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Intravenous Iron Versus Erythropoiesis-Stimulating Agents: Friends or Foes in Treating Chronic Kidney Disease Anemia?

Kamyar Kalantar-Zadeh, Elani Streja, Jessica E. Miller, and Allen R. Nissenson

Patients with chronic kidney disease (CKD), especially those requiring maintenance hemodialysis treatments, may lose up to 3 g of iron each year because of frequent blood losses. Higher doses of erythropoiesis-stimulating agents (ESAs) may worsen iron depletion and lead to an increased platelet count (thrombocytosis), ESA hyporesponsiveness, and hemoglobin variability. Hence, ESA therapy requires concurrent iron supplementation. Traditional iron markers such as serum ferritin and transferrin saturation ratio (TSAT) (ie, serum iron divided by total iron-binding capacity [TIBC]), may be confounded by non–iron-related conditions. Whereas serum ferritin <200 ng/mL suggests iron deficiency in CKD patients, ferritin levels between 200 and 1,200 ng/mL may be related to inflammation, latent infections, malignancies, or liver disease. Protein-energy wasting may lower TIBC, leading to a TSAT within the normal range, even when iron deficiency is present. Iron and anemia indices have different mortality predictabilities, in that high serum ferritin but low iron, TIBC, and TSAT levels are associated with increased mortality, whereas hemoglobin exhibits a U-shaped risk for death. The increased mortality associated with targeting hemoglobin above 13 g/dL may result from iron depletion-associated thrombocytosis. Intravenous (IV) iron administration may not only decrease hemoglobin variability and ESA hyporesponsiveness, it may also reduce the greater mortality associated with the much higher ESA doses that have been used in some patients when targeting higher hemoglobin levels.

Index Words: Transferrin saturation ratio; Erythropoiesis-stimulating agent; Intravenous iron; Ferritin; Inflammation

Erythropoiesis-stimulating agents (ESAs) are the medications of choice for the treatment of the erythropoietin deficiency that is believed to be the fundamental etiology of anemia of chronic kidney disease (CKD).[1,2] Since Medicare entitlement for dialysis was implemented in 1973 in the United States, one of the relatively expensive components of total patient care has been the cost of ESAs. For instance, in 2005, ESAs accounted for over $2 billion US dollars in costs for approximately 350,000 dialysis patients.[3]

However, for optimal hemoglobin synthesis and maintenance, both ESA and iron supplementation are required as shown in Figure 1.[4] Iron is indeed the core raw material for the production of the red blood cells (RBCs). Without iron, hemoglobin can be neither synthesized nor can RBCs be reproduced or maintained in the circulation at an adequate level. Hence, similar to a construction site, where both laborers and raw materials are needed simultaneously for the success of the building project, the RBC production in the bone marrow is dependent on both ESA and iron, as depicted in Figure 1. As a result, giving ESA without iron supplementation, or vice versa, is a suboptimal treatment strategy.

Estimated Annual Iron Requirement in CKD Patients

The amount of required iron to maintain stable iron availability in CKD patients is not clear.

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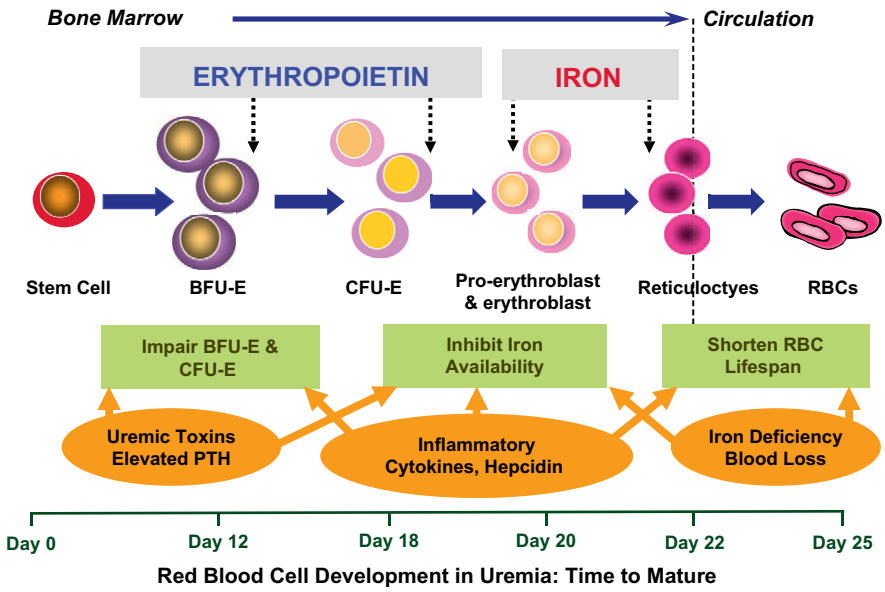

