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Iron therapy in chronic kidney disease: recent changes, benefits and risks

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Abstract

Anemia is a common complication in patients with chronic kidney disease (CKD), mainly due to inadequate renal production of erythropoietin. In hemodialysis (HD) patients this condition may be aggravated by iron deficiency (absolute or functional). The correction of this anemia is usually achieved by treatment with erythropoiesis stimulating agents (ESAs) and iron (oral or intravenous). Studies questioning the safety of ESAs (especially at higher doses), changed the pattern of anemia treatment in CKD patients. According to the new guidelines, when transferrin saturation is lower than 30% and ferritin lower than 500 ng/mL, a trial with iron should be started, to avoid therapy with ESAs or at least to reduce the doses needed to treat the anemia. Recent reports showed increasing ferritin levels, towards values above 800ng/mL, in CKD patients treated according to the guidelines. In this review we focus on the risks of the increased iron use to treat CKD anemia, namely, iron overload and toxicity, increased risk of infections, as well as mortality.

Keywords: Anemia; Chronic Kidney Disease; Hemodialysis; Intravenous iron; Iron therapy; Iron overload; Mortality.

1. Iron disturbances in hemodialysis patients

Anemia is a common complication in patients with chronic kidney disease (CKD). The number of CKD patients with anemia increases with the progression of renal dysfunction [1]. The main cause of anemia is the inadequate production of erythropoietin (EPO), a glycoprotein mainly produced by the kidney, responsible for the growth, differentiation and reduction of apoptosis of erythroid cells in the bone marrow [2]. Iron deficiency is another common cause of anemia in these patients [3]. The high frequency of blood analysis, the surgical procedures for vascular access and the blood loss into the hemodialyser and tubes during the dialysis procedure contribute to reduce iron stores. A CKD patient under hemodialysis (HD) therapy loses about 1-2 g of iron per year through these mechanisms. Inflammation is another hallmark of CKD that may lead to a “functional” iron deficient anemia, as we and others previously reported [4-10] . Actually, inflammation has been proposed to play an important role in disturbances in iron metabolism. It is known, as we found, that CKD patients under HD present high serum levels of hepcidin [6, 11], which has been described as a major regulator of body iron homeostasis. Hepcidin, synthesized by the liver, acts by inhibiting cellular iron efflux from hepatocytes, enterocytes and iron recycling macrophages, through binding to ferroportin, inducing its degradation [12]. Hepcidin synthesis is regulated by several proteins (Fig. 1), namely, hemochromatosis protein (Hfe), transferrin receptor 1 (TfR1), TfR2, hemojuvelin (HJV), bone morphogenic protein (BMP6), matriptase-2 and transferrin [13-15]. In the liver, diferric transferrin competes with TfR1 for binding to Hfe; in conditions associated with increased iron, more Hfe will be available to bind to TfR2; this complex, TfR2-Hfe, promotes HJV binding to

BMP6, triggering hepcidin synthesis. Moreover, hypoxia and EPO, as well as twisted gastrulation protein 1 (TWSG1), growth differentiation factor 15 (GDF15) and, more recently, erythroferrone, all produced by erythroblasts, are also important modulators of hepcidin synthesis, inducing a downregulation of hepcidin synthesis [16, 17]. Thus, HD patients under recombinant human EPO (rHuEPO) therapy might develop an iron deficient anemia due to several factors, as blood loss and inflammation.

2. Treatment of anemia

The first treatment used to correct anemia in CKD patients was blood transfusion. However, the risk of transfusion reactions (immunological sensitization), transmission of infectious agents and iron overload triggered the search for a better treatment of anemia [18].

The introduction of rHuEPO in the late 80's revolutionized the treatment of anemia of CKD, particularly of end stage renal disease (ESRD) patients. Since then, several erythropoiesis stimulating agents (ESAs) have been approved to treat the anemia of CKD patients, differing in their half-life (Table 1), which determines the frequency and route of their administration. They were, therefore, divided in "short-acting" and "long-acting" ESAs. Epoetin beta and alpha are "short-acting" ESAs, with identical amino acid and carbohydrate composition to EPO, that are given 3 times per week. Recently, biosimilar epoetins have been introduced in the market (epoetin zeta and theta), presenting therapeutic profiles similar to those of epoetin beta and alpha [19].

