Novel iron formulations for the treatment of Iron deficiency and Iron deficiency anemia

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DECLARATION:
Statement of Ethics:
Ethical approval is not required for this study in accordance with local or national guidelines.
Informed consent:
Informed consent is not required for this article in accordance with local or national guidelines.
Conflict of Interest:
The authors have no conflicts of interest to declare.
Funding sources:
No funding sources were used for this report.
Data Availability Statement:
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.
Acknowledgements:
Not applicable

Abstract- **Iron deficiency and iron deficiency anemia are one of the major public health problems affecting the quality of life and contributing to significant morbidity and mortality in the patient population. One of the major obstacles in the treatment of iron deficiency is non adherence to the treatment. Current literature further identifies the side effects of the current iron formulations as the main reason contributing to non adherence and treatment failure, hence making it an urgent need to identify newer drugs with less side effects.**
We have conducted a thorough literature search using Pubmed and Google Scholar and identified four oral and two intravenous iron preparations that yielded the maximum amount of published information. Then a second detailed analysis and information gathering was done on each identified iron preparation focussing on their efficacy and side effect profile.Finally, in this review we reconciled data from over 100 articles within the last ten years to compose subsections with information on each drug. Keywords used were 'Novel iron preparations', 'Ferric carboxy maltose', 'Ferric derisomaltose', 'Sucrosomial iron', 'Ferric citrate', 'Ferric maltol' and 'Liposomal iron'.
Data suggests that Oral formulations such as ferric maltol, sucrosomial iron and liposomal iron are associated with fewer side effects when compared to the conventional drugs. Whereas ferric citrate with its action on FGF 23 helps in the treatment of not only iron deficiency with or without anemia but also hyperphosphatemia in Chronic kidney disease. The gastrointestinal side effects of ferric citrate are higher when compared to the current iron medications. Intravenous formulations such as ferric carboxy maltose and ferric der isomaltose have shown to be effective in quickly correcting the iron levels and require lower doses when compared to other IV formulations.
In conclusion Liposomal and sucrosomial iron are the most effective oral formulations in terms of efficacy, absorption, associated with lower gastrointestinal side effect profile. Ferric citrate can be used in chronic kidney disease due to its favorable action on FGF 23 and phosphate levels. Ferric carboxy maltose and der isomaltose are intravenous formulations useful in cases requiring quick action and lower absorption or tolerance to oral iron.

Introduction and Background:

Anemia is a condition in which the red blood cell mass or hemoglobin (Hb) levels are low(Hb <13 g/dL in males, <12 g/dL in females, <11g/dL during pregnancy), reducing the ability of the blood to transport oxygen to tissues, resulting in weakness, fatigue, impaired concentration and poor work performance [1]. Anaemia has also been linked to preterm labor [2], low birth weight [2,3], child and maternal mortality [2-5], and impaired cognition in children [6,7].Anemia affects approximately 1.93 billion people, with developing countries accounting for 89 percent of the total

[9,10].Pathophysiology of anemia involves many factors of which Iron deficiency is the most common cause [8]. Iron deficiency is one of the leading causes of years lived with disability, according to the Global Burden of Diseases, Injuries, and Risk Factors Study 2016 (GBD 2016)[11].
The pathophysiology of iron deficiency and Iron deficiency anemia is summarized in figure 1[12].

