Clinical Aspects of Iron Use in the Anemia of Kidney Disease

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Iron deficiency occurs in the vast majority of patients with chronic kidney disease (CKD). The causes of iron deficiency in these patients are multifactorial. Main factors that contribute to iron deficiency in patients with end-stage renal disease (ESRD) are reduced intake and impaired intestinal absorption of dietary iron, blood losses, chronic inflammation associated with ESRD and/or increased iron requirements during therapy with erythropoiesis-stimulating agents (ESA).

Anemia is a common complication of CKD that can be corrected by ESA. Failure to achieve adequate iron stores and availability is the main cause of hyporesponsiveness to ESA therapy (1,2). The use of iron in combination with ESA is required for optimal management of the anemia of CKD. Management of iron status in patients with CKD involves excluding iron deficiency, providing adequate iron stores to allow patients to maintain target hemoglobin levels efficiently, and avoiding iron overload.

Utility of Markers of Iron Status

Serum ferritin of <15 μg/L in adults and of <12 μg/L in children with normal kidney function confirms the diagnosis of iron deficiency anemia, whereas ferritin levels >100 μg/L rule it out (3). Weiss and Gordeuk (4) defined absolute iron deficiency by serum ferritin levels <15 μg/L for men and <10 μg/L for women. In patients with CKD, the ferritin cutoff level for absolute iron deficiency is markedly higher by the experience that chronic inflammation increases serum ferritin. A serum ferritin target of 100 μg/L has a low sensitivity and specificity and may even underestimate the frequency and the severity of iron deficiency in hemodialysis patients (5). Therefore, serum ferritin levels ≥100 μg/L are recommended for patients with CKD and ≥200 μg/L for dialysis patients (2). Serum ferritin as a measure of iron storage in the body should be quantified every 3 mo in patients who are receiving ESA treatment and intravenous iron supplementation. This is required to establish whether an iron deficiency exists or too much iron supplementation is being administered. The upper limit of serum ferritin at which iron treatment should be withheld is not clear (6). High serum ferritin levels in patients with ESRD may be the result of inflammation, infection, malnutrition, or malignancy and not necessarily the result of iron overload (7). Iron deficiency in patients with ESRD probably is rare when serum ferritin is >500 μg/L but not excluded. Fishbane et al. (8) found that sensitivity of serum ferritin in excluding iron deficiency was 90% at 300 μg/L and 100% at 500 μg/L. In the study by Fernandez-Rodriguez et al. (9), sensitivity of serum ferritin was 92% at 300 μg/L and 98% at 600 μg/L. In a study by Chuang et al. (10), only 17% of iron-deficient hemodialysis patients had serum ferritin >300 μg/L. International guidelines recommend upper limits of serum ferritin at 500 μg/L (1,2) to avoid potential complications that are associated with iron therapy. Because patients who have hemochromatosis and serum ferritin <1000 μg/L do not have evidence of liver pathology (11), it is unlikely that patients with CKD may have any potential tissue damage associated with iron at ferritin levels ≤500 μg/L (or even higher). The situation in patients with ESRD, however, may differ from those with hemochromatosis, particularly if CKD is complicated by viral or bacterial infections. In dialysis patients, there is a significant correlation between serum ferritin and liver iron stores validated by magnetic susceptometry (12). It is interesting that almost half of all maintenance hemodialysis patients in the United States already have a serum ferritin >500 μg/L. Ferritin levels up to 1200 μg/L, however, do not increase all-cause death in hemodialysis patients (13). Therefore, an evidence-based guideline for the upper limit of serum ferritin is not available (14).

