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REVIEW

Iron in Chronic Kidney Disease and End-Stage Kidney Disease—Current Trends and Future Direction

Thomas McDonnell[1,2,*], Philip A Kalra[1,2]

[1]Donal O'Donoghue Renal Research Centre, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Salford, UK
[2]Division of Cardiovascular Sciences, Faculty of Biology Medicine and Health, University of Manchester, Manchester, UK
*Correspondence: thomas.mcdonnell@nca.nhs.uk (Thomas McDonnell)

Abstract

Anaemia is a frequent and serious complication in chronic kidney disease (CKD), affecting both non-dialysis-dependent (NDD) and dialysis-dependent (DD) patients. While erythropoietin (EPO) deficiency is the primary cause, iron deficiency (ID) also plays a crucial role. ID in CKD can be classified as either absolute, resulting from blood loss, or functional, driven by inflammation and elevated hepcidin levels, which trap iron in macrophages and hepatocytes, preventing its use in erythropoiesis. Elevated hepcidin also reduces dietary iron absorption in the gut, making oral iron supplements ineffective, particularly in advanced CKD. This review summarises the available intravenous (IV) iron formulations, discusses diagnostic definitions and treatment thresholds for ID in NDD and DD CKD, and explores potential future therapeutic directions.

Key words: iron deficiency; chronic kidney disease; functional iron deficiency; hepcidin; hypoxia-inducible factor prolyl hydroxylase inhibitors; intravenous iron; oral iron

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Introduction

Iron deficiency (ID) is a significant and frequently occurring complication in patients with chronic kidney disease (CKD), affecting both dialysis-dependent (DD) and non-dialysis-dependent (NDD) CKD. ID is associated with reduced quality of life, increased cardiovascular risk, and higher mortality (Drüeke and Parfrey, 2012; Stauffer and Fan, 2014). The pathophysiology of ID in CKD is complex, with both true ID secondary to blood loss and functional ID resulting from high hepcidin levels, common in CKD due to inflammation, impairing iron absorption and mobilisation (Batchelor et al, 2020). Treatment strategies focus on replenishing iron stores, either through oral or intravenous (IV) iron supplementation. Despite the availability of these treatments, managing anaemia and iron deficiency in CKD remains challenging due to the inflammatory milieu and iron sequestration (Batchelor et al, 2020). This review explores the current understanding of the epidemiology, pathophysiology, and treatment strategies for anaemia and iron deficiency in CKD, with a focus on the role of different iron therapies, including the emerging therapeutic potentials.

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Epidemiology of Anaemia and Iron Deficiency in CKD

Anaemia, defined as haemoglobin (Hb) of <120 g/L in women and <130 g/L in men, is a common complication of both NDD and DD CKD and is associated with worse quality of life (QoL), cardiovascular and mortality outcomes (Drüeke and Parfrey, 2012; Stauffer and Fan, 2014). Evidence from National Health and Nutrition Examination Survey (NHANES) data from 1999–2018 showed the prevalence of anaemia in NDD CKD stage 3–5 was 25.3%. Anaemia prevalence and severity both worsen as the estimated glomerular filtration rate (eGFR) declines. In CKD stages 3A to 5, the respective anaemia prevalence and mean haemoglobin levels are: 17.4% and 140 g/L in stage 3A, 41.0% and 131.4 g/L in stage 3B, 52.4% and 125.7 g/L in stage 4, and 66.1% and 119.7 g/L in stage 5. The proportion of patients with haemoglobin levels below 100 g/L also increases with advancing CKD stage, reaching 12.7% in stage 5 (Kovesdy et al, 2023). In DD CKD, anaemia is even more prevalent; 2021 UK renal registry data shows that 53.8% of people receiving kidney replacement therapy (KRT) had a Hb <100 g/L and >20% had a Hb <90 g/L (UK Renal Registry, 2023). The most significant mechanism contributing to the development of anaemia in CKD is erythropoietin (EPO) deficiency. The kidneys produce EPO in response to cellular hypoxia and stimulate erythropoiesis (Fehr et al, 2004). However, levels are reduced with decreasing nephron mass and dysregulation of the hypoxia-inducible factor-prolyl hydroxylase system leading to anaemia. Another important mechanism of anaemia in CKD is ID. ID in CKD can be the result of both true iron deficiency, "absolute ID", or an impaired utilisation of adequate iron stores, "functional ID" (a consequence of inflammation) (Batchelor et al, 2020). ID in CKD is very common (Fishbane et al, 2009); however, diagnosing and monitoring it in CKD is challenging because traditional biomarkers like ferritin are often elevated in CKD, leading to an underestimation of its prevalence with standard definitions. It is important to recognise and treat ID in CKD. Without adequate iron replacement, erythropoiesis-stimulating agents (ESA) supplementation will be less effective, and adequate iron supplementation allows for lower ESA doses (Macdougall et al, 2014; Yilmaz et al, 2011). This is of clinical importance as high ESA doses increase the risk of worsening hypertension, seizures, vascular access clotting, and are believed to contribute to death and cardiovascular events as well (Babitt and Lin, 2012; Pfeffer et al, 2009).

