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ORAL IRON SUPPLEMENTS AND IRON ABSORPTION PATHWAYS – SCIENTIFIC RATIONALE AND CLINICAL RELEVANCE

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ABSTRACT

Iron supplements are mainstay for prevention and management of anemia. Women, pregnant or not, in particular are vulnerable, and need regular clinical monitoring and care. A knowledge of different pathways of iron absorption and their regulation, helps in understanding the scientific rationale behind formulation, dosing, and response of different iron supplements. The amount of elemental iron, the absorption of the selected iron supplement, and the hemoglobin rise needed, are the parameters that help calculate the dosing amount and frequency. Conventional iron supplements like ferrous sulphate maybe lower on cost with acceptable efficacy and therefore suitable for initiating therapy especially in low socio-economic strata, but gastrointestinal adverse effects are common, that may compromise response and compliance. Advanced formulations like liposomal iron have shown higher bioavailability and tolerability among iron supplements, maintaining at least comparable efficacy to conventional ferrous supplements, and therefore can be the treatment of choice to initiate therapy in those where cost is not a factor, or as a switch when tolerability, compliance, or rise in hemoglobin and ferritin with conventional iron supplements is not satisfactory. For heme iron, comparative clinical studies are yet to show clinical benefits over conventional ferrous supplements, however it can still serve as another option available when gastro-intestinal side effects like constipation, limit the effectiveness of conventional iron supplements.

KEYWORDS: Iron, Ferrous salts, Ferric, Liposomal iron, Heme iron, Anemia, Hemoglobin.

INTRODUCTION

Iron is the key mineral required for the development of hemoglobin in the red blood cells. Iron can be derived in the diet from both plant and animal sources. All plant and animal derived foods contain non-heme iron, while heme iron is obtained only from animal foods like meat, fish, poultry, and eggs.[1] Heme iron has a higher bioavailability (20-25%) as compared to non-heme iron (10-15%) obtained from green leafy vegetables, nuts and lentils. Overall iron bioavailability is around 15-18% for mixed veg-nonveg diet. Therefore, less than $1/5^{th}$ of dietary iron is absorbed by the body.

Dietary deficiency of iron can lead to development of anemia, and implies a haemoglobin <12g/dL for non-pregnant and lactating women, and <11 g/dL for pregnant women. In India, anemia affects an estimated >40% of the population, considered severe category by WHO, as compared to a global average of around <25%.[2] The prevalence of anemia is 52-57% in women aged 15-49 years, implying 1 in every 2 women is anemic.[3] An estimated 20%-40% of maternal deaths in India are due to anemia. Anemia is a major public health problem in India contributing to maternal and child mortality, reduced physical performance, and adverse impacts on social and economic development.

Iron absorption pathways

The pathways for absorption of heme iron and non heme iron is different in the gut, as shown in Figure 1.[4,5] Iron exists in Fe^{3+} or ferric form in non-heme iron from plants, while it is in Fe^{2+} ferrous form chelated into a complex organic compound in heme iron.

Non-heme iron

Non-heme iron from diet is in ferric form. Ferric iron is insoluble at physiological pH. A lot of the ferric non-heme iron gets reduced to ferrous form in the acidic gastric environment by the action of vitamin C or amino acids.[4] The remaining ferric iron that reaches the duodenum, is reduced to ferrous form by the presence of duodenal cytochrome B (DcytB) at the brush border surface of intestinal cells, that acts as a ferrireductase and also uses vitamin C.

Therefore, vitamin C can enhance absorption of non-heme iron, while hypo or achlorhydria is associated with iron deficiency. Polyphenols in some plants and phytates found in cereals are the most potent dietary inhibitors of non-heme iron absorption, which can be counteracted significantly by the absorption enhanced by vitamin C.

Once in ferrous form, iron is taken up via the divalent metal transporter 1 (DMT1) at the apical surface that transports the ferrous iron into the enterocyte.[6] The DMT1 is regarded as the main transporter of ferrous iron from the gut into the enterocyte. However, this transporter also transports a number of other divalent ions, and there is an order for transport affinity that is possibly Mn>Cd>Fe>Pb-Co-Ni>Zn.[7] Therefore, DMT1 is a competitive and rate-limiting step in iron absorption.

