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Optimizing Anemia Management in CKD: A Focus on Ferric Carboxymaltose

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Anemia is commonly associated with chronic kidney disease (CKD) and associated with CKD progression, cardiovascular risk, mortality, poor quality of life and increased hospitalizations. Iron therapy and erythropoiesis stimulating agents (ESAs) are cornerstones in the management of anemia in CKD. There are various challenges associated with anemia management in CKD e.g. undertreatment, target hemoglobin level achievement, paradoxical outcomes with ESAs. Recent years, there has been shift in focus towards utilizing iron therapy compared to ESA in the management of anemia. Ferric carboxymaltose (FCM) is an intravenous iron preparation that has shown efficacy and safety for iron deficiency anemia management in CKD patients. Inj. FCM can be administered as high dose (1000 mg) in single administration and rapidly replenishes iron stores. It

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also avoids the need of ESA and in patients on ESA, it reduces up to 36% of ESA dose requirement. It also provides favorable adherence and overcomes limitations of oral iron (gastrointestinal side effects, reduced intestinal absorption of iron due to hepcidin). FIND-CKD trial has confirmed efficacy and safety of inj. FCM in CKD patients not on dialysis. However, REVOKE trial with iron sucrose in similar patient population was terminated early due to higher risk of serious adverse events observed in the iron sucrose group. Recent data indicating significantly less liver iron concentration with inj. FCM compared to iron sucrose may explain these apparent paradoxical results of FIND-CKD and REVOKE trials. Inj. FCM is also associated with less release of labile iron compared to iron sucrose and has not been associated with acute endothelial dysfunction unlike iron sucrose. Routine intravenous FCM treatment in an outpatient clinic of non-dialysis dependent (NDD)-CKD patients result in better correction of iron-deficiency anemia when compared to oral ferrous sulfate. Early treatment of anemia with inj. FCM has potential to improve outcomes. Inj. FCM will be beneficial to CKD patients with anemia across the spectrum, i.e. both CKD patients not on dialysis as well as patients on dialysis. Overall, the administration of intravenous ferric carboxymaltose appears to be the best answer available for addressing the challenges in the anemia management in CKD.

Keywords: Anemia in chronic kidney disease; injection ferric carboxymaltose; anemia management; intravenous iron.

1. INTRODUCTION

Chronic Kidney Disease (CKD) is an important global public health problem. It is a direct cause of morbidity and mortality. CKD also is an important risk factor for cardiovascular disease. It is highly prevalent with an estimated global prevalence of 9.1% and 697·5 million cases in 2017. “China and India account for almost a third of patients with CKD (132·3 million and 115·1 million cases for China and India respectively in 2017)” [1].

“As per Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline, anemia in adults with CKD is diagnosed when the hemoglobin (Hb) concentration is < 13.0 g/dl in males and < 12.0 g/dl in females” [2]. “One study from United States, estimated overall prevalence of anemia in CKD as 15.4% which was twice compared to general population’s prevalence (7.6%). Further, study reported increase in prevalence as disease advanced (from 8.4% at stage 1 to 53.4% at stage 5)” [3]. “The Indian Chronic Kidney Disease (ICKD) study in mild-to-moderate CKD (estimated glomerular filtration rate (eGFR) 15–60mL/min/1.73m^2, or >60mL/min/1.73m^2 with proteinuria) reported baseline anemia prevalence of 64.9% (n= 2539, total n=4056)” [4]. Another study from tertiary care hospital from India reported high prevalence of 82.4% among CKD patients (n= 589, total n= 715) [5]. Thus, anemia is commonly associated with CKD.

The causes for anemia in CKD can be multifactorial. The reasons include relative erythropoietin deficiency, iron deficiency, blood loss, inflammation, nutritional deficits (e.g. Vitamin B12 / folate) [6]. Iron deficiency and relative erythropoietin deficiency can be considered as common reasons for anemia in CKD. “In one Indian study, as high as 67.1% (392/ 584) non dialysis CKD patients with anemia had iron deficiency (functional or absolute) [7]. The causes for iron deficiency in CKD include poor gastrointestinal (GI) dietary iron absorption, blood loss, chronic inflammation and poor hepcidin clearance” [8].

2. IMPORTANCE OF ANEMIA IN MANAGEMENT OF CKD

2.1 Anemia as a Risk Factor for CKD Progression

Hypoxia is a state in which oxygen is not available in sufficient amounts at the tissue level to maintain adequate homeostasis. “Anemia associated with CKD induces and worsens hypoxia” [9]. It is proposed that tissue hypoxia leads to release of cytokines – e.g. transforming growth factor – beta (TGF-β), connective tissue growth factor (CTGF). These cytokines would increase fibrosis activity which results in kidney scarring. This process creates vicious cycle that would aggravate hypoxia and lead to progression of CKD [10]. Increased sympathetic activity due to anemia may also be contributing to CKD progression [11]. (Refer Fig. 1 – Pathophysiological mechanism of anemia leading to CKD progression).