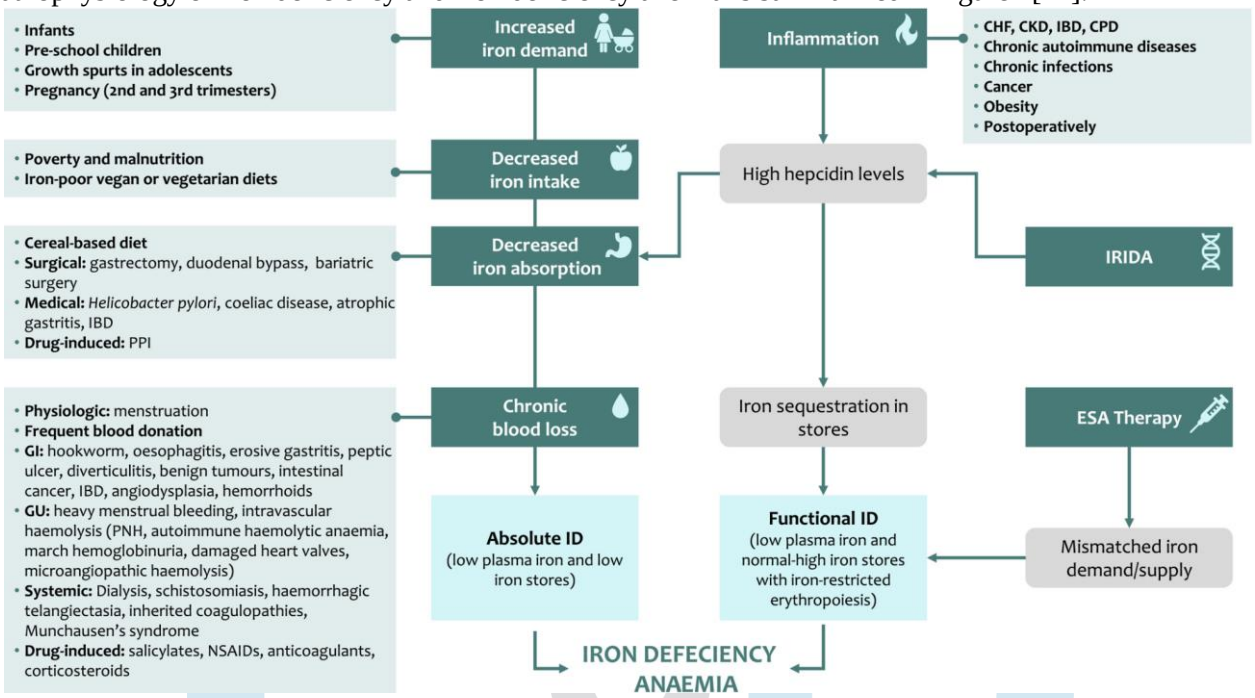
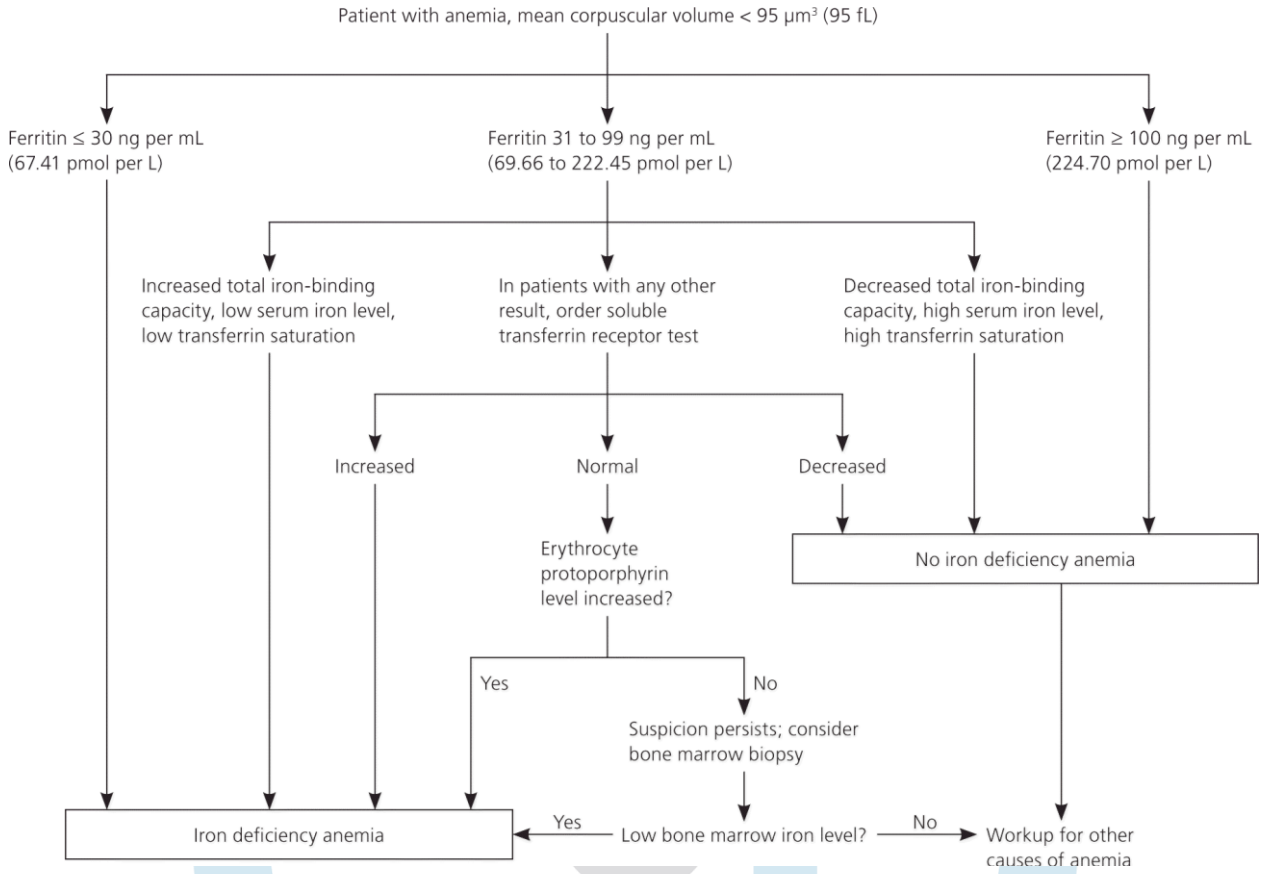


Figure 1

Various factors leading to iron deficiency anemia (IDA). CHF Chronic heart failure, CKD Chronic kidney disease, IBD Inflammatory bowel disease, CPD Chronic pulmonary disease, ESA Erythropoietin stimulating agents, IRIDA Iron refractory iron deficiency anemia, ID Iron deficiency, NSAIDS Non steroidal anti inflammatory drugs, PPI Proton pump inhibitors, PNH Paroxysmal nocturnal hemoglobinuria.