The need to improve formulations, in order to reduce the frequency of administration, led to the development of "long-acting" ESAs. Darbopoetin alpha

presents two additional N-linked carbohydrate chains compared to EPO, which increase its half-life and, therefore, allows its administration only once per week. In 2007, methoxy polyethylene glycolepoetin beta, a continuous EPO receptor activator (CERA) was introduced, presenting a half-life of about 130 hours, which reduced its administration for once per month [20]. Peginesatide, with a longer half-life, is a pegylated homodimeric peptide with no sequence homology to EPO [21]; it was the first synthetic peptide approved for the treatment of CKD anemia, in 2012; however, due to serious hypersensitivity associated reactions, the product was removed from the market in 2013.

The introduction of ESAs reduced the need for transfusions and improved the quality of life in CKD patients, as the treatment reduced the symptoms and the comorbidities associated with anemia [22] and slowed the progression of renal disease, increasing the time before replacement therapy [23]. Although the majority of the patients respond to ESA therapy, about 10% of CKD patients are hypo-responsive [24]. To overcome this reduced response, often referred as resistance, higher doses of ESAs are needed to achieve the target hemoglobin (Hb) levels [4-6].

One of the causes for hypo-responsiveness to ESAs is iron deficiency (Fig. 2), either absolute or functional [25]. Serum iron, transferrin and ferritin concentrations, as well as transferrin saturation (TSAT), are usually used to assess iron status. Plasma/serum ferritin concentration is the only non-invasive evaluation to assess iron stores. A ferritin value lower than 30 ng/mL in men or lower than 15 ng/mL in women are consistent with absolute iron deficiency [26]; a serum ferritin concentration higher than 300 ng/mL, along with anemia, indicates a functional iron deficiency, as usually occurs in CKD patients [6].

Serum iron and TSAT are useful to measure circulating iron, available for delivery to bone marrow erythroid cells, for Hb synthesis. In case of anemia, it is important to distinguish between absolute iron deficiency (low levels of iron, ferritin and TSAT), which usually is responsive to iron therapy, from a functional iron deficiency (high levels of ferritin and low iron and low/normal levels of TSAT) that results from an inflammatory state. Indeed, the inflammatory condition triggers the production of hepcidin, which inhibits iron absorption and mobilization, leading to the development/worsening of anemia in CKD patients [27].

Nowadays, the gold standard treatment for anemia in CKD patients is the administration of ESAs, associated with iron supplementation. When ESAs therapy was introduced, the patients were treated to normalize hematocrit (Ht) and Hb levels. However, the first clinical trial evaluating the outcomes of the patients, according to their Ht, showed that values higher than 42% were associated with increased number of deaths [28]. The publication of other three studies [29-31] reporting similar conclusions raised concerns about the risks associated with normalization of Ht, and about the risks associated with the higher ESA doses needed to achieve those Ht values. Considering the results of these studies, the Food and Drug Administration (FDA) launched in 2007 some safety advisories, recommending that patients should not exceed the Hb level of 12 g/dL [32]. Later, in 2012, the use of more conservative ESAs doses was recommended [33]. In accordance, the Kidney Disease Improving Global Outcomes (KDIGO) and the European Best Practice Guidelines (EBPG) Work Group made also an update to their guidelines, recommending that Hb levels should be 11-12 g/dL, without intentionally exceeding 13 g/dL and that a safer

use of ESAs should be adopted [24, 34]. Moreover, the “Clinical Practice Guideline for Anemia in Chronic Kidney Disease” [24] from KDIGO also stated that CKD patients with anemia should first start iron therapy rather than ESAs. They suggested that CKD patients should start iron supplementation when TSAT is lower than 30% and ferritin levels lower than 500 ng/mL; however, the upper safe serum ferritin level was not defined.

The use of iron is now a common practice in the treatment of anemia in CKD patients, in spite of the concerns about the increase in ferritin levels and tissue iron overload, due to the use of high/continuous iron supplementation.

3. Oral and intravenous iron

Supplementation of HD patients with iron is needed to maintain iron available for an adequate erythropoiesis. The decision for oral or intravenous (IV) iron treatment should balance the benefits and risks for the patient (Fig. 2).

Oral iron formulations (Table 2) are less expensive; however, the gastrointestinal side effects experienced by some patients (about 30%) may reduce the effect and adherence to treatment [35, 36]. Some studies reported that IV iron therapy increases both Hb and ferritin, while oral iron therapy increases Hb without increasing iron stores [35, 36]. Moreover, most of the clinical studies evaluating oral and IV administration reported that IV iron therapy leads to a higher increase in Hb than oral iron therapy [36, 37]**.**

IV iron therapy is better tolerated than oral iron therapy [35, 36], has more adherence and efficacy, but requires the existence of an IV access. It has been associated with hypersensitivity reactions that, although very rare, can be life-threatening [38]. The major risk factors for these hypersensitivity reactions

include a previous reaction to an iron infusion, a fast iron infusion rate, multiple drug allergies, severe atopy and systemic inflammatory diseases [38].