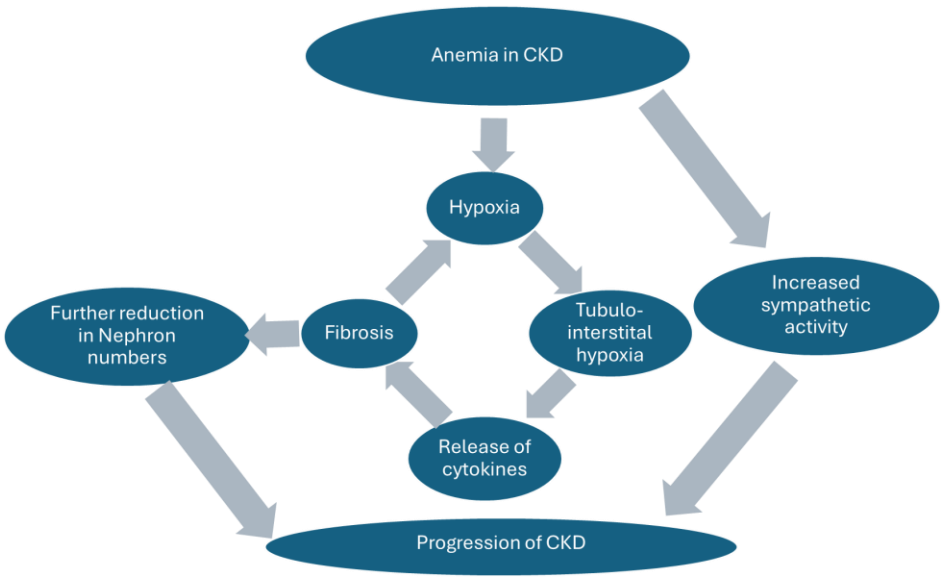

Fig. 1. Pathophysiological mechanism of anemia leading to CKD progression

Various clinical reports support the role of anemia as a risk factor leading to CKD progression. E.g. Chronic Renal Insufficiency Cohort (CRIC) study had 3919 participants of which 1859 (47%) had anemia at baseline. Analysis over median follow-up of 7.8 years revealed that individuals with anemia had higher risk for end stage kidney disease (ESKD) compared with those without (HR, 1.62; 95% CI, 1.24 to 2.11). "Anemia was independently associated with increased risk for incident ESKD and progression of CKD in this analysis" [11]. Another study found that patients with anemia had higher CKD stage advancement (43.5 per 100 patient-years compared to 27.5 per 100 patient-years for those without anemia). The same study also found a 40% estimated glomerular filtration rate (eGFR) decrease was higher in those with anemia versus those without anemia (18.1 versus 7.3 per 100 patient-years). "There was doubling of annual eGFR decline for patients with baseline anemia versus without (−0.6 versus −0.3 mL/min/1.73 m^2, respectively)" [12].

2.2 Anemia and Cardiovascular Risk in CKD

Patients with CKD bear a heavy burden of cardiac disease. Anemia increases the work of the heart and also reduces tissue oxygen delivery; thus, it could exacerbate cardiac injury. The development of left ventricular hypertrophy (LVH) is the most conclusive link between anemia and heart disease. Levin et al. studied 175 patients with non–dialysis-dependent CKD and found LVH in 38.9% of patients. "Each 1-g/dL lower Hb concentration was associated with 6% greater LVH in the study" [13]. "This is significant because LVH is independently and strongly linked to a higher risk of death" [6].

Cardiorenal syndrome (CRS) includes a spectrum of disorders of the kidneys and heart in which loss of function in one organ contributes to reduced function in the other organ. Anemia often develops in patients with CRS and leads to reciprocal and progressive cardiac and renal deterioration. Anemia is considered as an independent risk factor for the development and progression of both cardiovascular disease (CVD) and CKD. Cardiorenal anemia syndrome is a triad of heart failure, CKD, and anemia. Cardiorenal anemia syndrome is associated with adverse clinical outcomes, increased risk of hospitalization and mortality [14]. "Anemia seems to act as a mortality multiplier; that is, at every decrease in Hb below 12 g/dL, mortality increases in patients with CKD, cardiovascular disease, and those with both" [15].

2.3 Anemia and Mortality Risk in CKD

One systematic review included 191 studies to evaluate association of anemia and mortality (and other clinical outcomes) in CKD. Mean hazard ratios (HRs) (95% CI) for all-cause mortality in patients with CKD on dialysis with Hb <10, 10–12, and >12 g/dL were 1.56 (1.43–1.71), 1.17 (1.09–1.26), and 0.91 (0.87–0.96),

respectively. Similarly, HRs (95% CI) for the risk of all-cause mortality in patients with CKD not on dialysis with Hb < 10 g/dL and 10–12 g/dL were 1.70 (1.42–2.01) and 0.97 (0.92–1.01), respectively. “Authors concluded that anemia was consistently associated with greater mortality in patients with CKD” [16].

2.4 Anemia and Other Outcomes

“Anemia-related symptoms like fatigue, shortness of breath, insomnia, headaches, and reduced mental acuity impact on patients’ quality of life” [6]. “Anemia is also associated with higher hospitalization rates in CKD” [16].

3. CHALLENGES AND PARADOX OF ANEMIA MANAGEMENT IN CKD

Iron management and erythropoiesis stimulating agent (ESA) therapy are commonly used in the management of anemia in CKD.

3.1 Anemia Management in Real World – Challenge of Undertreatment

The effect of anemia in CKD on the clinical end points discussed above (section 2) highlights the importance of optimal anemia management. “In this regard, recent data indicate that CKD patients' anemia may be undertreated. E.g. the Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) reported that in United States, 68.0% of individuals with CKD with a hemoglobin concentration of <11.0 g/dL were not treated with iron or ESAs” [17]. Similarly, ICKD (Indian CKD) cohort (Indian patients with mild to moderate CKD)’s prescription pattern was analyzed (n=3966 with prescription details). Only 772 (31.1%) anemic subjects were taking iron supplements. Over 99% of the prescriptions were for oral iron agents. Only 112 (2.8%) had been prescribed an ESA. “Thus, authors reported low use of iron and ESA therapy in patients with anemia” [18].

