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An Indistinct Balance: The Safety and Efficacy of Parenteral Iron Therapy

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The National Kidney Foundation Dialysis Quality Initiatives (NKF-DOQI) Anemia Work Group developed clinical practice guidelines (1) that aimed to achieve a target hemoglobin level of 11 to 12 g/dl at the lowest cost by optimizing the erythron response to recombinant human erythropoietin (epoetin). Despite the use of epoetin to manage the anemia of chronic renal failure (CRF) (2–6), many patients remain at hematocrits below currently recommended levels. Persistence of suboptimal hematocrit levels despite administration of seemingly adequate doses of epoetin signifies an inadequate response to the agent. The most common cause for such *erythropoietin resistance* is an inadequate supply of iron to the bone marrow to sustain enhanced erythropoiesis (7–13).

The NKF-DOQI Anemia Work Group guidelines support the implementation of a proactive intravenous iron maintenance regimen. Given that gastrointestinal iron absorption is less than ongoing iron losses in the majority of hemodialysis (HD) patients, *functional iron deficiency* is likely to develop in most patients leading to an iron-limited erythropoiesis. We define functional iron deficiency as a pathophysiologic state in which the bone marrow's erythropoietic capacity to respond to epoetin is limited by iron release from storage depots. The result of such deficiency is utilization of higher and more costly doses of epoetin to overcome what is *errantly* perceived as relative resistance to epoetin. Parenteral iron is the treatment of choice in HD patients with either absolute or functional iron deficiency since oral iron therapy is nearly always ineffective in the dialysis population. In fact, the NKF-DOQI guidelines advocate aggressive detection and management of functional iron deficiency. An initial and careful scrutiny of the iron status of the dialysis patient is succeeded by the optimized delivery of parenteral iron and epoetin to achieve the desired level of erythropoiesis.

Excessive fear of the potential risks associated with iron therapy may lead the practitioner to adopt a skewed view of the role of iron and epoetin in the management of the anemia of CRF. In this venue, iron has a passive role that justifies maintenance of iron stores and transferrin saturation (TSAT) at low levels since epoetin resistance can be overcome by increasing epoetin dose. In this scenario, the means to achieve target hemoglobin levels of 11 to 12.5 g/dl become subsidiary to the goal because the benefits of anemia correction (*i.e.*, decreased mortality, decreased hospitalization, and improved quality of life) are gained only after attaining target hemoglobin levels. This rationalization underestimates the role of appropriate iron prescription, dismissing its cost effectiveness in the global management of the dialysis patient. Furthermore, hemoglobin levels are generally more stable over time during judicious application of iron, avoiding the fluctuating hemoglobin levels that are frequently present during epoetin-centric anemia management.

Reducing the epoetin dose in patients may attenuate several potentially untoward effects of epoetin. Epoetin may promote hypertension by inducing vascular constriction through enhanced endothelin-1 production and by reducing the vasodilatory response of resistance vessels by decreasing endothelial nitric oxide production (14). Furthermore, epoetin-mediated platelet-derived growth factor release by vascular smooth muscle cells (15) may promote atherogenesis and myointimal hyperplasia, particularly in vascular access grafts of HD patients. A more balanced view of risks and benefits associated with epoetin and iron in anemia management is depicted in Figure 1.

What is the relative safety of maintaining a higher ferritin level in HD patients through repeated administration of intravenous iron? Moreover, what levels of serum ferritin warrant concern for iron overload? Parameters that most frequently stimulate treatment by iron are a set of suboptimal iron indices, TSAT, and serum ferritin. Despite their wide application, these parameters frequently fail to detect functional iron deficiency (16–18). Several studies have explored the issue of whether increased risks exist for those end-stage renal disease (ESRD) patients whose ferritin levels consistently exceed 500 ng/ml (19) and for those who receive iron dextran continually (20–22). In this article, we will briefly review iron metabolism in ESRD patients and then critically examine those processes that inure functional iron deficiency, despite hyperferritinemia. We will conclude by focusing on the collective experience of intravenous iron administration in ESRD, contrasting the risks and benefits of conventional iron therapy.