IV iron therapy is preferred for patients under HD, as they have a vascular access already available that can be used for iron infusion. In non-dialysis (ND) CKD patients, oral iron may be preferred to preserve IV access. However, there is no consensus for the use of oral rather than IV iron as first line treatment in ND-CKD patients. Several studies have been performed [35, 37, 39, 40] to further clarify the efficacy and safety of oral *versus* IV iron supplementation in ND-CKD patients. Stoves et al. [39], in a follow-up study along 6 months of ND-CKD patients, found that the Hb response and ESAs requirements with IV iron (iron sucrose) or with oral iron (ferrous sulphate) supplementation were similar. In accordance, Charytan et al. [35] and Agarwal et al. [41] reported that both IV and oral iron therapies in ND-CKD patients resulted in similar Hb responses, but IV iron therapy showed better results in replacing iron stores. Conversely, Qunibi et al. [36], Van Wyck et al. [37] and the recently FIND-CKD study [40] found that IV iron is superior to oral iron therapy, as ND-CKD patients under IV iron therapy showed higher Hb levels and iron stores, as well as a higher improvement in their quality of life.

The efficacy of oral iron therapy can be compromised in CKD, as these patients usually present a low to mild degree of inflammation, which leads to an increase in hepcidin levels [6, 42]. This increase in hepcidin, by reducing gastrointestinal iron absorption and decreasing iron release from body storage sites, inhibits the use of iron for erythropoiesis and leads to an increase in ferritin (Fig. 1).

One of the concerns in IV iron therapy is that the used iron dose overcomes the binding capacity of transferrin, leading to an increase in non-transferrin bound

iron (NTBI). Moreover, as transferrin levels are usually reduced in CKD patients, this effect might be enhanced [6, 43]. The presence of NTBI can lead to the development of oxidative stress, increasing the pro-oxidant state of these patients. In case of co-existence of inflammation and cardiovascular (CV) disease, the oxidative stress may be even more enhanced. It has been also suggested that NTBI might be a source for iron deposition in organs [44-46].

The optimization of iron delivery, given the complications associated with IV iron therapy and the reduced oral iron adherence and efficacy, is an actual challenge to search and develop better iron formulations (Table 2). Recently, a treatment with oral liposomal iron showed to be a safe and efficacious alternative to IV iron in ND-CKD patients [47]. Iron–carbohydrate complexes (IV formulations), presenting lower hypersensitivity reactions than iron-dextrans complexes and allowing the gradual release of iron (instead of a cumulative iron dose), have been developed and approved [48].

3.1 Iron overload

Iron has essential roles in several physiological processes, including the synthesis of Hb and other hemeproteins. The body iron stores are tightly controlled, as there is no physiological mechanism of iron excretion. Iron can be stored in the body, as ferritin and hemosiderin. These forms are found in the macrophages of the reticuloendothelial system (liver, spleen and bone marrow) and in the parenchymal liver cells. Serum ferritin, TSAT and reticulocyte count are used to evaluate iron stores and bone marrow iron availability. Ferritin levels can be increased in case of inflammation and do not seem to be correlated with hepatic iron overload [49]. The first test used to evaluate iron availability to bone

marrow was performed by biopsy; as it is an invasive test, associated with some risks, it is used only to study specific iron disorders. The non-invasive techniques, as magnetic resonance imaging and magnetic susceptometry, are new tools to evaluate iron overload in CKD patients. However, these techniques do not distinguish between non-bound iron and iron stored in the macrophages of the reticuloendothelial system. Nowadays, the challenge is to find new markers and better techniques to predict iron overload [50].

The Dialysis Outcomes and Practice Patterns Study (DOPPS) [51] showed that the number of HD patients with IV iron supplementation increased in most countries; however, and even more important, the doses prescribed to these patients also increased in the past 10-15 years. Overall, the mean serum ferritin has increased over time, and the proportion of patients with serum ferritin values ≥ 800 ng/mL has also increased [51].