Iron deficiency also is accompanied by reductions in serum iron and transferrin saturation (TSAT) and by elevations in red cell distribution width, free erythrocyte protoporphyrin concentration, total serum iron-binding capacity (TIBC), and soluble transferrin receptor (sTfR) (15). Modern blood cell analyzers allow analysis of individual erythrocytes or reticulocytes with respect to cell volume and hemoglobin content. Even in patients with a mean cell volume <75 fl, up to 20 to 30% will not have iron deficiency but anemia of chronic inflammation. In patients with anemia and a mean cell volume >95 fl, there is a low probability that iron deficiency is present (3). sTfR is not affected by acute-phase response. In ESA-treated maintenance
dialysis patients, however, serum levels of sTfR reflect ongoing erythropoiesis but not iron availability (16). When a patient is noted to have an elevated sTfR, the clinician must determine whether it is due to iron deficiency or because the patient is on ESA therapy or has increased erythroblastic activity (17). Transferrin receptor-ferritin index >0.6, calculated by the ratio of sTfR to log ferritin levels, is recommended for the detection of iron deficiency and to predict the response to intravenous iron therapy in dialysis patients (18). TSAT (the ratio of serum iron to total serum iron-binding capacity) is a measure of circulating iron and is 15% or less (normal values 16 to 40%) in patients with iron deficiency. TSAT fluctuates widely as a result of diurnal variation in serum iron, and transferrin is affected by the nutritional status. TSAT decreases in the presence of acute and chronic inflammation, reflecting functional iron deficiency in patients with CKD (defined as TSAT <20% and normal or elevated serum ferritin levels). However, a TSAT >20% and/or a serum ferritin level >100 μg/L does not exclude iron deficiency, because specificity (TSAT <20%) and sensitivity (ferritin <100 μg/L) of these parameters for detection of iron deficiency is relatively low (17). Concerns with these targets exist for patients who have CKD and are not on dialysis, because fewer than one third of men with hemoglobin <12 g/dl and women with hemoglobin <11 g/dl at a creatinine clearance between 30 and 50 ml/min had ferritin ≥100 μg/L and TSAT ≥20% (19).

Erythrocyte and reticulocyte indices, such as the percentage of hypochromic red blood cells (RBC) and the reticulocyte hemoglobin content (CHr), provide direct insight into bone marrow iron supply and utilization. Determination of the percentage of hypochromic RBC (i.e., those with a cellular hemoglobin concentration <28 g/dl) as a marker of functional iron deficiency in dialysis patients during ESA therapy first was described by Macdougall et al. (20). Schaef er and Schaefer (21) found low levels of hypochromic RBC (<1%) in iron-overloaded patients and high levels of hypochromic RBC (>22%) in patients with severe iron deficiency. ESA treatment without iron supplementation induced an increase in hypochromic RBC from normal levels to 15.3%. This increase was reversed readily (5.5% after 4 wk) when intravenous iron was administered (21). Tessitore et al. (22) compared the diagnostic power of established tests of bone marrow iron availability (percentage of hypochromic RBC, CHr, erythrocyte zinc protoporphyrin, and sTfR) and of traditional indices (ferritin and TSAT). Their aim was to identify iron-deficient erythropoiesis patients who were on hemodialysis and maintenance ESA therapy and to identify best threshold values using the hemoglobin response to intravenous iron treatment. The authors demonstrated that hypochromic RBC >6% is the best currently available marker to identify maintenance hemodialysis patients who will have the best response to intravenous iron (22). Depletion of iron stores is one of the major reasons for anemia after kidney transplantation (23). Again, the percentage of hypochromic RBC was the most sensitive parameter for the detection of iron deficiency in this patient population. In 438 long-term kidney transplant recipients, having >2% hypochromic RBC was correlated positively with anemia, whereas serum iron, serum ferritin, and TSAT were not. The prevalence of iron deficiencies, as indicated by a percentage of hypochromic RBC of ≥2.5%, was 20.1% (24). The percentage of hypochromic RBC is an independent risk factor for mortality in kidney transplant recipients. Patients with >10% hypochromic RBC had twice the mortality risk as compared with patients with hypochromic RBC <5% (25). The percentage of hypochromic RBC is affected by inflammation. This parameter quantitatively reflects the integrated effects of iron stores, inflammation, and erythropoietic stimulation on iron availability in dialysis patients (26). An ideal marker of functional iron deficiency, however, should be independent of erythropoietic activity. Therefore, mature erythrocyte indices as new markers of iron availability have been proposed (27).