Pathophysiology of ID in CKD

The majority of the body's total iron stores come from macrophage recycling of destroyed red blood cells (RBCs) (20–25 mg/day), a process regulated by EPO (Batchelor et al, 2020). However, some exogenous iron is required and obtained through gastrointestinal absorption (1–2 mg/day) of dietary iron, although this is only ~10% of the daily iron intake. Nonheme dietary Fe^{3+} is reduced to Fe^{2+} by the cytochrome b-like ferrireductase Dcytb in the small intestine, where it can then be absorbed into the body via divalent metal transporter 1 (DMT1) located on the apical membrane of enterocytes in the duodenum and proximal jejunum. Ferroportin,

located on the basolateral side of the enterocytes, transports iron from the intestine into the bloodstream, where it binds to transferrin. Transferrin then transports iron into macrophages, predominantly in the liver and spleen, for storage, bound to intracellular ferritin. Iron can then be mobilised from the macrophages via ferroportin in the cell membrane to the bone marrow for erythropoiesis (Fig. 1) (Batchelor et al, 2020). This process of iron uptake and mobilisation is regulated by hepcidin, a peptide hormone synthesised (predominately) in the liver. Hepcidin reduces iron absorption in the gut by downregulating DMT1. It promotes the internalisation and degradation of ferroportin, blocking iron release into circulation from enterocytes and preventing the release of stored iron from macrophages, leading to reduced circulating iron levels (Portolés et al, 2021; van Swelm et al, 2020). In a homeostatic fashion, hepcidin production is increased by high iron levels and is suppressed by iron deficiency and hypoxia. However, inflammation and infection can also increase hepcidin production, and hepcidin levels are higher in CKD, as well as other chronic inflammatory conditions such as heart failure and inflammatory bowel disease (Zaritsky et al, 2009).

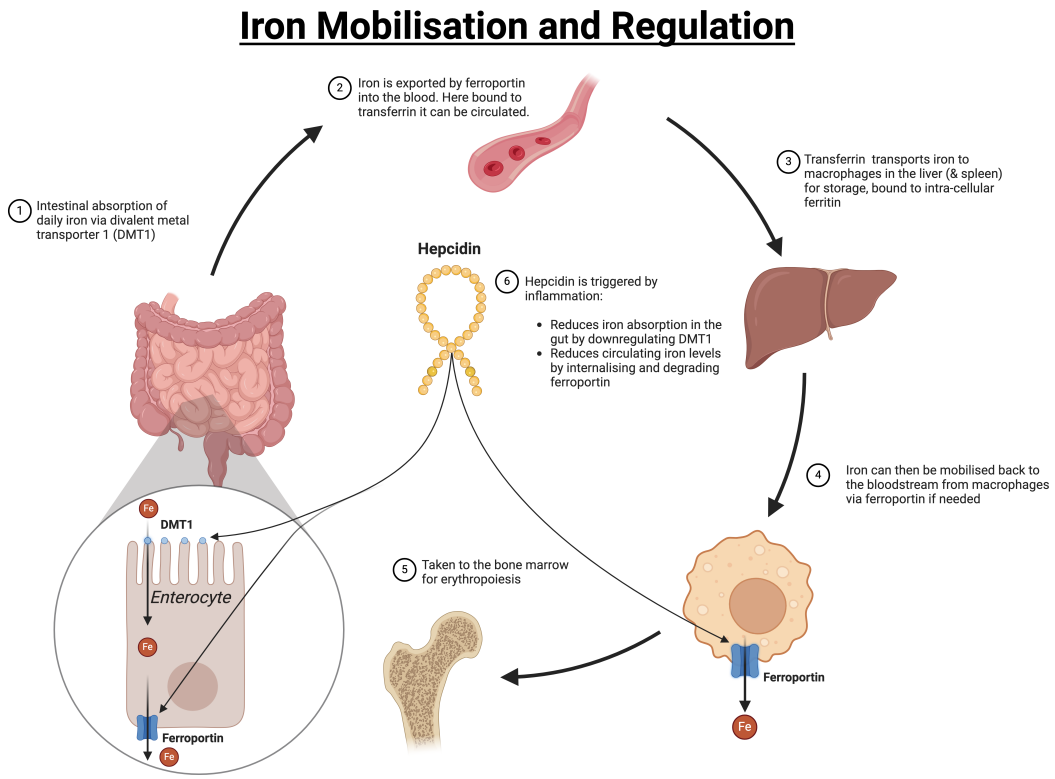

Fig. 1. Iron mobilisation and regulation. This figure illustrates the iron absorption and regulation process. DMT1, Divalent metal transporter 1. Created with BioRender 49 Spadina Ave (Toronto, Canada, https://www.biorender.com).

As stated previously, ID in CKD can be absolute (reduced total body stores of iron) or functional (impaired utilisation). In normal health, typical iron losses are 1–2 mg daily (far higher in menstruating women), with an iron balance maintained by intestinal absorption and mobilisation of stored iron. CKD patients are at

risk of absolute ID as they have increased iron losses in the form of bleeding from uremia-associated platelet dysfunction, phlebotomy, and in haemodialysis patients, blood loss in the extracorporeal circuit (Babitt and Lin, 2012). Higher hepcidin levels in CKD also reduce the gastrointestinal absorption of dietary iron, and exogenous ESA supplementation depletes iron stores by increasing erythropoiesis in a supply-demand mismatch (Batchelor et al, 2020). People with CKD also have a functional iron deficiency, where the total iron stores in the body are adequate for erythropoiesis; however, high hepcidin levels impair the utilisation of these iron stores by preventing the release and transport of macrophage-stored iron (Batchelor et al, 2020; Zaritsky et al, 2009). The result is that exogenous iron is almost ubiquitously required for both NDD and DD CKD-related anaemia and is essential in those receiving ESA to increase its efficient use (Drüeke and Parfrey, 2012).