Figure 1. Optimal red blood cell (RBC) production requires both erythropoietin (as the controlling factor) and iron (as the raw material). Several factors can impair RBC production; inhibit iron availability, and/or shorten RBC lie span (see text). BFU-E, burst-forming unit erythroid; CFU-E, colony-forming unit erythroid.

Despite interindividual variability, it is estimated that approximately 1 mg/d or 300 to 500 mg/y of iron is lost in every individual.[5] Most CKD patients, however, are subjected to frequent blood draws for laboratory testing, which is a major cause of substantial blood loss. In hemodialysis patients, weekly to monthly blood tests may result in up to a gram of iron loss each year.[5] Losing residual blood in the dialyzer tubing or catheters and accidental blood losses can further increase iron losses by approximately another 1 g. Slow chronic blood loss in the gastrointestinal tract because of platelet dysfunction and inadequate iron intake are additional contributors. Hence, up to 3 g of iron may be lost annually in an average chronic hemodialysis patient as shown in Figure 2.[1,6]

Assessment of Iron Status in CKD Patients

The most frequently used iron markers in CKD patients are serum iron; transferrin saturation ratio (TSAT), also known as the iron saturation ratio; and serum ferritin.[6] Some less frequently tested iron markers include bone marrow iron staining,[7,8] reticulocyte hemoglobin content,[9] percentage of hypochromic red cells,[10] soluble transferrin receptor,[11] erythrocyte zinc protoporphyrin,[12] and hepcidin.[13] Nevertheless, with the exception of serum iron, TSAT, and ferritin, the latter tests are rarely used beyond investigational purposes.

It is important to note that the 3 routinely measured markers of iron status are all imperfect in terms of specificity and/or sensitivity. Serum ferritin is an acute-phase reactant. Proinflammatory cytokines such as interleukin-1 beta and tumor necrosis factor α increase the synthesis of ferritin subunits through increased translation of preformed ferritin messenger RNA.[6,14] This inflammation-induced hyperferritinemia that provides more ferritin molecules to trap and immobilize iron may be one of the core components of so-called "functional iron deficiency."[15] The foregoing process may indeed be physiological in acute inflammation in which iron containment in the reticuloendothelial sites may mitigate the risk of infection, but it may be harmful under chronic inflammatory conditions by leading to iron immobilization and worsening anemia.[6] Hepcidin levels also increase under inflammatory circumstances.[13] Hence, anti-inflammatory interventions or hepcidin antibodies may be promising strategies to overcome the functional iron deficiency.[16]

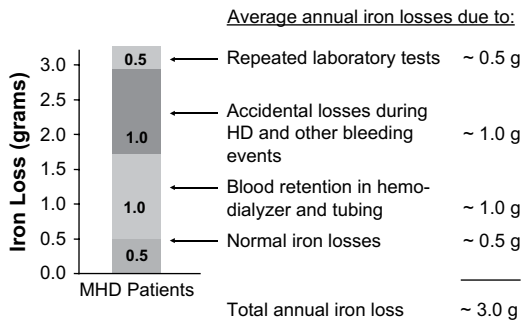

Figure 2. Estimated annual loss of iron in each chronic hemodialysis patient.

Nevertheless, although moderately high serum ferritin may be caused by inflammation, a low serum ferritin level (eg, <200 ng/mL) in hemodialysis patients is a rather specific marker of iron deficiency, as shown in the suggested algorithm in Figure 3.

