated regions (UTRs) of mRNA transcripts encoding proteins involved in iron metabolism.[45] When cellular (cytosolic) iron is low, IRPs bind to an IRE in the 5' UTR of the ferritin mRNA, which blocks translation and decreases protein levels. Also, when iron is low, the IRPs bind to an IRE in the 3' UTR of the DMT1 mRNA,[46] which enhances transcript stability, thus increasing protein synthesis. Conversely, when cellular iron is high, the IRPs do not bind to IREs, and therefore the ferritin transcript is translated normally and the DMT1 transcript is destabilized.[9,45] So, in summary, when cellular iron is low, iron import via DMT1 increases while iron storage in ferritin decreases; conversely, when intracellular iron is elevated, iron import via DMT1 goes down and iron storage via ferritin goes up. The other important cellular regulatory mechanism involves transcriptional regulation by the hypoxia-responsive transcription factor HIF2α. When cellular iron levels fall or when cells become hypoxic, such as during ID or IDA, the HIF2α protein is stabilized, which enhances transactivation of the genes encoding DMT1 and FPN.[47,48] HIF2α signalling thus increases vectorial iron flux in duodenal enterocytes, thus providing additional iron to replenish body iron stores and support enhanced erythropoiesis.

At the systemic level, intestinal iron absorption is regulated by the liver-derived peptide hormone hepcidin.[49] Hepcidin binds to FPN on the BLM of duodenal enterocytes,

causing its internalization and degradation, thereby limiting iron flux across the intestinal epithelium.[49,50] Hepcidin is produced mainly by hepatocytes, and its synthesis is regulated at the level of transcription by various stimuli.[50] The *HAMP* gene, encoding hepcidin, is downregulated in ID/hypoxia and when erythropoietic activity is enhanced, allowing increased absorption of enteral iron. When erythroid demand for iron is elevated, *HAMP* expression is attenuated by the hormone erythroferrone (ERFE), which is produced by erythroblasts in response to kidney-derived erythropoietin (EPO).[51] Conversely, when body iron stores are elevated and during infection and inflammation, *HAMP* expression is upregulated. In the inflammatory state, pro-inflammatory cytokines, such as IL-6, transactivate *HAMP*,[50] leading to higher hepcidin, which attenuates intestinal iron absorption. Notably, hepcidin also regulates cell-surface expression of FPN in cells that store and recycle iron (e.g. hepatocytes and reticuloendothelial macrophages of the spleen, bone marrow and liver).

EXOGENOUS AND ENDOGENOUS FACTORS THAT INFLUENCE IRON ABSORPTION

HI accounts for only ~10%–15% of total iron in western diets, but its absorption efficiency is higher, between 15% and 35%.[40] The remaining 85%–90% of total dietary iron is NHI, with lower bioavailability (2%–20% absorbed).[9,40] Numerous factors enhance (organic acids, dietary proteins, AAs)[40,52] or inhibit (polyphenols, phytates, oxalate, calcium)[9,53] NHI absorption (Table 1). HI absorption is less affected by these factors. Common oral iron supplements contain NHI salts, and thus iron absorption from these supplements can be influenced by dietary components (so dosing at least 30 min before a meal is recommended). Dietary (e.g. ascorbic acid) and endogenous (e.g. gastric acid, citrate) factors maintain NHI in the more soluble ferrous (Fe^{2+}) form, which promotes its absorption via DMT1.[40]

Iron absorption is decreased in individuals who have undergone gastric bypass surgery[3,5] or pancreaticoduodenal resection (i.e. the Whipple surgical procedure), due to a loss of the duodenal segment of the small intestine, which is the primary site of iron absorption. Use of proton-pump inhibitors and H_2 blockers inhibits gastric acid production, which decreases iron absorption, since gastric acid promotes the reduction of dietary ferric iron to ferrous iron, and ferrous iron transport via DMT1 is proton coupled.[3] Gastric acid production is also impaired in autoimmune atrophic gastritis and *Helicobacter pylori* infection, which also has a negative effect on the absorption of enteral iron.[54] Moreover, in patients with chronic inflammatory conditions, including, for example, inflammatory bowel disease (IBD) and coeliac disease,[3] hepatic *HAMP* is transactivated by pro-inflammatory cytokines. High hepcidin levels decrease serum iron, leading to the so-called anaemia of inflammation (or the anaemia of chronic disease).[55,56]

Diurnal variations in iron-related parameters have been reported in animals[57,58] and humans.[59] In (nocturnal) mice, liver iron was 30%–40% higher, and plasma iron was 20%–30% lower in the active dark period, as compared to the inactive light period.[58] In (diurnal) pigs, serum iron was low at 7:00 AM but peaked at 3:00 PM, which was concurrent with the peak of liver *Hamp* expression. Liver iron concentration peaked at 7:00 AM and was lowest at 11:00 PM. Expression of DMT1 and DCYTB in the duodenum and jejunum also

TABLE 1 Dietary and (patho)physiological factors that influence iron absorption.

Factor	Description	Outcome
Dietary and endogenous	Ascorbic acid, citric acid, lactic acid, meat/fish/poultry, amino acids, haem chelation	Enhance iron absorption
	Polyphenols, phytate, oxalate, calcium	Inhibit iron absorption
Physiological	Depletion of body iron stores/hypoxia and blood loss; Stimulation of erythropoiesis (EPO-ERFE signalling represses *HAMP*)	Low hepcidin High iron absorption
	High body iron stores, other physiological stressors	High hepcidin Low iron absorption
Genetic	*TMPRSS6* mutations causing iron-refractory iron-deficiency anaemia (IRIDA)	High hepcidin Low iron absorption
	SLC11A2 (encoding DMT1) mutations (humans and experimental rodent models)	Impaired iron absorption; severe IDA (Hb <5 g/dL in mice)
	Hereditary haemochromatosis; β-thalassaemia Relatively low hepcidin given body iron burden	Inappropriately high iron absorption; iron loading
Gastric	*Helicobacter pylori* infection, autoimmune atrophic gastritis, achlorhydria	Low iron absorption
Inflammatory	IBD, coeliac disease, other conditions typified by chronic inflammation (e.g. rheumatoid arthritis, cancer, Crohn's disease)	Transactivation of hepatic *HAMP*; high hepcidin and low iron absorption
Diurnal	Time-dependent variations in serum and liver iron; mRNA levels of iron metabolism-related genes thought to vary diurnally	Possible diurnal variations in iron absorption
Other	Bariatric surgery, proton-pump inhibitors (H_2 blockers), antacids, pancreaticoduodenectomy	Inefficient iron absorption; depletion of iron stores