Iron Deficiency

Pathogenesis of Functional Iron Deficiency

The inability to absorb iron in quantities sufficient to match the demands of heightened erythropoiesis constitutes the mechanism of functional iron deficiency in ESRD patients. Insuffi-

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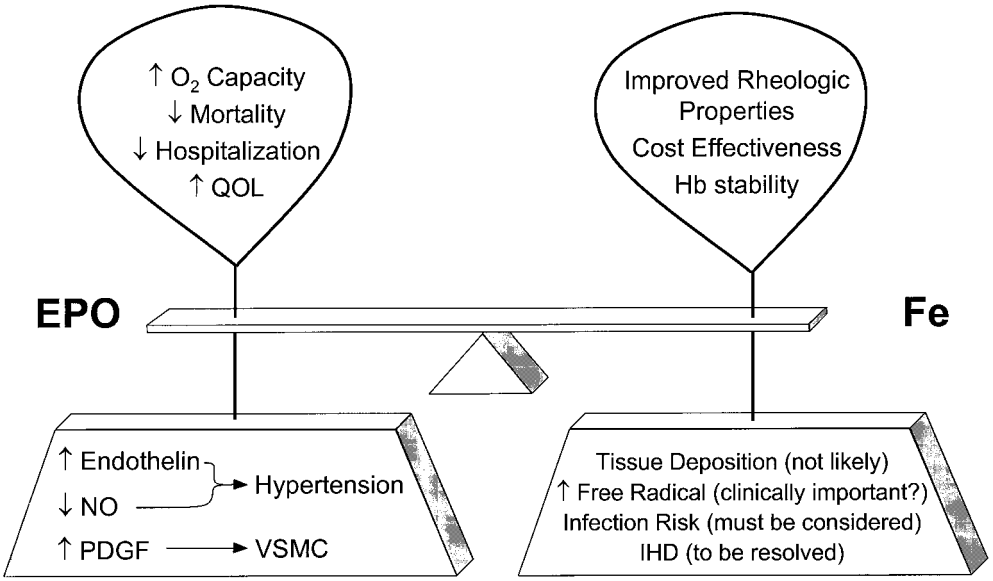

Figure 1. Relative benefits and risks of epoetin (EPO) and parenteral iron (Fe) use. Increasing hemoglobin to >10 g/dl by using EPO can reduce morbidity, mortality, and hospitalization, but may induce hypertensive effects or effects on vascular smooth muscle cells (VSMC) that may produce undesired effects on vascular access function. Similarly, parenteral iron may be associated with unwanted effects, but prevention of iron deficiency is cost-effective and may promote stability of hemoglobin, prevent multiple dosing changes in EPO, and improve blood flow through capillaries by improving the rheologic properties of red blood cells.

cient iron absorption may occur even when 200 mg of elemental iron is ingested. Iron absorption varies inversely with ferritin levels in healthy subjects and ESRD patients (23). In ESRD patients, ferritin levels exceeding 100 ng/dl do not guarantee adequate marrow iron storage and delivery. Furthermore, transferrin levels are frequently depressed in CRF. Subnormal transferrin levels limit enterocytic iron uptake. In ESRD, both evident as well as undisclosed inflammatory processes lower transferrin levels while reciprocally elevating ferritin levels. This combination precludes the requisite compensatory adaptive increase of gut iron absorption. Furthermore, intestinal iron absorption is decreased by gastric proton pump inhibitors and H_2-antagonists; by ingestion of dietary phytates, oxalates, carbonates, phosphates, and tannates (24); and by calcium-containing phosphorus-binding compounds that block iron uptake by enterocytes (25). Thus, current target hemoglobin levels cannot be achieved in ESRD patients by oral iron therapy (26). Finally, iron-replete individuals manifest decreased iron stores within 3 mo of epoetin treatment, thereby complicating the treatment of anemia (27).