It is interesting to note here that there is also a transporter for ferric iron on the apical surface called β_3-integrin and mobilferrin (β_3I/MF), the latter a calreticulin homologue.[8] Ferric iron being insoluble, and also that most of it gets reduced to ferrous form, this pathway has little physiological relevance and is used when some of the ferric iron is chelated by mucins on the duodenal brush border surface thereby maintaining it in the ferric state, available for transport across this pathway into the enterocyte. In the cytosol, this complex combines with flavin monooxygenase and β_2-microglobulin to form paraferritin (Pf), which has ferric reductase activity resulting in the conversion of the absorbed Fe^{3+} to Fe^{2+}. Recent evidence suggests that the paraferritin complex may also contain DMT1.[9]

Therefore, the intracellular labile iron pool inside the enterocyte is mainly ferrous iron Fe^{2+}. The exit of ferrous iron via the basolateral surface is a regulated process via a carrier protein called ferroportin 1 (FPN1).[10] Since FPN1 is under the influence of hepcidin, this represents another rate limiting step in iron absorption. Increased hepcidin during iron overload and inflammation/infection, decreases iron transport across the enterocyte, and the intracellular iron is stored as ferritin inside the cell that is eventually lost in faeces.[11,12] During iron deficiency states, hepcidin level falls and iron transport and absorption increases. Associated with ferroportin is a transmembrane copper-dependent ferroxidase called hephaestin, that oxidises ferrous Fe^{2+} form to ferric Fe^{3+} that binds to the blood transport protein transferrin.[10]

Heme iron

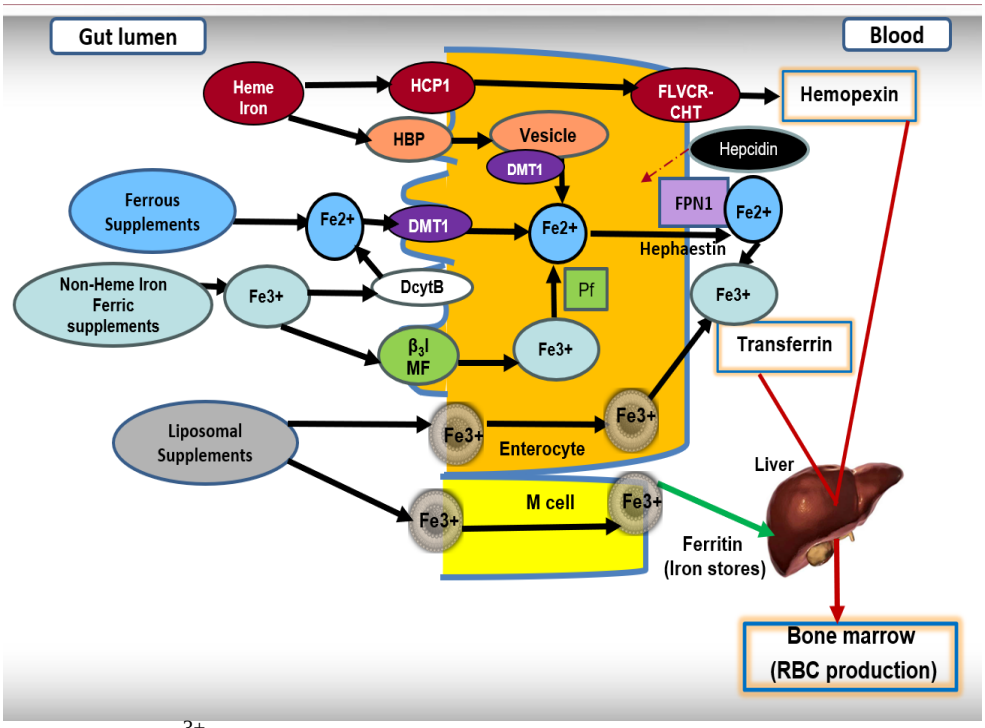
Two possible pathways have been studied and elaborated for heme iron. The first is a receptor mediated endocytosis.[5] A specific high affinity heme binding protein (HBP) has been characterized on the surface of villi in the intestinal cells. Once bound here, the heme iron is internalized as a vesicle that is akin to a lysosome. The heme is then catalyzed by heme oxygenase enzyme, and the released ferrous iron enters the intracellular labile iron pool (common for heme and non-heme iron). The presence of a DMT1 receptor on the surface of

