

The Fascinating but Deceptive Ferritin: To Measure It or Not to Measure It in Chronic Kidney Disease?

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Although the emergence of erythropoiesis-stimulating agents has revolutionized the anemia management of chronic kidney disease (CKD) in the past two decades, strategies to assess iron (Fe) status and to provide Fe supplementation have remained indistinct. The reported cases of hemochromatosis in dialysis patients from the pre-erythropoiesis-stimulating agent era along with the possible associations of Fe with infection and oxidative stress have fueled the “iron apprehension.” To date, no reliable marker of Fe stores in CKD has been agreed on. Serum ferritin continues to be the focus of attention. Almost half of all maintenance hemodialysis patients have a serum ferritin >500 ng/ml. In this ferritin range, Fe supplementation currently is not encouraged, although most reported hemochromatosis cases had a serum ferritin >2000 ng/ml. The moderate-range hyperferritinemia (500 to 2000 ng/ml) seems to be due mostly to non-Fe-related conditions, including inflammation, malnutrition, liver disease, infection, and malignancy. Recent epidemiologic studies have shown that a low, rather than a high, serum Fe is associated with a poor survival in maintenance hemodialysis patients. In multivariate adjusted models that mitigate the confounding effect of malnutrition-inflammation, serum ferritin <1200 ng/ml and Fe saturation ratio in 30 to 50% range are associated with the greatest survival in maintenance hemodialysis patients. Although ferritin is a fascinating molecule, moderate hyperferritinemia is a misleading marker of Fe stores in patients with CKD. It may be time to revisit the utility of serum ferritin in CKD and ask ourselves whether its measurement has helped us or has caused more confusion and controversy.

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The anemia of chronic kidney disease (CKD) is associated with poor outcome, including higher death risk in both maintenance dialysis patients (1) and individuals who have CKD stages 3 to 5 and are not yet on dialysis (2). With the introduction of the first erythropoiesis-stimulating agent (ESA; recombinant human erythropoietin) approximately two decades ago, the treatment of CKD-associated anemia was revolutionized. Since then, the anemia management has become one of the core components of the nephrology practice.

Two recent events have heightened further the importance of anemia management in nephrology: (1) The systematic definition of CKD and its stages, which first was presented in 2002 by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, and the subsequent intense campaign to increase awareness and education about the predialysis stages of CKD in almost 20 million Americans and many more throughout the world (3) and (2) the introduction of the newer ESA, including darbepoetin (4) and a few others in the pipeline, such as the continuous erythropoietin receptor activator (CERA), (5) with longer half-lives than recombinant human erythropoietin, leading to less frequent ESA

administration and making the outpatient treatment of CKD anemia more optimal.

Iron Status and Anemia Management

Despite the foregoing advances in CKD-associated anemia management, the one unresolved issue is the assessment of iron (Fe) status in patients with CKD. Fe assessment is an important endeavor, because hemoglobin synthesis is suboptimal without adequate background presence of Fe (6). Hence, no matter how aggressive the anemia management is attempted by means of generous ESA dosing and frequency, no successful hematopoiesis will be achieved as long as Fe stores are deficient.

Patients with CKD may lose Fe as a result of latent to overt gastrointestinal or other bleeding tendencies, frequent blood testing, and other blood losses, especially in patients who have CKD stage 5 and undergo hemodialysis. This leads to concomitant loss of Fe that amounts to 1.5 to 3 g/yr (7). Unless at least a similar amount of Fe is supplemented each year, ESA treatment is destined to be fruitless. Similarly, Fe supplementation without effective ESA treatment usually is unsuccessful because the mere provision of raw materials (Fe) without laborers and contractors (ESA) to build the house (hemoglobin) is in vain. Hence, both the ESA and Fe administrations are needed concurrently and continuously to treat CKD-associated anemia effectively and efficiently.