Normal iron transport and physiology is depicted in Figure 2A. The normal total circulating iron pool is 3 to 4 mg (28). Iron is bound and transported in plasma by the non-heme α1-globulin transferrin. During normal erythropoiesis, all of the circulating iron is bound to transferrin and iron is turned over 6 to 10 times daily (29); despite wide variation in iron stores, the iron pool remains remarkably stable. This observation suggests that iron release from macrophages is coordinately proportioned to tissue uptake that approximates 24 mg daily. One important function of macrophages, particularly Kupffer cells, is to recycle heme iron from senescent red cells back to transferrin (30). The mechanisms controlling macrophage iron output are unclear, but likely involve plasma epoetin-mediated increased generation of unsaturated transferrin that, in turn, results in greater iron extraction from macrophages.

Ferritin, a ubiquitous protein, exists as multiple tissue-specific isoforms. Its only known function is to sequester iron for storage. Plasma ferritin contains virtually no iron, whereas iron-overloaded cells contain ferritin and hemosiderin, likely a ferritin degradation product (26). Expansion of the intracellular pool of transit iron induces ferritin synthesis, but reciprocally decreases expression of cell surface transferrin receptors, thereby diminishing iron uptake. The opposite events occur during states of iron depletion. In the cell, iron regulatory proteins are tailored to "sense" iron in transit and to maintain it at physiologically appropriate levels.

Normally, plasma transferrin is 30 to 40% saturated by iron. In iron deficiency, elevated transferrin levels maintain the circulating iron pool despite the marked decrement in TSAT. Conversely, an iron-overloaded state is defined by a high serum iron level, notable decrement in circulating transferrin and markedly increased TSAT. During inflammatory states, circulating transferrin decreases, but because iron release from the reticuloendothelial system (RES) is retarded, TSAT changes little. Thus, the changes in serum ferritin and TSAT of ESRD patients mimic those inflammatory states. Anemic HD patients with concomitant inflammation that can be presumed on the basis of relatively higher C-reactive protein (CRP) levels absorb iron less readily from the gut than control patients, who do not manifest elevations of CRP (31).

Table 1 summarizes the diagnosis of absolute iron deficiency in healthy subjects and ESRD individuals. On average, the total iron binding capacity (TIBC) levels in ESRD patients