showed diurnal variations with peaks around 11:00 AM. Moreover, Nguyen et al.[59] showed that serum iron in humans was relatively high and stable between 8:00 AM and 3:00 PM, with peaks at 11:00 AM in adult men, 12:00 PM in adult women and children and 3:00 PM in teenagers. Moreover, fasting also influenced serum iron levels, with elevated serum iron noted after 10 h of fasting.[59] In another study, total iron-binding capacity (which reflects circulating transferrin levels), percent transferrin saturation (which reflects serum iron levels) and serum ferritin (which reflects total body iron stores) showed no clear diurnal variation in adult subjects.[60] Nonetheless, clinical diagnostic biomarkers of iron status may be influenced by the time of blood collection, and the timing of oral iron provision could impact the efficiency of its absorption and utilization.

GENETIC CONDITIONS ASSOCIATED WITH ALTERED IRON ABSORPTION

Intestinal iron absorption is inappropriately elevated in β-thalassaemia, which is an iron-loading anaemia, and in patients with the iron-loading disorder, hereditary haemochromatosis (HH). Conversely, iron absorption is repressed in some genetic conditions, such as iron-refractory iron-deficiency anaemia (IRIDA) and with mutations in *SLC11A2* (encoding DMT1). Although collectively, these disorders are uncommon, genetic iron overload or genetic ID could complicate iron supplementation strategies.[54] In β-thalassaemia patients, ineffective erythropoiesis, due to mutations in the β-globin gene (*HBB*), and increased demand for iron repress *HAMP* transcription in hepatocytes, leading to low circulating hepcidin levels, excessive intestinal iron absorption and iron loading.[61,62] Blood transfusion exacerbates iron loading in β-thalassaemia. Iron supplementation of an (anaemic) individual with enhanced intestinal iron absorption due to β-thalassaemia could exacerbate tissue/organ damage mediated by excess iron. HH is another genetic condition in which intestinal iron absorption is enhanced. Most cases of HH (~95%) arise from a homozygous C282Y mutation in the homeostatic iron regulator (*HFE*) gene.[63,64] HFE-related HH affects approximately 1 in every 200 persons of northern European ancestry, making it one of the most common genetic disorders. Rare cases of HH can also result from mutations in genes encoding haemojuvelin (HJV), hepcidin (HAMP) and transferrin receptor 2 (TFR2).[65] In HH patients, hepcidin production is inappropriately low given body iron status, leading to elevated iron absorption and iron accumulation in parenchymal tissues/organs.[66] Increased oxidative stress from iron overload increases the risk of developing liver damage, cardiomyopathy, diabetes, arthropathies and endocrinopathies. Iron supplementation of an individual with undiagnosed or early-stage HH could exacerbate iron loading and increase the risk of developing comorbidities from excess iron.

In IRIDA, another rare genetic disorder, hepcidin levels are elevated due to mutations in the gene encoding the protease matriptase-2 (encoded by *TMPRSS6*).[67–69] Matriptase-2 functions in a biochemical pathway that represses *HAMP* expression in hepatocytes. Low (or absent) matriptase-2 activity thus results in continuously elevated serum hepcidin levels, which decreases the absorption of enteral iron and leads to severe systemic iron depletion. Alternative approaches that bypass the intestinal absorptive defect, such as IV iron administration, would likely be more effective in IRIDA patients. Intestinal iron absorption may also be impaired in individuals with mutations in *SLC11A2*, encoding the DMT1 iron transporter.[70–74] Some patients with *SLC11A2* mutations developed ID but also hepatic iron overload. This was suggested to be due to the low residual activity of mutant DMT1 in the intestine, leading to the absorption of some iron, which then cannot be efficiently acquired by developing erythrocytes, leading to elevated serum iron and subsequent iron accumulation in the liver. In another, presumably DMT1-null patient, IDA but with no iron hepatic overload was observed, suggesting that their ID is related to impaired assimilation of dietary iron by intestinal DMT1 (combined with impaired iron utilization by developing RBCs).[75] Oral iron supplementation, or IV iron administration, would both likely be ineffective at correcting the ID/IDA in patients carrying deleterious *SLC11A2* mutations, since intestinal iron absorption *and* iron utilization by developing erythrocytes are both impaired.

STRATEGIES EMPLOYED TO ENHANCE THE EFFICACY OF ORAL IRON SUPPLEMENTATION

Iron supplementation: Dosing recommendations and frequency of administration

Different approaches to maximize the efficacy of oral iron supplementation, while minimizing mainly GI-related sides effects, are summarized in Table 2. The World Health Organization (WHO) provides population-based recommendations on the dosage and frequency of iron supplementation to prevent and control ID and IDA in at-risk groups at different life stages. These recommendations have been derived from the results of clinical trials using oral iron salts, most commonly $FeSO_4$, and are based upon the background level of anaemia in various settings. For example, in countries where the prevalence of anaemia is ≥40%, suggested daily intakes of elemental iron for three consecutive months in a year are as follows: 10–12.5 mg for infants and young children (6–23 months of age), 30 mg for preschoolers (24–59 months) and 30–60 mg for school-age children (5–12 years).[76] Additional WHO recommendations for other groups are summarized in Table 3. The WHO guidance can also logically serve as a framework to design individualized oral iron therapy regimens for patients that present at the clinic with ID or IDA.

A recent systematic review of published iron supplementation studies done in children and adolescents <20 years

TABLE 2 Strategies to enhance absorption of supplemental iron.