Iron deficiency represents a state of low tissue iron stores without manifesting into anemia. The diagnosis of iron deficiency in the absence of inflammation or infection, is by measuring serum ferritin levels. Ferritin levels of 30 mg/L are considered mild; in the presence of anemia, ferritin levels are usually lower (10-12 mg/L) [13]. When ferritin is unreliable, as it is in inflammation, no specific test exists to assess tissue deficiency in iron (e.g., cardiac or muscle). Clinical diagnosis is based on deterioration of a specific organ's function (for example, the heart) or on unspecific symptoms, the most common of which is fatigue. In some cases, such as heart failure, the diagnosis is based on a positive outcome after iron supplementation[14].
In functional deficiencies and IRIDA, measuring transferrin saturation and hepcidin might be useful [15].
The algorithm for the diagnosis of Iron deficiency anemia is shown in figure 2 [16]



According to WHO guidelines, adults require 120 mg of elemental iron per day for three months to treat iron deficiency anemia; children require 3 mg per kg per day, up to 60 mg per day [17]. After one month of treatment, an increase in hemoglobin of 1 g per dL indicates an adequate response to treatment and confirms the diagnosis. Adults should continue therapy for three months after anemia has been corrected to allow iron stores to replenish.
Available oral and injectable iron preparations are summarized in table 1 [16,18]
The amount of Elemental iron required is calculated by the following formula:
Elemental iron (mg) = 50 x (0.442[Desired Hb- Observed Hb]x lean body mass + 0.26 x lean body weight) [19].

Form	Formulation	Elemental Iron	Adult dose
Sodium ferric gluconate	Solution for injection	12.5 mg per ml	Based on weight and amount of desired change in hemoglobin
Iron dextran	Solution for injection	50 mg per ml	
Iron sucrose	Solution for injection	20 mg per ml	
Ferumoxytol	Solution for injection	30 mg per ml	
Ferrous fumarate	Oral tablet 324 mg	106 mg	1 tablet twice a day
Ferrous gluconate	Oral tablet 300 mg	38 mg	1-3 tablets, 2-3 times a day
Ferrous sulfate	Oral tablet 325 mg	65 mg	1 tablet 3 times a day

Low adherence due to gastrointestinal side effects is one of the most significant challenges in the treatment of iron deficiency anemia with the standard available oral agents. A double blind study conducted on 1496 subjects comparing the incidence of side effects in ferrous sulfate, fumarate and gluconate with placebo has summarized that the incidence

of side effects is similar and higher in all the three groups when compared to the placebo [21]. Low adherence is caused by unabsorbed non-heme iron, which causes ROS(reactive oxygen species)-mediated toxicity in the Gastrointestinal(GI) tract, resulting in abdominal pain, nausea, and constipation [22,23,25]. According to studies conducted in Ethiopia, Kenya, and Nigeria, low adherence due to unwanted side effects was the most common cause of treatment failure, rather than missed doses[22,24]. Hence more patients may receive and tolerate therapy if new oral iron formulations with fewer gastrointestinal side effects are developed.

Minor/moderate infusion reactions (nausea, pruritus, urticaria, flushing, back or thoracic pain) may occur in 1:200 infusions, and more serious reactions (hypotension, dyspnea) may occur in 1:200000 infusions[26]. Although IV therapy appears to be safe in general, the number of reported patients is usually insufficient to detect extremely rare anaphylactic reactions, such as those caused by high molecular weight iron dextran[27]. Their enigmatic pathogenesis has been attributed to the release of iron particles in the circulatory system and has been interpreted as a "complement activation-related pseudoallergy" [28].
The goal of this review is to identify newer iron formulations that may be superior to existing ones in terms of efficacy, adverse effects and number of doses that can be used in clinical practice in the near future.

ORAL FORMULATIONS:

Four oral formulations yielded the most literature output in our search of current data. These are Sucrosomial iron, liposomal iron, ferric citrate and ferric maltol.

Sucrosomial iron

Sucrosomial® iron is an oral formulation that contains ferric pyrophosphate delivered by a phospholipid and sucrester matrix (sucrosome®).

Mechanism of action

Sucrosomial Iron (SI) is composed of ferric pyrophosphate that is encased in a phospholipid and sucrester matrix. By including additional components (such as tricalcium phosphate and starch), the "sucrosome" is formed, providing increased stability and coating. By being gastro-resistant and preventing the contact of iron with the intestinal mucosa, this structure enables SI to reduce the likelihood of any adverse gastrointestinal effects.

Pharmacokinetics and pharmacodynamics

Enterocytes and M cells mediate intestinal Sucrosomial® iron absorption, which primarily takes place as intact particles and happens via the paracellular and transcellular routes. In comparison to oral iron salts, Sucrosomial® iron exhibits superior gastrointestinal tolerability and better intestinal iron absorption[29].

Bioavailability

In a study done by "Taratino et al." Data revealed that Sideral (Sucrosomial Iron) is substantially more bioavailable than ingredients from Lipofer, Sunactive, and Ferrous Sulfate, all of which are microencapsulated with Ferric Pyrophosphate, are used in Caco-2 cell mode[30].
In a study conducted by "Mafodda et al.", efficacy analyses have shown that response to treatment (increase in Hb >2 g/dL from baseline or achieving Hb ≥12 g/dL) was achieved by 71% of patients treated with IV iron and by 70% of patients supplemented with oral sucrosomial iron, with no statistically significant differences[31].

Safety

In comparison to traditional oral iron salts, SI possesses distinct structural, physicochemical, and pharmacokinetic properties, as well as a high rate of iron absorption and great gastrointestinal tolerability. SI is a formulation that is suited for the oral treatment of ID due to these characteristics, even in clinical settings. Even in clinical settings where IV iron is the typical therapeutic choice, SI is well tolerated and highly bioavailable compared to traditional iron salts because of its action in the gastrointestinal system[32].