3.2 Optimal Hemoglobin Level – Challenge to Define and Achieve, Paradox of Outcomes with ESA Trials

For more than 20 years, there has been debate regarding the "target" Hb for patients receiving ESA therapy. “Strong data from multiple randomized controlled trials indicates that Hb levels above 13 g/dL are harmful” [19-22]. Thus, there is paradox in management – while low hemoglobin (anemia) has poor outcomes, normalization of hemoglobin with ESA has not resulted in better outcomes in randomized controlled trials. The reasons for increased risk with ESA treatment to normal Hb targets are not clear. Very high ESAs doses required to normalize Hb concentrations may be contributing to this paradox. Contrary to expectations, patients who reached higher Hb concentrations in the studies had better outcomes, even though there was an increased risk in the higher Hb target groups. “Higher ESA doses that correlated most strongly with adverse outcomes in the studies” [6]. Guidelines suggest an upper limit of Hb as 11.5 in the USA or 12.0 g/dL in Europe. “The guidelines also stress the importance of individualizing the target haemoglobin” [2,23].

One CKD Outcomes and Practice Patterns Study (CKDopps) study analyzed 2,121 non dialysis (ND) -CKD stage 3-5 patients, at 43 nephrologist-run US and Brazil clinics. Lower Hb was strongly associated with greater CKD progression and mortality, even after extensive adjustment. Findings showed that Hb levels > 12 g/dL were associated with slower progression of CKD, greater survival, higher odds of being physically active, and better health-related quality of life (HRQOL). Additionally, an important finding of this work was that even moderate anemia (Hb levels from 10 to 12 g/dL) was associated with poorer HRQOL, rate of CKD progression, and mortality. Clinicians refrain from treating with ESAs to high Hb levels due to negative outcomes from randomized controlled trials (RCTs). “However, findings from this real-world analysis provide encouragement by indicating that maintaining Hb levels higher than the current recommendations may lead to improved HRQOL and greater physical activity levels, as well as lower risk of CKD progression” [24].

Overall, it appears that CKD patients with anemia, one should attempt to achieve and maintain Hb around 11.5 to 12 g/dL, preferably, if possible, without ESA. It is advisable to individualize the Hb target relative to the patient’s risks, basal conditions and preferences. Physicians need to balance the benefit and risk of therapy and achieve and maintain individual “target” hemoglobin. (Fig. 2A and 2B).

3.3 Challenge to Increase Awareness Regarding Early Anemia Treatment – Potential to Improve Outcomes

Kouji Kawai *et al* analyzed 2 Japanese databases to evaluate early intervention for

anemia in CKD. Patients initiated on long-acting ESA treatment were divided into early (hemoglobin levels ≥9.0 g/dl) and delayed (<9.0 g/dl) treatment groups. Delayed treatment was associated with higher risks of cardiovascular composite outcome, heart failure and all-cause mortality. "The results suggest the importance of early intervention before hemoglobin falls below 9.0 g/dl" [25]. An international study evaluated anemia management and mortality in the early dialysis period. About 53% of these patients had Hb <10 g/dL in Month 1 (<30 days after hemodialysis [HD] start). Despite minimal differences in Month 4 Hb, month 1 Hb was associated with first-year HD mortality (adjusted hazard ratio for 1 g/dL higher Hgb was 0.89; 95% confidence interval: 0.81–0.97). "Further, patients with lower Hb in Month 1 received higher doses of ESA, but not IV iron, over the first 3 months of HD. Compared with Hgb ≥ 11.0 g/dL at HD start, authors observed a 2-fold greater mortality rate for Hgb <8.0 g/dL and an 18–35% greater mortality rate for Hb 8.0–10.9 g/dL" [26]. Thus, more proactive approach to anemia management in advanced CKD may improve first-year survival on HD. Early anemia treatment has possible unrealized opportunities to reduce mortality in the high-risk period after dialysis initiation.

3.4 Limitations of ESA – Focusing CKD Patients not on Dialysis

Use of ESA has been associated with hypertension in CKD patients not on dialysis. One study by Noshad evaluated blood pressure change after erythropoietin injection in predialysis patients. "There was significant increase in mean systolic blood pressure from 133.01 ± 29.80 mm Hg before erythropoietin injection to 154.75 ± 23.96 mm Hg after injection (P = .01)" [27]. Similarly, study by Suttorp *et al* also confirmed the hypertensive effect of ESA. "There was higher requirement of antihypertensive drugs i.e. 0.77 (95% CI 0.63;0.91) more classes of antihypertensive drugs in pre-dialysis care patients with ESA (compared to without ESA)" [28].

