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Evaluating iron replacement therapies in pediatric CKD: A comparative analysis of oral liposomal iron, iron supported lactoferrin and IV iron Dextran

Nancy Kamboj [1], Aayush [2], Rida Asghar [3], Samreen Rizwan Ahmed Shaikh [4], Shelja Sharma [5], Srijamya [6,*] and Munawar Izhar [7]

[1] *Pt. B D Sharma University of Health Sciences, Rohtak, Haryana, India.*
[2] *NCR Institute Of Medical Sciences, Meerut, Uttar Pradesh, India.*
[3] *Lahore Medical and Dental College, Lahore, Pakistan.*
[4] *Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia.*
[5] *Rajasthan University of Health Sciences, Jaipur, Rajasthan, India.*
[6] *Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia.*
[7] *Department of Nephrology, Chicago Hospitals and Collaborative Research Institute, Chicago, Illinois, United States.*

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Abstract

CKD is defined as longstanding kidney damage and reduction in renal function. The global burden of CKD in the pediatric population is 15 per million, with congenital renal anomalies and hereditary disorders being the primary causes. Of these, 10% of patients require RRT. The development of anemia in chronic disease is a significant concern as the disease progresses. This condition exacerbates the pathological state by increasing the risk of infection, inevitably resulting in mortality.

The study aims to establish the comparative analysis of three types of iron replacement therapies including oral liposomal iron, iron supported lactoferrin and IV iron dextran by evaluating their safety and efficacy corresponding to the different stages of CKD in pediatric population.

A comparison between all three variants of iron replacement therapy shows oral liposomal iron provides higher bioavailability and tolerance but effective only in lower CKD stages. In IV iron dextran, rapid iron store replenishment has been observed, but with significant side effects, including the risk of severe hypersensitivity reaction. Conversely, oral iron-supported lactoferrin has demonstrated a maximal iron recovery response after six months of therapy, but with frequent gastrointestinal side effects.

Keywords: Chronic kidney disease; Pediatrics; Iron replacement therapy; Liposomal iron; Iron dextran

1. Introduction

Chronic kidney disease (CKD) is characterized by persistent pathological renal abnormalities due to loss of function or structure of the kidney. For the clinical diagnosis, CKD persists for 3 months or more, or a decrease in estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 mt. sq. [1,2].

CKD affects a large number of the population and its global prevalence, till 2017 was estimated to be 11.1% of the total population [3]. In the pediatric population, the estimated median prevalence is around 65 per million age-related

* Corresponding author: Srijamya

populations, and incidence around 9 per million age-related populations is observed for children <20 years old requiring renal replacement therapy (RRT).

The most common causes of CKD in children are congenital anomalies of the kidney and urinary tract (CAKUT) like renal agenesis, renal hypoplasia, renal dysplasia, and hereditary diseases like polycystic kidney disease, and Alport syndrome. Other causes include nephrotic and nephritic syndrome, vasculitis, benign tumors, and neoplasia [4, 5]. Most patients in the early stages of CKD are asymptomatic. Signs and symptoms manifest as the disease progresses to stage 4 or stage 5. Early symptoms can be nonspecific like nausea, vomiting, pruritis, loss of appetite, lethargy, stunted growth, and anemia [4]. Specific symptoms like proteinuria, oliguria, uremia metabolic acidosis, and electrolyte abnormalities along with azotemia and anuria in End Stage Renal Disease in CKD.

According to Kidney Disease Improving Global Outcomes (KDIGO) CKD Classification 2012, CKD can be classified into 6 categories based on GFR and additionally into 3 stages based on albumin levels in early morning spot urine samples, ultimately dividing each GFR-related category further based on albumin-creatinine ratio [2]. The criteria for classification of CKD are summarized in Table 1.

Table 1 The criteria for classification of CKD

Classification of CKD on the basis of GFR [2]

GFR Category	GFR(ml/min/1.73m²)
G1-NORMAL	≥90
G2-Mild Decrease	60-90
G3a-Mild to Moderate Decrease	45-59
G3b-Moderate to Severe Decrease	30-44
G4-Severe Decrease	15-29
G5- Kidney Failure	<15

Classification of CKD on the basis of Albumin Excretion Rate(AER) and Albumin-Creatinine Ratio(ACR) [2]

Category	AER (mg/24 hr)	ACR (mg/mmol)	ACR (mg/g)
A1-Normal to Mild Increase	<30	<3	<30
A2-Moderate Increase	30-300	3-30	30-300
A3-Severe Increase	>300	>30	>300

Diagnosis of CKD can be made by taking a comprehensive history and assessing various laboratory parameters like GFR, albuminuria, and Imaging studies.