CHr has been recommended as a surrogate marker of iron status and as an early predictor of response to iron therapy in hemodialysis patients (28,29). According to Fishbane et al. (30), a CHr <29 pg as measured by a Technikon H*3 blood analyzer indicates the presence of iron-deficient erythropoiesis. However, patients who had iron therapy on the basis of a CHr <32 pg already had an average of 23% reduction in their ESA requirements. Tsuchiya et al. (31) also reported that iron-deficient erythropoiesis already was present in hemodialysis patients at CHr values <32 pg, measured by the ADVIA-120 system. The authors favored quantification of hemoglobin and CHr (obtained from a single blood sample) as laboratory parameters necessary for control of iron supplementation and response to ESA (31). Brugnara et al. (32) compared reticulocyte and red cell measurements of hemoglobin content provided by the ADVIA 2120 and Sysmex XE 2100 analyzers in 1500 adult and pediatric dialysis patients. The authors demonstrated that with a reticulocyte hemoglobin cutoff level of 27.2 pg, iron deficiency can be diagnosed with a sensitivity of 93.3% and a specificity of 83.2% (32). A very low CHr cutoff of 26 pg has 100% specificity (no false positives) yet still a reasonably good sensitivity (33). High-fluorescence reticulocytes as assessed by flow cytometry represent immature reticulocytes and have been measured as an early indicator of erythropoietic activity. Combined use of CHr and high-fluorescence reticulocyte count allowed for very high accuracy in the early prediction of the response to intravenous iron therapy in hemodialysis patients, with a sensitivity of 96% and a specificity of 100% (10). However, neither CHr nor the percentage of hypochromic RBC has the ease of use, cost-effectiveness, and widespread availability of the traditional tests, such as ferritin and TSAT (34).

The best criteria of iron-deficient erythropoiesis is the response to intravenous iron products. It is the most widely accepted reference standard for clinical practice to identify patients who need iron to optimize ESA treatment (35). Response to iron therapy should be assessed by checking hemoglobin level after 2 to 4 wk. A 10- to 20-g/L rise in hemoglobin confirms iron deficiency (3).
Efficacy of Different Iron Administration Strategies

Iron can be supplemented orally or intravenously. In patients who have CKD and whose iron test results indicate iron deficiency, oral iron treatment should be initiated (5). Oral iron therapy is considered not only for patients with CKD but also for peritoneal dialysis patients and patients after kidney transplantation if mild iron deficiency should be corrected. Oral iron is absorbed best when given without food. Ferrous sulfate, 325 mg three times a day between meals, supplies 195 mg/g elemental iron (5). Alternatively, ferrous sulfate is recommended nightly at bedtime (4). Intestinal iron absorption is enhanced in patients with iron deficiency and declines with the correction of iron deficiency and re-accumulation of iron stores. Adverse effects such as constipation, diarrhea, nausea, or abdominal pain, probably as a result of induction of reactive oxygen species in the intestinal mucosa (36), limit compliance. Heme iron polypeptide is a new-generation oral iron product with reasonable efficacy and tolerability (37). It contains 12 mg of elemental iron per tablet. Intestinal iron absorption is impaired in patients with ESRD (38,39). Possible explanations are the use of phosphate binders and the inflammatory status of patients with CKD with stimulation of hepcidin. This peptide hormone controls whole-body iron content. Hepcidin is produced mainly in the liver in response to acute-phase reactions by proinflammatory cytokines but also in response to iron overload. Hepcidin inhibits intestinal iron absorption as well as the release of iron from macrophages (Figure 1). Whereas the first occurs via enterocyte divalent metal transporter-1, the latter is based on internalization and degradation of iron exporter ferroportin. In contrast, anemia, iron deficiency, and/or stimulated erythropoiesis strongly downregulates hepatic hepcidin production, allowing intestinal iron absorption and the release of iron from macrophages under these conditions (40). Uremia is a chronic inflammatory state, and increased hepcidin production under this condition may explain iron deficiency in the majority of patients with ESRD. This hypothesis is supported by the observation that intestinal iron absorption is adequate in iron-deficient and iron-replete peritoneal dialysis patients without evidence of inflammation or infection (41). Vitamin C deficiency may cause an impairment of intestinal iron absorption. Supplementation with vitamin C may correct this defect. The addition of ascorbic acid to a test meal fortified with isotopically labeled iron compounds resulted in a significant increase of intestinal iron absorption from either ferric pyrophosphate or ferrous sulfate (42).

Oral iron therapy may interfere with intestinal absorption of other drugs. Morii et al. (43) showed that oral co-administration of ferrous sulfate markedly impaired the intestinal absorption of mycophenolate mofetil in healthy Japanese subjects. A randomized crossover trial, however, failed to confirm this observation in European kidney transplant recipients who received long-term mycophenolate mofetil therapy (44). A second study in renal transplant recipients also failed to demonstrate any significant effects of oral iron supplementation on the absorption of mycophenolate mofetil (45).