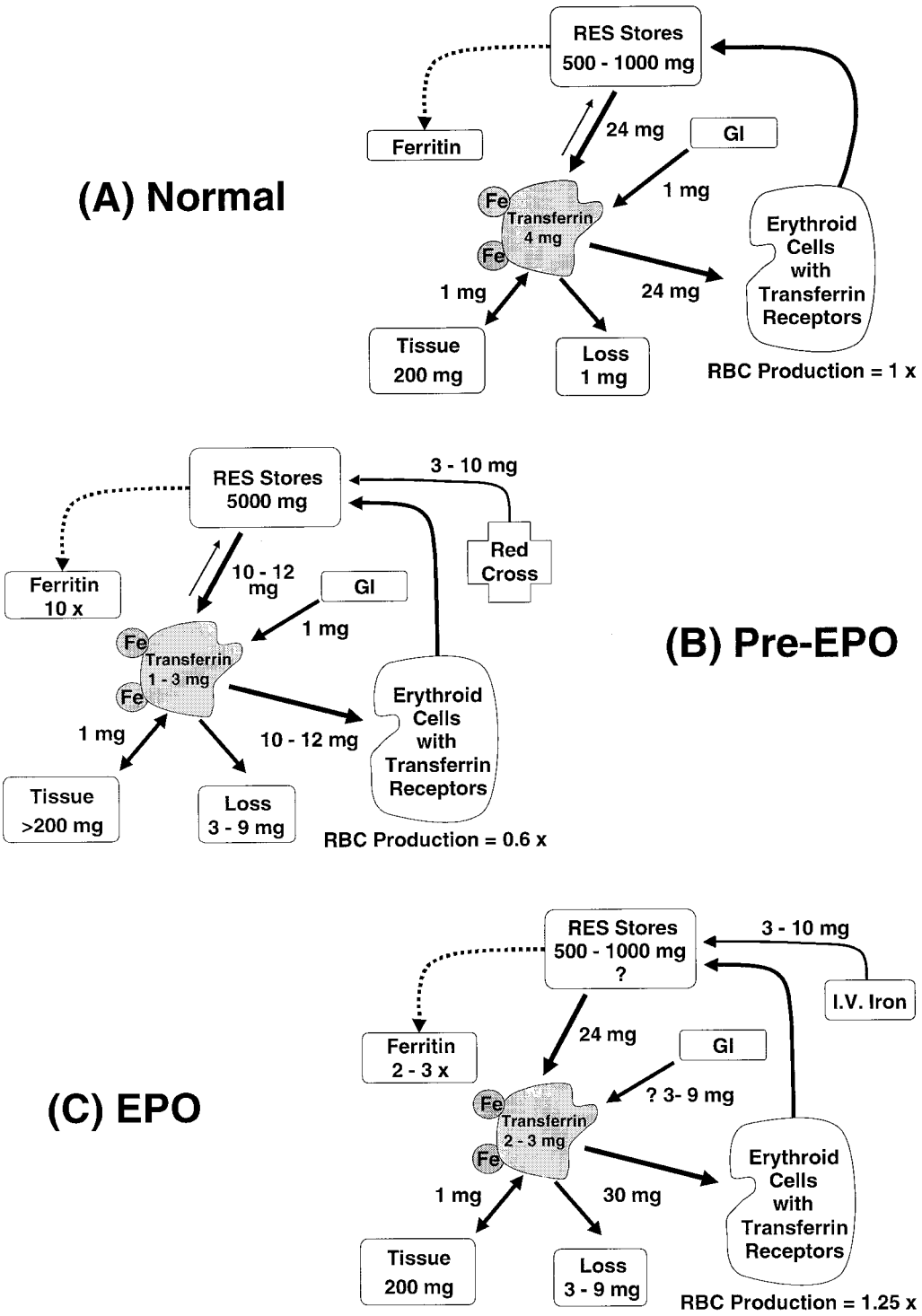

Figure 2. Iron metabolism in healthy men (Normal; Panel A) and end-stage renal disease (ESRD) male patients before epoetin (Panel B) usage and after epoetin (Panel C) usage for managing anemia. In healthy subjects (Panel A), basal daily erythrocyte production (1×) requires the delivery of 24 mg of iron from transferrin whose total circulating capacity is only 4 mg. External losses are low and therefore enterocyte absorption is also low. Before EPO use in ESRD (Panel B), erythrocyte production was reduced by 40% or more, and maintenance of hemoglobin depended on periodic red blood cell transfusion (Red Cross). Because of decreased transferrin levels and the absence of EPO-driven erythropoiesis, iron redistributed to the reticuloendothelial system (RES) and tissues. In the modern era (Panel C), erythrocyte production is frequently increased (1.25×) to maintain hemoglobin at 12 g/dl because of external dialysis-associated blood losses and shortened red cell survival. Greater delivery of iron is thus required in the face of decreased transferrin levels and some blockade of iron release from the RES. This necessitates the use of parenteral iron administration. RES and tissue overload is minimized because of the diversion of iron to the marrow by EPO-driven erythrocytosis.

Table 1. Comparison of iron absolute deficiency in healthy subjects and ESRD patients[a]

Parameter	Healthy Subjects	ESRD Patients
TIBC (mg/ml)	~350 to 430	~225 to 300
TSAT (%)	15	20
Serum iron (mg/ml)	53 to 64	45 to 60

[a] ESRD, end-stage renal disease; TIBC, total iron binding capacity; TSAT, transferrin saturation.

are decreased by nearly one-third from normal values (32). In ESRD, a TSAT of 20 to 30% indicates a substantial decrease in the circulating iron pool and is equivalent to a TSAT of 12 to 20% in nonuremic individuals. Iron uptake by developing erythrocytes is highly dependent on transferrin receptor density, in contrast to other tissues where uptake can accrue via receptor-independent pathways. We contend that the low TIBC of the ESRD patient represents one of the key forces that engenders functional iron deficiency because normal or supranormal erythropoiesis during epoetin therapy mandates greater-than-normal iron turnover (13). Such a low capacity system precludes sufficient iron uptake, in spite of adequate iron storage (32). Consequently, for the ESRD patient to maintain a total plasma iron pool comparable to healthy subjects, the TSAT must be maintained in the 30 to 50% range when the TIBC has declined by one-third. To achieve this, a therapeutic paradox arises. The physician must satisfy an increased requirement for iron delivery and optimize anemia management, yet incur no increased risk to the individual through enhanced iron administration (*primum non nocere*).