Clinical implications

Compared to traditional iron salts, SI is extremely bioavailable and well tolerated, especially in clinical settings where IV iron is the standard therapeutic choice. These comprise, among others, ID/IDA patients with cancer, inflammatory bowel illness[33], celiac disease[34], chronic renal disease[35-38], and those having bariatric surgery[39],obstetrics[40],cancer patients on chemotherapy[41].

Liposomal Iron

A new form of oral iron preparation known as liposomal iron, which contains ferric pyrophosphate and is enclosed in a phospholipid and lecithin membrane, exhibits high GI absorption, high bioavailability, and a lower incidence of side effects.

Mechanism of action

Utilizing cutting-edge technology and liposomes as the carrier, iron is directly absorbed in the intestine without coming into contact with the GI mucosa. The micronization procedure reduces the size of ferric pyrophosphate particles, increasing the solubility of iron.

Pharmacokinetics and pharmacodynamics

During processing, the molecule's surface area increases, which accelerates the rate of molecular dissolution.Furthermore, the micronized iron is contained in a lipid bilayer membrane comparable to biological membranes by a process known as microencapsulation.As a result, the liposome created has an iron-containing inner core and an outer bilayer membrane.The outer phospholipid bilayer protects against free radicals, interactions with alkaline fluids, bile salts, intestinal flora, and iron oxidation by mouth and/or stomach enzymes.Liposomes assist in targeted delivery by protecting the iron components in the core from oxidizing and deteriorating [42]. The liposome is directly absorbed in the small intestinal lumen by M cells (microfold cells) which are components of the lymphatic system.The liposome is then endocytosed by macrophages and transported to hepatocytes via the lymphatic system. Hepatocyte lysosomal enzymes dissolve the liposome, releasing the iron for utilization [43].

Liposomal iron (microencapsulated iron pyrophosphate in liposomal form) was utilized in a study to treat 30 postmenopausal females with iron deficient anemia (Haemoglobin, Hb 11.5 g/dL) who had unfavorable side effects from other iron supplements.After 8 weeks of supplementation, hemoglobin and hematocrit levels significantly increased, and the medication was well tolerated, with statistically significant decreases in the majority of the negative effects the patients had previously experienced [44].

Different processes may be helpful in absorption because the liposomal iron's outer membrane shares similarities with biological membranes in terms of composition. The various mechanisms of absorption include: 1) Simple adsorption, which raises the local concentration of liposomal contents at the intestinal membrane and causes absorption by diffusion or transporters; 2) Endocytosis, which leads to the breakdown of the liposomal membrane by intracellular lysosomes; 3) Fusion of the lipid bilayer to the plasma membrane and the release of the contents into the cytoplasm; and 4) Lipid exchange between the liposomal bilayer and plasma cell membraneThus, iron administration by liposomes may prevent iron carrier trafficking mediated by proteins. In the end, iron may be more bioavailable as a result[45].

The levels of malondialdehyde (MDA) and super-oxide dismutase (SOD) can change due to the conventional iron, which can exacerbate the oxidative damage. Liposomal iron is linked to lower MDA levels and higher SOD levels, according to studies. This could reduce the oxidative damage often associated with traditional iron preparations[46]. Traditional non-haem iron absorption may be hampered by dietary inhibitors, for example. In-vivo and in cell culture models have both demonstrated that the phytic acid in diets high in cereals and legumes prevents the absorption of iron. Due to technological advancements in processing and a new method of absorption, liposomal iron preparation provides improved iron distribution without being impacted by dietary inhibitors[47].

The benefits of liposomal iron

-When compared to regular ferric pyrophosphate, liposomal iron showed bioavailability ratios of 2.7 and 3.5, respectively [42].

-Liposomal iron supplements (microencapsulated iron pyrophosphate in liposomal form) were utilized to treat individuals who suffered negative side effects from other iron supplements. After 8 weeks of supplementation, hemoglobin and hematocrit levels increased significantly, and the medication was well tolerated, with statistically significant decline in most of the negative effects previously experienced by the patients [42].

-Conventional iron can alter the levels of malondialdehyde (MDA) and superoxide dismutase (SOD), increasing oxidative damage. According to research, liposomal iron is associated with reduced MDA levels and greater SOD levels. This has the potential to minimize the oxidative damage commonly associated with standard iron preparations [42].

-Traditional non-haem iron absorption may be restricted by things like dietary inhibitors. In-vivo and in cell culture models have both demonstrated that the phytic acid in diets high in cereals and legumes prevents the absorption of iron. Due to technological advancements in processing and a new method of absorption, liposomal iron preparation provides improved iron distribution without being impacted by dietary inhibitors[42].

Comparison with IV iron

Although the final increase in Hb was similar with both treatments, the short-term IV iron therapy increased Hb more quickly than liposomal iron did. The difference between the groups was statistically significant at the beginning of the treatment and vanished by the end.Following iron withdrawal, Hb concentrations in Group with IV iron remained steady while returning to baseline in the Oral liposomal group. In the IV group, there was a larger replenishment of iron reserves. While both groups adherence was comparable, the incidence of adverse events was significantly lower in the oral group (P 0.001).Constipation (4.5%) and diarrhea (4.5%) were the most common adverse effects in the OS group. In the IV group, Headache (18.2%), hypotension (12.1%), and infusion site response (12.1%) were the most common adverse events. There were no significant detrimental effects in either group. An equal proportion of patients in both groups demonstrated adherence at or above the 90% criterion.Although oral liposomal iron has a lower ability than IV

iron gluconate to refill iron storage sites and sustain elevated Hb levels after drug withdrawal, it is not inferior to IV iron gluconate in treating anemia in ND-CKD patients.
However, the low incidence of adverse effects associated with liposomal iron, its usefulness, and the generally cheaper cost of oral medication imply that this formulation may serve as the initial step in treating anemia in individuals with simple CKD[35].