Intravenous iron therapy unequivocally is superior to oral iron supplementation in hemodialysis patients (46–48), peritoneal dialysis patients (49–51), and patients with CKD (52,53). In patients who have CKD and hemoglobin <11 g/dl without ESA or without an increase in ESA dosage, intravenous iron administration raises the hemoglobin, stimulates a hemoglobin increase >1 g/dl hemoglobin more often, achieves or exceeds the target hemoglobin threshold of ≥11.0 g/dl more consistently, and replenishes iron stores more reliably than oral iron therapy (52). In two studies with patients who had CKD and were randomly assigned to either intravenous or oral iron, however, there was no significant difference in mean hemoglobin levels between the two groups at study conclusion (54,55). In hemodialysis patients with severe iron deficiency (pretreat-
ment TSAT values of 11%), an ESA dosage reduction of 70% is achievable when patients are supplemented adequately with parenteral iron (56). In hemodialysis patients, an aggressive iron dextran protocol (501 mg iron/mo during a period of 6 mo) resulted in an increase of TSAT >30% and dropped ESA dosage requirements by 40% as compared with a more moderate iron dextran protocol (176 mg iron/mo with a TSAT between 20 and 30%) (57). The patients in the high TSAT group, however, achieved mean serum ferritin levels of 730 μg/L (which is above the recommendations made before), whereas those in the low TSAT group had a mean serum ferritin of 297 μg/L (57). Iron dextran–treated hemodialysis patients were targeted to serum ferritin levels of 200 or 400 μg/L. In this study, mean ferritin levels of 299 μg/L and 469 μg/L were achieved. The higher ferritin group had 28% lower ESA dosage requirements (58). These data indicate that a more intensive iron therapy with ferritin levels in the upper recommended range (or even above it) is associated with a lower need for ESA. Data that were obtained from Medicare outpatient files that included 241,770 prevalent dialysis patients indicated that in 2002, a total of 84.4% of hemodialysis and 19.3% of peritoneal dialysis patients were administered intravenous iron. Ferric gluconate and iron sucrose have become the predominant form of therapy (59). Nevertheless, intravenous iron therapy still is underused in the ESRD patient population (60). The Predialysis Survey of Anemia Management (PRESAM) Study reported that 60% of patients who started dialysis between 1999 and 2001 were iron deficient (61). The Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated that 31 to 38% of hemodialysis patients in 2002 to 2003 presented with iron deficiency (62). Irving et al. (63) evaluated iron management of 1763 dialysis patients in six Australian renal units >4 yr after the implementation of the Caring the Australasians with Renal Impairment (CARI) guideline. The authors found a considerable variability among the units in achievement of iron targets: 30 to 68% achieved ferritin targets of 300 to 800 μg/L, and 65 to 73% achieved TSAT targets of 20 to 50%. Implementation barriers included lack of knowledge, lack of awareness of or trust in the CARI guideline, inability to implement the guideline, and inability to agree on a uniform unit protocol (63).

Vitamin C deficiency is common in patients who have ESRD and undergo regular dialysis therapy. Low ascorbic acid levels are the result of low dietary intake and intradialytic losses of vitamin C favored by the low molecular weight and the low albumin binding. The use of high-permeable dialyzer membranes is associated with convective and diffusive losses of vitamin C during hemodiafiltration (64). Low total vitamin C plasma predicts adverse cardiovascular outcomes (65) and, at least partially, the response to ESA therapy (66) among maintenance hemodialysis patients. Beneficial effects of intravenous administration of vitamin C have been reported in hemodialysis patients with iron overload (67,68) and functional iron deficiency (69) but also in dialysis patients with normal iron status (70). Up to 65% of the dialysis patients respond to intravenous vitamin C therapy with an increase in hemoglobin and/or a decrease in ESA dosage (70), but not all studies could confirm this finding (71). Attallah et al. (72) assessed the effect of vitamin C on ESA-hyporesponsive anemia in hemodialysis patients with unexplained hyperferritinemia. Treatment with 300 mg of intravenous vitamin C with each dialysis session caused a significant increase of hemoglobin and TSAT, whereas ESA dosage, iron-binding capacity, and C-reactive protein decreased significantly. The authors concluded that in hemodialysis patients with refractory anemia and hyperferritinemia, vitamin C improves responsiveness to ESA, either by augmenting iron mobilization from its tissue stores or through antioxidant effects (72).