Diagnosis of ID in CKD

While a bone marrow biopsy (BMB) remains the gold standard for diagnosing ID, it is invasive, painful, and impractical (Grote Beverborg et al, 2018). Therefore, ferritin is commonly used as a surrogate serum biomarker, with levels below 30 µg/L indicating iron deficiency in the general population (Snook et al, 2021). However, ferritin is an acute-phase reactant and serum levels increase in inflammation; during states of inflammation, hepcidin causes the internalisation of ferroportin, trapping iron bound to ferritin within macrophages, leading to elevated ferritin levels and making this threshold unreliable (Snook et al, 2021). Transferrin is the primary iron transporter in the blood. Transferrin saturation (TSAT)% is calculated as the ratio of serum iron to transferrin—reflecting the percentage of transferrin bound to iron. In ID, TSAT% is low (<20%), indicating that only a small proportion of iron is in the circulation and available for erythropoiesis (Snook et al, 2021). As transferrin is a negative acute-phase reactant (its levels decrease during inflammation), the British Gastroenterology Society advocates using the definition of TSAT% <20% and higher ferritin cuff off of <100 µg/L to diagnose ID in the context of inflammation (Snook et al, 2021). However, when using these criteria in people with NDD-CKD, 33% of cases of iron deficiency were missed compared to the gold standard of BMB (Stancu et al, 2010). This suggests that these criteria may not be sensitive enough to identify all cases of ID in CKD.

Diagnosing ID in CKD is a complex and challenging task. The definition can vary depending on dialysis status and whether the ID is functional or absolute. To address this issue, several biomarkers such as CHr (Content of Haemoglobin in Reticulocytes), %HRC (% hypochromic red cells) and RET-He (reticulocyte haemoglobin equivalent) in addition to TSAT% and ferritin have been tested and differing thresholds examined in both DD and NDD CKD. Erythrocyte and reticulocyte indices, %HRC and CHr, provide direct insight into bone marrow iron supply and utilisation and may be more predictive of response to IV iron (Mikhail et al, 2017).

In an RCT of haemodialysis patients, the thresholds for initiating IV iron based on CHr (<29 pg) were compared to traditional markers (ferritin <100 ng/mL or

TSAT% <20%). The study found that using a threshold of CHr <29 pg for iron replacement achieved similar haemoglobin levels while significantly reducing the amount of IV iron administered (Fishbane et al, 2001). Another study evaluated CHr as a diagnostic tool for assessing iron status in haemodialysis (HD) patients, comparing it with TSAT% and ferritin. A CHr <26 pg demonstrated higher sensitivity and specificity for detecting iron deficiency compared to ferritin and TSAT. Additionally, CHr levels were corrected within 48 hours of IV iron administration, making it a useful marker for iron repletion (Fishbane et al, 1997). RET-He and %HRC were also evaluated as markers, with RET-He showing moderate sensitivity and specificity in CKD patients on erythropoietin therapy. %HRC was useful, with a cut-off of >6% identifying iron deficiency (Auerbach et al, 2021; Karunarathne et al, 2022; Peerschke et al, 2014; Urrechaga et al, 2016).

As a result, the National Institute for Health and Care Excellence (NICE) and UK Kidney Association (UKKA) have suggested the following definitions for ID in CKD, ranked by preference, based on availability (Mikhail et al, 2017; Padhi et al, 2015):

- CHr <31 pg
- % HRC >6% (but only if processing of blood sample is possible within 6 hours)
- TSAT <20% and ferritin <100 µg/L (in those with NDD CKD or receiving peritoneal dialysis)
- TSAT <20% and ferritin <200 µg/L (in those receiving haemodialysis (HD))

Functional iron deficiency can also be diagnosed as a TSAT <20% and ferritin >100 µg/L or >200 µg/L in those with CKD not receiving HD and those receiving HD, respectively (Hain et al, 2023).

Oral vs Intravenous Administration

Iron can be administered in oral (PO) or intravenous (IV) form to those with absolute or functional ID of CKD. In the NDD CKD population, PO administration has obvious benefits as no intravenous access is required. However, PO iron can frequently result in gastrointestinal side effects (Düzen Oflas et al, 2020). Guidelines recommend a 1–3-month trial of oral iron in NDD CKD patients, considering factors such as the extent of iron deficiency, ease of venous access, previous response to oral iron, any adverse side effects and overall cost (Padhi et al, 2015).

The FIND-CKD study, a multicentre (and largest) trial comparing PO to IV iron in NDD CKD, randomised 626 participants not on EPO into three groups: IV iron (ferric carboxymaltose (FCM)) with high ferritin targets (400–600 µg/L), low ferritin targets (100–200 µg/L), or oral iron therapy. The primary endpoint—time to initiate other anaemia management or reach a haemoglobin target—was significantly improved in the high ferritin IV group compared to oral iron (hazard ratio (HR): 0.65; $p = 0.026$). No significant differences were seen in cardiovascular events, infection risk, or serious adverse events (Macdougall et al, 2014). Meta-analysis confirms these findings but indicates a higher incidence of allergic reac-

tions with IV iron, though variability exists in the type of IV iron used, and not all studies were powered for adverse events (O'Lone et al, 2019).

In the UK and Europe, the most common forms of IV iron preparations are iron sucrose (IS), ferric derisomaltose (FDI), and ferric carboxymaltose (FCM). These current IV iron formulations are considered very safe, with a low risk of serious adverse reactions (Wang et al, 2015). In contrast, older high molecular-weight iron dextrans carried a high risk of anaphylaxis. Despite the improved safety and tolerability of newer products, a very small risk still remains, and clinical practice still requires IV iron to be administered in settings equipped for emergencies. Less severe reactions, such as flushing and short-lived chest or shoulder pain (known as Fishbane reactions), occur in 0.5–1% of infusions and are likely linked to the release of free iron in the circulation or pseudo-allergy; these reactions are often misinterpreted as serious allergy but they can be effectively treated with slowing of the infusion rate or pre-medicated antihistamines (Auerbach and Macdougall, 2014).