The recent KDIGO Controversies Conference on Iron Management in CKD (San Francisco, 2014) recognized the entity of iron overload in HD patients. Actually, there are several studies reporting tissue iron accumulation in HD patients treated with ESAs and IV iron (Table 3) [49, 52-54]. Canavese et al. [52] found that 70% of HD patients presented mild-to-severe hepatic iron overload, although the same percentage of patients presented serum ferritin values below 500 ng/mL. Ferrari et al. [49] reported that 60% of HD patients presented liver iron concentration > 60 µmol/g (above the normal upper limit of 30 µmol/g) and 13% had liver iron concentrations > 130 µmol/g, which is usually found in patients with hemochromatosis; they also found that iron liver accumulation was correlated with cumulative iron dose, but no correlation was observed with ferritin or TSAT. Recently, two other studies found similar results

[53, 54]. Ghoti et al. [53] reported that 90% of HD patients presented mild to severe hepatic iron deposition and also iron deposition in the spleen. In the other study, 84% of the HD patients had hepatic iron overload, and in 30% of them iron overload was severe; moreover, iron liver content correlated with infused iron [54].

In spite of the widespread use of IV iron supplementation in HD patients, the safest dosing strategy is still poorly clarified, as well as its relation with serum ferritin levels, iron overload and mortality risk. Actually, only few studies addressed these questions, and presented controversial results (Table 3). Feldman et al. [55] found that HD patients receiving more than 1000 mg of IV iron in a period of 6 months presented a higher risk of death and hospitalization, compared to patients with no iron supplementation. In a follow-up study of 2 years, the same group evaluated the effect of each 6 months of iron exposure and did not find any association between the iron administrated and mortality, but found an association between iron dose and mortality at 12 to 18 months of treatment, for iron doses higher than 1800 mg [56]. In the first study of this group [55], only 17% of the HD patients received iron dosing above 1000 mg, whereas in the second study [56] this number rose to 48%. These authors also found an association between mortality and ferritin levels > 800 ng/mL in the 6 months prior to death, but this finding could result from confounding factors, such as inflammation and malnutrition [56].

Another observational study evaluating HD patients for a period of 2 years showed that serum ferritin levels in the range of 200 – 1200 ng/mL, TSAT between 30 – 50% and IV iron dose < 400 mg by month were associated with improved survival, suggesting that the association of high ferritin levels and

mortality could also result from confounding factors [57]. A recent study [58] evaluated the effect of a bolus of IV iron (consecutive doses ≥ 100 mg exceeding 600 mg during one month) *versus* maintenance of IV iron therapy (all other iron doses during the month), and also the effect of high (> 200 mg over 1 month) *versus* low dose of IV iron (≤ 200 mg over 1 month); after 1 month of iron exposure, the patients were studied for a follow-up period of 3 months; no significant associations of bolus *versus* maintenance dose or of high *versus* low dose IV iron with increased short-term CV morbidity and mortality were found.

Zitt et al. [59] found that increasing ferritin concentrations (> 800 ng/mL) in patients with normal C-reactive protein (CRP) concentrations were associated with decreasing mortality, whereas in patients with high CRP (> 0.5 mg/dL) values the increasing ferritin concentration were linked with increased mortality, suggesting that serum ferritin levels above 800 ng/mL are associated with increased mortality in case of concomitant inflammation. A 2-year follow-up study, by our group [6], found that HD patients presented several changes in iron metabolism (increased TSAT, ferritin and hepcidin and a decrease in iron and transferrin) and inflammatory markers (increased interleukin [IL]-6 and CRP). Patients who died during this follow-up period showed significantly lower values for transferrin and TSAT and increased levels of IL-6 and CRP. In the adjusted survival regression model, CRP was found to be a significant predictor of mortality.

The recently published observational DOPPS study [60] showed that HD patients receiving, along 4 months, 300 mg/month or even a higher dose of IV iron supplementation, compared with patients supplemented with 100 – 199

mg/month, presented increased hospitalization risk, all-cause mortality and CV mortality, regardless of serum ferritin or CRP concentrations.

Considering the controversial data in literature, there is a clear need to develop clinical trials with longer follow-up periods of HD patients to evaluate the effect of long-term cumulative IV iron doses and the impact of serum ferritin levels on all-cause and CV mortality. In accordance, a clinical trial, “The Proactive IV irOn Therapy for HaemodiALysis patients (PIVOTAL)”, has recently started, and the aim is to compare the effect of IV iron high-dose *versus* low-dose regimen on all-cause mortality, and to evaluate the incidence of non-fatal CV endpoints, in HD patients along 2 – 3 years follow-up [61]. Another aim of this study is to compare the effect of the two regimens on ESA dose requirements, red blood cells transfusions, complications of HD treatment, and quality of life of the patients.