Iron supplements	Chemical forms	Description/mode of action	Notes/potential limitations
Traditional iron salts	Ferrous ascorbate Ferrous fumarate Ferrous gluconate Ferrous sulphate Ferric formulations Others	Daily iron intake (WHO): • 30–60 mg for 3 consecutive months/yr for girls and women where prevalence of anemia is >40% • 30–60 mg to prevent or treat anaemia in pregnant women in areas with high prevalence	• Low fractional absorption • Adverse GI side effects • Poor adherence • Alternate day dosing may be most effective. • Vitamin C enhances absorption
Newer iron salt formulations	Slow-release iron Enteric-coated iron	Iron may be released in more distal gut segments (i.e. jejunum, ileum)	• Less efficient absorption • Possible adverse GI events
Complexed iron	Iron–polysaccharide complex (IPC)	Stable complex of ferric iron with a polysaccharide carrier	• Slower release of iron • Less effective than iron salts
	Plant and yeast ferritins	High bioavailability in humans	IHAT is a ferritin-core analogue
	Haem–iron polypeptide (HIP)	Haem moiety with short polypeptide chains; >1% iron	• Absorbed like dietary haem? • In vivo testing warranted
	Ferric maltol (trimaltol iron)	• Lipophilic iron chelate • Heteroaromatic complex with Fe	Efficacious in individuals refractory to treatment with iron salts
	Iron protein succinylate	• Highly soluble complex of iron bound to succinylated milk protein • Available since 1988; tested in >50 clinical and observational studies	• Iron released from protein shell by pancreatic proteases • Less GI side effects • Allergy to milk protein (e.g. casein) precludes use
	Hinokitiol	• Lipophilic iron chelator • Diffuses across cell membranes	Transfers iron when transporters are lacking
Micro-/nano-encapsulation of iron	Liposomal iron (ferric pyrophosphate)	• Phospholipid bilayer encapsulation • Nano-sized particles	• Absorbed into enterocytes by endosomal/lysosomal pathway • M cell/lymphatic pathway or macrophage uptake also possible • Additional in vivo testing is warranted for this class of iron supplements
	Sucrosomial iron (SI) (ferric pyrophosphate)	Matrix of phospholipids + sucrose esters of fatty acids	
	Nanoparticle (NP) iron (polyP-FeONPs)	Ferric hydroxide-polyphosphate nanoparticles	
AA-/peptide-based iron formulations	Iron–amino acid chelates and complexes (e.g. Fe-Gly)	Iron may be co-ordinately bound by or more loosely associated with AAs and/or peptides	Peptide transporters may mediate absorption of AA- and peptide-iron chelate

of age over the past 50 years considered the effect of dose, schedule and duration on the efficacy of oral iron therapy.[77] Most of these clinical trials (70%) utilized iron salts, including $FeSO_4$ (most frequently) and ferrous fumarate. Iron supplementation 1–2 times per week had similar efficacy in mitigating IDA compared to supplementation 3–7 times per week, while higher doses were more effective at improving anaemia compared to lower doses. Also, trials with longer duration and more frequent dosing were associated with a greater increase in serum ferritin levels, which reflects the restoration of body iron stores. Although this meta-analysis did not find an increased incidence of adverse outcomes associated with oral iron supplementation, negative side effects associated with oral iron supplementation have been described in other human trials.[14] In sum, weekly and more frequent iron supplementation at moderate to high doses was most effective at restoring iron balance while still avoiding adverse GI side effects.[14,77]

Recent studies, again mainly using oral iron salts, demonstrated that fractional iron absorption is higher at lower iron doses and when supplements are taken on alternate days.[29–31,78,79] Oral iron doses ≥60 mg in iron-deficient women triggered an increase in circulating hepcidin that persisted up to 24 h after dosing, thereby decreasing absorption of supplemental iron administered the following day by 35%–45%.[29,79] When administered twice daily, iron absorption from the second (afternoon) dose and the following morning's dose decreased while circulating hepcidin increased on the following day.[79] Of note, participants receiving daily supplementation had a 33% higher occurrence of GI side effects compared to those receiving alternate-day supplementation.[29] A systematic review by Pena-Rosas et al.[80] revealed that pregnant women receiving intermittent (2–3 times per week on non-consecutive days) oral iron supplementation (with or without other vitamins and minerals) had fewer side effects than with daily supplementation. No significant differences were observed between daily and alternate-day supplementation in terms of primary outcomes for infants, including low birth weight, preterm birth and neonatal death, or maternal anaemia at term. General recommendations for effective oral iron supplementation are discussed in detail below and summarized in Table 4.

TABLE 3 WHO population-based recommendations to prevent and control ID and IDA via oral iron supplementation.[a,b]

Life stage	Prevalence of anaemia in region (%)	Dosage of elemental iron[c]	Duration of therapy	Frequency of dosing	Link to current WHO guidelines
Infants and children	≥20	10–12 mg (6 months–4 years)	Throughout childhood from 6 months to 12 years	90 doses/6 months	WHO: 6 months–12 years
	20–40	25 mg (24–59 months) 45 mg (5–12 years)	Every other 3 months	Weekly	WHO: Children
	≥40	10–12.5 (6–23 months) 30 mg (24–59 months) 30–60 mg (≥60 months)	Three consecutive months in a year	Daily	WHO: Infants & Children
Women of reproductive age and adolescent girls	20–40	60 mg	Every other 3 months	Weekly	WHO: Menstruating Women
	≥40	30–60 mg	Three consecutive months in a year	Daily	WHO: Women and Adolescent Girls
Pregnant women	<20	120 mg	Throughout pregnancy	Weekly	WHO: Pregnancy
	20–40	30–60 mg	Throughout pregnancy	Daily	
	≥40	60 mg	Throughout pregnancy	Daily	
Postpartum women	≥20 gestational anaemia	Use guidelines for menstruating women or continue with pregnancy dosing	ASAP after delivery for 6–12 weeks or until menses resume	As per guidance selected	WHO: Postpartum Women

[a] WHO Guidance on Preventive Population-based Strategies to Control Anaemia Using Iron Supplementation.

[b] Haemoglobin concentrations should be measured prior to the initiation of supplementation to confirm non-anaemic status. For all anaemic individuals, follow national guidelines for the treatment of anaemia.