Death (33–35) and hospitalization rates (36,37) of ESRD patients vary inversely with hemoglobin levels. Collins *et al.* recently showed that HD patients whose hemoglobin levels decreased from 11 g/dl to <10 g/dl incurred increased risks for mortality and hospitalization (38). To obtain the benefits of maintaining the hemoglobin at 11 to 12 g/dl (Hct, 31 to 36%) for these patients, a more complete elucidation of the long-term risks of intravenous iron and a definition of the optimal parameters and tests for iron management will be required.

Diagnosis of Iron Deficiency

The distinction between functional and absolute iron deficiency is one of degree, as iron-limited erythropoiesis occurs in both circumstances. Functional deficiency precedes absolute deficiency and is defined by the delivery of less iron to the developing erythron than that required for optimal epoetin-driven erythropoiesis. In healthy subjects and iron-replete renal failure patients, ferritin and TSAT levels are significantly altered after only 1 wk of epoetin if the dose stimulates erythropoiesis above basal levels. Major *et al.* (39) demonstrated significant changes in iron metabolism within 7 d of epoetin therapy, even in iron-replete healthy subjects. Baseline iron indices were normal, and the reticulocyte hemoglobin content (HCr), reflecting iron delivery to the maturing erythrocyte, averaged 32 fmol/ml (normal range, 26 to 34 fmol/ml). Patients who received epoetin but no parenteral iron decreased their HCr from 32 to 31 fmol/ml and greatly decreased their serum ferritin levels. However, administration of a 200-mg dose of iron-saccharate abolished the constraint on erythropoiesis, reflected by an increase of HCr to 35 fmol/L and maintenance of serum ferritin. Similar data obtained by Eschbach *et al.* (2) are shown in Figure 3. Changes of iron parameters in

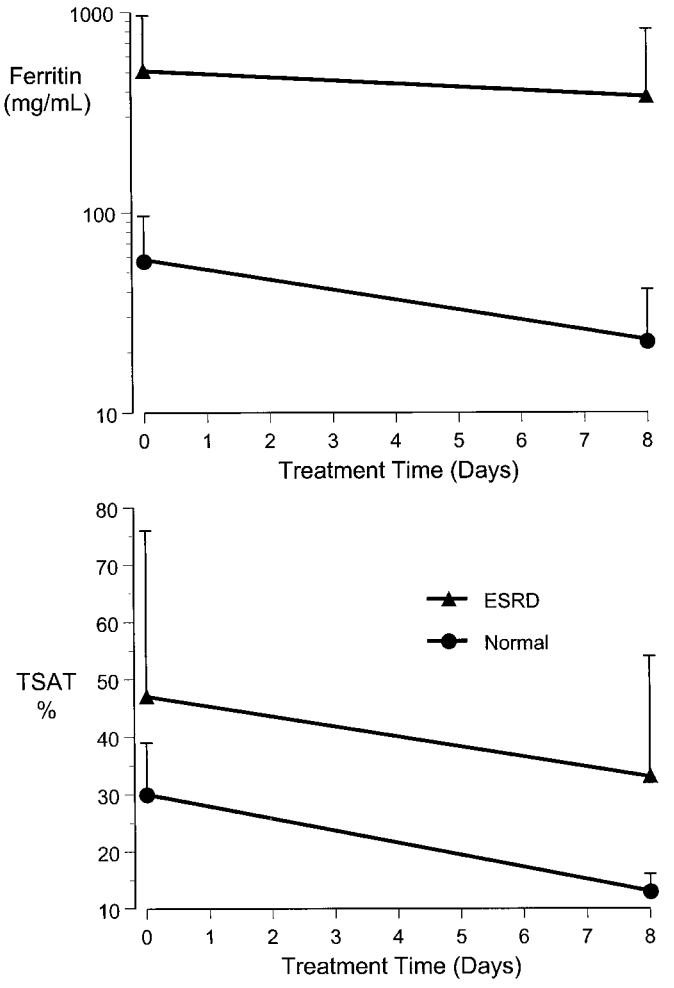

Figure 3. Changes in indices of iron delivery in healthy and ESRD subjects after administration of four doses of recombinant erythropoietin over 7 d. In "iron-replete" nonazotemic healthy individuals (●), transferrin saturation (TSAT) declines from 30% to <15%, whereas ferritin decreases from 58 ng/ml to almost 15 ng/ml. Both TSAT and ferritin levels approach those of absolute iron deficiency. In previously transfused ESRD patients with much greater iron stores (▲), the rate and magnitude of the changes in ferritin and TSAT are similar but start from higher levels. Adapted from *Kidney Int* 42: 407–416, 1992.

