

NEPHROLOGY

Rounds™

Iron Therapy in Chronic Kidney Disease

By BRADLEY M. DENKER, MD

Iron is essential for a wide variety of metabolic processes and is required for erythropoietin to effectively stimulate red blood cell production. However, iron (Fe) in solution is potentially highly toxic to vital cell structures and numerous mechanisms have evolved to minimize “free iron,” yet provide adequate supplies for heme-protein production. Iron can damage tissues by catalyzing the conversion of hydrogen peroxide to free-radical ions that attack cellular proteins, DNA, and membranes.¹ The necessity for Fe in fundamental physiologic processes and the potential for significant cellular damage in the “free” or unbound form has led to specialized mechanisms of absorption, delivery, and storage. Virtually all Fe that is not incorporated into heme-proteins is bound to 2 proteins: transferrin and ferritin. Iron bound to transferrin is the only mechanism for Fe transport in the circulation, while Fe bound to ferritin is confined to tissue storage. This issue of *Nephrology Rounds* reviews Fe homeostasis and monitoring, oral and intravenous Fe replacement, and potential Fe toxicity. Maintenance of adequate red blood cell mass requires both Fe and erythropoietin. The physiology and replacement of erythropoietin in kidney disease was reviewed in a prior issue of *Nephrology Rounds* (Vol. 2; Issue 3, March 2004).

Physiology of iron metabolism

Iron distribution and balance is summarized in Figure 1. An average adult male has ~50 mg/kg of total body Fe, while premenopausal women have lower levels (~38 mg/kg).² A majority of total body Fe is found in developing and circulating red blood cells (RBCs). In an average male with 3500 mg of total body Fe, approximately two-thirds (~2000 mg) is utilized in the RBC compartment (bone marrow and circulating RBCs; Figure 1). A small amount (10%-15%) of Fe is utilized in myoglobin and other heme-containing enzymes and cytochromes. The remaining one-third (approximately 1200 mg) is stored in tissues, predominantly the liver and macrophages of the reticuloendothelial system. The liver has first-pass access to dietary nutrients and can take up Fe that exceeds the binding capacity of transferrin. The reticuloendothelial macrophages ingest senescent RBCs, catabolize hemoglobin to scavenge Fe, and reload the Fe onto transferrin for re-use, Figure 1. In the steady state, oral intake equals gastrointestinal loss since there is no excretory pathway for Fe through the kidney or liver. Typically, only 1-2 mg/day are orally absorbed in the duodenum and proximal jejunum and, in the presence of Fe deficiency, this can increase several-fold.

The challenge in safely delivering Fe into the bone marrow for hematopoiesis is highlighted by the requirement for >20 mg/day just for steady state turnover of RBCs, but the total transferrin-bound pool is only 3-4 mg (Figure 1). Therefore, active transport of Fe from tissue stores to transferrin for delivery to the bone marrow is essential for hematopoiesis to occur. This fundamental concept is central to the understanding of Fe regulation (and deficiency) in kidney disease and it significantly affects issues related to Fe therapy and toxicity that will be discussed below. In solution, Fe exists in 2 oxidation states (Fe⁺² and Fe⁺³) that can donate or accept electrons, respectively. Under physiologic conditions, Fe⁺² is more soluble and absorbable, but can be readily oxidized to form insoluble Fe(OH)₃ polymers. Each molecule of transferrin has 2 high-affinity Fe⁺³ binding sites, and binding to the transferrin-receptor on developing erythrocytes results in receptor-mediated endocytosis, acidification, and release into the cytoplasm.³ In erythroid cells, Fe is taken up by mitochondria

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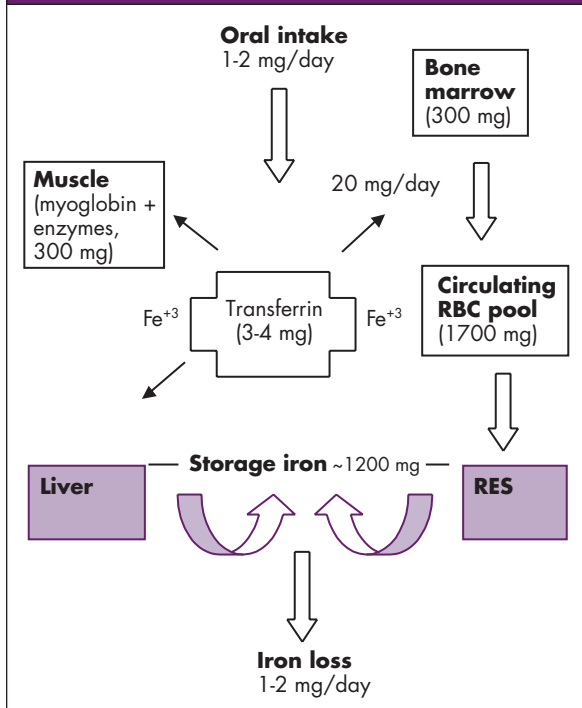
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Figure 1: Iron balance