Although a serum ferritin between 200 and 500 ng/mL can be associated with adequate iron stores when TSAT is >25%, moderately high ferritin levels, namely in the 500 to 1,200 ng/mL range, may be attributed to inflammation, infection, liver disease, malignancies, or other non–iron-related conditions. Hence, clinical workup, as suggested in Table 1, may be necessary to explain the underlying etiology of mild to moderate hyperrferritinemia.[17] Indeed, a recent randomized trial showed that the addition of intravenous (IV) iron gluconate to ESA therapy is effective in treating ESA hyporesponsiveness under such circumstances.[18,19] Nevertheless, caution is warranted when IV iron supplementation is considered with ferritin values >1,200 ng/mL because such high ferritin levels may be related to iron overload (Table 1).

Serum transferrin, also known as total iron-binding capacity (TIBC),[20,21] and serum iron[22] are both negative acute-phase reactants in that their levels tend to decrease during inflammation. In particular, the serum TIBC level is low in uremic malnutrition[20] or inflammation.[21] Even though the Kidney Disease Outcomes Quality Initiative guidelines recommend the use of TSAT (ie, iron divided by TIBC) as a screening tool for the assessment of iron stores in CKD patients,[23] TSAT can be significantly confounded by the frequent presence of the malnutrition-inflammation complex.[17] Because the denominator of TSAT (ie, TIBC) is a nutritional and/or inflammatory marker,[24,25] the utility of TSAT should be qualified if TIBC is low (eg, <200 mg/dL), as suggested by Figure 3. Of note, another important distinction between the CKD patients and general

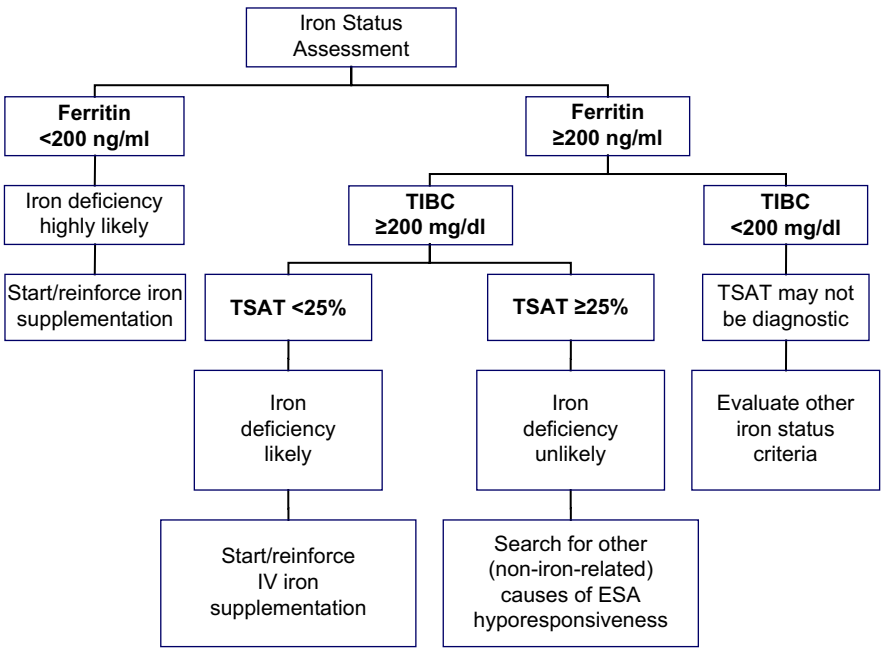

Figure 3. Algorithm of iron status assessment in CKD patients undergoing maintenance dialysis treatment.