Ferric maltol

A new oral iron replacement medication called ferric maltol is intended to improve iron absorption while minimizing gastrointestinal side effects brought on by unabsorbed free iron.When long-term therapy of chronic iron deficiency is necessary, ferric maltol is thought to be an efficient, practical, and well-tolerated treatment option for iron deficiency and iron-deficiency anemia.A compound of ferric iron and maltol (3-hydroxy-2-methyl-4-pyrone), a naturally occurring sugar derivative present in many foods and extremely selective for iron, is known as ferric maltol.Iron from ferric maltol was absorbed at least as well as ferrous iron, and it was better absorbed from the complex than from straightforward ferric salts . When ferric maltol was taken without food rather than with it, iron absorption was five times higher[48].
Maximum concentrations (Cmax) of iron in the plasma were reached in people with IBD within 2–3 hours of treatment due to the quick uptake . Following oral administration of ferric maltol, blood iron levels significantly increased in adults who were iron deficient, whereas there was significantly less absorption in individuals who were iron replete , indicating effective iron absorption with physiologic modulation of the uptake to fulfill the body's needs. Mean ferritin concentrations increased with time, showing that iron reserves were being replenished[49].
In a study conducted with “Pergola et al.” it was observed that at week 16, ferric maltol significantly raised hemoglobin levels compared to placebo, with an increase in serum ferritin, transferrin saturation, and iron levels while falling with a placebo. Hemoglobin levels were maintained in individuals who continued ferric maltol up to week 52 and rose in those who switched from placebo to ferric maltol.However, the limitation of the study was that there were too many female patients along with the heterogeneity of the ferritin levels[51].

Clinical implications of ferric maltol

In the AEGIS 1/2 IBD research, hemoglobin rose by 2 g/dL at week 12, and this level was maintained upto week 64[52]. A lesser increase in hemoglobin was observed in the CKD trial, which is indicative of the complicated interactions among inflammation, renal disease, and iron control in these individuals . Although the increase was significantly bigger with ferric maltol than with the placebo ($p = 0.01$), individuals with CKD who received treatment for up to 52 weeks saw their hemoglobin levels continue to rise over time.These findings showed that ferric maltol can effectively treat anemia and offer long-term iron supplementation in patients with underlying chronic inflammatory disorders[51].
The effectiveness of ferric maltol was unaffected by the severity of the underlying IBD or CKD activity, as determined by clinical index scores or inflammatory indicators such C-reactive protein, or by patients' usage of proton pump inhibitors for IBD[52-54].By weeks 12 (for IBD) and 16 (for CKD), measurements of ferritin concentration and TSAT show that ferric maltol can increase iron availability[52].In patients with underlying IBD or CKD, continuous ferric maltol therapy either resulted in levels of these iron availability markers rising or remaining stable for as long as a year . Ferritin levels in the IV ferric carboxymaltose arm of the IBD head-to-head study were high at week 12 and had slightly decreased by week 52; in contrast, levels in the ferric maltol arm increased significantly with continued treatment up to week 52, indicating steady replenishment of iron stores over time with this oral therapy[50].
After receiving ferric maltol for 12 weeks, the mean hemoglobin level in the phase IIIB study's pulmonary hypertension patients (n = 22) increased significantly by 2.9 g/dL, from 10.7 g/dL at baseline to 13.6 g/dL; ferritin and TSAT levels also increased significantly from baseline to week 12 (both p 0.001)[55].

Side effects

In studies with a longer-term follow-up, 331 patients were given ferric maltol for longer than 12 or 16 weeks (in the case of IBD or CKD, respectively), and 229 (or 69%) of them finished the course of treatment for up to 64 or 52 weeks (in the case of IBD) respectively. The most frequent causes of treatment discontinuation among patients who left the study early were adverse reactions (34/96 patients (35%) who stopped ferric maltol prematurely compared to 14/53 patients (13%) who stopped the placebo, and 2/19 patients (11%) who stopped IV ferric carboxymaltose), and physician or patient decision (28/96 (29%), 18/53 (34%), and 6/19 (32%), respectively).The most frequent side effects that caused patients with IBD or CKD to stop using ferric maltol during long-term treatment (up to 52-64 weeks) were gastrointestinal, including abdominal discomfort in 2-3% of cases (only in IBD), constipation in 1-2% of cases, diarrhea in 1-3% of cases, and nausea in 1-2% of cases. For comparison, 3% of IBD patients who received a placebo discontinued treatment early due to abdominal pain, and 2% did so due to diarrhea[51][52][56][57].