Vitamin C is metabolized partially to oxalate and excreted partially via glomerular filtration and active tubular secretion. Patients who are on regular dialysis treatment display markedly increased plasma oxalate levels as compared with healthy individuals, mainly because of the impairment of renal oxalate excretion. Vitamin C is supplemented either orally (1000 to 1500 mg/wk) to dialysis patients or intravenously in a dosage of 250 to 500 mg after the hemodialysis session thrice weekly (68,71,73). Plasma ascorbate and oxalate concentrations increase with the dosage of vitamin C that is administered to hemodialysis patients. The calcium oxalate saturation was exceeded by 40% of the hemodialysis patients during 6 mo of therapy with 500 mg vitamin C/dialysis administered intravenously, indicating the need for plasma oxalate measurements during long-term ascorbate therapy (73). Intravenous ascorbic acid medication results in a decline in sTfR with a parallel rise in TSAT, probably through iron mobilization from inert iron depots and the availability of intracellular iron for erythroid progenitors (74). In vitro, ascorbic acid increases intracellular labile iron pool, and iron mobilization to transferrin in human hepatoma HepG2 cells only in the presence of iron sucrose but not in the presence of iron dextran or ferric gluconate (75).

Critical Evaluation of the Risk of Iron Administration

Intravenous iron has been linked to infection risk. Bacteria can use iron to grow via siderophores and/or transferrin receptor, allowing them to acquire iron that is available in the bloodstream and/or urinary tract. Many specific types of bacteria have increased virulence and enhanced growth in iron-rich hosts (76).

Iron overload results in a decrease in chemotaxis and phagocytosis of polymorphonuclear leukocytes (PMNL) (77). A marked decrease in intracellular killing of bacteria was noted in hemodialysis patients with a serum ferritin >650 μg/L (78). Peritoneal dialysis patients who received high-dosage intravenous iron had impaired ability of PMNL to eradicate Escherichia coli bacteria (79). Both iron sucrose and ferric gluconate inhibit migration of PMNL through endothelial cells in doses equivalent to concentrations measured in the plasma of dialysis patients who were treated with these intravenous iron products. Greater impairment in PMNL migration was found when endothelial cells were incubated in vitro for iron sucrose as compared with ferric gluconate (80). Parenteral iron therapy exacerbates experimental sepsis (81).

Clinical data, however, are conflicting on the association between iron and infection. Teehan et al. (82) followed 132
hemodialysis patients up to 1 yr after the initiation of intravenous iron therapy for the outcome of bacteremia. Iron-replete patients (those with a TSAT value ≥20% and a ferritin level ≥100 μg/L) had a significantly higher risk for bacteremia as compared with hemodialysis patients who were not iron replete. Among 1455 hemodialysis patients, Kessler et al. (83) identified 230 episodes of infection in 203 individuals. Univariate analyses showed that significantly more patients with bacterial infection had iron overload, as indicated by plasma ferritin >1000 μg/L. In a second multicenter, prospective study, multivariate analyses showed that three parameters are significant independent risk factors for bacterial infection in dialysis patients: History of bacterial infection, type of vascular access, and serum ferritin level >500 μg/L (84). These data confirmed earlier findings that iron overload is associated with infectious complication in patients with ESRD (85–87). More intensive dosing of iron (defined as >10 vials of 100 mg iron dextran during a 6-mo period) was associated with significantly elevated rates of hospitalization and death as compared with hemodialysis patients who received <10 vials of iron (88). In contrast, no association between intravenous iron administration and mortality was observed when multivariable models were used (89). A multicenter, French, prospective trial in 988 hemodialysis patients did not find a correlation between ferritin of iron therapy with infection, although only 5% of patients had ferritin levels >1000 μg/L (90). Another study showed no difference in either hospitalization or infection in patients who had ESRD and a ferritin level >658 μg/L (57). In the study of Kalantar-Zadeh et al. (91), an elevated serum ferritin level was a strong predictor of hospitalization, and an increase of 500 μg/L in serum ferritin was associated with a 2.7-fold risk for death, probably as a result of the confounding effects of malnutrition and inflammation (14). In a quality-of-life study, hemodialysis patients who were randomly assigned to normal as compared with subnormal hemoglobin targets required higher dosages of intravenous iron sucrose but experienced no increase in mortality (92). Relative risk for mortality or hospitalization as a result of infection in hemodialysis patients who received iron sucrose in the Iron Sucrose Clinical Trial was lower as compared with that observed in the US Renal Data System historical control group (93). Because intravenous administration of iron increases the availability of this essential nutrient for microorganisms (94), intravenous iron therapy is not recommended in the setting of acute infection. Patients with chronic infection or chronic inflammation may develop iron deficiency and hyporesponsiveness to ESA therapy, resulting in the need for low-dosage intravenous iron administration. In patients with anemia of chronic disease, however, a major part of iron administered intravenously is transported into the reticuloendothelial system, where it is not really available for erythropoiesis (95).