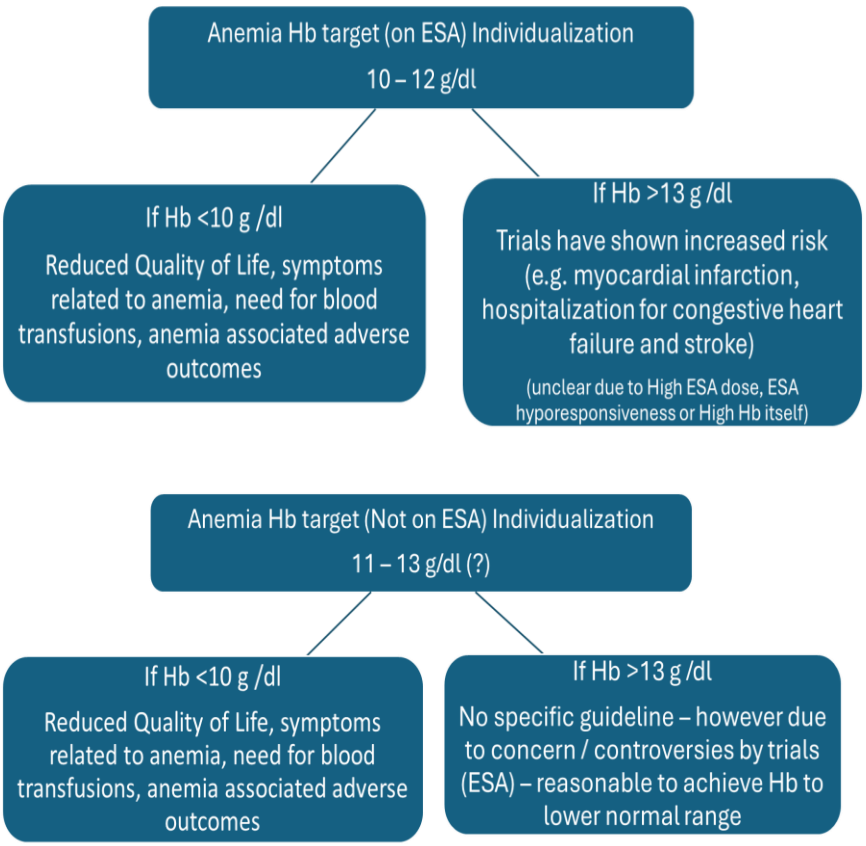

Fig. 2A. Anemia Hb target (on ESA); Fig. 2B. Anemia Hb target (not on ESA)

Pooled cohort of four observational studies was analyzed for risk of end-stage kidney disease (ESKD) and death in patients with non-dialysis CKD with use of different types of ESAs. Results reported increased risk of a composite endpoint of ESKD (dialysis or transplantation) or all-cause death at higher ESA doses. "Authors suggested that ESA treatment should aim at correcting anemia by using the lowest efficacious dose" [29]. Thus, whenever possible, attempt should be made to delay the initiation of ESA in CKD patients not on dialysis. Further, ESA should be used at the lowest efficacious dose.

3.5 Challenges with Frequently Used (Oral) Route of Iron Administration in CKD Patients not on Dialysis

Oral iron is most frequently used for iron deficiency anemia management in CKD patients not on dialysis due to convenience. However, there are several limitations for oral iron:

3.5.1 Frequent gastrointestinal (GI) adverse events

"About 65% patients developed GI side effects in one Indian study of CKD patients not on dialysis. Constipation (46.7%), diarrhea (6.7%), discolored faces (6.7%) GI hemorrhage (4%) were reported GI side effects in the study" [30].

3.5.2 Poor therapeutic adherence

"There is a high rate of discontinuation of treatment with oral iron. Nonadherence rate with daily oral iron has been estimated to ranging from 10 to 32%" [31].

3.5.3 Absorption may be affected due to inflammation (hepcidin)

Hepcidin is the key hormonal regulator of iron homeostasis. It exerts effects on ferroportin, protein that exports iron from the inside of the cell to the outside of the cell. Hepcidin controls the uptake of iron from the gut and its release from the iron stores. Increased hepcidin concentrations block intestinal iron absorption. CKD patients commonly have elevated levels of hepcidin. The likely reasons include decreased kidney clearance of circulating hepcidin and increased levels of systemic inflammation that stimulate hepcidin expression. "The reduced efficacy of oral iron in patients with CKD is explained by hepcidin-induced blockade of iron absorption in the intestine. (Fig. 3)" [32].

3.5.4 Other medications / food can reduce absorption of oral iron

"There is high prevalence of potential drug-drug interactions among CKD patients" [33]. The intestinal absorption of oral iron is reduced when administered with calcium carbonate. This is because calcium carbonate increases the gastrointestinal pH. Oral ferrous sulfate and oral calcium carbonate was the most common potential drug interaction reported in patients with CKD [32]. As calcium carbonate is commonly used as phosphate binder in CKD, this interaction can be of clinical interest. Sodium bicarbonate, another commonly used drug in CKD, also decreases iron absorption. "One study from India in CKD patients also identified One Indian study in CKD patients – iron and calcium carbonate & iron and sodium bicarbonate as potential major severity (Type D) interaction" [34].

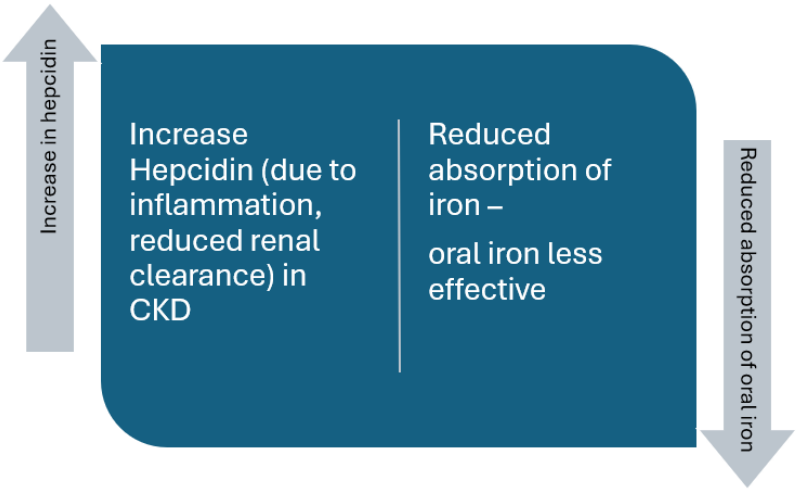

Fig. 3. Hepcidin and reduced efficacy of oral iron

"Food can also interfere with iron absorption, e.g. proteins coming from milk and dairy products impair iron absorption" [35].