In the steady state, Fe intake and losses are equivalent and represent only a few milligrams/day. In Fe-deficient states, gastrointestinal absorption can be modestly increased (see text). Most Fe is in developing RBCs (bone marrow) or in the circulating RBC pool. Circulating Fe exists only bound to transferrin and this pool is limited to 3-4 mg. Since >20 mg/day is needed for steady state erythropoiesis, this pool must completely turn over 5-6 times/day. Functional Fe deficiency occurs when the demand for Fe in the bone marrow to support accelerated hematopoiesis exceeds the capacity for delivery by transferrin. Fe is stored in the liver and the reticuloendothelial system (shaded boxes) and represents about one-third of total body Fe. Serum ferritin reflects storage Fe, while the transferrin saturation (see text) indicates the circulating Fe pool.

where it is incorporated into protoporphyrin to make heme. In non-erythroid cells, released Fe is stored as ferritin or hemosiderin. Ferritin is composed of 2 peptides that form a shell capable of binding up to 4,500 Fe molecules, although the mechanisms for release of ferritin-bound iron are not well understood.⁴

Iron balance is significantly altered in renal disease. Fe absorption is normally regulated by body Fe stores and the rate of erythropoiesis, but is limited by the gastrointestinal tract. The protein hepcidin is produced by the liver and, in the presence of elevated iron stores, prevents gastrointestinal iron absorption and blocks release from the reticuloendothelial system. Inflammatory states, such as infection, stimulate cytokine release (particularly IL-6) resulting in elevated hepcidin levels. This is the likely mechanism blocking effective iron utilization in the anemia of chronic disease.⁵ There are conflicting data

regarding whether Fe absorption is increased or decreased in patients on dialysis.⁶ Nevertheless, Fe demand is significantly increased in dialysis patients who have an estimated Fe loss of 1000-3000 mg/year through blood loss on dialysis and from phlebotomy. In addition, RBC lifespan is reduced in renal disease, requiring more rapid RBC turnover to maintain a given hemoglobin concentration. Finally, the use of recombinant human erythropoietin (rHuEpo) accelerates RBC differentiation and production, resulting in “functional iron deficiency.”² This occurs when increased RBC iron requirements exceed the available supply of Fe, even in the presence of storage Fe (Figure 1).

Assessing/monitoring iron stores

There are multiple challenges in accurately determining Fe stores in kidney disease patients. Clinicians need to consider circulating Fe in plasma (available Fe), “total” Fe stores (tissue compartment), and Fe utilization in the bone marrow (erythropoiesis). The circulating Fe pool (available for movement between storage and utilization in the bone marrow) is only 3-4 mg and is bound to transferrin. The only measurement available to assess this pool is the transferrin saturation (TSAT), which is determined by serum Fe/TIBC (total iron-binding capacity) x 100.

In healthy patients undergoing phlebotomy, there is little change in serum Fe levels until stores are exhausted and serum Fe falls to <50 µg/dL.⁷ Transferrin increases linearly to approximately 400 µg/dL and transferrin saturation falls to <16%. The “gold standard” for determining Fe deficiency is bone marrow staining, but even this invasive test is not absolute. One study in 20 dialysis and 5 chronic kidney disease (CKD) patients correlated bone marrow Fe with transferrin saturation and ferritin.⁸ Overall, a TSAT <20% was 88% sensitive and 63% specific. Excluding patients with hypoproteinemia (transferrin <150 mg/dL) improved TSAT sensitivity to 100% and specificity to 80%. Although an easy test to obtain with reasonable sensitivity and specificity, it cannot diagnose functional Fe deficiency that occurs during rhEpo therapy.

