

# Iron deficiency in chronic kidney disease and the new generation of intravenous iron

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**Abstract:** Anemia is the most common complication of chronic kidney disease (CKD) and the main cause of poor prognosis in CKD patients. Iron deficiency (ID) is the second most important factor in the occurrence of anemia in CKD besides EPO deficiency, and iron is currently the main treatment for iron deficiency in patients with CKD anemia. Iron supplements are divided into intravenous iron and oral iron supplements. Oral iron is often ineffective due to its gastrointestinal side effects and low absorption efficiency. Traditional intravenous iron can only be administered in small single doses due to safety restrictions. New intravenous iron agents have emerged. This article provides a brief overview of current iron metabolism in chronic kidney disease, causes of iron deficiency, iron status and new intravenous iron agents available.

**Keywords:** iron deficiency, anemia, chronic kidney disease, iron

## 1. Introduction

CKD has become a major public health problem worldwide, and anemia is one of the most common complications in CKD patients. It is estimated that the prevalence of CKD accounts for about 13.0% of the adult population in the United States and 10.8% in China, and more than 50% of CKD patients have combined anemia<sup>[1]</sup>. Anemia in CKD is associated with decreased quality of life, cardiovascular disease, hospitalization, cognitive impairment, and increased mortality<sup>[2]</sup>. Effective erythropoiesis is dependent on erythropoietin (EPO) and iron sufficiency. ID plays an important role in the development of anemia in CKD, and because of this, treatment of ID is essential for the successful management of anemia in CKD. The treatment of CKD anemia with ID is now mainly based on supplementation, but the emergence of new intravenous (IV) iron agents in recent years has brought new hope for the treatment of CKD patients who cannot tolerate oral iron and who are not treated well due to the side effects or inconvenience of traditional IV iron. This review will outline the causes of iron metabolism and ID in CKD, iron status and diagnostic criteria, and the relative benefits and risks of various the new generation of IV iron, with the aim of drawing attention to CKD anemia.

## 2. Iron metabolism and causes of iron deficiency in CKD

Iron is an important element involved in human metabolism. Based on its ability to accept and transfer electrons, an adequate amount of iron is essential for many important biological reactions, including oxygen transport, cellular respiration and DNA synthesis, while iron overload can also cause severe oxidative stress and tissue damage<sup>[3, 4]</sup>. Due to the important role of iron in the organism, its uptake, transport and metabolism are tightly regulated. Because the body has no natural iron excretion mechanism, the regulation of iron homeostasis is mainly accomplished by regulating absorption<sup>[5]</sup>. ID in CKD is often associated with elevated hepcidin, inadequate iron intake and increased iron consumption.

### 2.1. Circulating concentrations of hepcidin

Hepcidin is a small peptide hormone consisting of 25 amino acids synthesized and secreted by the liver<sup>[6]</sup>, degraded by renal filtration, and acts by binding to ferroportin. Ferroportin regulate all major flows of iron into the plasma and extracellular fluid (including transfer of dietary iron from duodenal

enterocytes to plasma, release of circulating iron from spleen and hepatic macrophages, and release of stored iron from hepatocytes). Iron-regulator binds to ferroportin and mediates their endocytosis into cells for degradation. Loss of ferroportin correspondingly reduces intracellular iron transport to the plasma and extracellular fluid<sup>[7]</sup>. Heparin levels are controlled by various factors such as iron stores<sup>[8]</sup>, hypoxia<sup>[9]</sup>, inflammation<sup>[10]</sup> and erythropoiesis<sup>[11]</sup>. In CKD due to decreased renal clearance, increased inflammatory cytokines and decreased erythropoietin levels<sup>[11, 12]</sup>, heparin levels are elevated, resulting in a decrease in circulating iron. Elevated heparin also induces reduced iron absorption in the gastrointestinal tract, further exacerbating ID in CKD.

## **2.2. Inadequate iron intake**

The elevated iron regulator in CKD also induces a decrease in iron absorption in the gastrointestinal tract, coupled with the fact that CKD patients are often accompanied by poor nausea, reduced dietary intake, malnutrition, and insufficient iron intake, increasing leading to iron deficiency.

## **2.3. Increased iron consumption and loss**

CKD patients are often treated with erythropoiesis-stimulating agents (ESAs) for anemia, which accelerates the production of red blood cells and exceeds the ability to adequately mobilize iron from stored iron, often causing functional ID<sup>[13]</sup>. The frequent blood draws and blood left in the dialysis line during dialysis in CKD patients lead to iron loss. Moreover, CKD patients are often combined with abnormal platelet function and gastrointestinal bleeding, further causing iron loss<sup>[14, 15]</sup>.

## **3. Iron status**

The definition and diagnosis of ID and anemia in CKD is based on 3 main parameters: Hemoglobin (Hb); transferrin saturation (Tsat), an indicator of circulating iron, and Storage iron --serum ferritin (SF). Iron status is divided into absolute ID and functional ID in CKD. Absolute ID is defined as a severe reduction or absence of iron stores in the bone marrow, liver and spleen and is defined as Tsat <20% and SF <100 µg/l in non-dialysis-dependent CKD (NDD-CKD) or SF <200 µg/l in dialysis-dependent CKD (DD-CKD). Functional iron deficiency is defined as normal or increased total body iron stores that cannot be incorporated into erythroid precursor cells for erythropoiesis. It is usually diagnosed in clinical situations: Tsat <20% and SF >100 µg/l in NDD-CKD, SF >200 µg/l in DD-CKD. Although the parameters currently used are unreliable for estimating body iron stores or predicting response to therapy. New assays are still being researched and developed to more accurately diagnose absolute and functional ID and to monitor the response to treatment of ID<sup>[16]</sup>.