Each IV iron preparation has distinct advantages depending on the clinical situation. For example, in NDD CKD, a single dose of FDI (20 mg/kg) can be given with no upper dose limit, preventing multiple attendances to the hospital, whereas FCM is limited to 1 g/dose. However, few patients would require more than 2 doses (Batchelor et al, 2020).

One side effect almost exclusive to FCM is hypophosphataemia. FCM is thought to increase intact fibroblast growth factor 23 (FGF23) levels, a phosphaturic hormone made in osteocytes that inhibits phosphate reabsorption in the renal proximal tubule. In advanced CKD, FGF23 levels are already elevated, rising in response to reducing nephron mass to maintain normal plasma phosphate concentrations. Hence, whereas hypophosphatemia with FCM is not a concern in CKD stage 4 and worse, in those with well-preserved kidney function FCM can often lead to phosphate concentrations $<$0.6 mmol/L. FCM was compared to FDI in 245 people with normal kidney function in two trials (trial A of 123 patients and trial B of 122 patients). After administration of FDI, 1000 mg, on day 0 or FCM, 750 mg, infused on days 0 and 7. At any point during the 35-day follow-up period. Rates of hypophosphatemia with FDI vs FCM were 7.9% vs 75.0% in trial A and 8.1% vs 73.7% in trial B (Wolf et al, 2020). Though the hypophosphatemia seen with FCM is less of a concern in those with advanced CKD, the obligate rise in FGF23 in dialysis patients may be. FGF23 has been shown to directly induce pathological hypertrophy in cardiomyocytes, while blocking FGF23 receptors can attenuate left ventricular hypertrophy (LVH) (Faul et al, 2011) and higher FGF23 levels are independently associated with mortality in dialysis patients (Gutiérrez et al, 2008). Another effect of FGF23 is the down-regulation of the 1α-hydroxylase enzyme, leading to vitamin D deficiency; cases of osteomalacia have been seen in patients receiving repeated doses of FCM (Vilaca et al, 2022).

The FERWON study examined the safety and efficacy of a single dose of iron isomaltose 1000 ("Monofer®", now known as FDI) compared to a median of 5 $\times$ 200 mg IS doses in a large cohort of NDD CKD patients. The single dose of the FDI induced a non-inferior 8-week haematological response but with a faster time to Hb

target at weeks 2 and 4, with comparably low rates of hypersensitivity reactions and a significantly lower incidence of composite cardiovascular adverse events (dominated by lower rates of congestive heart failure with FDI) (Bhandari et al, 2021b). The National Institute for Health and Care Excellence (NICE) guidelines recommend high-dose, low-frequency IV iron formulations for those with NDD CKD (Padhi et al, 2015).

A flowchart of when to choose PO vs IV iron therapy is included (Fig. 2).

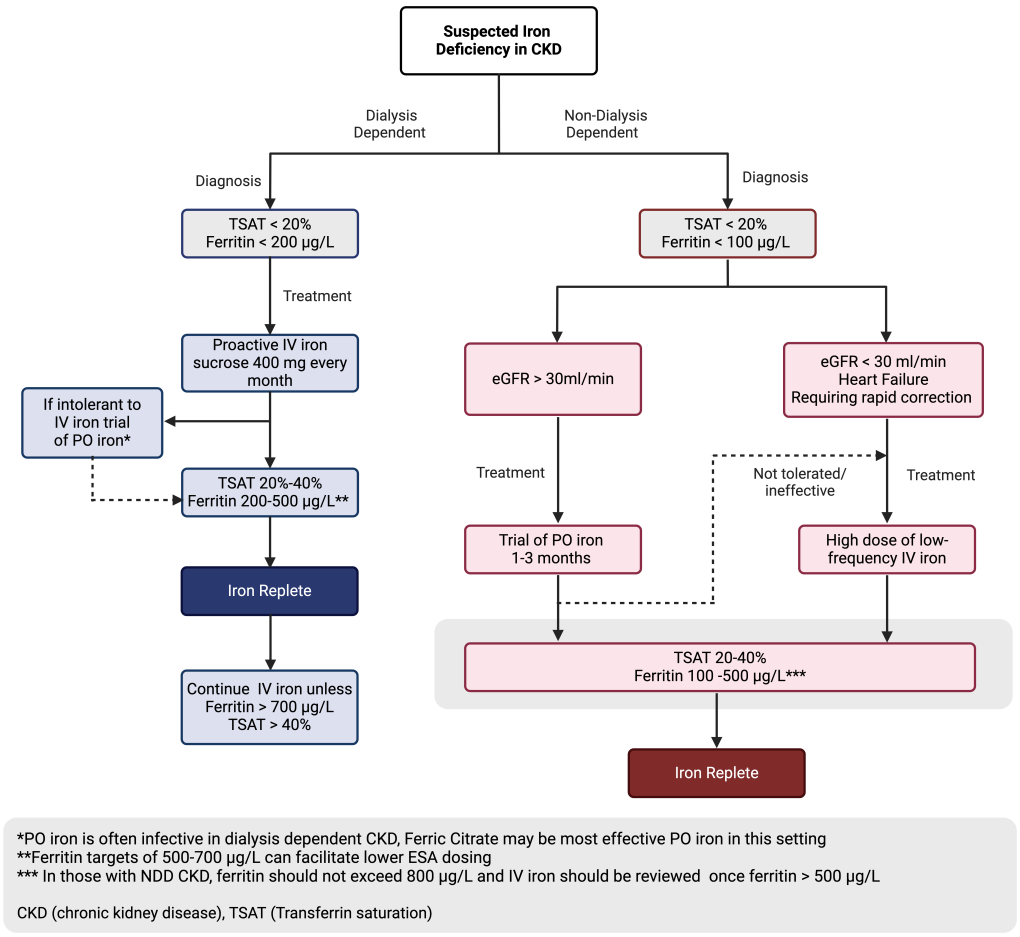

Fig. 2. Diagnosis and management of iron deficiency in chronic kidney disease (CKD). PO, oral; IV, intravenous; eGFR, estimated glomerular filtration rate. Created with BioRender 49 Spadina Ave (Toronto, Canada, https://www.biorender.com).