the internalized vesicle is postulated to be the mechanism of intracellular iron release. Heme uptake and binding capacity of HBP increases with iron deficiency.

The other pathway for heme iron absorption is via heme carrier protein (HCP-1) on the enterocyte cell membrane.[13] This appears to be coupled with folate transport (proton-coupled folate transporter/heme carrier protein 1 - PCFT/HCP1). The heme iron entering the cell via this pathway exits the basolateral surface via the FLVCR choline and heme transporter 1, and binds to hemopexin, the transport protein for heme in the plasma. FLVCR acts as an overflow valve for excess heme to prevent cellular toxicity due to oxidative stress.

The different, dual, and relatively non-competitive pathway of absorption may explain the higher bioavailability of heme iron.

Both ferric iron via transferrin, and ferrous iron complex in heme via hemopexin, reach the liver, where iron is stored as ferritin, or released into the circulation to reach the bone marrow via transferrin, based on the rate and need-availability of iron for erythropoiesis.[14,15]



Fe^{2+}: Ferrous Iron; Fe^{3+}: Ferric iron; HCP1: Heme Carrier Protein 1; HBP: Heme Binding Protein; FLVCR-CHT1: Feline leukemia virus C receptor choline and heme transporter 1; DMT1: Divalent Metal Transporter 1; FPN1: Ferroportin 1; DcytB: Duodenal cytochrome B; β_3I: β_3Integrin; MF: Mobilferrin; Pf: Paraferritin

Figure 1: Iron Absorption Pathway.

Oral iron supplements

Oral Iron supplements are usually available in combination with folic acid and vitamin B12, so in order to address both RBC maturation and hemoglobin formation, and prevent masked macrocytic anemia. Non-heme supplements may often also have added vitamin C.

Ferrous supplements

Ferrous salts are the conventional oral iron supplements being used for a long period of time.[16,17] They all more or less show similar iron bioavailability of around 10-15%, as they are absorbed through the DMT1 pathway in the small intestine. The absorption is lower when taken with food, however the tolerability is better. Ferrous salts differ mainly in the amount of elemental iron, as shown in Table 1. The greatest bane of iron salts has been its adverse effects of metallic taste, and gastrointestinal side effects like nausea, indigestion and constipation, seen because of a large portion of unabsorbed iron in the gut, and its irritant property. This leads to loss of efficacy and frequent changes in prescription of ferrous supplements.

Table 1: % Elemental iron in ferrous salts.[16,17]

Ferrous Salt	% Elemental Iron
Ferrous Sulphate (hydrated)	20
Ferrous Sulphate (Desiccated)	32
Ferrous Fumarate	33
Ferrous Bisglycinate	20
Ferrous Ascorbate	15
Ferrous Gluconate	12
Ferrous Succinate	35

To increase hemoglobin (Hb) by 1g%, around 250mg of absorbed iron is needed.[18] Oral iron doses ≥60 mg in iron-deficient women, and doses ≥100 mg in women with iron deficiency anemia IDA, stimulate an acute increase in hepcidin that is maximum after the morning dose, and persists for 24-48 h. Therefore, it is better to give iron as a single morning dose, not to be repeated in afternoon and evening, and to give higher doses >60mg on alternate days, for best absorption and tolerability.[16] With such oral supplements, it can take at least 2-3 months, to increase the Hb by around 2g%, and up to 3-6 months to replenish ferritin stores.[19] While ferrous sulphate may be low on cost, among the ferrous salts, absorption may be highest for ferrous ascorbate due to the intrinsic presence of ascorbic acid.[20] A study showed that at 3 months ferrous ascorbate intake resulted in a significantly higher hemoglobin rise and lower nausea, constipation and epigastric pain as compared to ferrous sulphate.[21] Ferrous ascorbate