## **4. Iron**

The treatment of ID in CKD is mainly aimed at the treatment of anemia caused by ID. Among them, iron is the main treatment for iron deficiency anemia (IDA) in CKD. For patients with CKD with ID, both oral and IV iron supplements are available. The KDIGO guideline suggests that IV iron is usually more effective than oral iron for DD-CKD, but the choice between oral and IV iron is more delicate for NDD-CKD. The KDIGO recommends that clinicians "choose the route of iron supplementation based on the severity of iron deficiency, availability of intravenous access, response to previous oral iron therapy, side effects of previous oral or IV therapy, treatment compliance, and cost."<sup>[17]</sup>

### **4.1. New-generation (third-generation) IV iron**

For most patients with IDA, the full course of IV iron dosing is 1 g. Most IV iron doses require 5-10 doses of 100-300 mg<sup>[18]</sup>. Third-generation IV iron has a faster dosing rate and larger single dose than conventional IV iron (iron gluconate, iron sucrose, etc.), which include Ferumoxytol, iron isomaltoside (IIM) and ferric carboxymaltose (FCM). They all consist of an iron core that is covered by a carbohydrate shell whose properties allow the new generation of IV iron to be administered in higher single doses than conventional IV iron, as its shell-core structure binds iron atoms more tightly to control the release of iron by stable complexation and reduces the production of free iron<sup>[19]</sup>. Third-generation IV iron has reduced the incidence of systemic allergic reactions, but controversy persists regarding hypersensitivity reactions, cardiovascular events, and hypophosphatemia<sup>[13]</sup>.

#### 4.1.1. Ferumoxytol

Ferumoxytol was approved by the FDA in 2009 for the IV treatment of IDA in adult CKD [20] and is the first of new generation of IV iron that reduces the incidence of systemic allergic reactions and reduces the release of free iron. It was approved by the FDA for single 510 mg dose administration. Ferumoxytol at 1020 mg has been reported to be safe to administer within 15 minutes, allowing for adequate iron supplementation in a single visit<sup>[18]</sup> and has shown the lowest amount of detectable free iron after a single injection reported by Ferumoxytol in comparison with conventional IV iron approved in the United States (iron gluconate, iron sucrose) <sup>[21]</sup>.

Provenzano et al <sup>[22]</sup> found that ferumoxytol increased Hb levels and SF levels much more than oral iron in a phase III randomized controlled trial of 230 patients with CKD anemia with ID. Macdougall et al<sup>[23]</sup> in a Ferumoxytol versus iron sucrose(IS) treatment for IDA in a safety and efficacy study in CKD, found that 1020 mg ferumoxytol applied in two divided doses was superior to 1000 mg IS applied in multiple doses in terms of improvement in hematological parameters. In terms of safety, several studies <sup>[20, 22-24]</sup> have reported fewer treatment-related adverse effects in patients using Ferumoxytol compared to conventional iron (iron sucrose, oral iron).

#### 4.1.2. FCM

FCM was originally approved by the FDA in 2013 and consists of iron hydroxide surrounded by and tightly bound to carboxymaltose<sup>[25, 26]</sup>. The FDA initially approved a dose of 15 mg/kg of FCM on days 0 and 7 for individuals weighing  $\leq 50$  kg and 750 mg for 2 doses for individuals weighing  $> 50$  kg, but in 2021, the FDA approved 1000 mg as a single replacement dose for FCM.

In the REPAIR-IDA trial comparing the efficacy and safety of FCM with IS in NDD-CKD with IDA, it was found that the Hb elevation was significantly faster in the FCM group than in the IS group. In terms of safety, the serious adverse events were similar between the two groups. However, hypophosphatemia was found more frequently in the FCM group <sup>[27]</sup>. In the FIND-CKD trial comparing the efficacy and safety of FCM versus oral iron in patients with non-dialysis CKD anemia with ID<sup>[28]</sup>, it was found that FCM improved Hb levels more rapidly in patients with CKD and that there were no differences in cardiovascular or infectious adverse events between the FCM and oral groups.

#### 4.1.3. IIM

IIM was approved by the FDA in 2020. In composition, IIM is hydroxy iron oxide encased in an exfoliating maltose shell and is approved for a single injection of 1000 mg.

The FERWON-NEPHRO trial was conducted to compare the administration of 1000 mg of total iron to NDD-CKD with IDA patients with a faster increase in Hb levels in the IIM group for a single dose and in the IS group for five doses. In terms of safety, the overall incidence of adverse was similar in the IIM and IS groups. Patients treated with IIM experienced significantly fewer composite cardiovascular events than IS patients (4.1% and 6.9%, respectively [ $p = .025$ ]), and the time to first composite cardiovascular event was significantly longer in the IIM group ( $p = .019$ ).<sup>21</sup> This may be related to the fact that ID impairs mitochondrial respiratory function in cardiomyocytes, which impairs myocardial systolic and diastolic function, and that aggressive correction of iron deficiency is effective in improve mitochondrial function in cardiomyocytes<sup>[29]</sup>. However, because the FERWON-NEPHRO trial was an 8-week trial, the effect of IIM on long-term cardiovascular safety cannot yet be described. The ongoing large clinical trial, the 5 IRONMAN trial, may provide an answer to the question of the long-term cardiovascular safety of IIM<sup>[30]</sup>.

## 5. Conclusion

In CKD, functional and absolute ID often leads to anaemia, and iron supplementation is necessary for effective haemoglobin synthesis. Third-generation IV iron has fewer allergic reactions and fewer short-term adverse cardiovascular events than conventional IV iron. Because these IV iron preparations can be given in a single large dose, they are more suitable for NDD-CKD to reduce the number of infusion centers and venipunctures. And third-generation IV iron is more cost-effective than traditional IV iron in economic research. However, adverse effects such as hypophosphatemia require further research.

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