Treatment of Side-Effects of Iron Therapy

As indicated above, oral iron frequently results in gastrointestinal side effects, and accordingly cessation of therapy is common. The frequency of intolerance and poorer iron absorption in more advanced CKD, with accompanying inflammation and hepcidin upregulation, is the reason why oral preparations are not often given to patients with stage 4 or worse CKD. The only dialysis patients who would be trialled with oral iron would be those found allergic to IV iron. As already de-

scribed, serious allergy including anaphylaxis is now rare with modern IV irons. Algorithms exist for addressing non-anaphylactic allergy (Achebe and DeLoughery, 2020), and these encompass the use of anti-histamines and steroids in moderate to severe situations. The so called Fishbane reaction is more frequently seen and is believed to be caused by mast cell degranulation with histamine release, and may have origins related to the osmolality and/or ionicity of the administered IV solution (Lyberg et al, 2022). Hence, the appropriate response to this side effect is to stop the IV iron infusion, reassure the staff and patient of the non-seriousness, and then once symptoms have settled restart the infusion at a slower (e.g., half speed) rate. Hypophosphataemia is far more likely to be seen with ferric carboxymaltose than with other IV iron preparations but this is most unlikely to be clinically important in patients with advanced CKD where phosphate retention is usually the rule. Serious hypophosphataemia (serum phosphate concentration $\leq$0.6 mmol/L) will be seen in people with well-preserved eGFR (e.g., >45 mL/min) but the management is uncertain as the benefit of phosphate supplementation tends to be short-lived with phosphaturia, driven by increased intact FGF23, persisting for several weeks (Schaefer et al, 2022).

Iron Use in NDD CKD

As described previously, a 1–3-month trial of PO iron for people with NDD CKD with an eGFR >30 mL/min is considered appropriate by some clinicians. However, gastrointestinal side effects are common, and IV iron is more efficacious in cases of severe anaemia or advanced CKD (Macdougall et al, 2014). In these cases, a high-dose, low-frequency IV iron formulation should be chosen, and serum ferritin levels should be kept below 600 µg/L, with treatment evaluated if ferritin exceeds 500 µg/L (Padhi et al, 2015).

In 2006, the Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE) studies examined the safety of higher haemo globin targets in NDD-CKD patients. The CHOIR trial showed a 34% increase in cardiovascular events at a higher haemoglobin target of 13.5 g/dL, while the CREATE trial found no cardiovascular benefit but an increased risk of end-stage renal disease (Drüeke et al, 2006; Singh et al, 2006). Both studies prompted the FDA to lower recommended haemoglobin targets and ESA-treated patients have a haemoglobin target of $\leq$120 g/L.

As it is the higher ESA use, not the higher Hb target, that is detrimental, if an NDD-CKD patient does not require ESA, then there is no upper limit for haemoglobin. One question, then, is whether to treat the non-anaemic iron-deficient NDD CKD patient. The 'Iron and Heart trial' gave a single dose of FDI vs placebo to non-anaemic, iron-deficient (according to the NDD-CKD definition; ferritin <100 µg/L or TSAT <20%) patients with CKD stages 3b-5. There was no significant impact on functional capacity, oxidative stress, or inflammation (Bhandari et al, 2021a). Three subsequent trials examined this question in a heart failure population: FAIR-HF (Anker et al, 2009), CONFIRM-HF (Ponikowski et al, 2015) and IRONMAN

(Kalra et al, 2022). FAIR-HF and CONFIRM-HF showed improved functional capacity in a CKD subgroup. IRONMAN was the largest of the trials, significantly reducing heart failure hospitalisation in those with an eGFR <60 mL/min. Hence, there is evidence that in NDD CKD patients with co-morbid heart failure and iron deficiency but no anaemia IV iron therapy can be given to improve their functional status and reduce heart failure-related hospitalisations.

Iron Use in DD CKD

Before ESA therapy, patients with DD CKD frequently received RBC transfusions, masking any potential iron deficiency. With the introduction of ESAs and the subsequent reduction in RBC transfusions, it became evident that maintaining the haemoglobin response to ESA therapy required regular IV iron supplementation. In the 1990s, high Hb targets were pursued with ESA treatment based on the belief that increasing Hb levels would not only improve patient-reported quality of life and reduce the need for transfusions, as shown in early studies, but also decrease morbidity and mortality (Hung et al, 2014). To support this practice, boluses of IV iron were administered at the end of a haemodialysis session every 2–4 weeks, with UK ferritin targets set at around 400–500 µg/L. However, there was emerging evidence as to the negative effects of high-dose ESA.

The Normal Hematocrit Trial (1993) was the first to explore the effects of normalising hematocrit in haemodialysis patients. It was halted early due to increased risks of death or nonfatal myocardial infarction in patients with a target hematocrit of 42%, along with higher rates of vascular access thrombosis (Besarab et al, 1998). The TREAT study (2009) then demonstrated an increased risk of stroke and recurrent cancer, with no reduction in cardiovascular events, in the group randomised to a haemoglobin target of 13 g/dL (Pfeffer et al, 2009).