3.2 Iron toxicity

Data in literature strongly suggest the risk of tissue iron overload in HD patients, although the underlying pathophysiological mechanisms are less clear, especially in case of IV administration of iron. The infusion of iron may overwhelm the capacity of the iron binding proteins, allowing iron to become free in circulation and/or to increase iron stores. It is known that free iron can react with hydrogen peroxide leading to the production of hydroxyl radicals that are able to trigger oxidative modifications in lipids, proteins and DNA. Indeed, the literature supports that after IV iron injection in HD patients a transient increase in oxidative stress occurs, as shown by the increase in plasma lipid peroxidation [62] and oxidative modification of proteins [63]. Actually, different

markers of oxidative stress are significantly increased in CKD patients [64, 65] and are involved in the progression of renal disease [66].

Several diseases have been associated with oxidative stress, such as the CV diseases [67, 68], which are the major cause of death in HD patients. It has been hypothesized that the oxidative stress induced by IV iron infusion could favor atherosclerosis and endothelial cell damage. Reis et al. [69] found that in dialysis patients the carotid intima media thickness correlated with serum ferritin and with the IV iron dose, corroborating the previous hypothesis. Studies in rabbit models found that the more extensive atherosclerotic lesions contained a higher concentration of iron and that the formation of these lesions may be accelerated by free radical production, caused by increased iron levels [70, 71]. Kuo et al. [72] reported that CKD patients who had received IV iron sucrose preparation presented increased superoxide production by circulating mononuclear cells, increased expression of soluble adhesion molecules, and of mononuclear-endothelial adhesion molecules, when compared with untreated CKD patients or healthy subjects. In the same study, the authors corroborated their results by showing that mice with uninephrectomy treated with IV iron presented increased tissue superoxide production, increased expression of tissue cell adhesion molecules, endothelial adhesiveness and exacerbated atherosclerosis in the aorta. These effects seem to be dependent on IV iron formulation used, as reported by Toblli et al. [73].

NTBI might be important for extrahepatic iron deposition and toxicity, namely, in the kidney. Progressive tubulointerstitial damage and renal fibrosis are common pathways in the development of CKD and iron deposition could favor these lesions. Indeed, iron accumulation is observed in the proximal tubule in human

CKD [74], as well as in rats with nephropathy [75-78], and seems to be associated with the progression of CKD. In a study by our group, using a rat model of nephrectomy, we found iron deposition in tubules, along with extensive tubulointerstitial lesions [78]. Recently, in a similar model, Naito et al. [76] reported that the animals with renal failure, treated with oral iron chelators, showed a reduction in interstitial fibrosis, suggesting that renal iron accumulation is associated with renal interstitial fibrosis, promoting the progress of renal disease.

3.3 Association of iron therapy with infection

In vitro studies show a relationship between the availability of iron and bacterial virulence, as iron is important for bacteria multiplication in the host. Therefore, clinical conditions associated with iron excess in the host may increase the risk for infection [79]. Clinical studies reported different results about the linkage of IV iron therapy with infection. One study observed a significantly higher rate of bacterial infection with higher IV iron saccharate dose, but not with higher frequency of dosing administration [80]. A one year follow-up study of HD patients, examined the relationship between iron stores, IV iron dosing and bacteremic risk, and found that patients with higher iron stores had a significantly higher risk of bacteremia; however, they did not find an IV iron dose-response relationship [81]. Brewster et al. [82] reported that IV iron did not significantly increase the rate of microorganism growth within catheters or the development of blood infections with iron supplementation. After the recent changes in the pattern of IV iron treatment [24], Bansal et al. [83] in a 2 year follow-up study of HD patients treated with IV iron found a significant increase in

TSAT and in serum ferritin; however, it was not associated with an increase in the incidence of infectious complications. In a retrospective cohort study of HD patients, those receiving bolus *versus* maintenance iron therapy were at increased risk of infection-related hospitalization [84]. Recently, Kuragano et al. [85] found that patients with a higher ferritin level had a higher risk of infectious disease than those with lower ferritin level. They also found that the risk of infection and hospitalization were significantly higher among patients who were treated with high weekly doses of IV iron, compared with no iron. An observational study that included 14078 patients reported the possibility of infection-related mortality with higher iron doses [86].