Management of CKD primarily depends on the cause of the CKD, avoiding risk factors, health education, lifestyle adjustments, and/or pharmacotherapy interventions. In severe and refractory cases, Renal Replacement Therapy options like hemodialysis, peritoneal dialysis, and renal transplantation are the treatment options.

As the disease advances, anemia worsens because of a lack of erythropoietin (EPO) and irregular iron control, necessitating the use of supplements. The choice of iron supplement is specific to the patient's profile. The study seeks to compare the effectiveness, safety profiles, and results of Oral Liposomal Iron, IV iron Dextran, and oral iron-supported Lactoferrin and identify the general principles of use and advantages of one over the other in specific conditions related to pediatric CKD.

2. Oral liposomal iron

Liposomes are composite structures of an aqueous core with a phospholipid bilayer. Their utility lies in their ability to mobilize and their flexible configuration, aligning with the biological functioning of the human body [6]. Micro ionized iron is encapsulated in the lipid bilayer membrane to form liposomal iron (Fig 1.1). This microencapsulation process helps with enhanced stability and absorption of iron with less side effects [7].

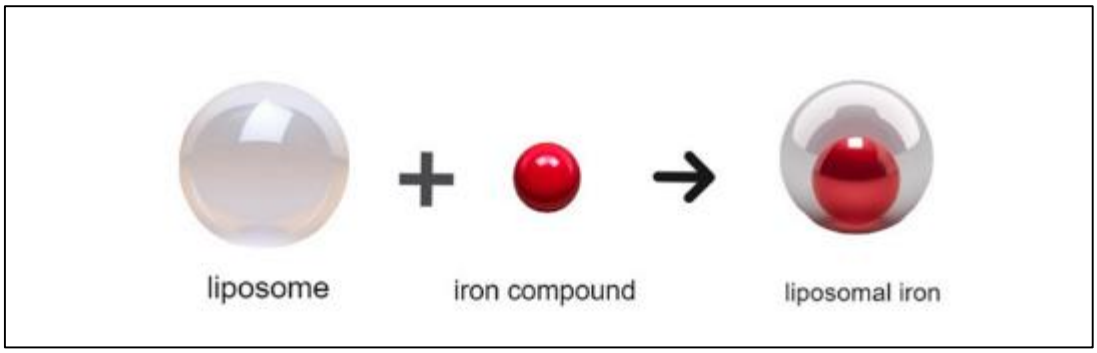

Figure 1 Formulation of liposomal iron

Liposomes are taken up by M cells in the small intestine after passing through the stomach unchanged and reach the liver embodied in macrophages via lymphatics (Fig.1.2). Although Iron transit is decreased with increase in size of liposomes, this mechanism results in enhanced bioavailability and lesser side effects [6].