In response to these studies, nephrology practice shifted toward lower ESA dosing. Ironically, despite none of these trials focusing on iron therapy, increased iron use and higher ferritin targets emerged to help reduce ESA doses. In the United States, anaemia management evolved to target higher ferritin levels (around 900–1000 µg/L) in dialysis patients to reduce cardiovascular risks associated with higher ESA usage (Hung et al, 2014). Adopting these higher ferritin targets and increased iron dosing raised concerns from clinicians about long-term safety, particularly the risk of infection. Laboratory studies have shown that high iron concentrations could impair the function of lymphocytes and neutrophils, potentially lowering immune response. Additionally, there were hypothetical concerns regarding atherosclerotic cardiovascular disease. This risk is based on iron's redox activity, where the conversion between ferric and ferrous states can produce oxygen free radicals, which are known to contribute to oxidative stress and vascular damage leading to atherosclerosis (Li and Zhang, 2021).

The PIVOTAL study from the UK examined the safety of high-dose iron regimes: high-dose IS was administered in a proactive fashion (400 mg monthly unless the ferritin concentration was >700 µg/L or TSAT% ≥40%) vs low-dose reactive strategy (0 to 400 mg monthly) only administering IS if the ferritin concentration was

<200 µg/L or a TSAT% <20%. The result was positive, with reduced mortality and major adverse cardiovascular events (MACE) in the proactive high-dose arm, a significant reduction in myocardial infarction, heart failure hospitalisations and no increase in infection risk. The proactive arm also received fewer blood transfusions and received lower doses of ESAs (Macdougall et al, 2019).

UKKA definition of adequate iron status is (Mikhail et al, 2017)

- Serum ferritin 200–500 µg/L
- TSAT 20%–40%
- HRC <6%, or CHr/RET-He >31 pg

The UKKA recommends administering regular IV iron unless ferritin exceeds 700 µg/L or TSAT >40%. Targeting ferritin of 500–700 µg/L can help facilitate lower ESA dosing.

A frequently encountered and challenging scenario, particularly in the HD patient, is one where ferritin levels are >700 µg/L with the patient still anaemic with TSAT typically <20%, often on high doses of ESA. It is recognised that such patients are at higher all-cause mortality risk (Kuragano et al, 2020). These patients are very inflamed with resulting functional ID. As described previously, the patient may have adequate iron stores. However, they cannot be utilised, as hepcidin internalises and degrades ferroportin (the only known iron exporter), locking iron into macrophages bound to ferritin. Numerous studies have shown that ESA dosage is inversely related to iron stores, and both absolute or functional ID is the main cause of ESA resistance (Besarab et al, 2000; Coladonato et al, 2002; Kalantar-Zadeh et al, 2003). We also know that targeting higher TSAT%, 30%–50%, compared to aiming for 20%–30%, reduces ESA dose requirement by 40% (Besarab et al, 2000). However, the question remains regarding the safety of increasing IV iron when ferritin levels are high (>900–1000 µg/L). The DRIVE 1 study (and the 6-week extension DRIVE 2) evaluated this (Coyne et al, 2007; Kapoian et al, 2008). Patients on high-dose ESA therapy with ferritins of 500–1200 ng/mL (median 761 ug/mL), TSAT% ≤25% (median 19%), and haemoglobin ≤110 g/L were randomised to either eight consecutive 125-mg ferric gluconate doses or placebo. Those receiving iron had higher Hb and more rapid Hb response. DRIVE 2 showed significantly lower ESA dose requirement and Hb >110 g/L persisting during follow up. Adverse events were higher in the placebo group. There were no differences when subgrouping for those with very high ferritins >800 µg/L. As described in the previous sections, there is a major difference in the iron treatment approach in different sub-sections of the CKD population. Fig. 3 summarises this.

Future Trends, HIF-PHIs, Ferric Citrate and Hepcidin Blockers

As described previously, hepcidin is the key protein adversely affecting iron mobilisation in CKD. Treatments that can lower or bypass high hepcidin levels have the potential to utilise the body's endogenous iron stores and reduce the need for intravenous iron supplementation.