The type of IV iron formulation might have also an impact in the rate of infection, as suggested by Sirken et al. [87], that found a higher bacteremia rate with iron sucrose than with ferric gluconate; however, a relationship between IV iron dose and bacteremia was not supported. Randomized clinical trials are needed to assess the effect of cumulative IV iron doses and the risk of infection-related mortality.

4. Conclusions

The new protocol for anemia management, in accordance with the recent published guidelines “Clinical Practice Guideline for Anemia in Chronic Kidney Disease” from KDIGO [24], contributed to an increase in the frequency and in the dose of iron used to treat anemia of CKD patients. Higher values of TSAT and ferritin have been found in dialysis patients, raising concerns about iron overload. Data reported in literature alerts to the safety of cumulative higher iron doses in dialysis patients, as they seem to be associated with increased risk of

iron overload, toxicity and infection, which can lead to an increased risk of mortality in these patients. Actually, there is a need to clarify the effect of the actual iron dosing in CKD patients and its effect on mortality.

Practice points

- Iron deficiency (absolute or functional) is a common cause of anemia in CKD patients.
- The number of HD patients with IV iron supplementation and the prescribed doses increased in the past years.
- The prevalence of HD patients with ferritin levels above 800 ng/mL has increased.
- Iron overload in HD patients has been reported in several studies; however, the relationship between iron overload and mortality risk is not clear.
- Serum ferritin is not always a predictor of iron overload, due to confounding factors, as inflammation and malnutrition.
- Non-invasive techniques, as magnetic resonance imaging and magnetic susceptometry, are new tools to evaluate iron overload in CKD patients.

Research agenda

- Clinical trials to evaluate the association between high iron doses, iron overload and mortality risk in HD patients.
- Basic and clinical research is still needed to find better markers and assays to evaluate iron overload.

Conflict of Interest Statement

The authors report no conflicts of interest.

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Figure Legends

Figure 1. Iron absorption and regulation of iron metabolism. Diet iron is present as either heme iron (Fe2+) or nonheme iron (Fe3+). Nonheme iron (Fe3+) must first be reduced to Fe2+, by duodenal cytochrome B (DcytB), before it can be transported by the divalent metal iron transporter 1 (DMT1). Once inside the enterocyte, the newly absorbed iron enters the intracellular iron pool. If the iron is not required by the body, it is loaded onto the iron storage protein ferritin. Iron required by the body is transferred across the basolateral membrane by ferroportin (FPN). The export of iron also requires the ferroxidase hephaestin (HEPH). Iron is transported by transferrin (Tf) to the local where it is needed, as in bone marrow to erythropoiesis. The senescent erythrocytes are phagocyted by macrophages recycling iron. Hepcidin the main regulator of iron metabolism (by blocking FPN action) is synthesized by the liver and regulated by several stimulator (+) and inhibitor (-) factors, as transferrin saturation (TSAT), inflammation, anemia, erythropoiesis and hypoxia. BMP6 – Bone morphogenetic protein 6; BMP-r – BMP receptor; HFE – hemochromatosis protein; HIF – hypoxia inducible factor; HJV – hemojuvelin; IL6 – Interleukin 6; IL6-r- IL6 receptor; TFR –Transferrin receptor.

Figure 2. Iron deficiency and treatment. Iron deficiency can be absolute or functional according to transferrin saturation (TSAT) and ferritin values. Oral or intravenous (IV) iron can be used to correct iron deficiency depending on patients characteristics.