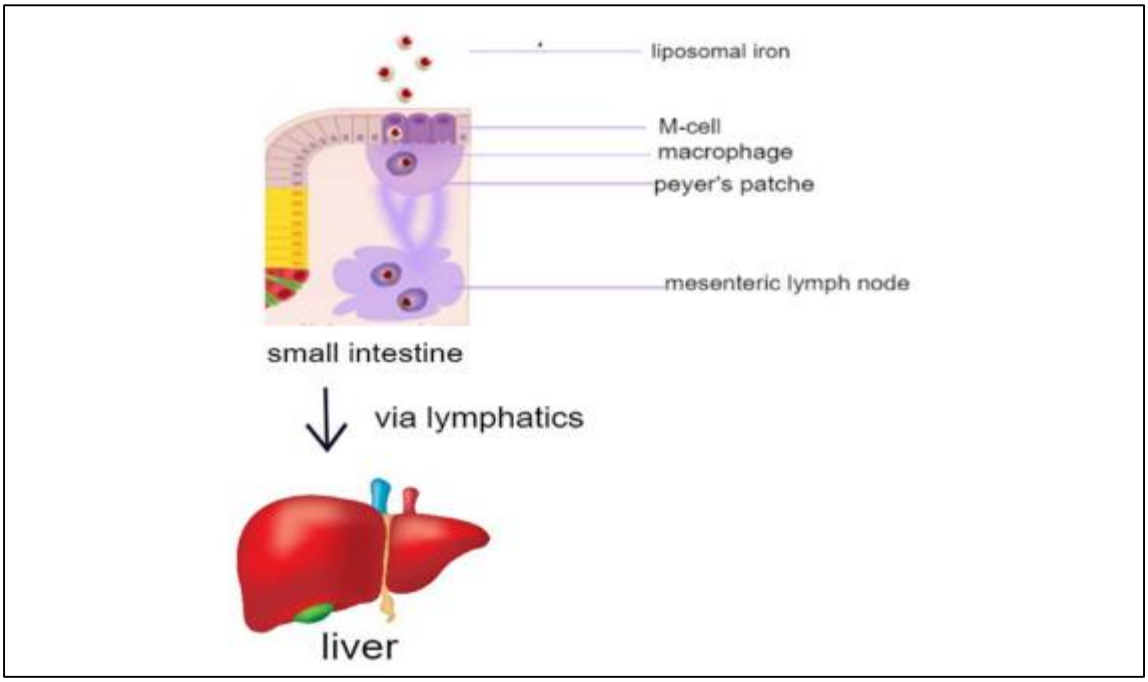

Figure 2 Oral liposomal iron intake

In vitro preparation of liposomal iron supplements with iron salts such as FerrumLek, iron sulfate and iron gluconate have been developed to examine the best encapsulation efficiency, which in turn results in decreased cytotoxicity and reactive oxygen species formation [8]. These qualities are responsible for limiting the adverse effects and better tolerability. Liposomal ferrous glycinate was found to be superior to ferrous glycinate in bioavailability whereas liposomal pyrophosphate iron showed better absorption than free pyrophosphate iron, iron sulfate and iron gluconate [6]. Single blinded randomized controlled trial (RCT) study showed oral liposomal iron to be as effective and safe as IV iron and resulted in decreased requirement of erythropoiesis stimulating agents in pediatric CKD patients [7].

3. Oral iron-supported Lactoferrin

Lactoferrin, a glycoprotein found in various bodily secretions and notably abundant in milk, is known for its robust iron-binding ability. Structurally, lactoferrin outmatches serum transferrin by having a 300-fold higher affinity for iron. This quality allows lactoferrin to retain iron across a wide pH range and contributes to iron homeostasis [9]. The mechanism of oral action of oral Iron-supported Lactoferrin is given in Fig 1.3.

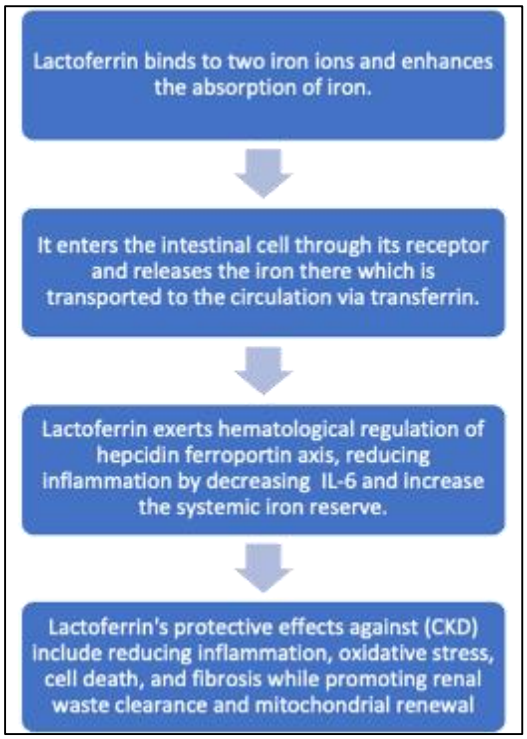

Figure 3 Mechanism of Action of Oral Iron-supported Lactoferrin

A recent study reported a significant improvement in hemoglobin (Hb) levels in CKD patients with lactoferrin supplementation [10]. Over six months following the initiation of lactoferrin intervention, a progressive increase in Hb levels was observed. Specifically, after two months of treatment, patients exceeded the target Hb level of 12 g/dl, with the number of patients reaching this threshold continuing to climb to 15 by the six-month mark. Interestingly, this improvement in Hb levels allowed for a reduction in the erythropoietin dosage, with the dose being halved and subsequently discontinued as patients maintained their normal Hb levels (table 2). Quantitatively, the increase in Hb levels from baseline was substantial and statistically significant each month after six months of lactoferrin administration. These findings highlight lactoferrin's potential as an adjunct treatment associated with CKD, supporting its role in enhancing iron absorption and utilization [11].