[c] 60 mg of elemental iron = 300 mg of ferrous sulphate heptahydrate, 180 mg of ferrous fumarate or 500 mg of ferrous gluconate.

Oral iron salts

Iron salts have been used for hundreds of years to treat anaemic patients and remain the mainstay treatment for IDA globally.[81] Ferrous iron compounds have been suggested to be more effective than ferric iron compounds,[82,83] most likely since ferrous iron (Fe^{2+}) is the main DMT1 substrate and DMT1 accounts for most NHI absorption.[84] Dissolved oxygen in the fluids bathing the apical surface of enterocytes could promote oxidation of some proportion of enteral ferrous iron to Fe^{3+}, which would then have to be solubilized and reduced by endogenous or dietary factors (e.g. gastric acid or ascorbic acid) or enzymes (e.g. the DCYTB ferrireductase). Ferrous iron is subsequently assimilated via the DMT1/FPN pathway, which is subject to systemic regulation by hepcidin (Figure 1A). Since iron from these ionic iron compounds is inefficiently absorbed, intakes several times above the typical RDA for iron may be required for adequate repletion. High-dose supplementation with iron salts elevates the concentration of unabsorbed iron in the gut lumen, which can irritate and damage the mucosa, thus leading to numerous, mainly GI side effects.[14] Recent research efforts have compared the efficacy of iron salts to other oral iron formulations. For example, one clinical trial among pregnant women of gestational age 12–26 weeks with moderate anaemia compared oral iron treatment with $FeSO_4$ to an iron hydroxide polymaltose complex and ferrous ascorbate.[85] Outcomes demonstrated that all three oral therapies showed comparable efficacy and safety profiles. Also, a recent meta-analysis concluded that iron supplementation with lactoferrin, an iron-binding protein in human milk, was superior to $FeSO_4$ for correcting IDA.[86] Furthermore, enteric coating has been utilized to encapsulate iron salts like $FeSO_4$, aiming to slow down the release of iron[87] while reducing GI side effects. One caveat to this approach, though, is that iron may be primarily released in the mid- to distal small intestine rather than the duodenum, where iron absorption is most efficient.[28,29]

Iron supplements including vitamin C (ascorbic acid)

Ascorbic acid (vitamin C) has been evaluated as an enhancer of NHI absorption.[88] Ascorbate donates an electron to promote the reduction of ferric iron in the acidic pH of the proximal intestine,[88] thus enabling the absorption of ferrous iron via DMT1. Consumption of iron supplements with orange juice is often recommended; thus, not surprisingly, oral iron supplements containing ascorbic acid are commercially available.[89,90] Earlier work conducted in humans using radiolabelled iron in meals containing fruits

TABLE 4 General guidelines for oral iron therapy to treat ID and IDA.[a]

- Iron supplementation is typically the initial logical approach to correct ID/IDA
- Oral iron therapy approaches are preferred for ID/IDA children, adolescents and other at-risk groups (e.g. pregnant women), since this obviates the need for IV iron, which is typically administered in a monitored (clinical) infusion setting
- Over-the-counter, oral iron supplements come in a variety of chemical forms and formulations (Table 3)
  - Iron salts are frequently used for oral iron therapy due to their established safety profiles and cost-effectiveness.
    - Adverse GI-related side effects may occur with provision of iron salts, reducing compliance
  - Complexed (e.g. iron–amino acid chelates) or encapsulated forms (nanoparticle iron) of supplemental iron are reported to cause fewer GI-related side effects and have better absorption but are likely to be more expensive.
  - Enteric-coated or slow-release forms of iron may be poorly absorbed (due to iron release in the distal GI tract)
- Absorption of dietary and supplemental iron can be influenced by endogenous and dietary factors:
  - Ascorbic acid may increase the solubility/bioavailability of iron and thus enhance absorption
  - Food and medications can inhibit absorption; take iron 30 min before eating or 2 h before taking medications
    - Methyldopa/levodopa, fluoroquinolones, penicillin and tetracyclines may decrease absorption
  - Polyphenols in tea, phytate/oxalate in vegetables, calcium and antacids/acid blockers may blunt absorption
  - Iron absorption may be reduced in gastric bypass patients and those undergoing pancreaticoduodenectomy
- Patients should be advised on the chemical form of iron to take, the dosage and the conditions and schedule of dosing
  - Population-based recommendations by the WHO provide guidance for iron dosing (Table 2)
  - Alternate-day dosing may maximize fractional absorption, increase efficacy and reduce adverse GI side effects
    - For over-the-counter iron supplements, it is best to choose those that are certified against the American National Standard, NSF/ANSI 173 (NSF Supplement Certification) or those with the USP Verified Mark (USP Verified Mark). ConsumerLab.com also tests supplements and provides consumer information (CL Certification Seal)
- Follow-up with patients is critical after recommending oral iron therapy; a laboratory workup will help determine efficacy
- Effectiveness (and compliance) can be determined by reticulocyte count, blood haemoglobin and serum ferritin
  - Reticulocytosis may be evident 7–10 days after the initiation of an oral iron supplementation regimen
  - Mean corpuscular haemoglobin (MCH) content (in picograms) will likely increase within 3–4 days of initiating therapy
  - Total blood haemoglobin may increase after 2–3 weeks; increases of 0.7–1.0 g/dL per week indicate effectiveness
  - Adequate iron replacement has typically occurred when serum ferritin levels reach ~100 μg/L; however:
    - Baseline serum ferritin may vary at different developmental stages and also according to ethnic background
    - Inflammation increases serum ferritin, independent of changes in iron status
- If Tx is ineffective after a few weeks, compliance should be assessed, and patients should be evaluated for blood loss or poor absorption/utilization; referral to a gastroenterologist or haematologist may be needed to diagnose the underlying cause
- IV iron may be a reasonable alternative in some circumstances (see Indications For Parenteral Iron Therapy: Table 3)
  - IV iron may be the preferred primary approach in chronic kidney and heart disease populations

[a]Physician's guide to oral iron supplements; iron supplementation.