Table 1. Recommended Interpretation of Serum Ferritin Levels in CKD Patients

Serum Ferritin Range	<200 ng/mL*	≥200 but <500 ng/mL	≥500 but <1,200 ng/mL	≥1,200 ng/mL
Common conditions in CKD patients	Absolute iron deficiency (most common); ferritin deficiency syndrome*	Likely associated with both absolute and functional iron deficiency	Most commonly associated with inflammation, infection, liver disease, or malignancy	Iron overload may have overwhelmed the effect of inflammation on serum ferritin
Association with iron stores	↓ferritin ← → ↓iron	↑ferritin ← ? → ↓↑iron	↑↑ferritin ← ? → ↑↓iron	↑↑↑ferritin ← → ↑iron
What serum ferritin means	Serum ferritin = iron	Serum ferritin = inflammation + iron + others	Serum ferritin = inflammation + iron + others	Serum ferritin = iron
Recommended course of action	De novo IV iron administration or increasing the IV iron dose is usually indicated irrespective of TSAT	Maintenance of IV iron supplementation (eg, 100 to 500 mg/mo) is indicated to target TSAT between 25% and 50%	Check liver enzymes, assess serum CRP and MIS, rule out latent infection or malignancies. If ESA hyporesponsiveness persists, iron administration may be beneficial especially if TSAT<25%	Iron supplementation should generally be avoided, especially if TSAT >50%

NOTE. In NDD-CKD patients or those undergoing PD, the cutoff level of <100 ng/mL has been suggested by KDOQI guidelines.[57]
Abbreviations: CRP, C-reactive protein; MIS, malnutrition inflammation score.
*The ferritin deficiency syndrome can be present if serum ferritin level is <50 ng/mL (see text).

Table 2. Comparing the "ESA Hyporesponsiveness" and "Functional Iron Deficiency" ("Iron Hyporesponsiveness") in CKD Patients

Characteristic Features	ESA Hyporesponsiveness	Functional Iron Deficiency (Iron Hyporesponsiveness)
Inflammation	High levels of CRP and inflammatory cytokines	High levels of inflammatory cytokines and hepcidin
Nutritional status	Signs of PEW: low albumin and TIBC, high MIS, low appetite, low protein intake	PEW is more likely
Iron stores	Ranging from depleted (iron deficiency) to iron overload	Apparently adequate iron status but trapped (immobilized) in RES
Serum ferritin	<200 ng/mL in iron deficiency >500 ng/mL in most cases	>500 ng/mL
Serum TSAT (iron saturation)	Usually normal to high (>25%)	Usually <25%
Circulating hepcidin	May be increased	Usually increased
Response to increasing ESA dose alone	Limited response, may lead to thrombocytosis and CV events if iron stores are depleted	Limited response
Response to IV iron	Expected if ESA treatment is combined with IV iron repletion	Greater response is expected
Response to anti-inflammatory (eg antihepcidin) interventions	Improved erythropoiesis expected but no clinical data available	Improved erythropoiesis expected but no clinical data available.
Other interventions	Active vitamin D or calcimimetics to correct hyperparathyroidism Nutritional support if PEW	Vitamin C supplementation (mixed data)

Abbreviations: RES, reticuloendothelial system; MIS, malnutrition-inflammation score; PEW, protein-energy wasting; TSAT, transferrin saturation ratio; CV, cardiovascular.

population is that both iron and TIBC tend to decrease in iron deficiency anemia of CKD,[21] whereas in non-CKD individuals with anemia, iron decreases whereas TIBC increases simultaneously, making the TSAT fraction even smaller.

Functional Iron Deficiency Versus ESA Hyporesponsiveness

ESA hyporesponsiveness is a well-known condition that is associated with chronic inflammation;[26] however, the concept of "functional iron deficiency" is somewhat less clear[27] and is based on the notion that iron supplementation during ESA therapy may be less effective in patients with high serum ferritin.[27] As shown in Table 2, there are similarities and differences between ESA hyporesponsiveness and functional iron deficiency, which can also be referred to as "iron hyporesponsiveness." Both conditions appear to be associated with hyperferritinemia[28,29] and an increased level of hepcidin.[13,30] However, in iron hyporesponsiveness, serum TSAT is usually low (<25%), leading to the paradoxic association of high ferritin with low TSAT,[17] whereas the ESA hyporesponsiveness may be associated with iron deficiency (ferritin <200 ng/mL), inflammation, or other conditions.[26] Anemic hemodialysis patients with the paradoxic iron markers (ie, ferritin >500 ng/mL but TSAT <25%) and ESA hyporesponsiveness may still benefit from IV iron supplementation.[18]