It may be argued that intravenous iron products may have an adverse impact on patients with CKD via a potentiation of systemic inflammation. In the setting of acute traumatic muscle damage in mice, iron therapy caused proinflammatory effects that were evaluated by an increase in the production of TNF-α (96). Two important clinical studies, however, demonstrated that intravenous iron therapy within international recommendations may even display anti-inflammatory effects in maintenance hemodialysis patients (97) and also in patients with rheumatoid arthritis (98). In hemodialysis patients, intravenous iron sucrose therapy resulted in an increase of plasma IL-4 levels and in a decrease of TNF-α levels. There was a direct correlation between IL-4 and TSAT and an inverse correlation between TNF-α and TSAT in these patients (Figure 2). Hemoglobin levels increased in hemodialysis patients with the increase of IL-4 and the decrease in TNF-α. In contrast, ESA dosage decreased with the increase of IL-4 and the decrease in TNF-α (97). These data indicate that intravenous iron therapy within international recommendations results in downregulation of proinflammatory immune effector pathways and stimulation of the anti-inflammatory cytokine IL-4. Intravenous iron therapy improves renal anemia by two different mechanisms: First, directly via iron supply for (the ESA-stimulated) erythropoiesis; and, second, indirectly via the reported anti-inflammatory properties. However, iron-mediated weakening of the Th-1 immune effector function (estimated by lowered TNF-α production) with a subsequent strengthening of the Th-2–mediated immune effector function (estimated by increased IL-4 production) is an unfavorable condition for patients with ESRD in the case of acute infection and malignant disease (97). These data also argue for a withdrawal of iron supplementation under these conditions.

Intravenous iron products may impair kidney function in patients with CKD. Induction of passive Heymann nephritis in rats resulted in a marked increase in nonheme iron content of kidney cortex and tubules. It is interesting that an iron-deficient diet caused a significant reduction of nonheme iron level in the glomeruli and also a significant decrease in proteinuria (99). Intravenous iron products caused induction of monocyte chemoattractant protein-1 (MCP-1) in renal and extrarenal tissues under artificial experimental conditions (intravenous injection of 2 mg of iron sucrose or ferric gluconate into mice with a body weight of 20 to 25 g corresponding to >5000 mg of iron sucrose or ferric gluconate for a 75-kg patient). Because MCP-1 has profibrotic properties, negative implications for CKD progression by intravenous iron products have been suggested (100). In patients with CKD, intravenous administration of 100 mg of iron sucrose caused transient proteinuria and urinary excretion.

![Figure 2. Association between iron status and cytokine levels in patients with ESRD (97). TSAT, transferrin saturation.](image-url)
of tubular enzymes (101). The study by Leekley et al. (102) could not demonstrate proteinuria or albuminuria despite generation of oxidative stress by the infusion of 125 or 250 mg of ferric gluconate measured by plasma and urinary malondialdehyde (103). A single dose of 100 mg of iron sucrose infused over 5 min resulted in a transient increase of MCP-1 in plasma and urine of patients with CKD with an average estimated GFR of 26 ± 7.2 ml/min (103). The clinical relevance of this finding is unclear. Importantly, nondiabetic patients with CKD and a GFR of 36.2 ± 5.2 ml/min per 1.73 m² and mean ferritin levels of 98 µg/L (range 24.8 to 139.0 µg/L) had a remarkably stable kidney function (GFR 37.2 ± 0.9 ml/min per 1.73 m² 1 yr later) after the administration of 2400 mg of iron sucrose within 1 yr (200 mg/mo iron sucrose intravenously) (104). In addition, van Wyck et al. (52) showed that intravenous iron is at least as safe as oral iron in preserving GFR in anemic patients with CKD. Patients who had CKD and were given intravenous iron sucrose 300 mg/mo up to 6 mo showed a rate of decline of renal function that was not different from that seen in patients who were given oral iron (54). Finally, patients who had CKD and were assigned to oral iron therapy showed a significant decline in creatinine clearance but not their counterparts who were given intravenous iron dextran 100 mg twice monthly up to 3 mo (105). Nevertheless, more clinical data and long-term data are needed to exclude that intravenous iron therapy impairs kidney function in patients who have CKD and are not on dialysis or in renal transplant recipients. No effect of either intravenous iron or oral iron on C-reactive protein could be found (54).