suggested that ascorbate led to a dose-dependent increase in iron absorption.[91] Also, 40–50 mg of ascorbate contained in 100 mL of orange juice and administered with ^{59}Fe-labelled food items, including bread and tea, increased iron absorption by ~3-fold.[92] Another study reported a 2.5-fold increase in iron absorption in meals taken with orange juice.[92] A systematic review by Heffernan et al.[89] confirmed that iron absorption was enhanced when study participants consumed test meals containing ascorbic acid. Additionally, in long-term ascorbate supplementation studies, an increase in Hb levels was observed compared to baseline measurements.[89] Another recent randomized clinical trial in 400 adults with IDA, however, found that vitamin C did not increase the efficacy of iron repletion. Study participants were supplemented with 100 mg of ferrous succinate (an iron salt) every 8 hours, but the magnitude of iron absorption and the rate of haemoglobin recovery were the same with and without the addition of ascorbate.[93] Nonetheless, consumption of vitamin C with meals (and with iron supplements) is a reasonable recommendation for individuals at risk for ID, especially since foods containing vitamin C have additional health-promoting properties and supplemental vitamin C is inexpensive, safe and produces minimal, if any, negative side effects (even at doses many times above the RDA).[94]

Iron–polysaccharide complexes

The IPC has been developed as an oral iron supplement for use in humans, with fewer purported side effects as compared to iron salts.[95,96] IPCs, which are isolated from plants or chemically synthesized, are composed of a polysaccharide carrier complexed with ferric iron atoms and have variable structures and physiochemical properties.[96] IPC formulations have been evaluated for use in correcting IDA.[15,16] In a seminal study, IPC was compared to $FeSO_4$ (both used at 3 mg iron/kg body weight, once daily) for restoring Hb levels in infants and young children with nutritional IDA.[16] After 12 weeks of treatment, $FeSO_4$ increased Hb levels more effectively (11.9 g/dL vs. 11.1 g/dL), resolved IDA more frequently (29% vs. 6%) and caused less diarrhoea (35% vs. 58%). Another recent randomized trial compared ferrous fumarate to ferric IPC (both with ascorbic acid) in a 12-week intervention study in individuals with IDA. Ferrous fumarate was significantly more effective at increasing haemoglobin and serum ferritin, while minimal side effects were noted with both supplements. The decreased efficacy of IPC may be due to less efficient intestinal absorption,[97] possibly due to the release of iron from the complex in more distal portions of the small intestine (where iron absorption is less efficient).[98] Ionic iron released from the IPC in the stomach or proximal small intestine is most likely