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Markers of Fe Status in CKD

Table 1 shows the current markers of Fe status that can be used to assess Fe stores in patients with CKD. The most routinely used Fe markers in patients with CKD include serum Fe; iron saturation ratio (ISAT), which also is known as transferrin saturation ratio; and serum ferritin. Although the bone marrow Fe staining is the reference standard, it is a semiquantitative measure and rarely is used beyond investigational purposes (8–10). Similarly, direct liver Fe store assessment requires the invasive procedure of liver biopsy, although the indirect assessment *via* the superconducting quantum interference device (SQUID) may be a promising method that currently can be accessed only in very few centers (11). Other nontraditional but much less frequently used Fe markers in patients with CKD include reticulocyte hemoglobin content (12,13), percentage of hypochromic red cells (14,15), soluble transferrin receptor (16), erythrocyte zinc protoporphyrin (17), and hepcidin (18). With the exception of serum Fe, ISAT, and ferritin, none of the foregoing measures currently are available routinely in the United States; neither is their reimbursement uniformly regulated. Moreover, their cutoff levels for the detection of Fe deficiency *versus* Fe overload in patients with CKD is far from clear. Finally, most of these so-called measures of Fe stores are susceptible to being confounded by inflammation or other non-Fe-related factors (see Table 1) (19). Hence, enthusiasm toward nontraditional Fe measures has remained low, leaving serum ferritin and ISAT as the routine measures of Fe markers in individuals with CKD.

The Molecule Ferritin

Ferritin is the main storage molecule for Fe and nature's solution to the difficult chemistry of Fe and oxygen, because it stores Fe in a safe and soluble manner that allows for regulated release of Fe and mitigates the risk for oxidation *via* free Fe atoms (6,20). Ferritin molecule is a hollow sphere with an external diameter of 12 to 13 nm (Figure 1). The outer shell is composed of 24 heavy (H) and light (L) polypeptide chains, the so-called ferritin subunits, folded into four-helix bundles (20,21). The center cavity of the molecule, 7 to 8 nm in diameter, is the Fe storage site and connected to the surface of the molecule by two types of channels, the three-fold channels and the four-fold channels, formed at the intersection of the L and H subunits (Figure 1). The central cavity in each ferritin molecule can hold as many as 4500 Fe atoms. Ferritin molecule has an average molecular weight of 450,000 Da, but when fully loaded with Fe, the molecule has a molecular weight of up to 800,000 Da (20,22). Hemosiderin is the condensed form of ferritin.

The transport and processing of Fe within the fascinating ferritin complex machinery are incompletely understood. Fe normally exists in solution as ferrous [Fe(II) or Fe²⁺] or ferric [Fe(III) Fe³⁺] ions or complexes. It is believed that Fe needs to be reduced to Fe(II) to enter the ferritin sphere through the hydrophilic three-fold channels; subsequently, it is oxidized to Fe(III) to remain stored inside ferritin molecules (20,22). Whenever Fe is needed, stored Fe inside ferritin is reduced back to Fe(II) to be transported out of ferritin (Figure 2). The molecule ferritin has eight sites for entry of Fe, three to 24 sites for the

Table 1. Markers of Fe stores in patients with CKD^a

Fe Stores Marker	Advantages	Limitations
Bone marrow Fe <i>via</i> biopsy	Gold standard	Invasive, painful, semiquantitative
Liver Fe <i>via</i> biopsy	Gold standard	Invasive, risk for complications, semiquantitative
Liver Fe <i>via</i> SQUID	Noninvasive, safe	Investigational; limited experience in CKD
Serum ferritin	Low levels are highly specific for Fe deficiency	Moderately high levels are mostly due to non-Fe-related conditions
Serum transferrin saturation ratio (ISAT)	More reliable than ferritin, higher sensitivity than ferritin	Denominator (TIBC) can be low in malnutrition and/or inflammation
Serum Fe	Direct measurement of circulating Fe	Diurnal fluctuation, can be low in inflammation
CHr	Measures immediate incorporation of Fe into reticulocytes	Limited data in CKD, cutoff level debatable
PHRC	Similar to CHr (see above)	Samples cannot be shipped to outside laboratories
sTfR	Correlates with transferrin receptors on erythroblasts	Mixed results, unknown cutoff levels
ZnPP	May be less confounded by inflammation	Affected by non-Fe-related factors such as lead level
Hepcidin	May detect the presence of functional Fe deficiency	Currently no reliable assay for its serum measurement

^aCHr, reticulocyte hemoglobin content; CKD, chronic kidney disease; Fe, iron; ISAT, iron saturation ratio; PHRC, Percentage of hypochromic red cells; SQUID, superconducting quantum interference device; sTfR, Soluble transferrin receptor; TIBC, total iron binding capacity; ZnPP, erythrocyte zinc protoporphyrin.