also exhibited significantly higher hemoglobin rise at 1 month compared to ferrous fumarate, and iron polymaltose.[22] Overall, ferrous ascorbate and ferrous bisglycinate showed significant and higher rise in hemoglobin and lower gastrointestinal side effects at 2 months compared to ferrous sulphate and ferrous fumarate.[23]

Ferric supplements

Ferric iron is given in the form of chelates or complexes to maintain its state and enable its absorption across the less rate limiting β_3I/MF pathway. These include ferric pyrophosphate, ferric-amino acid chelates like ferric tris-glycine chelate, ferric glycinate, and carbonyl iron.[16,17] These chelated ferric salts often claim better absorption and tolerability as compared to the conventional ferrous salts, however there is lack of adequate scientific studies to support this.[16] The ferric salts are also more expensive than the ferrous salts.

A part of these complexes break-down in the gut releasing the ferric iron that is insoluble, and part of which gets reduced to ferrous state in the stomach and duodenum brush border. In the enterocyte, the iron from these salts anyway enters the common labile ferrous pool, and the final exit from the enterocyte is still dependent on the FPN/hepcidin pathway. Therefore, the overall absorption of ferric salts is in fact considered lower than standard ferrous sulphate and other ferrous salts.[24] Ferric iron coupled with sugar complexes like polymaltose or maltol (iron polymaltose complex -IPC or ferric maltol), gives the ferric iron compound a better stability and portability compared to conventional ferric compounds. Ferric maltol has shown absorption and efficacy that may be comparable to ferrous iron supplements, with a possible reduction in gastrointestinal adverse effects, though this still needs further clinical substantiation.[25] However other studies showed that ferrous salts (ascorbate, fumarate and sulphate) give better hemoglobin rise at 1-3 months compared to IPC.[21,22]

Liposomal iron

This is a newer technology, whereby the iron salt is enclosed in a liposome that refers to micronized particles surrounded by a phospholipid bilayer similar to the cell membrane structure in human cells.[26] The liposomal protection allows the iron to overcome the gastric environment, preventing early degradation and inactivation. This enables direct absorption of liposomal iron through the cell membrane of the enterocyte through the process of diffusion, vesicular fusion or phago-endocytosis.[27] This obviates the need for transport carrier proteins both at the apical and basolateral surface, and their rate limiting/competitive implications and control by hepcidin respectively. Further, liposomal iron can also be absorbed through M

cells in the small intestine without specific transporters, that are richly supplied by lymphatics and thereby, directly deliver the absorbed iron to the liver, enabling more effective replenishing of ferritin stores. The liposomal technology not only enhances iron absorption across the intestine 2.5-4 times as compared to conventional ferrous/ferric salts, but also adds two other benefits – dosing can be flexible with relation to frequency and relation to meals, and gastrointestinal irritation and side effects as well as unpleasant taste are minimized due to the enclosed structure of the iron salt within the liposome, and improved absorption.[26,28]