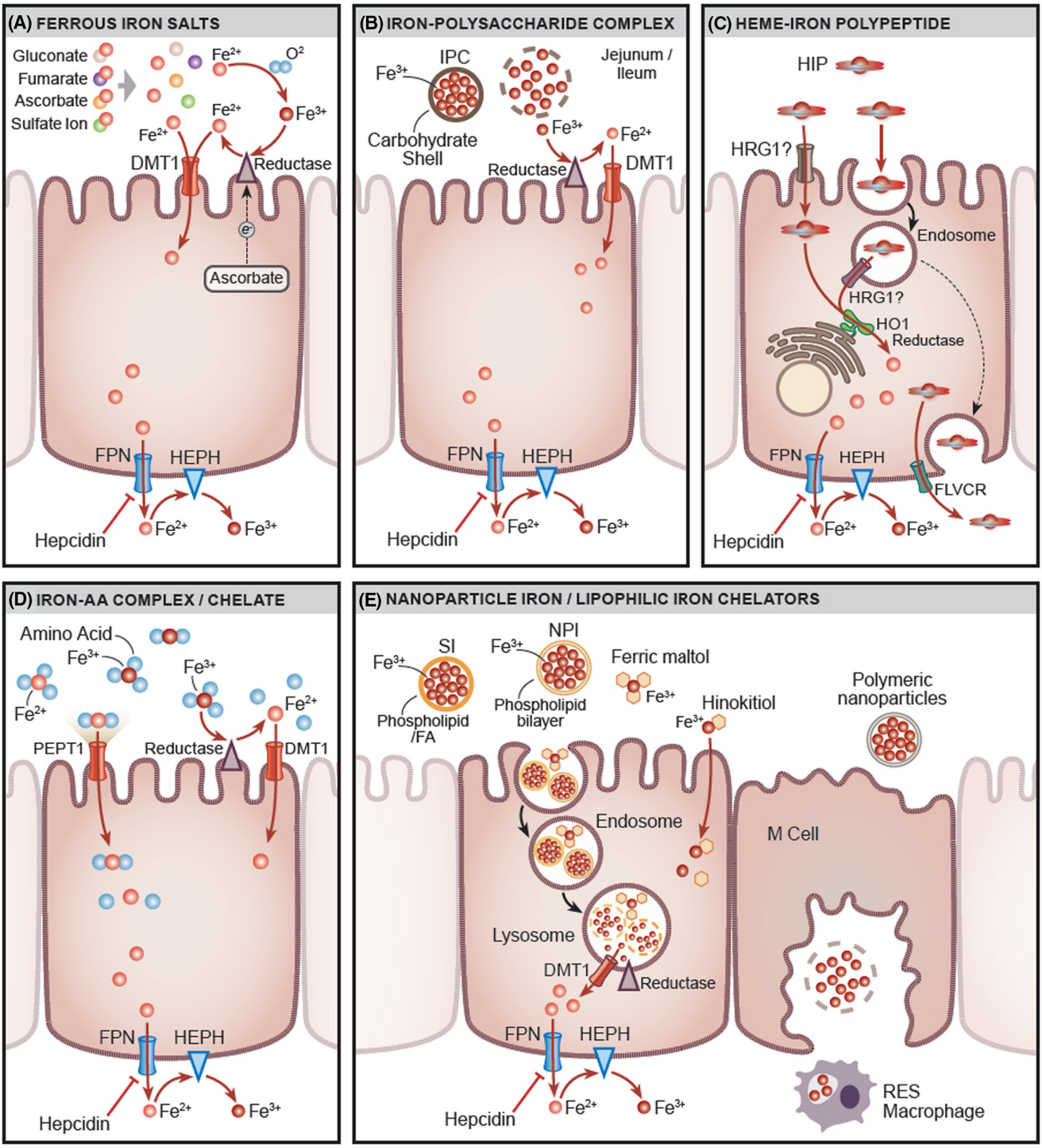

FIGURE 1 Oral iron supplements and pathways of absorption. Ferrous iron salts (A) ionize within the intestinal lumen, and iron is then absorbed via the DMT1/FPN pathway. Some ferrous iron may be oxidized and require reduction prior to absorption. The iron–IPC slowly dissolves in the gut lumen (B), thus releasing ferric iron, which is then reduced and absorbed by the DMT1/FPN pathway. Absorption may be less efficient as some iron is liberated from the carbohydrate shell in more distal gut segments. Haem–iron polypeptide (HIP) may be absorbed like dietary haem (C). This process likely involves a BBM haem transporter/receptor, possibly HRG1, intracellular HO1, a reductase and possibly a BLM haem exporter. Details of this process, for haem, or for HIP, remain to be clarified. Amino acids and peptides are known to enhance iron absorption (D). Iron–AA complexation may increase iron bioavailability by delivering iron to the surface of enterocytes, where free iron is absorbed via DMT1. Iron–AA chelates (e.g. Fe-Gly) may be absorbed intact via AA/peptide transporters (e.g. PEPT1) and then hydrolysed within enterocytes, thus liberating free iron. Sucrosomial iron (SI) and nanoparticle iron (NPI) are likely absorbed via endocytosis, followed by dissociation within lysosomes and iron transport into the cytosol, possibly via DMT1 (E). The lipophilic iron chelate ferric maltol may also be absorbed by this pathway, followed by breakdown in enterocytes or it could traverse cells intact and be taken up by resident tissue macrophages (not shown). There is also evidence that some of these forms of iron can be absorbed via intestinal M cells and then taken up by macrophages of the reticuloendothelial system (RES). Hinokitiol probably allows iron to simply diffuse across membranes, followed by iron release to other iron-binding ligands within enterocytes (E).

absorbed into duodenal enterocytes via the DMT1/FPN pathway and is thus subject to regulation by hepcidin (Figure 1B).

Ferritin

Plant ferritins, or phytoferritins, are abundant in soybeans, peas and other legumes and are considered highly bioavailable dietary sources of iron for humans. As such, iron-rich phytoferritins have been proposed as novel iron supplements.[99–102] Attempts have also been made to increase ferritin levels in legumes to further enhance their iron-storing capacities for possible use as oral iron supplements.[103] Studies in humans and experimental animal models suggested that the mechanism of iron absorption from ferritin was via a pathway distinct from the DMT1/FPN non-haem iron and the haem–iron absorption pathways,[104] possibly involving endocytosis followed by lysosomal degradation and iron release into the cytosol.[105,106] Ferritin is composed of light and heavy chains, and ferritin heavy chains (FHCs) have been proposed as the main form that binds to the cell surface, is internalized, and eventually releases bioavailable iron. Surprisingly, the uptake mechanism into cells could involve transferrin receptor 1 (TFR1),[107] but this is probably not important for dietary iron acquisition from ferritin since TFR1 expression is likely restricted to cells of the intestinal crypt (and not absorptive enterocytes).[108] Nonetheless, a recent report described a novel iron supplementation approach using nutritional yeast containing a FHC–iron complex that effectively repleted iron-deficient rats and monkeys.[109] Testing this product in humans is clearly an imperative. Furthermore, a novel NP ferritin-core analogue, iron hydroxide adipate tartrate (IHAT), was demonstrated to be effective at iron repletion and mitigate the unfavourable GI side effects typical of ferrous iron supplementation.[110,111] In iron-deficient pregnant mice, oral IHAT and ferrous sulphate were equally effective at increasing maternal haemoglobin, hepatic iron and total fetal iron, and neither supplement increased biomarkers of oxidative stress.[112] IHAT may be taken up intact by endocytosis at the apical membrane of enterocytes, independent of DMT1,[113] but in vivo verification is necessary to confirm this possibility. A recent double-blind, randomized, placebo-controlled clinical trial in The Gambia compared IHAT (20 mg Fe) to $FeSO_4$ (12.5 mg Fe) and placebo in children 6–35 months with IDA. IHAT was shown to be as efficacious as $FeSO_4$, but with a lower incidence of diarrhoea compared to $FeSO_4$ and no increased adverse events compared to placebo. The authors concluded that IHAT is an affordable and safe iron supplementation strategy that could be advantageous over using iron salts, particularly in low-income countries.[114]

Haem–iron polypeptide

HIP is produced by digesting porcine or bovine haemoglobin with proteolytic enzymes, resulting in a highly soluble haem moiety with short polypeptide chains containing >1% iron.[115] HIP is predicted to be absorbed by the same molecular pathway as dietary haem.[116] This pathway likely involves receptor-mediated endocytosis, export from endosomes and degradation by cytosolic HO1, thus liberating iron from the protoporphyrin ring within the cell[117] (Figure 1C). Iron export would then be mediated by FPN and subject to regulation by hepcidin. Alternatively, HIP, like haem, could be exported (and/or exocytosed) from enterocytes intact (possibly by FLVCR) and then catabolized in the liver. Iron absorption from HIP taken with a meal was higher in 14 test subjects, as compared to ferrous fumarate, and moreover, iron absorption from HIP was higher in those with lower serum ferritin values.[118] Also, in a randomized, controlled trial in adults on peritoneal dialysis, after 6 months of iron supplementation, serum ferritin levels were significantly lower in the HIP group than in an $FeSO_4$ group; however, the cost of HIP was sevenfold higher.[17,18] Further human trials with HIP are clearly necessary and warranted.