Conclusion and future implications

Ferric maltol, an oral iron replacement therapy, is approved for the treatment of individuals with iron deficiency with or without anemia in both Europe and the United States[58-60]. Ferric maltol, regardless of the underlying condition, is an effective and efficacious oral therapy for patients with iron deficiency and anemia, according to consistent data in

a variety of contexts, including IBD, CKD, and pulmonary hypertension. Future studies should confirm the clinical effects of ferric maltol on iron insufficiency without anemia or in other situations. Nevertheless, we feel that ferric maltol is a viable therapeutic choice for individuals in whom long-term, practical, and well-tolerated management of anemia is desired, with the exception of those suffering an IBD flare and those needing urgent iron replacement (best accomplished with IV iron).

Ferric Citrate

Ferric Citrate is an oral iron-based compound with distinctive chemical characteristics and a mechanism of action that render it dual effective as a therapy in patients with CKD. It has been approved as a phosphate binder for the control of serum phosphate levels in adult CKD patients treated with dialysis and as an iron replacement product for the treatment of iron deficiency anemia in adult CKD patients not treated with dialysis[61].

Pharmacokinetics and pharmacodynamics

The recommended starting dose of ferric citrate is 1g/day but can go up to 4g/day safely[62].

In research by Sinsakul et al., hemodialysis patients are recruited over the course of two periods: period 1 with patients taking 6 to 15 tablets of a binder with phosphorus levels more than 2.5 mg/dl, and period 2 with patients taking more than or equal to 12 pills per day of a binder with phosphorus levels of ≥ 3.5 mg/dl (ferric citrate consumption of 4.5g per day in period 1 and 6g per day in period 2). After 4 weeks, individuals tolerated ferric citrate well and showed no significant adverse reactions that were related to exposure[63].

Clinical Implications

By lowering FGF-23 and increasing hemoglobin and iron parameters, ferric citrate lowers serum phosphate levels. In a study by Block et al., Comparing ferric citrate with placebo in non-dialysis dependent CKD patients, ferric citrate significantly reduced serum phosphate at 16 weeks only in patients with elevated baseline serum phosphate levels (4.5 mg/dL) compared to placebo ($p = 0.006$) and had no effect on serum phosphate in patients with serum phosphate levels that were within the population reference range. By altering TSAT, ferric citrate partly decreased intact FGF23 and C-terminal FGF23[64].

Ferric citrate decreases the PTH level in patients with non dialysis dependent CKD. A study shows that in patients receiving ferric citrate, serum PTH significantly decreased compared to baseline, with no change in serum FGF23 levels[65].

In research by Maruyama et al., two CKD patient groups receiving hemodialysis were randomly assigned to receive either lanthanum carbohydrate (a non-iron based phosphate binder) or ferric citrate, and the results were monitored for 24 weeks. After 24 weeks, individuals receiving ferric citrate had considerably lower FGF-23 levels than those receiving lanthanum carbohydrate. The levels of blood phosphate and serum PTH did not alter significantly. While lowering the necessary dose of ESA, ferric citrate improved hemoglobin, serum iron, ferritin, and transferrin saturation—effects that were not seen in individuals taking lanthanum carbohydrate[66].

Ferric citrate reduces the need for ESA dosage in CKD patients in addition to controlling phosphate. In a study by Yokoyama et al., patients undergoing haemodialysis and receiving erythropoiesis-stimulating agents (ESA) and non-iron-based phosphate binders were randomly assigned to receive 24 weeks of FC or to continue receiving non-iron-based phosphate binders (control). According to the study, ferric citrate decreased ESA dosage and RDW without significantly affecting hemoglobin levels when compared to control ($p = 0.03$). In comparison to the controls, there was no difference in phosphate levels[67].

Adverse effects

In a study compared with placebo, Ferric citrate contributed to higher rates of gastrointestinal adverse effects such as diarrhea, constipation, and nausea[68].

Intravenous iron:

Intravenous (IV) iron is the preferred treatment for patients with iron deficiency anemia (IDA) who require rapid replenishment of iron stores or in whom oral iron is not tolerated or effective.

Ferric derisomaltose (FDI; also known as iron isomaltoside), ferric carboxymaltose (FCM), Iron sucrose (IS) and ferumoxytol (FER), are successful treatments for iron deficiency anemia.

Iron isomaltoside:

Mechanism of action

Iron isomaltoside 1000 (Monoferric), now known as ferric derisomaltose, is a carbohydrate (isomaltoside) that combines with iron to produce a matrix structure that allows for regulated iron release in the body.

Pharmacokinetics and pharmacodynamics

Iron isomaltoside is available in 1 mL, 5 mL, and 10 mL vials with a concentration of 100 mg/mL elemental iron. Iron isomaltoside 1000 can be dosed in two ways: first, using the Ganzoni formula, which accounts for individual patient

weight, assumed iron stores, and target and actual hemoglobin levels; and second, using a dosing table[table-1], resulting in doses of 1,000 mg, 1,500 mg, or 2,000 mg[69].

Patients < 70 kg l If hemoglobin ≥ 10 g/dL: l If hemoglobin < 10 g/dL:	 1,000 mg 1,500 mg
Patients ≥ 70 kg l If hemoglobin < 10 g/dL: l If hemoglobin < 10 g/dL:	 1,500 mg 2,000 mg

Table-1

Up to 500 mg of iron isomaltoside 1000 can be given as a bolus injection once a week at a rate of 250 mg per minute. If the total needed iron dose as an infusion exceeds 20 mg iron/kg body weight, the dose should be divided into two administrations spaced at least a week apart. A single dose of more than 1,500 mg is not advised.