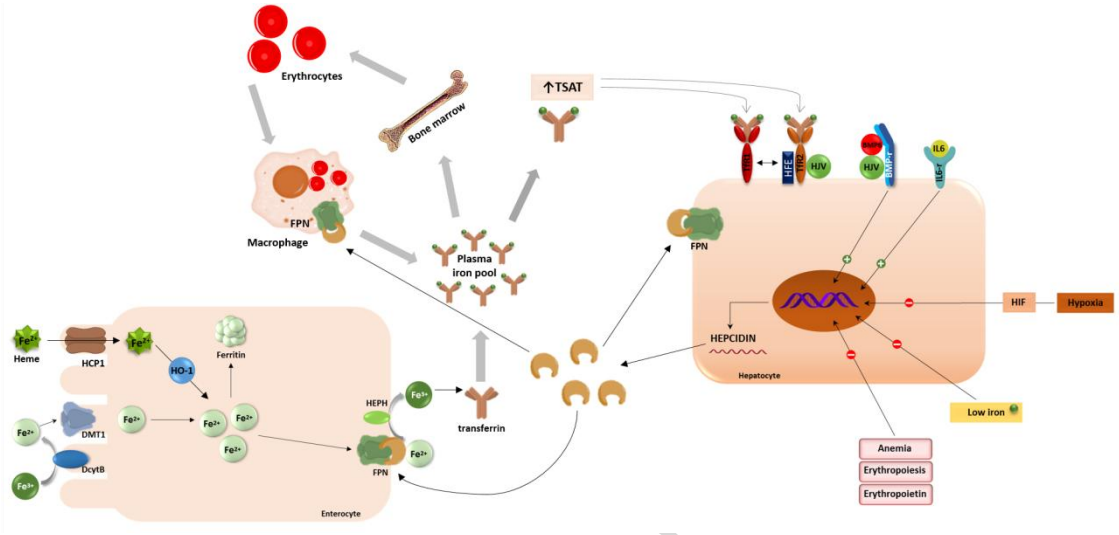

Figure 1

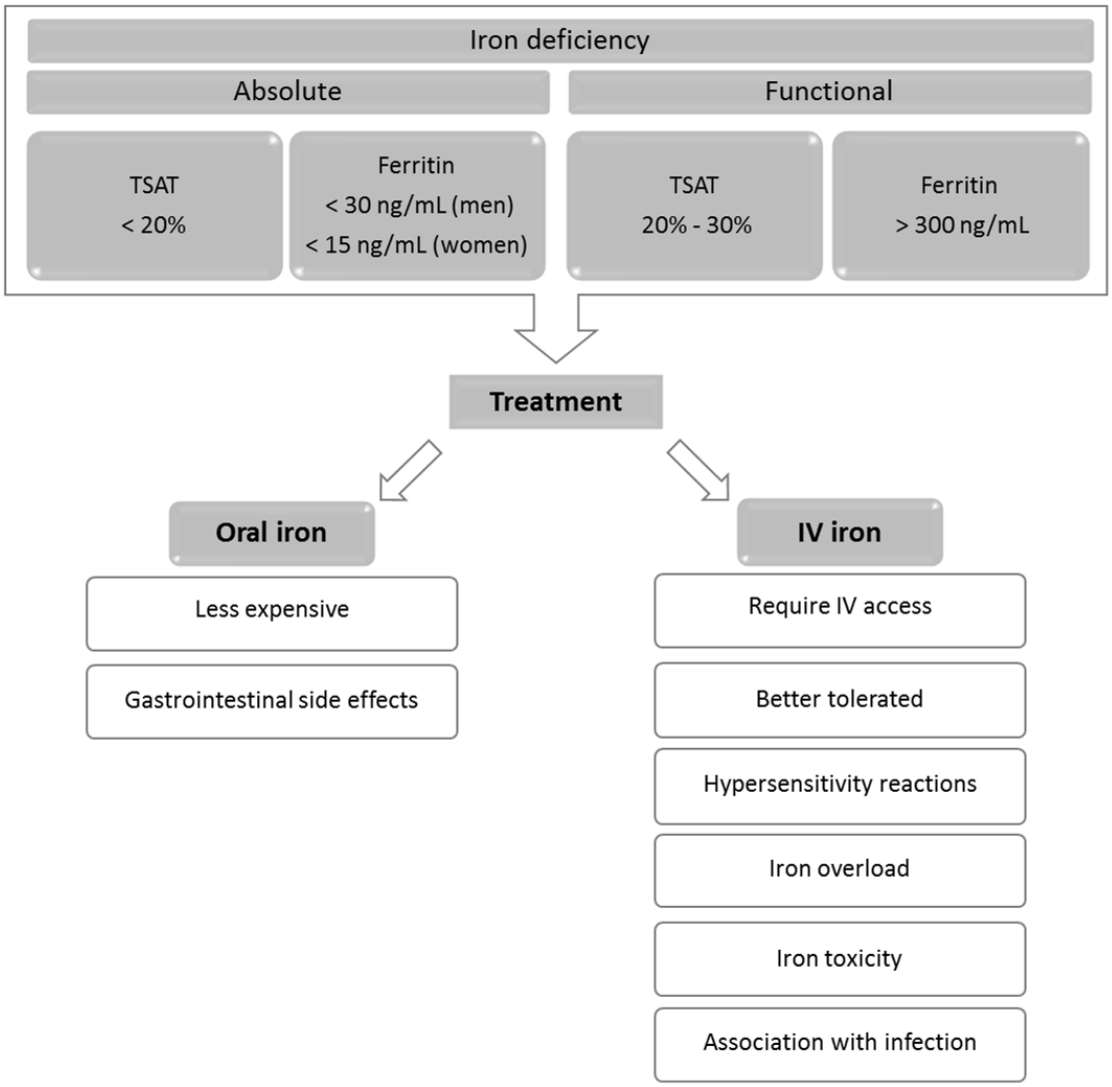

Figure 2

Table 1 – Erythropoiesis-stimulating agents approved for CKD anemia treatment

Short-acting	Long-acting
Epoetin beta	Darbopoetin alpha
Epoetin alpha	Methoxy polyethylene glycolepoetin beta
Epoetin zeta	
Epoetin theta	

Table 2 – Iron supplements approved for CKD anemia treatment

Oral	Intravenous
Ferrous sulfate	Iron sucrose
Ferrous gluconate	Ferumoxytol
Ferrous fumarate	Ferric carboxymaltose
	Iron dextran

Table 3 – Studies evaluating iron overload and mortality risk associated with intravenous iron therapy in dialysis patients

	Year	Patients	Iron dose/Follow-up time	Outcome	Ref.
Iron overload	2012	HD patients (n=119)	100 mg of iron sucrose (2-3x/w - induction phase; 1x/w every 4 w - maintenance phase) 60 mo follow-up	• 84 % of patients with hepatic iron deposition, 30% of them with severe iron overload • Iron liver content correlates with infused iron	[54]
	2012	HD patients (n=21)	100 mg (ferric saccharate) 1-3x/w 12 mo follow-up	• 90% of patients with mild-to-severe hepatic iron deposition • 95% of patients with splenic iron deposition • 14% patients with pancreatic iron deposition	[53]
	2011	CKD patients (n=25)	50 to 200 mg/mo for 12 mo	• Liver iron concentration: 60% of patients > 60 umol/g; 13% of patients > 130 umol/g (reference value 30 umol/g)	[49]
	2004	HD patients (n=40)	31.25 mg ferric gluconate complex 10 patients: maintenance iron at least 6 mo 30 patients: without iron therapy at least 2 mo (after ferritin > 500 ug/L)	• 70% of patients with mild-to-severe hepatic iron overload • 70% of patients with ferritin < 500 ng/mL	[52]