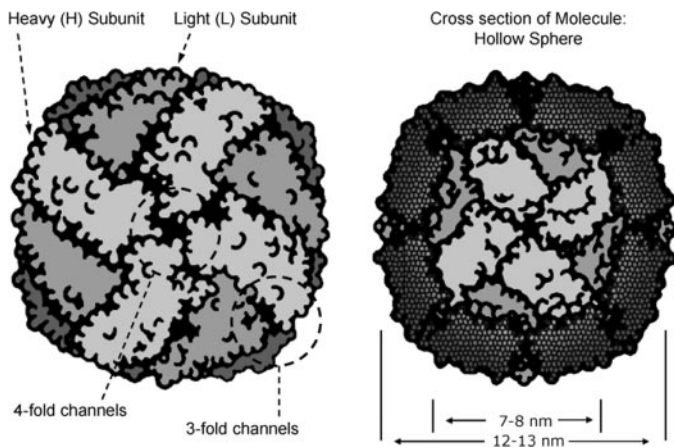


Figure 1. Schematic representation of serum ferritin. Ferritin is a spherical shell that consists of 24 subunits (or peptide chains) folded into ellipsoids, connected through noncovalent bonds. Two types of subunits are heavy (H) subunits and light (L) subunits. The subunits pack to form a hollow sphere approximately 7 to 8 nm in internal diameter with walls that are approximately 12 to 13 nm in external diameter. Among the important structural features of ferritin is the presence of two types of channels (three-fold and four-fold) that occur in the protein wall at the intersection of the subunits.

oxidation of Fe to its Fe(III) state, several sites for translocation and mineral attachment and mineralization, and eight sites for Fe exit from the molecule (20). Reducing agents such as dihydroxyfumarate (DHF- $C_4H_4O_6$) can be used for the reduction of Fe(III) to Fe(II) in the Fe-mineral core of ferritin to simulate *in vivo* chemical processes under *in vitro* conditions (Figure 2).

The foregoing Fe chemical processes under the presence of ferritin are critical for life, because the deletion of the gene for ferritin leads to early embryonic death (23). It is interesting that a so-called “ferritin deficiency syndrome,” or *Ferritinmangel-Syndrom*, has been described mostly in the German-language literature. This seems to be a rare and somewhat questionable condition in menstruating women and associated with fatigue, psychologic lability, restless leg, sleep disturbances, headache and neck pain, and a serum ferritin level <50 ng/ml but no overt anemia. This condition seems to improve with Fe supplementation (24,25).

Ferritin Synthesis: The Role of Inflammation

Under normal amounts of body Fe loading, most cells contain little ferritin, whereas cells in the reticuloendothelial system (RES) may contain larger amounts of ferritin (6). In the latter cells, a large amount of dormant ferritin mRNA may exist. When Fe enters the cell, the mRNA is processed and ferritin H and L subunits are produced rapidly (26). The process is regulated by the interaction between noncoding sections of the mRNA (Fe-responsive elements) and cytoplasmic Fe regulatory proteins (26).

During the acute-phase response, proinflammatory cytokines such as IL-1 β and TNF- α increase the synthesis of both H and L subunits of ferritin through an increased translation of pre-