Mortality Predictability of Indices of Iron and Anemia

Several observational studies have shown that higher levels of serum ferritin, especially values above 1,200 ng/mL, are associated with increased mortality in hemodialysis patients,[31,32] whereas lower levels of serum TIBC[21] or iron[22] are linked to increased death risk. The TSAT (ie, iron divided by TIBC) shows a U-shaped or reverse J-shaped association with mortality.[32] The observation that

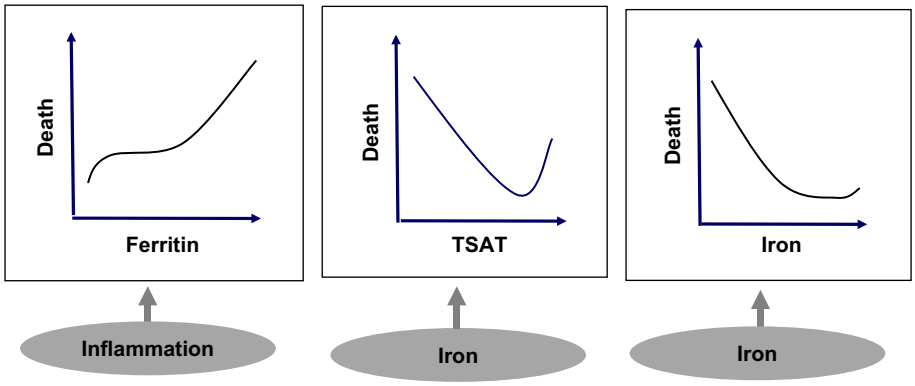

Figure 4. Schematic representation of the mortality predictability of frequently used iron markers in CKD patients undergoing maintenance dialysis treatment. Data from Kalantar-Zadeh et al.[32]

these conventional markers of iron status have different and even opposing mortality associations, as shown in Figure 4, is yet another reason to believe that these iron markers cannot be considered as robust criteria to assess iron status in these patients. Otherwise, they would exhibit similar associations with outcome. Notwithstanding the multivariate analyses, the residual confounding may still have contributed to the mortality differences of the said iron markers.

Several recent, randomized, controlled trials have shown that targeting hemoglobin levels above 13 g/dL to "normalize" hemoglobin in CKD patients are paradoxically associated with worse outcomes.[33-36] A recent retrospective study of 58,058 hemodialysis patients also showed that achieved hemoglobin levels between 11.5 and 13 g/dL were associated with the lowest death risk.[37] It is not clear as to why hemoglobin levels above 13 g/dL in both observational[37] and interventional[38] studies are associated with increased mortality. A recent observational study showed that the administration of high ESA doses without the provision of adequate iron was associated with increased platelet count.[39] In the aforementioned study of 36,735 hemodialysis patients, within each increment of hemoglobin, serum ferritin levels were lower in those with relative thrombocytosis (platelet count >300,000/mm^3) compared with non-thrombocytotic patients, as shown in Figure 5.[39] It was concluded that the higher likelihood of relative thrombocytosis, especially among patients who received exceptionally high ESA doses and hemoglobin above 13 g/dL, might predispose to an increased risk of thromboembolic events.[39] It is also important to note that several other observational studies indicated improved survival in dialysis patients who receive any dose of ESA versus none.[37] Receiving maintenance IV iron supplementation up to 400 mg/mo is also associated with greater survival compared with the absence of IV iron administration or IV iron administration exceeding 400 mg/mo.[32]

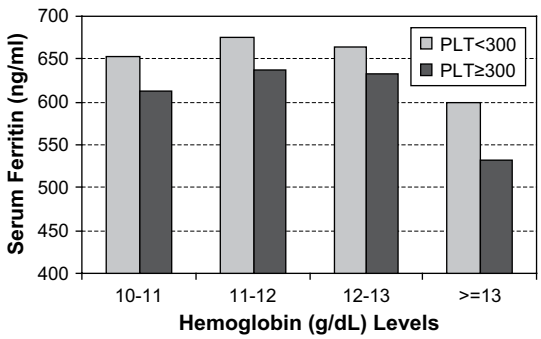

Figure 5. Serum ferritin in 36,735 chronic hemodialysis (HD) patients with hemoglobin (Hb) >10 g/dL. Data from Streja et al.[39]