Table 2 The gradual increase in Average blood Hemoglobin(g/dl) after the infusion of Oral Lactoferrin in Children with CKD stage 2-4 for 6months

Average value of Blood Hb (g/dl) among the studied cases	**Percentage change found each month** **Percentage Change (Before-After/Before)×100**
1 month: Before: 9.8 µmol/l After: 10.9 µmol/l	11.22%
2 months: Before: 9.8 µmol/l After: 11.9 µmol/l	21.43%

3 months: Before: 9.8 µmol/l After: 12.6 µmol/l	28.57%
4 months: Before: 9.8 µmol/l After: 13.0 µmol/l	32.65%
5 months: Before: 9.8 µmol/l After: 13.3 µmol/l	35.71%
6 months: Before: 9.8 µmol/l After: 13.7 µmol/l	39.80%

4. IV iron Dextran

IV iron dextran restores hemoglobin and iron levels by extracting iron and dextran from the bloodstream. Macrophages absorb iron dextran through endocytosis in the reticuloendothelial system. Acidic lysosomes break down the iron dextran, releasing ferrous iron (Fe[2+]). DMT1 helps transport Fe(2+) into the cell, while ferroportin moves it into the bloodstream or stores it with ferritin.

In RCT by Aggarwal et al demonstrated that IV iron dextran was superior to oral iron sulfate in terms of increasing iron parameters and hemoglobin levels [14]. Iron dextran has been shown to be safe and beneficial in pediatric patients' clinical trials. It has been approved by the FDA for use in children ≥4 months of age, and numerous studies have attested to its beneficial effects in this age group [17,18].

Low molecular weight (LMW) INFeD and High molecular weight (HMW) Dexferrum are FDA approved iron dextran formulations used in adults and pediatrics for iron deficiency anemia (IDA) when oral iron is intolerable or ineffective. Both can be administered via IV push at 50 mg/min or IM injection (<100 mg by Z-Track). They share similar safety profiles, including anaphylaxis warnings and the requirement of a test dose with observation for one hour. Both are compatible with nonlipid parenteral nutrition. Common adverse reactions include hypotension, flushing, chest pain, headache, weakness, dizziness, nausea, vomiting, diarrhea, arthralgia, and malaise.

Before the first complete dose, a test dose of 10 mg for newborns under 10 kg, 15 mg for children between 10 and 20 kg, or 25 mg for adults and children above 20 kg is administered. Patients are monitored for an hour after this test dose. It is recommended to take this precaution before the initial iron dextran administration. The complete dose should be given over 30 seconds (INFeD) or 5 minutes (DexFerrum). Maintenance doses may vary depending on the patient's needs.

Total replacement doses of iron dextran can be calculated using the formula:

$$\text{Dose in mL [50 mg/mL]} = 0.0442 \times \text{LBW [kg]} \times (\text{desired Hgb} - \text{observed Hgb}) + (0.26 \times \text{LBW [kg]})$$

where Hgb represents hemoglobin levels in g/dL and LBW stands for lean body weight.

The HMW iron dextran formulation has been linked to the highest rate of anaphylactic-type events. These severe allergic reactions can cause bronchospasm, low blood pressure, swelling in the mouth or throat, loss of consciousness, excruciating pain, and spasms in the muscles. They can also result in acute respiratory failure and cardiovascular collapse [15,16].

5. Discussion

According to the KDIGO guidelines, CKD is identified by the presence of kidney damage, either structural or functional, or by a decline in GFR below 60 mL/min/1.73-meter square of body surface area for more than 3 months [19]. Anemia

is a common and challenging complication of CKD in children. The primary contributing factors of CKD in pediatric population includes endogenous erythropoietin and iron deficiency. There are ongoing debates regarding the most effective method of administering iron therapy. As far as we know, this is the initial literature review that utilizes up-to-date data to examine the relative effectiveness and safety of different methods and compositions of iron in chronic kidney disease among children.

Several RCT were examined, and specific criteria for inclusion were established to evaluate the safety and effectiveness of the three different iron formulations. Pediatric population (age < 18 years) of CKD Stage greater than Stage 1 receiving EPO therapy with/without hemodialysis were included. Liposomal iron, with higher bioavailability and less side effects, is associated with notable decrease in EPO when given for more than 3 months. It is considered equally efficacious and safe as IV iron dextran and iron supported lactoferrin in children. It can be considered as a therapeutic option for patients requiring RRT [20].

Oral lactoferrin has shown promising results in the treatment of iron-deficiency anemia in pediatric patients with CKD stages 2 to 4. Study reveals when combined with EPO therapy, oral lactoferrin improved various blood parameters such as Hb (39.80% improvement in 6-month therapy), erythrocytes, serum iron, serum ferritin, and total iron binding capacity (TIBC). These results were observed to be more effective when compared to the use of IV iron. Specifically, the cases in Stage 4 exhibited the lowest level of improvement, followed by those in Stage 3, while the highest level of improvement was observed among cases in Stage 2. The effect of oral lactoferrin diminishes as CKD progresses. Therefore, the use of oral iron supported lactoferrin is not recommended for patients with higher CKD stages. There are certain side effects that are commonly observed, such as constipation and GI discomfort [21].