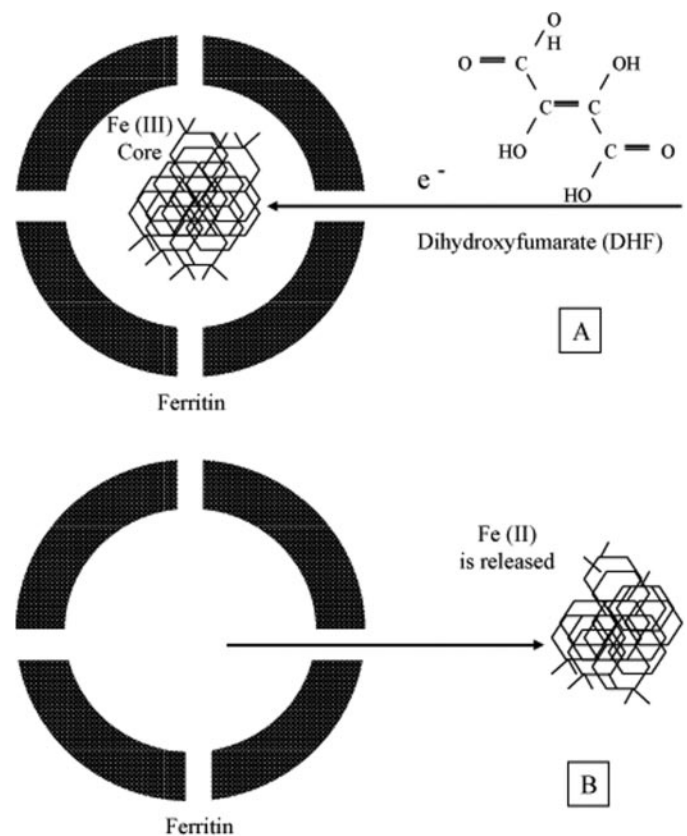


Figure 2. Iron (Fe) normally exists in solution as ferrous (Fe^{2+}) or ferric (Fe^{3+}) ions or complexes. Dihydroxyfumarate (DHF) as the reducing agent can be used for the reduction of Fe^{3+} to Fe^{2+} in the iron-mineral core of ferritin. DHF may enter through a channel or may transfer an electron to the mineral core. After Fe^{3+} is reduced to Fe^{2+} , Fe^{2+} leaves the protein *via* the hydrophilic three-fold channel.

formed ferritin mRNA (22,27,28). IL-1 β induces ferritin mRNA translation *via* a translational enhancer region located upstream from the segments that code for the ferritin H and L polypeptide chains (27,29–31). Rogers *et al.* (30) showed that IL-1 β induces ferritin gene expression by translational control of its mRNA, but this inflammatory induction of ferritin synthesis is different from the Fe-dependant ferritin gene expression in that it requires the background presence of some cellular Fe. It is not clear why ferritin synthesis is increased under inflammatory conditions. Hypothetically, higher amounts of ferritin may trap more body Fe and protect the individual against worsening infection, the start of which invariably is associated with inflammation. Hence, inflammation-induced hyperferritinemia may result in a so-called “functional Fe deficiency,” which may be useful in “acute” inflammation by Fe containment in the RES sites but harmful under “chronic” inflammation by leading to refractory anemia such as in CKD or other chronic disease states.

The permissive role of minimal Fe in regulating inflammatory synthesis of ferritin is consistent with recent clinical and epidemiologic findings in patients with CKD: Under *absolute* Fe deficiency, serum ferritin almost always is low, even in the

presence of inflammation, but once the minimal required Fe is available, ferritin regulation becomes a function of non-Fe-dependent factors such as inflammation (32). The foregoing hypotheses may explain why most studies have found a superior specificity for a low serum ferritin in diagnosing Fe deficiency, whereas its sensitivity is inferior (6,9). Hence, a low ferritin level (*e.g.*, <200 ng/ml in hemodialysis patients or <100 ng/ml in nondialyzed patients with CKD) is a reliable indicator of Fe deficiency, whereas a normal to moderately high serum ferritin does not rule out Fe deficiency or indicate adequate or too much Fe on board (32).

Serum versus Tissue Ferritin

It is important to acknowledge that ferritin is *not* an Fe transport molecule. Ferritin only stores Fe in the tissue but has almost no role in transporting Fe between storage sites and the RES. The latter function usually belongs to transferrin, also known as total iron binding capacity (TIBC) (33). Whereas tissue ferritin clearly plays a role in intracellular Fe handling, the role of serum ferritin is less clearly understood, even though serum ferritin frequently is measured as a marker of Fe stores. The processes by which ferritin enters circulation are not completely known. It is speculated that serum ferritin results from the leakage of tissue ferritin (21,34). The concentration of serum ferritin is the result of the balance between its leakage, which is related directly to intracellular Fe metabolism and other factors, such as inflammation (see above), and its clearance, which is conducted mainly in liver and other RES organs. Hence, liver dysfunction (*e.g.*, chronic hepatitis B or C) and inflammatory conditions in patients with CKD may confound the clearance and/or the synthesis of ferritin, thereby increasing serum ferritin levels as a result of circumstances that are not related to Fe metabolism.

There are other subtle but probably clinically significant differences between the tissue and serum ferritin; serum ferritin seems to be more glycosylated and may include less of the H subunit (34). Although according to some studies serum ferritin may contain a significant amount of Fe that may vary in relation to Fe status or inflammation and tissue injury (35,36), most studies indicate that serum ferritin has little or no Fe (21). The negligible or no Fe content of serum ferritin, if true, is in sharp contradistinction to the general belief that moderately high levels of serum ferritin indicates “too much” Fe in the blood.

Hyperferritinemia in CKD: High Fe or Inflammation?