Kim et al., observed that the pharmacokinetics of iron isomaltoside in IBD patients followed first order kinetics[70].

Clinical Implications

Iron isomaltoside 1000 is indicated for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance or unresponsiveness to oral iron therapy. Iron isomaltoside shows a rapid improvement in hemoglobin. iron, and ferritin when compared to oral sucrose and oral iron.

Iron isomaltoside has been shown to improve the regeneration of hemoglobin levels and prevent anemia in non-anaemic patients undergoing cardiac surgery. Patients received 1000mg of i.v. iron isomaltoside before undergoing cardiac surgery and had an increased hemoglobin concentration one month post-surgery when compared with the placebo group ($p = 0.012$). This tends to improve the anemia, and the patient group that received iron isomaltoside tended to be more non-anaemic than the placebo group[71].

Iron isomaltoside is also beneficial in the treatment of women suffering from severe fatigue following a postpartum hemorrhage. In a clinical study done by Holm et al., a single dosage of iron isomaltoside was associated with a statistically significant and clinically significant drop in physical fatigue within 12 weeks postpartum. It also has a similar safety profile to standard oral iron therapy[72].

Intraoperative infusion of iron isomaltoside was proven to successfully reduce postoperative anemia in patients having total knee arthroplasty. Yoo et al., conducted a study in which the treatment group receiving total knee arthroplasty received iron isomaltoside (dosage 1136 +/- 225) I.V. over 30 minutes during surgical wound closure. When compared to the placebo group, the incidence of anemia at 30 days following total knee arthroplasty was significantly lower in the treatment group, with high levels of hemoglobin, serum ferritin concentration, and transferrin saturation. It indicates the involvement of iron isomaltoside in patient blood management treatments for reducing postoperative anemia[73].

Holm et al., conducted an RCT comparing RBC transfusion with iron isomaltoside in individuals with postpartum anemia. Women with postpartum hemorrhage greater than 1000 ml and hemoglobin levels between 5.6 and 8.1 g/dl were randomly assigned to receive a single dose of 1500 iron isomaltoside and an RBC transfusion. Although there was no significant difference between groups on the fatigue and depression scales, RBC transfusion was associated with greater hemoglobin and lower iron levels on day 1 compared to iron isomaltoside, which had higher hemoglobin and repletion of iron stores in weeks 3–12. With RBC transfusions, reticulocytosis is inhibited, but iron isomaltoside recipients exhibit increased reticulocytosis[74].

A single dosage of iron isomaltoside 1000 mg showed a rapid improvement in hemoglobin from baseline to immediately before the third blood donation in a first-time female blood donor ($p<0.0001$) with a similar safety profile as placebo in a trial conducted by Brask et al.[75].

Comparison:

When compared to orally administered iron, iron isomaltoside has demonstrated a quick rise in hemoglobin. In a study conducted by Gunnar et al., (2017) comparing isomaltoside with oral iron, it was shown that the isomaltoside infusion had a quicker commencement of hemoglobin response ($p = 0.03$) and a sustained impact on hemoglobin in both groups.

Compared to oral iron, iron isomaltoside was better tolerated, and it also significantly decreased fatigue. Both groups had a clinically insignificant incidence of hypophosphatemia[76].
When compared to IV formulations, FDI is demonstrated to be superior. It is less likely to cause fibroblast growth factor 23-mediated hypophosphatemia. In research comparing FDM with FCM,patients receiving FCM showed a higher incidence of hypophosphatemia with elevated PTH than those receiving FDM ($p<0.01$)[77]. Aside from hypophosphatemia, patients using FCM are more likely to have adverse symptoms such as nausea and headaches.
In addition, FDI overcomes iron sucrose to achieve a quick hemoglobin response. When compared to iron sucrose, it can induce a quick hemoglobin response with fewer and higher doses[78]. According to one study, FDI improves quality of life while reducing administration and adverse event expenses as compared to iron sucrose[79]. In addition to the minimal risk of hypophosphatemia, studies suggest that FDI reduces cardiovascular adverse events in individuals with iron deficiency anemia when compared to iron sucrose and ferric carboxymaltose[80].

Adverse Effects:

Further research is required to study the adverse effects of iron isomaltoside.

Ferric carboxy maltose (FCM)

Iron replacement product ferric carboxymaltose is an iron carbohydrate complex with the chemical name polynuclear iron (III) hydroxide 4(R)-(poly-(1o4)-O-D-Dglucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate [81].

Mechanism of action:

Ferric carboxymaltose is a colloidal iron (III) hydroxide complexed with carboxymaltose, an iron-releasing carbohydrate polymer, which enables controlled iron delivery to the targeted tissues [81].

Safety:

There are several studies regarding safety, tolerability and comparative efficacy of ferric carboxymaltose with other intravenous and oral iron formulations [82,83] .
According to a study conducted by Bailie et.al in 2010 [82], administration of FCM (15mg/kg, maximum of 1000mg) over 15 minutes was well tolerated and associated with minimal risk of adverse reactions in patients with iron deficiency anemia [82].

FCM was approved for clinical use in 2007 in Europe but the US Food and Drug Administration (FDA) approved ferric carboxymaltose injection (Injectafer; American Regent) in July 2013 for the treatment of iron-deficiency anemia in adult patients who have an unsatisfactory response to oral iron or who are intolerant of oral iron, as well as in adult patients with non-dialysis-dependent CKD [81,86].