IV Iron dextran, approved by the FDA in children ≥4 months of age, is widely used due to its safety and efficacy in the pediatric population. Studies have shown faster and greater iron replenishment in body via IV dextran therapy in CKD pediatric population as compared to the other two formulations of iron [22]. But it is associated with comparatively serious anaphylactoid like reactions like respiratory compromise and hypotension, which are less frequent in pediatric patients receiving hemodialysis. After iron withdrawal in patients with IV dextran, the hemoglobin remains stable as compared to oral liposomal iron in which it is recovered to baseline.

There are various methods for administering iron, each with its own set of benefits and drawbacks. The patient's profile including CKD Stage, complications etc determine the appropriate method of iron administration. Literature suggests that intravenous iron is superior to liposomal iron or iron-supported lactoferrin for infants who are undergoing hemodialysis. In contrast, oral formulations should be avoided for children with GI issues, as they may result in constipation, nausea, and GI distress. The comparative analysis for side effects and clinical significance of each iron formulation is mentioned in Table 3. There is a need to develop more large scale RCT to facilitate comprehensive and comparative study for the available iron formulations.

Table 3 Efficacy and Clinical significance of different iron formulations in different CKD stages

	Liposomal iron	**Iron supported Lactoferrin**	**IV Iron Dextran**
Adverse Effects	Diarrhea (4.5%) Constipation (4.5%)	Constipation (44.4%) Diarrhea (4%) GI upset (53.3%)	Hypersensitivity reactions (respiratory compromise, hypotension)
Clinical significance	Effective in CKD Stage 5	-More effective in lower CKD stages	-Effective in all stages of CKD

6. Result

With a variety of etiologies, including congenital defects and inherited disorders, CKD in children poses serious health risks. As the disease progresses, specific symptoms like anemia, proteinuria, and electrolyte imbalances become evident. In the early stages of CKD, symptoms are nonspecific. The diagnosis and staging are based on several factors, including imaging investigations, albuminuria, and eGFR.

EPO insufficiency and iron dysregulation cause anemia to worsen in CKD. As the illness progresses, iron supplementation becomes essential. This comparative study assessed the safety and effectiveness of IV iron dextran, oral liposomal iron, and oral iron-supported lactoferrin in different CKD stages in pediatric population.

Oral liposomal iron has enhanced bioavailability and tolerance as compared to IV iron dextran. Oral liposomal iron significantly increases Hb levels compared to baseline (mean increase of 1.9 g/dL).

Hb levels significantly improve with oral iron-supported lactoferrin during a six-month period, allowing for a lower dosage of EPO but cannot be used in higher stage of CKD. Over the course of six months, the average percentage change in blood hemoglobin levels increased gradually, rising from 11.22% at one month to 39.80% at six months.

Although IV iron dextran replenishes iron reserves quickly, there is a chance that patients may experience severe allergic reactions.

Abbreviations

- chronic kidney disease (CKD);
- estimated glomerular filtration rate (eGFR);
- renal replacement therapy (RRT);
- congenital anomalies of the kidney and urinary tract (CAKUT);
- Kidney Disease Improving Global Outcomes (KDIGO);
- erythropoietin (EPO);
- randomized controlled trial (RCT);
- hemoglobin (Hb);
- Low molecular weight (LMW);
- High molecular weight (HMW);
- iron deficiency anemia (IDA);
- total iron binding capacity (TIBC)

7. Conclusion

The comparative analysis done in this study shows significant understanding on how various iron replacement treatments may be used to treat anemia in different stages of CKD in pediatric population. CKD is progressive in nature and can lead to complications like anemia, which can affect treatment outcomes and quality of life in children, there are a lot of challenges associated with the condition.

Comparing oral liposomal iron to conventional IV iron dextran, it was found to be more acceptable and effective choice in terms of absorption. It demonstrated efficacy in raising Hb levels without requiring concurrent EPO drugs, suggesting effective treatment plan for higher stages CKD patients with multiple complications.

Similarly, oral iron-supported lactoferrin showed efficient rise in Hb levels in earlier stages CKD patients over longer time with noticeable GI side effects. This emphasizes its value as a substitute, especially for low stage CKD patients with less complications.

However, IV iron dextran necessitates cautious administration procedures due to the potential for severe hypersensitivity reactions, despite its efficacy in restoring iron reserves within a shortened timeframe.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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