Serum ferritin is a widely utilized marker of storage Fe although, in renal patients undergoing bone marrow biopsy, a ferritin <200 mg/dL was 100% specific, but only 41% sensitive.⁸ Therefore, low ferritin levels are virtually diagnostic for Fe deficiency, but since ferritin is a marker of inflammation (particularly common in renal disease patients), high ferritin levels do not exclude Fe deficiency. Ferritin levels fall with administration of rhEpo to 50%-75% below baseline and there may be a more labile pool of storage Fe in equilibrium with the erythropoietic compartment.⁴ Finally, tissue ferritin and serum ferritin are not identical. Serum ferritin is glycosylated, while tissue ferritin is not, yet both are detected with standard assays, raising issues of interpretation.⁹

The diagnosis of functional Fe deficiency is ultimately made by the response to Fe replacement. The challenge is detecting functional Fe deficiency in patients receiving rhEpo with available laboratory measurements. A prospective study of 50 dialysis patients found that in those who responded to Fe replacement (ie, were functionally iron deficient), transferrin saturation and ferritin had a sensitivity and specificity of <80%. However, in patients who did not respond to increased doses of rhEpo, using a transferrin saturation of <27% or ferritin <300 µg/L offered a sensitivity of >90%.¹⁰ This suggests that dialysis patients who are not adequately responding to rhEpo should have transferrin saturation increased to >27% to exclude functional Fe deficiency.

Other laboratory tests have been investigated for identifying functional Fe deficiency. The percentage of hypochromic RBCs increases in dialysis patients receiving rhEpo, and values >10% (normally <2.5%) are compatible with functional Fe deficiency. This value can be obtained from the red cell distribution width (RDW) obtained with every hemogram. The RDW reflects the distribution of the mean cell volume (MCV) and hypochromic RBCs will appear larger than normochromic ones. However, increased hypochromic RBCs also occur in patients with increased numbers of normal reticulocytes and young RBCs. The reticulocyte hemoglobin content (CHr) is another hematology test that may be useful for diagnosing functional iron deficiency, and predicted a response to Fe repletion in dialysis patients (sensitivity 100%, specificity 80%). However, it is not yet routinely available in most laboratories. Zinc protoporphyrin (ZnPP) is another direct measure of Fe availability to the bone marrow, but also has significant limitations.

Although not perfect markers, serum ferritin and transferrin saturation are reasonable parameters for assessing Fe stores and the circulating Fe pool, respectively. Currently, there are no readily available laboratory tests to diagnose functional Fe deficiency. To exclude functional Fe deficiency in patients receiving rhEpo, Fe replacement should be initiated even with transferrin saturation and ferritin levels above suggested limits. Current Dialysis Outcomes Quality Initiative (DOQI) guidelines are for a target hemoglobin of 11-12 g/dL, transferrin saturation ≥20%, and ferritin ≥100 ng/mL.¹³ The concern for Fe overload in the setting of elevated ferritin levels will be discussed below.

Replacing iron

Oral Fe preparations are safe, but limited by side effects and gastrointestinal absorptive capacity. Fe⁺² is absorbed more rapidly due to its increased solubility, although absorption does not appear to be affected by the specific ferrous salt (fumarate, succinate, or gluconate). Gastrointestinal intolerance, usually constipation, often leads to poor patient compliance, and absorption is further

Table 1: Available intravenous iron preparations. The 2 available iron dextrans differ in molecular weight.

Iron preparations	Molecular weight (kDa)	Half-life (hours)	How supplied	Direct to transferrin	Test dose
Iron dextran	96/267	48 h	100 mg	No	Yes
Iron gluconate	350	1 h	62.5 mg	No	No
Iron saccharate	40	6 h	100 mg	Yes	No

reduced if taken with food and/or phosphate binders. Fe absorption is increased if taken with ascorbic acid since it reduces ferric (Fe⁺³) to ferrous (Fe⁺²) iron and prevents formation of insoluble Fe compounds in the gut. However, ascorbic acid is a precursor for oxalates that can accumulate in dialysis patients. Several studies have demonstrated that oral Fe is not adequate to maintain Fe stores in dialysis patients,^{14,15} although one study comparing 4 different oral Fe preparations found that Fe supplementation may maintain adequate stores in the short term.¹⁶ In addition, there were no significant differences in side effects among any of the tested formulations, including Fe polysaccharate.¹⁶

Multiple parenteral Fe formulations are now available for Fe replacement (Table 1) and most dialysis patients will require intravenous Fe replacement. All Fe preparations have demonstrated efficacy in repleting Fe stores, although their pharmacokinetics and potential side effects vary.