Mortality	2015	HD patients (n=32 435)	4 month-follow up of IV iron dose: < 300 mg/mo *versus* ≥ 300 mg/mo	• ↑ mortality among patients with higher doses of IV iron (≥ 300 mg/mo over 4 months), regardless serum ferritin or CRP values	[60]
	2014	dialysis patients (n=235)	7.6 years-follow up with continuous maintenance iron therapy once/w in varying doses: 12.5 mg (minimum dose) to 62.5 mg (maximum dose)	• ↑ mortality with ferritin levels > 800 ng/mL in case of concomitant inflammation (CRP > 0.5 mg/dL)	[59]
	2013	HD patients (n=117 050)	3 mo-follow up after 1 mo exposure to: high dose (> 200 mg) *versus* low dose (1-200 mg) bolus (consecutive doses ≥ 100 mg exceeding 600 mg during one month) *versus* maintenance dose	• no significant associations of bolus versus maintenance dose or high dose *versus* low dose IV iron with increased short-term cardiovascular morbidity and mortality	[58]
	2005	HD patients (n=58 058)	Iron gluconate effect in a 2 year-follow up, with different iron dose categories: 0 mg/mo; 1 to 199.9 mg/mo; 200 to 399.9 mg/mo; > 400 mg/mo	• ferritin 200-1200 ng/mL, TSAT 30-50% and IV iron dose < 400 mg/mo associated with improved survival	[57]
	2004	HD patients (n= 27 280)	Effect of iron administration in a 2 year follow-up, with iron doses categories at each 6 mo: >0 to 700 mg; > 700 to 100 mg; > 1000 to 1800 mg; > 1800mg	• no association between iron administrated and mortality • association between iron dose and mortality at 12 to 18 months of treatment, for doses > 1800 mg • association between mortality and ferritin > 800 ng/mL in the 6 months prior to death	[56]

	2002	HD patients (n= 10 169)	number of 100-mg vials of iron during 6 mo	• ↑ risk of death and hospitalization with IV iron > 1000 mg	[55]

CRP – C reactive protein; HD – hemodialysis; IV – intravenous; mo - month; w – week.