Iron–amino acid and iron–peptide chelates and complexes

Early studies on iron biology in experimental laboratory animals established that higher protein intake stimulated intestinal iron absorption, and it was thus hypothesized that protein breakdown products, including peptides and/or AAs, facilitate iron absorption.[20] Certain AAs were also shown to stimulate electrolyte and fluid absorption in conditions requiring oral rehydration.[119] The mechanism of action involved, at least in part, increased expression of electrolyte transporters on the BBM of enterocytes.[120,121] Previous investigations have also exemplified the potential of individual AAs and short peptides to stimulate iron absorption. For example, certain AAs and dipeptides enhanced iron transport in Caco-2 cells, which model the human enterocyte.[122] Moreover, DMT1 knockdown in Caco-2 cells impaired absorption of iron from ferrous *bis*-glycinate (Fe-Gly) (an iron-diglycine chelate), suggesting that iron and glycine disassociated prior to Fe^{2+} being imported by DMT1.[19] Furthermore, blind loop studies were conducted in experimental animals to evaluate the influence of AAs on iron absorption. The duodenum of anesthetized rats was ligated, and $^{59}FeSO_4$ in combination with one of nine different AAs was injected into the intestinal loops. Blood samples were obtained periodically for 1 h thereafter, and ^{59}Fe activity was quantified. Outcomes showed that all tested AAs increased ^{59}Fe absorption and ^{59}Fe in the liver, with asparagine, glutamate, glutamine and histidine being most effective.[20] Another recent investigation found that a four AA (4AA) formulation consisting of aspartate, glutamate, glutamine and glycine: (1) increased DMT1 expression on the BBM of duodenal enterocytes (by immunoblotting); (2) increased ^{59}Fe flux and decreased the K_m for iron absorption in mouse duodenal epithelial sheets mounted in an Ussing chamber; and (3) promoted ^{59}Fe absorption in short-term, oral gavage

studies in mice.[21] Additional experimentation implicated DMT1 as the mediator of increased iron transport in the presence of the four AAs.[21] Another iron–protein complex, IPS, contains 5% ferric iron bound to modified casein (a milk protein), and has been utilized for iron supplementation in humans and animal models, with efficacy similar to $FeSO_4$ being reported.[26,123–125] This formulation purportedly maintains the iron–protein complex in the acidic milieu of the stomach, thus limiting iron interaction with the mucosa and minimizing GI side effects. Ferric iron is subsequently released from the protein matrix at the more neutral pH found within the lumen of the proximal small intestine and then absorbed via the DMT1/FPN pathway (and thus subject to regulation by hepcidin).

Recent iron supplementation studies in humans and experimental animals have been carried out with the aim of comparing traditional iron salt formulations to AA/peptide–iron chelates.[126] One investigation compared the efficacy of an iron–AA chelate, containing 15 mg of iron, to ferrous fumarate, containing 115 mg of iron, in treating IDA in 150 pregnant women when administered daily for 12 weeks starting in the second trimester of pregnancy.[22] The iron–AA chelate and ferrous fumarate resulted in similar levels of iron repletion; however, the iron–AA chelate raised blood haemoglobin levels faster and had better tolerability among participants, with 60% of women receiving ferrous fumarate reporting constipation compared to 41.3% of women receiving the iron–AA chelate. Interpreting these outcomes is challenging, however, since the dose of elemental iron varied significantly between treatment groups. An additional clinical trial compared iron–AA/-short peptide chelates to ferrous sulphate and found no statistical difference in regards to tolerability or adverse side effects.[127] Furthermore, in another recent clinical trial, ferrous *bis*-glycinate (Fe-Gly) was tested for the prevention of IDA in pregnancy. Pregnant women received 25 mg of iron as Fe-Gly or 50 mg of iron as $FeSO_4$ daily ($n = 40$/group) from 15 to 19 weeks of gestation to parturition.[128] Outcomes showed similar efficacy with both forms of supplemental iron. Participants receiving Fe-Gly reported fewer gastrointestinal complications; however, interpretation of this outcome is again challenging since the doses of iron varied by twofold. Moreover, a recent systematic review evaluated clinical trials that tested iron supplementation using ferrous *bis*-glycinate as compared to various iron salts.[129] Fe-Gly was more effective at increasing Hb levels in pregnant women, and fewer adverse GI events were reported.[129] These authors concluded that additional clinical trials comparing Fe-Gly to other iron supplements are required in other, more diverse populations and geographical locations before Fe-Gly could be widely recommended and utilized.

Another important consideration is the mechanism by which AAs/peptides promote the absorption of NHI (Figure 1D). In the gut lumen, iron–AA/–peptide complexation may maintain the solubility of iron and promote the reduction of ferric iron to ferrous iron.[130] These effects would likely promote iron absorption via the DMT1/FPN/hepcidin pathway should the complex disassociate at the surface of enterocytes. Another possibility is that AAs/peptides remain bound to iron and facilitate uptake via AA or peptide transporters (e.g. PEPT1), which, therefore, may not involve DMT1.[130] Another iron–AA chelate mentioned above, Fe-Gly, is produced in the laboratory by the reaction of reduced iron with glycine in the presence of citric acid. The resulting Fe-AA chelate consists of Fe^{2+} bound to two glycine molecules via covalent and co-ordinate covalent bonds.[131] This chelation process creates a stable complex between iron and glycine, enhancing the bioavailability and absorption of iron. Intestinal absorption of Fe-Gly was hypothesized to involve uptake via the dipeptide pathway followed by hydrolysis within intestinal enterocytes (thus liberating free iron). Further clarification of the mechanistic processes involved in AA-/peptide-mediated iron absorption awaits additional experimental evaluation and is the focus of ongoing investigations.

In sum, AA–/peptide–iron chelates and complexes may be advantageous due to better tolerability and more efficient absorption. These properties may be attributed to the fact that iron bound to AAs or peptides is less reactive, less likely to cause mucosal irritation and other adverse GI side effects and less likely to interact with other digestive components, thus increasing bioavailability.[126] The positive outcomes of the studies outlined above collectively provide the rationale for further investigation on the influence of AA/peptides on intestinal iron absorption, with the goal of developing more effective oral iron supplementation approaches.