transfused HD patients parallel those of healthy subjects, the latter becoming iron deficient within 7 d. ESRD patients who have never received blood rapidly become iron deficient during epoetin therapy as do healthy subjects (3,13). Thus, epoetin can increase marrow demand for iron to an extent greater than that which can be provided by RES iron output, thus resulting in ineffective erythropoiesis from functional iron deficiency

Ongoing dialysis-associated blood losses reduce ferritin levels with time, even in iron-overloaded patients (21). Epoetin accelerates the decline of iron stores as iron is mobilized into newly formed erythrocytes. (Blood losses and therefore iron losses increase at the increased hematocrit.) Common threshold values for iron repletion therapy in HD patients are a TSAT $<$20% or a ferritin level $<$100 ng/ml (1), but these parameters are frequently inadequate to detect functional iron deficiency (16,17,40). This conclusion is reinforced by a recent Veterans Administration study (41,42) of 170 HD patients who received 240 courses of iron dextran. A course of iron consisted of 10 successive 100-mg doses of iron dextran administered at dialysis. An increase in hemoglobin to the same epoetin dose or a decrease in epoetin dose needed to maintain target hemoglobin in response to a course of iron was used to detect the presence of functional iron deficiency (18). Data analysis (42) produced no clear cutoff values for ferritin (*i.e.*, 100 to 300 ng/ml or TSAT 12 to 20%) that could be used to either positively or negatively predict the presence of functional iron deficiency with more than 80% certainty. Therefore, there is no absolute level of TSAT or ferritin diagnostic of functional iron deficiency. Others have established that functional iron deficiency may occur at TSAT values approaching 30% (3,18) or ferritin levels of nearly 600 ng/ml (43–48).

Thus, it is not surprising that a large cross-sectional study found that hemoglobin directly correlated with serum iron, inversely with ferritin, but not at all with TSAT (44). Even at a mean ferritin of 871 ng/ml, parenteral iron treatment could increase the hematocrit by up to 11% when TSAT was increased from 20 to 32% (45). Perhaps the HCr that increases within 2 wk of iron treatment may provide an early clue to iron-limited erythropoiesis and lead to more effective iron therapy (46–48). In Europe, the percentage of hypochromic cells is used to reflect functional iron deficiency. However, its diagnostic utility is offset by the relatively long interval (weeks to months) that passes before therapy is prompted. Presently, the only way to definitively exclude functional iron deficiency is by evaluating the erythropoietic response to additional parenteral iron (18,49).

Parenteral Iron Therapy

Efficacy

Many studies indicate that adequate iron stores are critically necessary to achieve optimal responses to epoetin. Patients enrolled in the earliest epoetin studies tended to be iron-overloaded. These subjects' ferritin levels decreased from initial values of nearly 1400 ng/ml to 800 ng/ml during the initial 3 mo of treatment. A continued decline to $<$200 ng/ml occurred during the subsequent 3 yr of monitoring (50). These declines of ferritin reflected progressive utilization of iron stored during the corrective and maintenance phases of treatment. Tarng *et al.* (51) disclosed that those patients who achieved target hemoglobin levels originally maintained on average ferritin of 1582 ng/ml and TSAT of 51%. By contrast, patients failing to achieve target hemoglobin levels had significantly lower mean ferritin and TSAT values of 141 ng/ml and 25%, respectively.