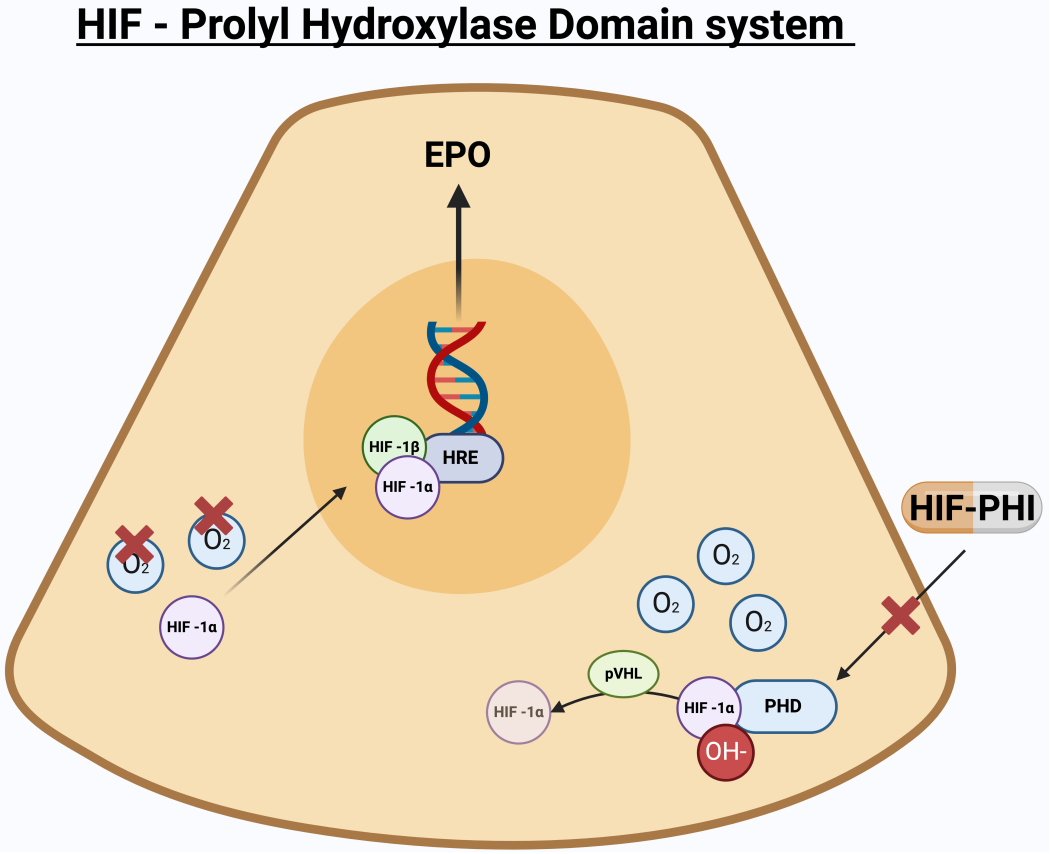

Fig. 3. HIF-prolyl hydroxylase domain system. This figure depicts the hypoxia-inducible factor (HIF) pathway, which regulates erythropoietin (EPO) production in response to oxygen levels. HREs, Hypoxia response elements; PHD, prolyl hydroxylase domain; pVHL, Von Hippel-Lindau; HIF-PHIs, prolyl hydroxylase inhibitors. Created with BioRender 49 Spadina Ave (Toronto, Canada, https://www.biorender.com).

The hypoxia-inducible factor (HIF) system plays a key role in maintaining haemoglobin in normal health but it is dysregulated in CKD leading to anaemia (Fig. 3). HIF consists of HIF1α and HIF1β subunits, with HIF1α being nearly absent under normoxic conditions. HIF-α is regulated by prolyl hydroxylase domain-containing proteins 1–3 (PHD1–3). In normoxic conditions, PHD hydroxylates HIF1α, marking it for ubiquitination by the von Hippel-Lindau (pVHL)-E3-ubiquitin ligase complex, leading to proteasomal degradation. However, in hypoxic conditions, PHD activity is inhibited, with stabilisation of HIF1α. HIF1α can then translocate to the nucleus, which binds to HIF1β, forming a complex that attaches to hypoxia response elements (HREs) on DNA. This complex activates the transcription of several hypoxia-sensitive genes in the kidneys and liver, including the *EPO* gene, increasing EPO production (Batchelor et al, 2020; Portolés et al, 2021). It also activates several other genes that are critical in iron metabolism, including stimulation of transferrin generation which leads to an increase in total iron binding capacity (TIBC). Not only this, but HIF reduces hepcidin production in the liver, downregulating its adverse effects upon iron transport, increasing the availability of iron in the circulation by facilitating its release from intracellular ferritin, stored in macrophages and hepatocytes, and by increased intestinal absorption (Yang et al,

2023). HIF therefore increases endogenous EPO levels as well as the transcription of genes that promote the dietary uptake of iron (Haase, 2013). The HIF prolyl hydroxylase inhibitors (HIF-PHIs) work by inhibiting the PHD enzymes, increasing HIF-α and EPO. In phase 2 and 3 trials of the HIF-PHIs, hepcidin levels appeared to be lower, and patients randomised to the HIF-PHI required a reduced quantity of IV iron and had an improved effectiveness of PO iron (Wang et al, 2023). A network meta-analysis by Yang et al (2023) included 15 trials involving 5 different HIF-PHI and 3228 participants showed that compared to ESAs, HIF-PHIs reduced hepcidin, ferritin and TSAT, but increased transferrin. There appeared to be heterogeneity in the effect of the 5 different HIF-PHIs in decreasing hepcidin with daprodustat having the greatest effect compared to darbepoetin. This systematic review emphasised the point that the alteration in the iron metabolic parameters should be considered 'dynamically'; the decrease in ferritin is a marker of iron release from storage and the reduction in TSAT, which would be considered a negative effect with a 'static' view of iron metabolism, was brought about by an increase in TIBC but better iron delivery.

Typically, PO iron is both ineffective and non-tolerated in DD CKD patients (Pergola et al, 2019). However, ferric citrate, an iron-containing phosphate binder, may show promise. Ferric citrate improves Hb levels in iron-deficiency anaemia in high hepcidin mouse models, enhancing iron absorption even when ferroportin levels are low (Hanudel et al, 2022). A previous study has suggested that ferric citrate might bypass the traditional hepcidin-ferroportin pathway or that the citrate component may help to loosen tight junctions between enterocytes (Hanudel et al, 2022). However, this study showed that the iron absorption with ferric citrate was predominantly ferroportin-dependent, and the preparation did not significantly lower hepcidin levels (Hanudel et al, 2022). This is corroborated by a study of Japanese haemodialysis patients treated with ferric citrate, despite there being an inverse relationship between iron absorption and hepcidin levels, ferric citrate still increased ferritin, Hb, and TSAT% levels and was well tolerated (Tomosugi et al, 2023). The ability of ferric citrate to increase iron parameters in a high-hepcidin population has been established (Lee et al, 2015). More impressively, it has also been shown to reduce the need for IV iron and ESA. In an open-label trial, ferric citrate demonstrated a 25% reduction in ESA dosing, along with a significant decrease in cumulative IV iron use in a haemodialysis population (Yokoyama et al, 2014). When compared to an active control, a study involving 441 haemodialysis patients further reinforced these findings. In this study, ferric citrate (n = 292) was compared to an active control (n = 149) for its efficacy as a phosphate binder and its impact on iron parameters. Results revealed that patients in the ferric citrate group required less IV iron and ESA, while achieving higher levels of ferritin, TSAT, and haemoglobin compared to the control group (Lewis et al, 2015).