Fear of Iron

IV iron administration offers several advantages in the treatment of CKD-associated anemia such as improving ESA hyporesponsiveness[26,40] and reducing hemoglobin variability.[41] There are also other non–anemia-related salutary effects

Table 3. Presumed Advantages and Disadvantages of IV Iron Administration in CKD Patients

Advantages of IV Iron in CKD
Reducing ESA dose
Improving ESA hyporesponsiveness
Mitigating hemoglobin variability
Mitigating risk of thrombocytosis
Reducing likelihood of blood transfusion
Circumventing the need for oral iron supplementation
Beyond anemia effects
Treatment of restless leg
Improving cognitive function
Decreasing death risk (?)*
Disadvantages of IV Iron in CKD
Short-term adverse events
Iron overload
Increased risk of infection
Increased oxidative stress
Increased death risk (?)*

*Both decreased and increased death risk have been postulated with IV iron administration.

of iron supplementation such as improving restless leg syndrome[42,43] or decreasing the risk of death as shown by some epidemiologic studies.[32] However, there appears to be a substantial degree of "iron apprehension" in the nephrology community because of the presumptive association of iron with infection, oxidative stress, and hemochromatosis (Table 3).[6] A clinical trial performed almost 3 decades ago in 137 iron-deficient individuals in Somalia showed a 5 times higher risk of infection in those who received iron compared with placebo.[44] In the pre-ESA era, there were hemochromatosis case reports ascribed to frequent blood transfusion or iron administration to anemic dialysis patients.[45,46] In vitro studies indicate an association between iron and oxidative stress.[47,48] Finally, a limited number of observational studies imply an association between high serum ferritin and infection[46,49] or mortality,[31] and in others between iron administration and indices of cardiovascular disease[50] and death in dialysis patients.[51]

In the general population, a possible link between high levels of iron markers and poor cardiovascular outcomes was reported.[52] However, more robust epidemiologic studies did not confirm any risk of coronary heart disease with high TSAT. Indeed, a possible inverse association of iron stores with overall and cardiovascular mortality in the general population has been noted.[53,54] A recent study in dialysis patients documented that a low, rather than a high, serum iron is associated with a higher death risk.[22] To date, no randomized controlled trial has been conducted to examine the risk of infection or death as a result of IV iron administration in CKD patients. A recent clinical trial revealed that the level of the inflammatory cytokine tumor necrosis factor α decreased in those dialysis patients who received IV iron compared with those who did not receive any IV iron.[55] The investigators of a preliminary study that indicated a tendency toward increased death risk in dialysis patients who received higher doses of IV iron[51] could not confirm this stated association in time-varying marginal structural models that controlled for confounding by indication.[56] Another epidemiologic study in 58,058 hemodialysis patients found that administered IV iron up to 400 mg/mo was associated with greater survival.[32] Hence, in the post-ESA era, there has been no convincing evidence against or for an association between iron and mortality in CKD.

Conclusions

In summary, we suggest that both iron and ESA are required for optimal management of anemia in CKD patients. Chronic hemodialysis patients may require up to 3 g of iron each year to compensate for their blood loss. The current iron markers are confounded by non–iron-related conditions and their levels may be misleading. Although serum ferritin $<$200 ng/mL is a rather specific test for the diagnosis of iron deficiency, ferritin levels between 200 and 1,200 ng/mL may be associated with inflammation, malignancies, liver disease, and other non–iron-related factors. Uremic malnutrition may be associated with a low TIBC $<$200 mg/dL, leading to erroneously normal-looking TSAT even in the face of iron deficiency. High serum ferritin and low iron, TIBC, and TSAT levels are associated with an increased mortality risk in epidemiologic studies. The link between targeting or achieving hemoglobin values above 13 g/dL and increased mortality may be caused by iron depletion–induced thrombocytosis, a consequence of using high ESA doses without

adequate iron administration. Hence, a maintenance ESA therapy strategy requires the maintenance supplementation of iron and vice versa.

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