It is estimated that almost half of all maintenance hemodialysis patients in the United States have a serum ferritin >500 ng/ml (37). Extremely high serum ferritin levels, usually >2000 ng/ml, usually are indicative of Fe overload, also known as hemosiderosis (32,38). Most reported cases of Fe overload in dialysis patients, however, are from the pre-ESA era, when blood transfusion was practiced much more frequently to treat anemia (39–41). In most of reported Fe overload cases in dialysis patients, serum ferritin levels were in ranges between 2000 and 10,000 ng/ml or even higher (39,42,43). Nevertheless, moderately high levels of serum ferritin (up to 2000 ng/ml) have not

been found to be associated with excessive tissue Fe store in postmortem autopsies (43). Even though a recent study indicated a mathematically significant correlation between serum ferritin and liver Fe stores using the indirect imaging known as SQUID (11), it seems highly unlikely that serum ferritin levels <2000 ng/ml are associated with clinically significant increase in body Fe stores in patients with CKD.

The increase in serum ferritin during inflammation, infection, liver disease, malignancies, and other non-Fe-related conditions (Table 2) may hinder the ability to assess the Fe status in CKD under the concurrent presence of foregoing conditions (6). Serum ferritin is a marker of malignancy, such as in neuroblastoma (44,45), renal cell carcinoma (46,47), or Hodgkin’s lymphoma (48). Hyperferritinemia also is associated with liver dysfunction, probably because liver is the main organ to clear circulating ferritin molecules (49). High ferritin levels have been reported in patients who had CKD with glomerular disease and proteinuria (50). Chronic inflammation is common in patients with CKD, and up to 40 to 70% of patients with CKD may have increased C-reactive protein (CRP) levels on a chronic basis (51). Hence, inflammation probably is the most common confounder in CKD-associated hyperferritinemia and may contribute to it more strongly than Fe (32,52). There are many other, similar models of hyperferritinemia in chronic disease states, including rheumatoid arthritis, in which Fe deficiency is present in >50% of patients yet serum ferritin levels are normal or increased (53).

In patients with CKD, hyperferritinemia is paradoxically associated with ESA hyporesponsiveness and a more severe anemia (54,55). In a recent study, Kirschbaum (56,57) found that 34% of hemodialysis patients with elevated serum ferritin had inflammation as the probable cause of the increased ferritin level. In another recent observational study in 82 hemodialysis patients, those with a serum ferritin >800 ng/ml had a significantly higher CRP level and a worse malnutrition-inflammation score compared with patients with a serum ferritin <800 ng/ml (32). Serum ferritin concentration was higher in malnourished patients as assessed by the subjective global assessment (32). A significant association between serum CRP and ferritin that was independent of age, gender, race, and diabetes was found. Multivariate models showed that both CRP and ISAT, independent of each other, correlated significantly with serum ferritin. These findings suggest that a moderately high serum ferritin is not

Table 2. Conditions that may be associated with hyperferritinemia in patients with CKD

Condition	Serum Ferritin Range (ng/ml)
Fe overload (hemosiderosis)	>2000
Inflammation	200 to 2000
Infection	200 to 2000
Liver disease	200 to 2000
Malignancies	200 to 2000

just a mere marker of Fe stores but more an indicator of inflammation and/or malnutrition as well as other non-Fe-related conditions in patients with CKD (32):

$$\uparrow \text{ Ferritin} = \text{ Fe} + \text{ inflammation} + \text{ other factors}$$

Serum Ferritin and Mortality in CKD

Examining prospectively collected historical data of a large national dialysis patients database with 58,058 hemodialysis patients in the United States over a 2-yr observation period (July 2001 through June 2003), we recently found that after extensive time-dependent and multivariate adjustment including for malnutrition-inflammation-cachexia syndrome (MICS) surrogates, the presence of serum ferritin levels between 200 and 1200 ng/ml was associated with the lowest all-cause and cardiovascular death risk (Figure 3) (37). Hence, the previously observed associations between moderately high levels of serum ferritin and mortality in unadjusted and case mix-adjusted models (52) seem to be due mostly to the confounding effects of malnutrition and inflammation, because additional adjustments for surrogates of MICS mitigate or even reverse some of these associations.

An association between dialysis morbidity, including risk for infection, and Fe overload reflected by a high serum ferritin also have been reported (58). However, the related studies had small sample size and did not control extensively for confounders. Hyperferritinemia-associated morbidity might be due to non-Fe-related factors. Because serum ferritin is a positive acute-phase reactant (32), hyperferritinemia-associated increased risk for infection and death may be a mere epiphenomenon. Therefore, considering high ferritin levels as the primary cause of increased mortality in the setting of inflammation or infection and preventing optimal anemia management with intravenous Fe for serum ferritin levels >500 (59) or >800 ng/ml (60) may be irrational.