Iron dextran: Two Fe dextrans are available for use (Dexferrum, Luitopold Pharmaceuticals; and INFed, Schein Pharmaceuticals). The half-life of the Fe dextrans is relatively long at 1-3 days, potentially overwhelming the uptake mechanisms in the reticuloendothelial system and elevating serum Fe and ferritin for days after a 500 mg infusion. Both dextrans are similar in effectively repleting Fe in hemodialysis patients.¹⁷ Iron dextrans have also been effectively utilized in Fe-deficient peritoneal dialysis (PD) and CKD patients with single 1000 mg infusions (over 4 hours). Until recently (1999), these were the only iron preparations available and significant side effects were reported with these compounds. Severe anaphylactic reactions (~0.7%), including some deaths, have been reported with iron dextran,¹⁸ leading to potential undertreatment of Fe deficiency.

Iron gluconate: (Ferrlecit, Schein Pharmaceuticals) was approved in 1999 for use within the United States and has been used in Europe for >40 years. It contains 62.5 mg of Fe in complex with sodium gluconate and is considered to be relatively unstable, allowing rapid release of Fe in comparison with other preparations (serum half-life ~1 hour). The complex is provided in a sucrose solution, but is not to be confused with iron sucrose (discussed below). It has been shown to be safe and effective in hemodialysis patients

with only minor side effects.¹⁹ A direct comparison with Fe dextran revealed a much lower adverse event rate²⁰ and side effects were comparable with controls.

Iron sucrose: (Venofer, American Reagent Laboratories) has been used worldwide for many years and was approved for use in the United States in November, 2000. It was shown to be effective and safe in a North American clinical trial.²¹ Iron sucrose is a polynuclear Fe hydroxide sucrose complex with a serum half-life of 5-6 hours.²² Unlike Fe dextrans and gluconate, Fe sucrose follows 2 different distribution pathways after injection:

- the expected uptake in the reticuloendothelial system
- some dissociates within the serum and is directly bound to transferrin, raising the potential for additional side effects from free Fe.

Overall, the side effect profile is similar to Fe gluconate, and a retrospective analysis of healthy volunteers and dialysis patients in Switzerland found a 0.1% incidence of reversible hypotension and no deaths.²³ One study suggested that there is transferrin oversaturation (>80%) for several hours after Fe sucrose administration,²² but this was not documented in a recent study on dialysis patients.²⁴ One in vitro study found similar oxidative potential in all Fe preparations, but the only one with increased cellular toxicity was with Fe sucrose.²⁵

The optimal delivery schedule for intravenous Fe that prevents functional Fe deficiency, yet minimizes potential harm, has not been identified. Multiple studies have demonstrated the effectiveness of intravenous Fe therapy and most have shown reduced rhEpo dosing and increased hemoglobin with maintenance dosing. A composite analysis of 13 studies through 1999 demonstrated that there was a 42% decrease in rhEpo dose and 18% increase in hemoglobin concentration²⁶ and current DOQI guidelines recommend replacement with 1 gm of Fe over 8-10 consecutive dialysis sessions in Fe-deficient patients, and maintenance Fe therapy of 25-125 mg/week.¹³ A randomized trial revealed that increasing TSAT to 30%-50% led to less functional Fe deficiency and a 40% reduction in rhEpo dosing.²⁷ However, there was a trend toward significantly higher ferritin (658 ng/mL) levels in these patients, and current guidelines suggest holding all Fe therapy if the TSAT is >50% and/or the ferritin is >800 ng/mL.

All 3 forms of available intravenous (IV) Fe therapy have been utilized in PD and CKD patients on rhEpo. In a study in PD patients, a single infusion of 1 gm of Fe dextran over 4 hours was superior to oral Fe therapy and resulted in higher hematocrits on lower rhEpo doses.²⁸ Iron gluconate administered at 125 mg/week was safe and effective in PD and CKD

Table 2: Potential side effects of intravenous iron therapy

Cardiac arrest	Palpable purpura
Hypotension	Arthralgias
Pulmonary edema	Headache
Bronchospasm/ laryngospasm	Nausea/vomiting/ diarrhea
Stridor	Swelling
Urticaria/pruritis	Myalgias
Dyspnea/wheezing	Skin flushing
Abdominal/chest pains	Edema

patients,²⁹ and doses of Fe sucrose from 200-500 mg administered weekly were well-tolerated and effective in CKD and PD patients.³⁰

Toxicity of intravenous iron

There are two areas of concern with administration of IV iron. The first are short-term side effects occurring within minutes to days of Fe infusion. Table 2 lists the short-term adverse reactions to Fe therapy. The second area of concern relates to the long-term toxicities of Fe overload with organ damage in liver, pancreas, and heart, potential increases in infection rates, and risk of myocardial infarction and cancer. Adverse reactions may be towards “free” iron or to the carrier. The most serious adverse reactions to Fe dextran are thought to be from the dextran moiety and may relate to mast cell degranulation without immune complex involvement.³¹ There is little direct evidence that free Fe exists at clinically significant levels and increased non-transferrin-bound Fe is likely a methodological artifact.³² Symptoms of arthralgias, abdominal pain, chest pain, myalgias, rash, and facial redness, as well as hypotension, tend to be related to the rate of Fe administration.