Other iron safety issues include tissue oxidation and atherosclerosis. *In vitro*, iron sucrose exerts a greater inhibitory effect on endothelial cell proliferation than lower molecular weight iron dextran, probably as a result of overexpression of proteins that are related to the cell-cycle arrest and apoptosis stress pathways (106). These findings are in agreement with *in vitro* data of Zager et al. (107) that demonstrated that iron sucrose inhibits aortic endothelial cell proliferation and showed more cytotoxicity than other iron compounds that are used for intravenous iron therapy. Whole-animal studies showed that intravenous administration of iron dextran in rats with chronic renal failure induces oxidative stress (108). An exacerbation of oxidative stress occurs after intravenous infusion of iron sucrose in dialysis patients, as demonstrated by an increase in plasma concentrations of malondialdehyde (109). Increased blood levels of non–transferrin-bound iron and/or its redox-active part have been found in patients with ESRD (110–112) but also in normal volunteers (113) after intravenous injections of iron products. In normal volunteers, free iron release was associated with increased reactive oxygen species in plasma and reduced flow-mediated forearm blood flow (113). In peritoneal dialysis patients, intravenous infusion of 300 mg of iron sucrose also caused peripheral vasodilation that was confirmed by an increase in forearm blood flow. However, the increase in non–transferrin-bound iron and redox-active iron caused by iron sucrose therapy did not influence vascular reactivity to intra-arterial acetylcholine, glycerol-trinitrate, or L-N-mono-methyl-arginine (112). Iron sucrose injection in hemodialysis patients led to free iron in serum and oxidative stress, which could be attenuated by pretreatment with vitamin E (114). Intravenous iron therapy induced protein and albumin oxidation (115,116) and correlated with plasma levels of advanced oxidation protein products as well as carotid artery intima thickness of dialysis patients (117). Ferric gluconate modifies β₂-microglobulin (118) and fibrinogen (119) as a marker for oxidative stress. Intravenous administration of 100 mg of iron sucrose in patients with CKD increased malondialdehyde as a marker of lipid peroxidation (101). However, not all studies found evidence of enhanced oxidative stress caused by parenteral iron therapy in patients with ESRD (111,120). Hemodialysis therapy is associated with an increase of peroxide levels. This rise in plasma total peroxides, however, is not increased further by concomitant intravenous injection of 100 mg of iron sucrose (111). The authors concluded that this increase was related to hemodialysis rather than intravenous iron. Parenteral infusion of iron sucrose during hemodialysis had no effects on the expression of leukocyte surface molecules and did not increase the production of reactive oxygen species (120).

**Evaluation of Various Iron Preparations**

Iron dextran, ferric gluconate, and iron sucrose distinguish clinically by differences in pharmacokinetics, maximum dose size, maximum rate of infusion (121), and the rate of adverse reactions (122–126). Adverse reactions to parenteral iron range from minor to life-threatening. A search of the Gambro Health-care US medical database during a 16-mo period from January 1999 to April 2000 revealed an incidence of reactions to iron dextran that required resuscitative medications to be 0.035% (seven of 20,213 iron dextran–naïve dialysis patients). Importantly, the life-threatening adverse reactions to iron dextran were reported in five dialysis patients in response to the test dose and in two dialysis patients in response to the first treatment dose, indicating that the risk is confined to incident patients. Adverse reactions that were serious enough to be reported to the database occurred in 0.7% of 48,509 dialysis patients who received iron dextran, yielding an intolerance incidence of 0.5% per year (127). These data closely approximate the results of a previous report of 165 serious events in 841,252 exposures (adverse drug event rate 0.0196%) that were based on the Fresenius Medical Care North America database (124). Serious adverse reactions for iron dextran were 11.6 to 57.9 per million exposures published using the large voluntary reporting database of the World Health Organization (126).