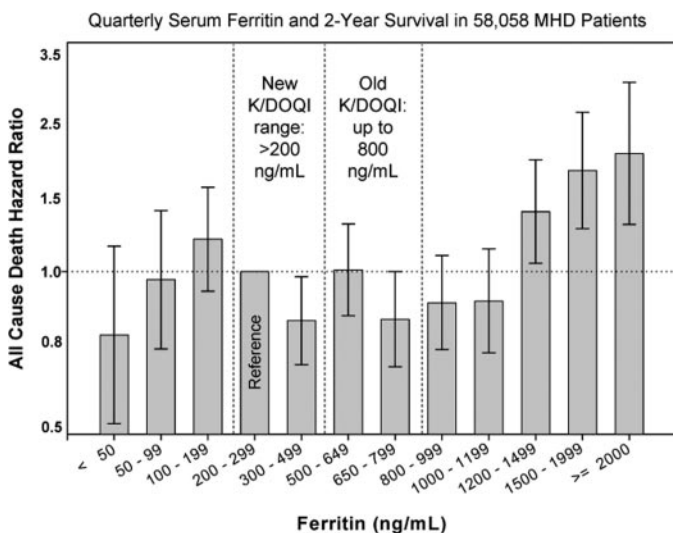


Figure 3. Multivariate adjusted association between serum ferritin and all-cause mortality in 58,058 maintenance hemodialysis patients in DaVita dialysis facilities between July 2001 and June 2003. Based on data from reference (37).

What Is the Best ISAT Range?

The K/DOQI guidelines recommend an ISAT >20% as the target of anemia management in CKD (60). The recent epidemiologic study in the 58,058 hemodialysis patient cohort showed that ISAT in the range of 30 to 50% was associated with the best survival (Figure 4) (37). Although this range essentially is within the recommended guidelines (59,60), ISAT levels between 20 and 30% were associated with higher death risk when compared with ISAT levels >30% (37). However, it is important to note that ISAT is not a measured entity but a mathematical derivation of two other measures: Serum Fe divided by TIBC. Serum TIBC is a negative acute-phase reactant and a marker of MICS and poor outcome in dialysis patients (33,51,52). In Fe deficiency, the TIBC level tends to be elevated in individuals without kidney disease, whereas serum Fe and TIBC levels change parallel to each other in hemodialysis patients ($r = 0.30$) (37). In addition to uremia, ISAT can be significantly confounded by MICS, because the denominator of ISAT (TIBC) is a nutritional and/or inflammatory marker (61,62). Hence, the association between ISAT levels of >50% and increased death risk (see Figure 4) may be an artificial finding and a mere reflection of the known association between low TIBC levels (which erroneously increases the calculated ISAT value) and death risk in patients with CKD (37).

The “Iron Apprehension”

Whereas the dosage and the frequency of ESA administration usually can be decided flexibly by the practicing nephrologists, there seems to be less limited tolerance toward Fe administration in the treatment of patients with CKD. There are several reasons for this so-called “iron apprehension”: (i) A clinical trial that was performed almost three decades ago in 137 Fe-deficient individuals in Somalia showed that the risk for infection in those who received Fe supplementation was almost five

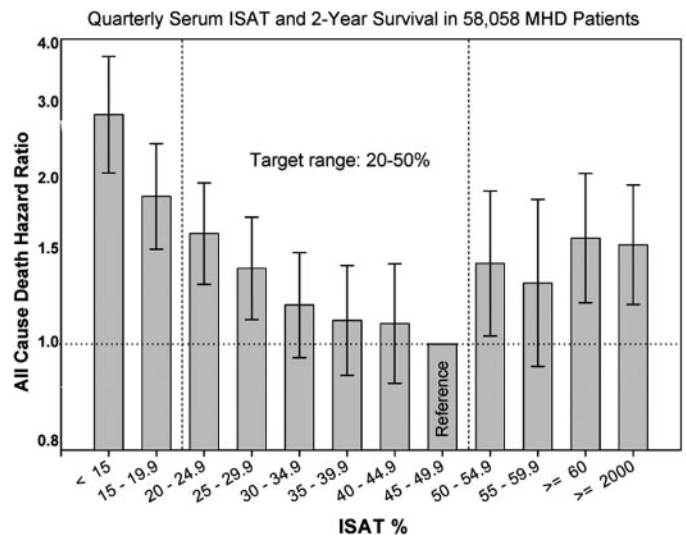


Figure 4. Multivariate adjusted association between serum iron saturation ratio (ISAT) and all-cause mortality in 58,058 maintenance hemodialysis patients in DaVita dialysis facilities between July 2001 and June 2003. Based on data from reference (37).