4. FERRIC CARBOXYMALTOSE – NEWER GENERATION INJECTABLE IRON

Recent years there has been shift in the focus on anemia management in CKD with more emphasis on iron and less on ESA. "In patients with early CKD and iron deficiency, iron *per se* may be sufficient to improve the anemia" [36].

4.1 Ferric Carboxymaltose Introduction

Ferric carboxymaltose is an intravenous iron preparation that has been authorized for the treatment of iron deficiency in multiple countries. "It is formulated as a colloidal solution of polynuclear iron (III) oxyhydroxide stabilized by the carbohydrate polymer carboxymaltose. Ferric carboxymaltose is specifically formulated to provide controlled delivery of iron to the macrophages of the reticuloendothelial system in the liver, spleen, and bone marrow" [37].

Ferric carboxymaltose had replenished iron stores and corrected anemia in various populations with iron-deficiency anemia, like patients with chronic kidney disease, chronic heart failure, inflammatory bowel disease, postpartum iron-deficiency anemia and perioperative anemia. "Intravenous ferric carboxymaltose was generally well tolerated, with a low risk of hypersensitivity reactions" [37].
A very large dose of ferric carboxymaltose, (equivalent to 1,000 mg of iron) can be administered intravenously within a brief duration of 15 minutes.

4.2 Inj. Ferric Carboxymaltose - Evidence in Iron Deficiency Anemia of CKD

"Several randomized, open-label, multicenter trials have examined the efficacy of intravenous ferric carboxymaltose in patients with chronic kidney disease and iron-deficiency anemia" [38-42].

4.2.1 Inj. FCM studies in non-dialysis dependent CKD

A randomized trial (FIND-CKD) of intravenous ferric carboxymaltose versus oral iron in patients with non- dialysis-dependent CKD was conducted by Iain C. Macdougall *et al*. It was 56-week, open-label, multicenter, prospective study. Patients were randomized (1:1:2) to intravenous (IV) ferric carboxymaltose (FCM), targeting a higher (400–600 µg/L) or lower (100–200 µg/L) ferritin or oral iron therapy. The primary end point was time to initiation of other anemia management (ESA, other iron therapy or blood transfusion) or hemoglobin (Hb) trigger of two consecutive values <10 g/dL during Weeks 8–52. The primary end point occurred in 23.5% patients (n=36) in the high-ferritin FCM and 31.8% patients (n=98) in oral iron groups [hazard ratio (HR): 0.65; 95% confidence interval (CI): 0.44–0.95; p = 0.026]. There was also a significantly greater increase in Hb with high-ferritin FCM versus oral iron (p = 0.014). "Significantly greater proportion of patients achieved an Hb increase ≥1 g/dL with high-ferritin FCM versus oral iron (HR: 2.04; 95% CI: 1.52–2.72; P < 0.001)" [39].

One single center, retrospective observational study was carried out to evaluate the efficacy of FCM compared with oral ferrous sulfate for the treatment of iron-deficiency anemia in non-dialysis-dependent (NDD) -CKD patients (n=349). At 18 months, hemoglobin, serum ferritin and TSAT values increased significantly from baseline in the FCM group compared with the ferrous sulfate group. ESAs dose and rate of infusion decreased only in the FCM group. There was up to 36% ESA dose reduction with inj. FCM while oral ferrous sulfate group reported up to 17% dose increase of ESA. "This study highlights routine intravenous FCM treatment in an outpatient clinic of NDD-CKD patients result in better correction of iron-deficiency anemia when compared to ferrous sulfate" [43].

4.2.2 Switching iron sucrose to ferric carboxymaltose in hemodialysis (HD) patients

Hofman *et al* performed a retrospective audit on records of 221 stable HD patients from different HD centers in the Netherlands, who were switched from iron sucrose to FCM on a 1:1 ratio. Hemoglobin increased while the weekly iron dose was significantly lower when patients received FCM compared to iron sucrose (48 vs 55 mg/week, P = 0.04). Furthermore, the ESA dose was reduced during FCM, while hemoglobin levels increased. "Authors suggest one can correct iron status parameters more efficiently with FCM, at a lower dose, and as such a putative iron overload can be prevented" [44].

4.2.3 Safety and tolerability of inj. FCM

Intravenous ferric carboxymaltose was generally well tolerated and is associated with a low risk of hypersensitivity reactions. “There is lower risk of gastrointestinal adverse effects and results in generally better tolerability than oral ferrous sulfate” [37].

4.3 Paradox in FIND-CKD and REVOKE Trial Results – Recent Findings Providing Explanation

In the FIND-CKD trial of FCM (as discussed above), there was no difference in cardiovascular or infectious events between FCM and oral iron group. However, REVOKE trial with iron sucrose was terminated early. REVOKE trial randomly assigned patients with stage 3 and stage 4 CKD and iron deficiency anemia to either oral ferrous sulphate or intravenous iron sucrose. The independent Data and Safety Monitoring Board observed less chance of finding differences in the primary outcome (measured glomerular filtration rate), along with a higher risk of serious adverse events in the iron sucrose group. There was a higher incidence rate ratio of serious cardiovascular events (2.51, 1.56-4.04) and infections leading to hospital admissions (2.12, 1.24-3.64) in the intravenous iron sucrose group compared to oral iron group. “Thus, there is discrepancy in cardiovascular events and infections between FIND-CKD and REVOKE trials” [45].

The following recent findings probably explain the paradox.