Another promising strategy for addressing anaemia in the context of inflammation and elevated hepcidin levels is to target and reduce hepcidin directly. While a comprehensive review of the mechanisms by which this could be achieved is beyond the scope of this article, a detailed review is referenced (Sagar et al, 2021). Several medications targeting hepcidin have advanced through phase 1 and 2 clin-

ical trials. A Hepcidin-binding protein, Anticalin PRS-080, is a small engineered protein designed to neutralize hepcidin by binding to it and which has been tested in HD patients (Renders et al, 2019). Another promising agent, NOX-H94 (Lexaptepid Pegol), a synthetic oligonucleotide (Spiegelmer), has reached phase 2 trials in ESA-resistant HD patients, showing efficacy in increasing serum iron levels by blocking hepcidin's interaction with ferroportin (Macdougall et al, 2015).

Anti-hepcidin monoclonal antibodies, such as LY2787106, have completed phase 1 trials in patients with cancer-related anaemia, demonstrating improved iron mobilisation and anaemia (Vadhan-Raj et al, 2017). Small molecules like Guanosine Diphosphate (GDP) offer another approach by binding to and reducing hepcidin expression, preventing its interaction with ferroportin and thereby promoting iron release into circulation. Additionally, antagonists of the BMP pathway and ferroportin stabilisers are being explored alongside repurposed drugs such as Interleukin-6 (IL-6) inhibitors and Janus Kinase 2/Signal Transducer and Activator of Transcription 3 (JAK2/STAT3) inhibitors, which are known to lower hepcidin levels (Sagar et al, 2021).

Though these therapies are not yet commercially available, their potential to directly modulate hepcidin could be transformative for CKD patients, and those with other inflammatory conditions, particularly those with high ferritin levels who remain unresponsive to erythropoiesis-stimulating agents (ESAs) and for whom the utility of intravenous iron is uncertain. However, any therapeutic targeting hepcidin reduction must carefully consider the balance between improving iron homeostasis and mitigating the possible off-target effects on immune function.

Conclusion

ID is common in all forms of CKD, with increasing prevalence with advancing stages of CKD. Defining ID in CKD is challenging due to the inflammatory nature of CKD and the fact that ferritin is an acute-phase reactant. Alternative biomarkers such as CHr $<$31 pg or %HRC $>$6% may be more sensitive and better guides to therapy; however, their use is limited by availability. Oral iron can be used successfully in the early stages of CKD. However, it is ineffective when the eGFR reduces due to increasing hepcidin levels and patient symptomatology. When administering IV iron to those with NDD CKD, a high dose of low-frequency iron should be used with a ferritin target between 200–600 µg/L. In HD patients, the ferritin upper range is now 700 µg/L in the UK. Some HD patients may be anaemic, on high-dose ESA therapy and have ferritin levels $>$700 µg/L and TSAT $<$20%. This group of patients is at high risk of all-cause mortality and could benefit from a higher ferritin strategy with close follow-up. The future of iron therapy in CKD may involve reduced reliance on IV iron: HIF-PH inhibitors show promise in lowering hepcidin and potentially reducing IV iron needs, ferric citrate has emerged as a promising oral iron option in HD, and hepcidin blockers, although not yet available, are likely to play a key role in treatment in the coming decades.

Key Points

- Iron deficiency (ID), both in its absolute form (where iron stores are truly depleted) and its functional form (where iron stores are present but not effectively utilised), is prevalent across all stages of CKD.
- Traditional definitions of ID in CKD are often unreliable due to the inflammatory nature of CKD, with ferritin acting as an acute-phase reactant, which can mask true iron deficiency.
- In NDD CKD, a 1–3-month trial of oral iron is appropriate for those with an eGFR >30 mL/min; however, intravenous iron is recommended if oral iron is poorly tolerated, anaemia is severe, if eGFR falls below 30 mL/min, the patient is receiving ESA or has heart failure.
- In HD patients, most of whom will be receiving ESA therapy, proactive iron supplementation is essential. Adequate iron status is defined as ferritin between 200–500 µg/L and transferrin saturation (TSAT) between 20–40%. However, IV iron should be continued unless ferritin exceeds 700 µg/L or TSAT >40% and a ferritin target of 500–700 µg/L facilitates lower ESA dosing in practice.
- HD patients on high-dose ESA therapy who remain anaemic with ferritin levels >700 µg/L and TSAT <20% are likely experiencing functional ID with significant inflammation. Continued iron supplementation can be administered cautiously, though these patients are at higher mortality risk.
- The future of iron therapy in CKD may involve reduced reliance on IV iron: HIF-PH inhibitors show promise in lowering hepcidin and potentially reducing IV iron needs, ferric citrate has emerged as a promising oral iron option in HD, and hepcidin blockers, although not yet available, may play a key role in treatment in the coming decades.

Availability of Data and Materials

Not applicable.

Author Contributions

TM and PAK designed the manuscript. TM wrote the manuscript and PAK provided senior review. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

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