times higher than those who received placebo (63); (ii) in the pre-ESA era, there have been frequent reports about the risk and consequences of Fe overload as a result of blood transfusion or Fe administration to anemic dialysis patients (64,65); (iii) several *in vitro* studies have indicated the association between Fe supplementation and oxidative stress in cell cultures (66,67); and (iv) a limited number of observational studies have indicated an association between high serum ferritin and infection (65,68) or mortality (52) and between Fe administration and indices of cardiovascular disease (69) or death risk (70) in dialysis patients.

As a result of the foregoing concerns, the K/DOQI guidelines seemed to be conservatively prudent with regard to the recommendations that pertain to the intravenous Fe supplementation in patients with CKD. However, despite initial reports that indicated possible associations between higher Fe marker levels and poor cardiovascular outcome in the general population (71), more robust epidemiologic studies did not show an increased risk for coronary heart disease with higher ISAT but, on the contrary, indicated a possible inverse association of Fe stores with overall and cardiovascular mortality in the general population (72,73). Similarly, recent studies in dialysis patients showed that a low, rather than a high, serum Fe is associated with higher death risk (74).

It is important to note that to date, no randomized, controlled study has been conducted to substantiate the risk for increased infection or death as a result of intravenous Fe administration in dialysis patients. Indeed, a recent clinical trial showed that in dialysis patients who received intravenous Fe, the level of the inflammatory cytokine TNF- α was decreased when compared with those who did not receive any intravenous Fe (75). The authors of another study that initially showed an increase death risk linked to increased serum ferritin in dialysis patients (52) showed that this risk was due mostly to the confounding effect of the MICS (37), a condition that is highly prevalent in patients with CKD. Similarly, the authors of the preliminary study indicating a tendency toward higher death risk in dialysis patients who received higher dosages of intravenous Fe (70) revised their initial conclusions when they used time-varying marginal structural models that adjusted for bias by indication (76).

A recent epidemiologic study in 1283 hemodialysis patients showed that a low, rather than a high, serum Fe was significantly associated with higher mortality and hospitalization (74). Another epidemiologic study in 58,058 hemodialysis patients found that compared with those who did not receive any intravenous Fe, administered intravenously, Fe up to 400 mg/mo was associated with improved survival (37). Although patients who received intravenous Fe had significantly different demographic, clinical, and laboratory features at baseline, the survival benefits of intravenous Fe was relatively consistent in different subgroups of hemodialysis patients, including those who had high ferritin but low ISAT values (37). These findings seem to be inconsistent with the notion that excessive intravenous Fe is deleterious by leading to oxidative stress and predisposition to infection. However, most reports concerning

adverse effects of Fe in patients with CKD are based on *in vitro* studies (67).

Moderate Hyperferritinemia in CKD

The clinical significance of serum ferritin measurement in patients with CKD seems to be somewhat different than in the general population, and the current guidelines to use serum ferritin for Fe overload screening might be flawed when applied to the CKD population (40). Using such arbitrary upper limits as 500 or 800 ng/ml to recommend withholding Fe administration in patients with CKD may be scientifically flawed, because moderately high levels of serum ferritin do not necessarily indicate Fe overload but most likely inflammation, infection, malnutrition, liver disease, and/or other non-Fe-related factors in CKD. The MICS, rather than Fe overload, seems to be the main contributor to moderate hyperferritinemia in CKD and a marker of refractory anemia including ESA hyporesponsiveness in these individuals.

Given the undeniable scientific evidence pertaining to the significant contribution of non-Fe-related factors such as inflammation to hyperferritinemia in CKD, the utility of measuring serum ferritin as a routine test of Fe stores in patients with CKD is highly questionable. Moderately high levels of serum ferritin are not *per se* an indicator of Fe overload and should not be regarded as a means to restrict Fe supplementation for optimal anemia management. A low Fe status may be as harmful as, if not more harmful than, the hyperferritinemia. In the previously reported cases of Fe overload in dialysis patients, the reported serum ferritin levels were well above the currently observed ranges in patients with CKD, usually in 2000- to 10,000-ng/ml range (42).