Most commonly available and studied liposomal iron preparation is ferric pyrophosphate, available as preparations usually containing 28-35mg elemental iron. Studies have shown around a 2g% Hb rise in 2 months, with a 17% rise in hematocrit, and a marked reduction in gastrointestinal side effects with liposomal ferric pyrophosphate when compared to previous conventional iron supplements being taken.[29] In a comparative study in pregnant women, versus ferrous sulphate, liposomal ferric pyrophosphate showed significantly higher Hb and ferritin, compared to ferrous sulphate at 28-32 weeks, and in post-partum period.[30] Liposomal iron has also shown better efficacy than ferrous sulphate in correction of anemia of chronic inflammatory disease in young women. After treatment at 3 months, liposomal ferric pyrophosphate showed a median hemoglobin of 11.5 g% (vs 9.5 g% for ferrous sulphate) and median ferritin was 260 ng/ml (vs 100 ng/ml for ferrous sulphate) with a decrease in ESR and CRP not seen with ferrous sulphate, and minimal side effects as compared to ferrous sulphate.[31] In a study comparing liposomal iron with ferrous sulphate in patients of iron deficiency anemia and inflammatory bowel disease, the increase in Hb was 1.9g% and 0.9g% respectively for liposomal iron and ferrous sulphate at 12 weeks, with more number 62.5% showing an increase of >1g% in liposomal iron group versus 33.3% in ferrous sulphate group.[32]

Sucrosomial Iron (SI) is an innovative oral iron formulation in which ferric pyrophosphate is protected by a phospholipid bilayer plus a sucrester matrix (sucrosome). A study in pregnant women, showed significantly higher Hb and ferritin levels at 28 weeks and in the postpartum period with SI as compared to ferrous iron while fewer women from the SI-28mg developed anemia (10 vs 25%), compared to ferrous iron.[33] Liposomal ferrous salts like ferrous sulphate and ferrous glycinate are also available, however there is no comparative evidence currently.

Heme iron supplements

As already discussed, heme iron may show higher bioavailability due to independent absorption pathways, while the complexed nature and higher absorption may also help reduce gastrointestinal adverse effects. An Indian real-world study showed that in non-pregnant women, the average rise in Hb at 3 months was 1.17, 2.06 and 3.28 (g%), in groups with baseline mild, moderate, and severe anemia, while in pregnant women, the average Hb rise was 2.70 and 3.53 (g%) in groups with baseline moderate and severe anemia.[34] Another study revealed similar results in women who were non-compliant to conventional iron supplements, with moderate anemia who showed Hb rise of 1.15g/dl, 1.48g/dl (non-pregnant, pregnant) and severe anemia who showed Hb rise of 1.56g/dl, 2.75g/dl (non-pregnant, pregnant).[35] The rise in Hb was highly significant in both pregnant and non-pregnant women with baseline moderate and severe anemia, while the treatment adverse event related discontinuation rate was less than 1% in both studies.

The evidence from comparative studies with conventional iron supplements is low.[36] At 6 months, ferrous salts were no different from heme iron in transferrin saturation, and were better in improving ferritin levels in a study in peritoneal dialysis patients with anemia. Heme iron was also comparable in efficacy to higher dose ferrous fumarate in pregnant women, but caused lesser constipation (14 vs 35%). Heme iron tablets are usually available with elemental iron in the range of 6-18mg, and also have the advantage of flexible dosing with relation to frequency and meals.

CONCLUSION

Iron supplements have a central place in management of anemia. Women, pregnant or not, in particular are vulnerable, and require regular follow-up. A knowledge of different pathways of intestinal iron absorption and their regulation, helps in understanding the scientific rationale behind formulation, dosing, and response of different iron supplements. The amount of elemental iron, the approximate percentage of absorption of the selected iron supplement, and the Hb rise needed, are the parameters that help calculate the dosing amount and frequency. Conventional iron supplements especially ferrous sulphate is low-cost with acceptable efficacy and therefore suitable as starting therapy mainly in low socio-economic strata, however these are often accompanied by gastrointestinal poor tolerability reducing compliance and clinical effectiveness. Liposomal iron scores in higher bioavailability and minimal side effects among iron supplements, maintaining at least comparable efficacy to

conventional ferrous supplements, and therefore can be the treatment of choice to initiate therapy in those where cost is not a factor, or as a switch when tolerability, compliance, or rise in hemoglobin and ferritin with conventional iron supplements was not satisfactory. For heme iron, comparative clinical studies are yet to show clinical benefits over conventional ferrous supplements, however it may be considered as another option in the armamentarium for those with moderate to severe anemia, and increased gastro-intestinal side effects like constipation, with conventional iron supplements.

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