Liposomal/microparticle, NP oral iron delivery

Liposomes are an effective drug carrier system; their biocompatibility, biodegradability and low toxicity make them suitable for delivering drugs or nutrients. Iron delivery via liposomes is a promising approach to improve iron absorption.[23–25,132] Liposomal iron is prepared by microencapsulation of iron within a liposomal phospholipid bilayer,[25] resulting in nano-sized particles (100–1000 nM in diameter). Microencapsulation is purported to stabilize the inorganic iron atom and increase bioavailability and absorption, while producing fewer negative side effects.[25,132] Liposomal/NP iron is likely absorbed into enterocytes by endocytosis or via the M cell/lymphatic pathway, as detailed below (Figure 1E).[133] In patients with IBD, daily supplementation with oral liposomal iron taken twice daily for 8 weeks (28 mg/day) improved Hb levels, TSAT and serum iron values.[132] Another recent clinical trial evaluated the efficacy of microencapsulated liposomal ferric pyrophosphate containing 14 mg of iron (plus ascorbic acid and vitamin B_{12}) taken twice daily for 12 weeks by women with IDA ($n = 558$). The authors reported a significant increase in Hb levels from 8.71 ± 2.24 g/dL to 10.47 ± 1.69 g/dL; however, the lack of a positive control group makes interpretation challenging.[24] Additionally, sucrosomial iron (SI), which is made up of ferric pyrophosphate covered by a matrix of phospholipids plus

sucrose esters of fatty acids, has also been proposed for oral iron supplementation.[81] In time-course studies monitored up to 5 h, rats administered 5 mg/kg iron as SI (Sideral® RM [SRM, Sucrosomial® Raw Material Iron]) displayed higher iron bioavailability when compared to ferrous pyrophosphate salts.[134] In another study in piglets, SI showed better potential as an iron supplement to treat IDA compared to iron oxide NPs.[135] Furthermore, NP encapsulation of iron, such as in iron oxide NPs[135] and ferric hydroxide-polyphosphate NPs,[136] is another emerging approach to improve iron absorption in oral therapy. As with microencapsulation, NP encapsulation is thought to confer stability and enhance iron absorption with fewer side effects. Rats administered a single oral dose of ferric hydroxide-polyphosphate NPs at 2 mg Fe/kg body weight demonstrated better absorption (1.7-fold higher) relative to $FeSO_4$.[136] Also, a recent study has evaluated the safety and efficacy of iron NPs in humans.[111]

Iron liposomal/NPs and SI may be absorbed into enterocytes via macropinocytosis/endocytosis of whole NPs, followed either by lysosomal degradation and iron release into the cytosol or possibly exocytosis of intact NPs across the BLM.[113,135] Absorption could also be mediated by microfold (M) cells that are present throughout the gut-associated lymphoid tissue of Peyer's patches (Figure 1E).[137] After transfer to the blood, intact iron NPs and SI would likely be taken up by resident tissue (RE) macrophages in the liver and spleen, where the particles could be decomposed, thus liberating free iron for utilization, storage or release into the bloodstream.

Lipophilic iron chelates

Trimaltol iron (ferric maltol) and other lipophilic iron–chelator complexes may provide therapeutic advantages for the treatment of IDA.[138] Such iron-binding molecules were first discovered and tested many years ago,[139] but have only recently been approved for clinical use in humans. Synthetic, lipophilic iron chelators form heteroaromatic complexes with ferric iron, and have been shown to transfer iron across cell membranes and increase iron absorption in experimental animal models. The iron–maltol complex is probably absorbed intact into enterocytes via endocytosis, and the complex is either broken down within enterocytes or in the lamina propria of the intestinal villus (Figure 1E). Any iron liberated from the complex within enterocytes would be exported by FPN and thus subject to regulation by hepcidin. Intact iron-maltol in the interstitial fluids could be taken up by tissue-resident macrophages, in which the complex would be broken down, liberating Fe^{3+}.[138] Ferric maltol was effective at repleting iron-deficient patients with IBD who did not respond to oral iron salt supplementation.[15] In another recent human trial, ferric maltol was effective at repleting iron-deficient IBD patients after 8 days of treatment.[140] Additionally, maltol iron effectively repleted iron-deficient individuals that did not respond to $FeSO_4$ treatment[141] and was superior to $FeSO_4$ in another clinical trial.[142] Overall, ferric maltol treatment appears to be equally effective or better than iron salt formulations, which is an important advance in the investigation of oral iron supplementation.

Hinokitiol, a lipophilic, natural product isolated from the essential oil of the *Chamaecyparis taiwanensis* (Taiwan Hinoki) tree, can chelate iron and other metals. Grillo et al. reported that hinokitiol restored iron transport into, within and/or out of cells lacking functional iron transporters.[143] For example, hinokitiol promoted intestinal iron absorption in DMT1-deficient Belgrade rats and in FPN-deficient flat-iron mice and facilitated haemoglobinization in DMT1- and mitoferrin-deficient zebrafish. These authors proposed that hinokitiol utilizes electrochemical iron gradients to move iron across cellular membranes without the assistance of a membrane protein or transporter. More details about the mechanism were recently described by Ekaputri et al., who showed that hinokitiol acts as a substitute transmembrane iron transporter that releases iron trapped in liver macrophages (Kupffer cells) and forms a complex with iron, which facilitates red blood cell maturation.[144] These findings suggested that the hinokitiol-iron chelate could be utilized to increase iron absorption in individuals who are refractory to oral iron supplementation; also, hinokitiol could enhance the absorption of dietary NHI.

CONCLUSIONS AND FUTURE PERSPECTIVES

Despite decades-long research on oral iron supplementation, ID and IDA remain leading public health concerns worldwide. Recent scientific efforts have led to the development of improved treatment approaches for IDA; however, additional research is required to ensure the efficacy and non-toxicity of newer oral iron formulations that may be more effective at lower doses and produce fewer negative side effects. Also, it may be important to only treat individuals that are iron deficient or anaemic, since early-life iron supplementation of non-anaemic or iron-replete individuals may have negative effects on the gut microbiome,[145] increase the risk of infection and reduce growth in infants[146] and impair cognitive development in children.[147] A detailed understanding of the molecular mechanisms by which various chemical forms of iron are absorbed in the intestine will undoubtedly facilitate the development of improved oral iron supplementation approaches in the future.

AUTHOR CONTRIBUTIONS

JFC and POE-U conceptualized the review and organized its content. POE-U wrote the first draft, and all authors worked on subsequent drafts. All authors provided intellectual input and approved the final, submitted version of the paper.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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