With widespread ESA administration to patients with CKD since early 1990s, there has been many fewer reported, if any, cases of Fe overload in patients with CKD despite much more rigorous use of intravenous Fe (42). Therefore, we suggest considering the algorithm presented in Table 3 when dealing with the interpretation of serum ferritin measurement in dialysis patients. Nevertheless, such recommendations are amenable to errors and misinterpretations. Hence, an ultimate solution, even though somewhat radical, may be to abandon measuring serum ferritin in patients with CKD or to measure it only to be used as a specific Fe deficiency marker (<100 ng/ml in most patients with CKD and <200 ng/ml in hemodialysis patients).

Although the results of the epidemiologic studies may have major clinical implications, the observational nature of such studies prompts caution in interpreting and generalizing their findings. Interventional studies including randomized clinical trials are required to ascertain (1) whether in patients with CKD and a low serum ISAT and moderately high serum ferritin, intravenous Fe administration can effectively increase serum Fe and (2) whether such an interventional increase in serum Fe improves clinical outcome in these individuals. To our knowledge, at least one major randomized, clinical trial, the so-called "dialysis patients' response to intravenous Fe with elevated ferritin" (DRIVE) study (77), is currently being conducted to address these important questions.

Table 3. Our recommended interpretation of serum ferritin levels in CKD patients who undergo maintenance dialysis treatment

	Serum Ferritin Range (ng/ml)			
	Ferritin <200	Ferritin >200 and <500	Ferritin >500 and <2000	Ferritin >2000
Common conditions in CKD	Absolute Fe deficiency (most common), ferritin deficiency syndrome ^b	May be associated with both absolute and functional Fe deficiency.	Most commonly associated with inflammation, infection, liver disease, or malignancy.	Fe overload overwhelms the effect of inflammation on serum ferritin.
Association with Fe stores	↓ ferritin ↔ ↓ Fe	↑ ferritin ← ? → ↓ ↑ Fe	↑ ↑ ferritin ← ? → ↓ ↑ Fe	↑ ↑ ↑ ferritin ↔ ↑ Fe
What serum ferritin means	Serum ferritin = Fe	Serum ferritin = inflammation + Fe + others	Serum ferritin = inflammation + Fe + others	Serum ferritin = Fe
Recommended course of action	Fe supplementation	Maintenance Fe supplementation is indicated if ISAT <50%	Check serum CRP, liver enzyme, assess MIS, and rule out latent infection or malignancies. If ESA resistance persists, then Fe administration may be beneficial if ISAT <50%	Fe supplementation should be avoided.

^aAdapted from reference (32). CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; MIS, malnutrition-inflammation score.

^bThe ferritin deficiency syndrome can be present if serum ferritin level is <50 ng/ml (see text).

Conclusion

Because the conundrum of the utility of serum ferritin for the management of CKD anemia, especially the debate over its upper threshold, seems to be far from over, as our final remarks, we draw readers' attention to the recent recommendations by the K/DOQI guidelines (78) and compare it with the independent opinions stated recently by Fishbane *et al.* (6). "In the opinion of the [K/DOQI] Work Group, there is insufficient evidence to recommend routine administration of intravenous Fe if serum ferritin level is greater than 500 ng/ml. When ferritin level is greater than 500 ng/ml, decisions regarding intravenous Fe administration should weigh ESA responsiveness, hemoglobin and transferrin saturation level, and the patient's clinical status" (78).

The conclusions stated by Fishbane *et al.* (6) in a recent review article are the following: "The decision as to the upper limit for serum ferritin at which Fe treatment should be withheld requires a careful balancing between potential benefits and risks to patients. As discussed, current knowledge with respect to Fe safety is incomplete and inadequate. The literature relating to Fe deficiency and the efficacy of intravenous Fe treatment at higher levels of serum ferritin is similarly inadequate for guiding evidence-based practice. Therefore, we conclude that (1) it is not possible to have an evidence-based guideline for the upper limit of serum ferritin; (2) no specific level of serum ferritin, not 500 ng/ml or 800 mg/ml, or some other number, should be stated as an upper limit for Fe treatment. Given the lack of support from the literature, any attempt to set an upper limit would be arbitrary and would not serve to improve the

quality of treatment. When making Fe treatment decisions when serum ferritin is greater than 500 ng/ml, however, we would encourage the clinician to balance the possibility of benefit against considerations of risk in the context of the individual patient."

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