Clinical implications

Ferric carboxymaltose (FCM) is an effective alternative for the treatment of iron deficiency anemia in patients who cannot tolerate or respond to oral iron and it can be administered in fewer doses when compared to other intravenous iron preparations.

FCM in treatment of Iron deficiency anemia:

FCM has the advantage of short treatment period, higher compliance, lower incidence of adverse effects and cost effectiveness when compared to the available standard treatment.

Clinical implication	Dose	Efficacy	Safety	Conclusion
Anemia of pregnancy	20 ml equivalent to 1000 mg iron infusion. Maximum dosage 1500mg [91].	Improvement of hemoglobin in 3 to 6 weeks after infusion [84-91] Fatigue scores improved over 12 weeks [86].	Mild temporary adverse effects noted in a small percentage of women [85,87-89]. No serious adverse effects reported in both mother and fetus [84- 91].	If i.v iron is required in the second and third trimesters of pregnancy, FCM is the drug of choice [89].

Postpartum anemia	FCM with 1000 mg iron dosage [92] . Maximum 2500mg [94].	Improvement in hemoglobin and ferritin levels within 2 weeks of infusion	Mild adverse effects noted. No serious adverse effects reported [92, 94-97]. Serious adverse events in two study participants reported (Raised AST and ALT) [93]. There are no safety concerns in breast-fed infants [92].	FCM is not inferior to the iron sucrose in the treatment of IDA in the postpartum period and it also has the advantage of lower incidence of side effects, short treatment period and cost effectiveness [97].
Restless leg syndrome (RLS) [98-103].	FCM with 500 to 1000 mg iron	IRLS severity scale ,PLM index and sleep quality improvement. Quality of life improved.	No serious adverse effects noted [98-103], Serious adverse effects reported are considered unrelated to treatment [99].	FCM is a safe and effective treatment option for RLS.
Iron deficiency in Chronic kidney disease(CKD) [104, 38,108]	FCM with 200mg iron for HD-CKD patients [106]. FCM with 1000mg iron for non dialysis dependent CKD patients [106].	Improvement in Hb, ferritin and TSAT.	No serious adverse effects related to the intervention found. Transient low phosphorus levels without clinical symptoms were noted in some patients [105].	Correction of iron deficiency anemia by FCM is safe in patients with non dialysis dependent CKD.
Iron deficiency due to inflammatory bowel disease (IBD)	FCM having 1000 mg or 500 mg iron[109] 15 mg/kg of iron in pediatric dose [111]	Improvement in Hb and resolution of anemia	No serious adverse events were noticed. Mild adverse effects in 2 patients which resolved after discontinuation of	FCM is effective in correction of IDA and ID in both adult and pediatric patients with IBD [109-112]. FCM also prevents recurrence of

			the infusion [111,112]	anemia for a long time compared to placebo (single blind study) [110]
Heart failure	FCM with 200 mg to 1000 mg iron[14, 116]	Improvement of quality of life, exercise capacity and lowers hospitalization rates due to worsening HF [14,115 -118]	No serious adverse effects reported [14,113,115,117]	Treatment with FCM in heart failure patients and iron deficiency regardless of anemia improves quality of life with sustained benefits [14,115] There are ongoing clinical trials like HEART FID trial to explore the role of long term treatment with FCM in patients with HFrEF and ID [116, 117]

ID: Iron deficiency, IDA: Iron deficiency anemia, AST: Aspartate aminotransferase, ALT:Alanine aminotransferase, IRLS:International restless legs study group severity rating scale, PLM index: Periodic limb movement index, HD CKD:Hemodialysis dependant chronic kidney disease, TSAT:Transferrin saturation, Hb:Hemoglobin, HEART FID: Ferric carboxy maltose in heart failure with iron deficiency, HFrEF:Heart failure with reduced ejection fraction.

Adverse effects:

The most common side effect of FCM is hypophosphatemia which takes more than 3 months to resolve in the majority of patients. Risk factors for hypophosphatemia are shown to be normal kidney function and more severe iron deficiency anemia [119].

Conclusion

In this article, we aim to compare the available iron formulations in terms of treatment compliance, side effects, and efficacy. We draw the conclusion that IV iron formulations are superior to oral iron in the quick correction of hemoglobin, compliance, and the absence of gastrointestinal side effects after analyzing over 100 publications in the current available literature. FCM and FDI are the best IV formulations currently on the market. FCM has an advantage over FDI since there are no known contraindications to using it during pregnancy, whereas studies are required to use FDI during pregnancy. Despite the possibility of hypophosphatemia with FCM, there aren't many studies that show FDM to be superior over FCM. Sucrosomial iron and liposomal iron are the best among available oral preparations, with others more involved as phosphate binders. We conclude FCM is superior among all the available iron formulations.

Areas of further research:

The formulations we listed in this article are still new with the exception of ferric carboxy maltose and needs more research and clinical trials to evaluate the long term effects of each iron preparation in patients with iron deficiency or iron deficiency anemia. Ferric carboxy maltose has been widely studied and is also used in regular clinical practice. However its effect on morbidity and mortality in patients with chronic conditions still needs to be studied. Although ferric derisomaltose has an advantage over FCM in regards to the risk of hypophosphatemia, further research is required to demonstrate both its use in pregnancy and superiority to FCM.

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