4.3.1 Significantly less liver tropism for FCM compared to iron sucrose

Dialysis patients with liver iron accumulation experience an increase in hepcidin production, which has been linked to an elevated risk of cardiovascular events and mortality. Furthermore, recent studies have demonstrated that dialysis patients with liver iron accumulation experience an increase in the liver fat fraction, which can lead to the development or worsening of fatty liver disease. Rostoker Guy *et al* compared the pharmacokinetics of liver accumulation of ferric carboxymaltose and iron sucrose. Liver iron concentration (LIC) was analyzed in 54 dialysis patients by magnetic resonance imaging. There was a substantial rise in LIC in patients who received intravenous iron sucrose at doses of 1.2 g or 2.4 g ($p < 0.001$, Wilcoxon test). However, there was no significant increase in LIC detected in patients treated with FCM ($p > 0.05$, Wilcoxon test). The absolute differences in LIC were 25 µmol/g in the 1.2 g iron sucrose group compared with only 5 µmol/g in the 1 g ferric carboxymaltose ($p < 0.0001$, Kruskal–Wallis test). These findings may override apparent paradoxical data of FIND-CKD and REVOKE trials. The high safety and potential beneficial consequences of FCM may be due to weak accumulation in liver compared with that of iron sucrose. “Further, avoidance of the development or aggravation of fatty liver disease with FCM might be of value in patients with known non-alcoholic fatty liver disease, overweight patients, and those with dysmetabolic iron overload syndrome” [46].

4.3.2 Labile iron release, endothelial dysfunction and inflammation – less with FCM

Injectable ferric carboxymaltose (FCM) forms stable and strong complexes that tightly bind iron and do not leak significant quantities of labile, non-transferrin-bound iron (NTBI) into the bloodstream prior to being taken up by macrophages. Consequently, the likelihood of experiencing infusion reactions due to labile iron is reduced and inj. FCM is well-tolerated even when high dosages are administered. “Compared with third-generation irons (e.g. inj. FCM) the lower molecular weight iron sucrose complexes have lower complex stability and release larger amounts of NTBI into the blood” [47]. An *in vivo* comparison of labile iron potential of IV iron preparations was conducted by Jahn *et al*. They used Ferrozine®-method for determination of detectable labile iron in human serum as a percentage of total dose given. “The labile iron release with iron sucrose (200mg) was approx. 7 times higher compared to FCM (3.5% vs 0.5%)” [47,48].

There has been concern that IV iron might cause endothelial damage and promote atherosclerosis by generating oxidative stress. “This can have potential consequences of long-term cardiovascular toxicity and nephrotoxicity” [49]. A prospective, crossover study in patients with CKD stages 3-5 (n=31) evaluated acute effects of iron sucrose and inj. FCM on endothelial function by flow-mediated vasodilatation assessment. The arterial reactivity significantly decreased only after iron sucrose infusion ($p=0.01$) but not after FCM ($p=0.27$). “Authors concluded endothelial dysfunction seems to be acutely induced by a single dose of intravenous iron sucrose, but not by FCM” [50].

Table 1. Key features of inj. FCM for iron deficiency anemia in CKD

Key features of inj. ferric carboxymaltose (FCM) for iron deficiency anemia in CKD
Significantly increases hemoglobin and transferrin saturation (TSAT) (compared to baseline)
Rapidly replenishes iron stores
Delays / avoids need of ESA; Reduces dose requirement of ESA (upto 36%)
Overcomes limitations of oral iron (gastrointestinal side effects, poor adherence, decreased gastrointestinal absorption due to hepcidine)
Good safety profile
Favors adherences (High dose in single administration)
Fewer administrations are required to reach target Hb; Fewer doses requirement (compared with iron sucrose)
Less liver iron accumulation – potentially contributing to safety (compared to iron sucrose)
Less release of labile iron (7 times less compared to iron sucrose)
Not associated with acute endothelial dysfunction (unlike iron sucrose)

Prats M et al. evaluated acute and sub-acute effect of ferric carboxymaltose on inflammation and adhesion molecules in patients with predialysis chronic renal failure (n=47). "There were no significant changes in any of the studied inflammatory (C-reactive protein, interleukin-6) or endothelial markers (intercellular adhesion molecule [ICAM] and vascular adhesion molecule [VCAM]) during acute (after 60 minutes) or subacute (after 3 weeks and 3 months) evaluation" [51].

5. CONCLUSIONS

Anemia can have profound impact in CKD as it is associated with CKD progression, cardiovascular risk and poor quality of life. Iron deficiency is one of the common reasons for anemia in CKD and injection iron therapy would be sufficient to increase hemoglobin in most patients. Considering above and as "fate of patients on dialysis, to a great extent, is sealed in predialysis period," proactive approach has potential to improve outcomes. In recent years, there has been a shift from ESA to more of iron use. While oral iron is readily available, inexpensive, and when taken and tolerated is effective. Unfortunately, this combination is an exception rather than rule. Thus, intravenous injection can be considered as preferred choice and inj. ferric carboxymaltose is an attractive option. Single large dose (up to 1000 mg) of inj. FCM can be administrated in a short period. Key features of inj. FCM as described earlier have been summarized in table 1.