Early (pre-rhEpo) studies with dialysis patients suggested a link between Fe excess and infection³³⁻³⁵ but, considering the dramatic effect on Fe metabolism that is induced with rhEpo, these relationships have been questioned. Some more recent epidemiologic studies have suggested a link between IV Fe administration and mortality,³⁶ but recent re-analysis suggests that these associations may have been confounded.³⁷ In addition, a recent study found that low serum Fe correlated with hospitalizations and mortality in >1280 dialysis patients.³⁸

Nevertheless, significant concern exists about toxicity in these patients, particularly for cardiovascular disease and infection. Free Fe could result in a number of reactions, leading to increased oxidative stress. Superoxide generation from white blood cells during inflammatory processes could catalyze the

Fenton reaction ($\text{Fe}^{+3} \rightarrow \text{Fe}^{+2}$) leading to the generation of free hydroxyl-radicals that generate reactive oxygen species and lipid oxidation. Although there is little evidence that these processes occur in vivo, in dialysis patients with cardiac disease, randomized to normal hematocrit (42%) versus 30%, there was higher mortality in the normal hematocrit group.³⁹ One of the differences between the two groups was the amount of Fe administered. There was a 2.4 odds ratio of mortality for patients who received IV Fe dextran and more Fe was administered to the normal hematocrit group. Some studies have correlated the increased risk of myocardial infarction in men with ferritin levels,⁴⁰ but others have failed to confirm this association.⁴¹ A prospective study in dialysis patients failed to find a relationship between ferritin and cardiovascular death, and an autopsy study of hemochromatosis patients found less coronary artery disease than in age-matched controls.⁴²

Numerous in vitro studies have postulated tissue toxicity from Fe and increased infectious potential.⁴³ Neutrophils from hemodialysis patients and hemochromatosis patients with elevated ferritin levels >650 ng/mL, all had significant inhibition of intracellular bactericidal effects.⁴⁴ However, large-scale clinical observations have not firmly linked an increase in infectious risk to IV Fe. The prospective EPIBACDIAL study examined risk factors for infection in hemodialysis patients. Anemia, a prior episode of infection, immunosuppressive therapy, and dialysis through a tunneled catheter were all associated with increased risk of infection. However, there was no correlation with Fe therapy.⁴⁵ A further retrospective analysis of this patient cohort confirmed the absence of a correlation between Fe use and infectious risk.⁴⁶

Conclusion

Iron supplementation is essential in most dialysis and CKD patients treated with rhEpo. The benefits of anemia correction are well-established and Fe replacement is effective and safe. Oral Fe is safe, but probably ineffective in most patients and limited by side effects. There are several IV Fe choices, all with proven efficacy, although Fe dextrans are associated with a higher incidence of serious adverse reactions. Short-term risks of non-dextran preparations appear similar and quite low.⁴⁷ There are some differences in pharmacokinetic profiles and in vitro toxicity between Fe gluconate and Fe sucrose, but additional studies are necessary to distinguish different safety profiles in vivo. The fact that both compounds have been in use for >40 years outside the United States suggests that any differences in the safety profile are likely to be minor. The long-term risks of Fe therapy remain to be determined, but data to date fail to clearly demonstrate increased risks of infection and there is little

evidence for significant free Fe and increased cardiovascular events. However, in patients with known cardiovascular disease, aggressive Fe therapy should be undertaken with caution. In those with active infection, the risk of Fe administration is unknown, but these patients are likely to be rhEpo-resistant and transfusions should be considered for the short-term. There is general agreement that maintenance Fe therapy is effective in reducing functional Fe deficiency, increasing the efficiency of hematopoiesis, and reducing rhEpo requirements. However, the exact schedule for delivery needs to be optimized for each patient and there should be regular monitoring of Fe stores. According to current DOQI guidelines, Fe therapy should be discontinued with a TSAT >50% and/or ferritin >800 ng/mL.

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