The newer preparations of intravenous iron, ferric gluconate, and iron sucrose may have a lower risk for adverse drug events as compared with iron dextran (128). Three multicenter studies that were performed with iron sucrose in the United States found no serious adverse drug events and no severe hypersensitivity reactions (93,123,129), although patients with a history of intolerance to another iron agent that was administered before study enrollment have been included. A single life-threatening reaction was observed in one of 2534 prospectively examined hemodialysis patients who were administered a single 125-mg ferric gluconate dose (per-exposure and per-patient serious adverse drug events rate 0.04%) (125). Among 143 iron
dextran–sensitive hemodialysis patients who were exposed to ferric gluconate, three (2.1%) had suspected allergic reactions, including one patient with serious adverse drug events (0.7%). Among 2194 iron dextran–tolerant hemodialysis patients, however, adverse drug events to ferric gluconate were seen only in some patients (0.3%), and none had serious reactions (125). Chertow et al. (130) calculated the absolute rates of life-threatening reactions as 0.6, 0.9, 3.3, and 11.3 per million for iron sucrose, ferric gluconate, lower molecular weight dextran, and higher molecular weight dextran. Bailie et al. (131) used the Freedom of Information surveillance database administered by the Food and Drug Administration, together with market research data, to review adverse events of intravenous iron preparations that are available in the United States. All-event reporting rates were 29.2, 10.5, and 4.2 reports/million 100-µg dosage equivalents for iron dextran, ferric gluconate, and iron sucrose, respectively. All-fatal-event reporting rates for these three iron compounds were 1.4, 0.6, and 0.0 (131). Comparing the safety results of available intravenous iron agents, however, requires great caution, because clinical trials to compare safety of the products directly have not been performed so far, and most published studies represent retrospective analyses of charts or databases (5). Nevertheless, life-threatening and other adverse drug events are less frequent and less severe with the use of nondextran iron formulations. Iron sucrose carries probably the lowest risk for hypersensitivity reactions (131,132). The anaphylactoid reactions involving hypotension, dyspnea, back pain, flushing, and anxiety are predominantly to dextran (133). Iron dextran, however, still is in use worldwide, and many nephrologists claim that it can be used safely.

The safety and the efficacy of ferumoxytol, a semisynthetic carbohydrate-coated iron oxide, was studied recently in a phase II clinical trial (134). Rapid intravenous injection (30 mg/s iron) offers such a therapy for patients who have CKD and are not on dialysis or patients who undergo peritoneal dialysis. Adverse drug events included constipation, chills, tingling, delayed pruritic erythematous rash, and transient pain at the injection site in some patients (134). Ferumoxytol injected at 60 mg/min was well tolerated in the majority of the patients. The drug half-life in normal individuals and hemodialysis patients increased with increasing dosage from 9.3 to 14.5 h. Ferumoxytol was not removed with hemodialysis (135).

Agarwal et al. (101) administered 100 mg of iron sucrose over 5 min, whereas Macdougall and Roche (136) found that administration of 200 mg of iron sucrose as an intravenous bolus injection of 2 min is a practical dosing regimen in patients with CKD, but seven patients experienced hypotensive reactions under these conditions. Some authors recommend infusion of 200 to 500 mg of iron sucrose over up to 1 to 4 h. In Europe, the recommended upper ferric gluconate dosage is 62.5 mg per injection. In the United States, most studies have been performed using 125 mg of ferric gluconate injected within 10 min. Leehy et al. (102) infused 125 mg of ferric gluconate over 1 h and 250 mg of ferric gluconate over 2 h. Up to 20 mg/kg body wt iron dextran can be administered as a single dose. These data indicate an enormous flexibility in the actual dose regimen. Thrice-weekly, weekly, every-other-week, once-monthly, or less frequent schedules are used to provide 25 to 125 mg/wk or 100 to 1000 mg of intravenous iron within 12 to 16 wk, depending on needs (34).

Conclusion
Diagnosis of iron deficiency and guidance of iron supplementation should be made in stable patients with ESRD by ferritin and TSAT measurements at 3-mo intervals. Minimum levels are defined as serum ferritin >100 µg/L and TSAT >20%; recommendations for target values are 200 to 500 µg/L for ferritin and 30 to 40% for TSAT. The percentage of hypochromic RBC or alternatively CHR should be determined whenever possible. Minimum levels for the percentage of hypochromic RBC and CHR are <10% and >29 pg, respectively, whereas recommended target values are <2.5% and 35 pg. Intravenous administration of iron is mandatory for the majority of patients with ESRD, because oral iron supplementation often is not sufficient. Optimal monitoring of iron-treated patients balances the safety and the efficacy of parenteral iron therapy (137). Intravenous iron products are administered safely within the recommended international guidelines (1,2) but not without adverse drug events. Nondextran iron preparations are preferable because of a reduced incidence of serious adverse drug events (138).

Disclosures
None.

References

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