Overall, management of anemia in CKD is associated with multiple challenges. Inj. ferric carboxymaltose is an effective and well tolerated option. If used proactively, it has potential to avoid / delay the need of ESA. It also provides adherence as single administration under observation. It also overcomes the limitations of oral iron. Amongst injectable irons, inj. ferric carboxymaltose has favorable profile (less release of labile iron, less liver iron accumulation compared to iron sucrose). Considering the above, inj. ferric carboxymaltose seems to be the best answer currently available to address challenges and paradox associated with anemia in CKD.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, Adebayo OM, Afarideh M, Agarwal SK, Agudelo-Botero M, Ahmadian E. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The lancet. 2020;395(10225):709-33.
2. McMurray J, Parfrey P, Adamson JW, Aljama P, Berns JS, Bohlius J, Drüeke TB, Finkelstein FO, Fishbane S, Ganz T, MacDougall IC. Kidney disease: Improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney International Supplements. 2012:279-335.
3. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PloS one. 2014;9(1): e84943.
4. Kumar V, Yadav AK, Sethi J, Ghosh A, Sahay M, Prasad N, Varughese S, Parameswaran S, Gopalakrishnan N, Kaur P, Modi GK. The Indian chronic kidney disease (ICKD) study: baseline characteristics. Clinical kidney journal. 2022;15(1):60-9.
5. Zaawari A, Tejaswini KL, Davina GD, Singanaveni A. Prevalence of anemia among chronic kidney disease patients in India: a single-centre study. Int J Basic Clin Pharmacol. 2022;11(404):2319-003.
6. Fishbane S, Spinowitz B. Update on anemia in ESRD and earlier stages of CKD: core curriculum 2018. American Journal of Kidney Diseases. 2018;71(3): 423-35.
7. Vikrant S. Etiological spectrum of anemia in non-dialysis-dependent chronic kidney disease: A single-center study from India. Saudi Journal of Kidney Diseases and Transplantation. 2019;30(4):932-42.
8. Hain D, Bednarski D, Cahill M, Dix A, Foote B, Haras MS, Pace R, Gutiérrez OM. Iron Deficiency Anemia in CKD: A Narrative Review for the Kidney Care Team. Kidney Medicine. 2023;100677.
9. Habas Sr E, Al Adab A, Arryes M, Alfitori G, Farfar K, Habas AM, Akbar RA, Rayani A, Habas E, Elzouki A, ERRAYES A. Anemia and Hypoxia Impact on Chronic Kidney Disease Onset and Progression: Review and Updates. Cureus. 2023;15(10): e46737.
10. Nangaku M, Eckardt KU. Pathogenesis of renal anemia. Seminars in nephrology 2006; 26(4):261-268
11. Saraf SL, Hsu JY, Ricardo AC, Mehta R, Chen J, Chen TK, Fischer MJ, Hamm L, Sondheimer J, Weir MR, Zhang X. Anemia and incident end-stage kidney disease. Kidney360. 2020;1(7):623-30.
12. Wittbrodt ET, James G, Kumar S, van Haalen H, Chen H, Sloand JA, Kalantar-Zadeh K. Contemporary outcomes of anemia in US patients with chronic kidney disease. Clinical kidney journal. 2022;15 (2):244-52.
13. Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. Am J Kidney Dis. 1996;27(3):347-354.
14. McCullough PA. Anemia of cardiorenal syndrome. Kidney International Supplements. 2021;11(1):35-45.
15. McCullough PA, Lepor NE. The deadly triangle of anemia, renal insufficiency, and cardiovascular disease: implications for prognosis and treatment. Reviews in cardiovascular medicine. 2005;6(1):1-0.
16. Palaka E, Grandy S, van Haalen H, McEwan P, Darlington O. The impact of CKD anaemia on patients: incidence, risk factors, and clinical outcomes—a systematic literature review. International journal of nephrology. 2020;(1):7692376.
17. Wong MMY, Tu C, Li Y, et al. Anemia and iron deficiency among chronic kidney disease stages 3-5ND patients in the Chronic Kidney Disease Outcomes and Practice Patterns Study: often unmeasured, variably treated. Clin Kidney J. 2020;13(4):613-624.
18. Prasad N, Yadav AK, Kundu M, Sethi J, Jaryal A, Sircar D, Modi GK, Kamboj K, Sahay M, Gopalakrishnan N, Kaur P. Prescription practices in patients with mild to moderate CKD in India. Kidney International Reports. 2021;6(9): 2455-62.
19. Besarab A, Bolton WK, Browne JK et al. The effects of normal as compared with low hematocrit values in patients with

cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339:584–90.
20. Drüeke TB, Locatelli F, Clyne N et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006;355:2071–84.
21. Singh AK, Szczech L, Tang KL et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085–98.
22. Pfeffer MA, Burdmann EA, Chen CY et al.; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019–32.
23. European Best Practice guidelines for the management of anaemia in patients with chronic kidney failure. Nephrol Dial Transplant. 1999;14(Suppl):1–50.
24. Hoshino J, Muenz D, Zee J, Sukul N, Speyer E, Guedes M, Lopes AA, Asahi K, van Haalen H, James G, Dhalwani N. Associations of hemoglobin levels with health-related quality of life, physical activity, and clinical outcomes in persons with stage 3-5 nondialysis CKD. Journal of Renal Nutrition. 2020;30(5):404-14.
25. Kawai K, Ishii M, Kokado Y, Horikawa T, Hoshino J. Outcomes of Early Versus Delayed Anemia Treatment in Nondialysis-Dependent CKD. Kidney International Reports; 2024.
DOI: 10.1016/j.ekir.2024.04.030
26. Karaboyas A, Morgenstern H, Waechter S, Fleischer NL, Vanholder R, Jacobson SH, Sood MM, Schaubel DE, Inaba M, Pisoni RL, Robinson BM. Low hemoglobin at hemodialysis initiation: an international study of anemia management and mortality in the early dialysis period. Clinical kidney journal. 2020;13(3):425-33.
27. Noshad H. Blood pressure increase after erythropoietin injection in hemodialysis and predialysis patients. Iranian Journal of Kidney Diseases. 2013;7(3):220-5.
28. Suttorp MM, Hoekstra T, Mittelman M, Ott I, Franssen CF, Dekker FW. Effect of erythropoiesis-stimulating agents on blood pressure in pre-dialysis patients. PLoS One. 2013;8(12):e84848.
29. Minutolo R, Garofalo C, Chiodini P, Aucella F, Del Vecchio L, Locatelli F, Scaglione F, De Nicola L. Types of erythropoiesis-stimulating agents and risk of end-stage kidney disease and death in patients with non-dialysis chronic kidney disease. Nephrology Dialysis Transplantation. 2021; 36(2):267-74.
30. Agrawal S, Sonawane S, Kumar S, Acharya S, Gaidhane SA, Wanjari A, Kabra R, Phate N, Ahuja A. Efficacy of oral versus injectable iron in patients with chronic kidney disease: a two-year cross-sectional study conducted at a rural teaching hospital. Cureus. 2022;14(7): e27529.
31. Pasupathy E, Kandasamy R, Thomas K, Basheer A. Alternate day versus daily oral iron for treatment of iron deficiency anemia: a randomized controlled trial. Scientific Reports. 2023;13(1):1818.
32. Gutiérrez OM. Treatment of iron deficiency anemia in CKD and end-stage kidney disease. Kidney International Reports. 2021;6(9):2261-9.
33. Olumuyiwa JF, Akinwumi AA, Ademola OA, Oluwole BA, Ibiene EO. Prevalence and pattern of potential drug-drug interactions among chronic kidney disease patients in south-western Nigeria. Niger Postgrad Med J. 2017;24:88-92.
34. Panneerselvam P, Kotakala CM, Ravichandiran D. Drug-Drug Interactions among Chronic Kidney Disease patients in a tertiary hospital. Medica Innovatica. 2021 Jul 1;10(2):34-40
35. López MA, Martos FC. Iron availability: An updated review. International journal of food sciences and nutrition. 2004;55(8): 597-606.
36. Macdougall IC. Anaemia in CKD-treatment standard. Nephrology Dialysis Transplantation 2024;39(5):770-777
37. Keating GM. Ferric carboxymaltose: a review of its use in iron deficiency. Drugs. 2015:101-27.
38. Onken JE, Bregman DB, Harrington RA, et al. Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: the REPAIR-IDA trial. Nephrol Dial Transplant. 2014;29(4):833–42
39. Macdougall IC, Bock AH, Carrera F, et al. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. Nephrol Dial Transplant. 2014;29(11): 2075–84.
40. Qunibi WY, Martinez C, Smith M, et al. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency

anaemia of non-dialysis- dependent chronic kidney disease patients. Nephrol Dial Transplant. 2011;26(5):1599–607
41. Schaefer RM, Khasabov NN, Todorov NG, et al. The efficacy and safety of intravenous ferric carboxymaltose compared to iron sucrose in haemodialysis patients with iron deficiency anaemia (abstract no. MP375). In: 45th Congress of the European Renal Association and the European Dialysis and Transplant Association; 2008.
42. Charytan C, Bernardo MV, Koch TA, et al. Intravenous ferric carboxymaltose versus standard medical care in the treatment of iron deficiency anemia in patients with chronic kidney disease: a randomized, active-controlled, multi-center study. Nephrol Dial Transplant. 2013;28(4):953–64
43. Cirillo L, Somma C, Allinovi M, Bagalà A, Ferro G, Di Marcantonio E, Bellelli S, Dallari LA, Ballo P, Dattolo PC. Ferric carboxymaltose vs. ferrous sulfate for the treatment of anemia in advanced chronic kidney disease: an observational retrospective study and cost analysis. Scientific reports. 2021;11(1):7463.
44. Hofman JM, Eisenga MF, Diepenbroek A, Nolte IM, van Dam B, Westerhuis R, Bakker SJ, Franssen CF, Gaillard CA. Switching iron sucrose to ferric carboxymaltose associates to better control of iron status in hemodialysis patients. BMC nephrology. 2018;19:1-8.
45. Auerbach M, Gafter-Gvili A, Macdougall IC. Intravenous iron: a framework for changing the management of iron deficiency. The Lancet Haematology. 2020;7(4):e342-50.
46. Rostoker G, Lepeytre F, Merzoug M, Griuncelli M, Loridon C, Boulahia G, Cohen Y. Differential pharmacokinetics of liver tropism for iron sucrose, ferric carboxymaltose, and iron isomaltoside: A clue to their safety for dialysis patients. Pharmaceutics. 2022;14(7): 1408.
47. Bhandari S, Pereira DI, Chappell HF, Drakesmith H. Intravenous irons: from basic science to clinical practice. Pharmaceuticals. 2018;11(3):82.
48. Jahn MR, Andreasen HB, Fütterer S, Nawroth T, Schünemann V, Kolb U, Hofmeister W, Muñoz M, Bock K, Meldal M, Langguth P. A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer®), a new intravenous iron preparation and its clinical implications. European journal of pharmaceutics and biopharmaceutics. 2011;78(3):480-91.
49. Kassianides X, Hazara AM, Bhandari S. Improving the safety of intravenous iron treatments for patients with chronic kidney disease. Expert Opinion on Drug Safety. 2021;20(1):23-35.
50. Mehedinti AM, Lipan M, Stancu S, Mircescu G, Capusa C. Acute effects of iron sucrose and iron carboxymaltose on endothelial function in nondialysis chronic kidney disease patients. American Journal of Therapeutics. 2022;29(2):e175-81.
51. Prats M, Font R, García-Ruiz C, Cabré C, Muñoz-Cortés M, Nogués MR, Jariod M, Romeu M, Martínez-Vea A. Acute and sub-acute effect of ferric carboxymaltose on inflammation and adhesion molecules in patients with predialysis chronic renal failure. Nefrología (English Edition). 2013;33(3):355-61.

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