Intravenously administered iron as iron dextran, iron gluconate, iron-hydroxide sucrose complex, or ferric saccharate is processed by the RES before its transferrin-mediated transport to the marrow and other tissues (Figure 2A). The most commonly used parenteral iron regimen uses intermittent dosing. Typically, 0.5 to 1.0 g of elemental iron is provided in divided doses when critical thresholds for TSAT or ferritin levels are reached (52–55). This scheme and modifications of single total dose infusion (54) are typically administered intermittently, on an "as needed" basis. These strategies are suboptimal. Several recent studies have established that maintenance parenteral iron administration as opposed to an "as needed" strategy achieves target hematocrits with lower epoetin doses, presumably abrogating the iron-limited erythroid response to epoetin (13,32,46,47,56–66). Our studies (32) have determined that maintenance iron treatment, with an average iron dose of 58 mg/wk (range, 20 to 150 mg/wk) for 72 wk, safely decreased the erythropoietin dose by 40%. Others have advocated for HD session-based iron dosing in 15- to 20-mg doses (58–60,67) or, for those patients being initiated into hemodialysis, iron therapy alone during the initial management phase (68). Other groups affirm the use of intravenous iron in pre-ESRD (69) and peritoneal dialysis patients (70,71). In CAPD patients, a single 1-g infusion over 4 h is well tolerated (72). Our experience has shown that peritoneal dialysis patients require approximately 700 mg of parenteral iron yearly, compared to dialysis patients who receive an average of 2.5 g yearly as maintenance therapy.

The efficacy of iron has been amply demonstrated. In one striking example, iron treatment alone successfully combated the anemia of HD patients (68). Patients with no stainable marrow iron increased their hemoglobin levels from 7.5 to 11.0 g/dl within 1 yr and to 12.6 g/dl by 2 yr without epoetin, following iron saccharate therapy at a weekly dose of 62.5 mg. The TSAT increased from 21 to 35% as ferritin increased from 268 to 393 ng/ml. Two control groups who received neither oral iron alone nor supplemental iron could not correct their anemia and required monthly packed red cell transfusions of 36 to 53 ml.

The magnitudes of the reductions in epoetin dose associated with parenteral iron administration have varied significantly among studies. The results are summarized in Figure 4. Averaged over 13 studies, ferritin increased from a pretreatment mean of 209 to 447 ng/ml after iron restoration, while mean TSAT increased from 22 to 35%. Overall, hemoglobin increased 18% while epoetin dosage decreased by 42%. Rosen *et al.* (73) and Senger and Weiss (66) noted 75% reductions in epoetin dose when intermittent monthly iron dosing of 100 mg was used. Two studies have shown the potential cost benefit of maintenance iron therapy that is generated by reducing epoetin

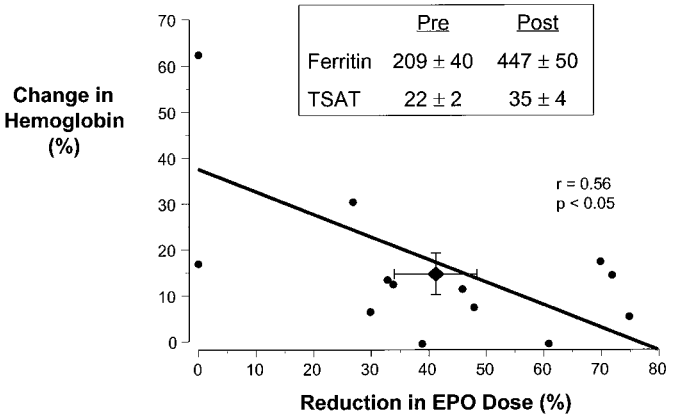

Figure 4. Regression analysis of 13 published studies examining the effect of parenteral iron therapy in ESRD hemodialysis patients. Parenteral iron protocols increased the ferritin from 209 to 447 ng/ml and the TSAT from 22 to 35%. On average, the EPO dose was decreased by 42% with an 18% increase in hemoglobin.

dose (64,65). Even patients with elevated ferritin levels benefit from parenteral iron and can reduce their epoetin doses (45,74).

We maintain that the optimal application of maintenance iron therapy in patients on fixed doses of erythropoietin requires judicious proportioning of iron delivery to the marrow, marrying it to the rate of erythropoiesis. Excessive transferrin saturation does not enhance erythropoiesis. The very high TSAT (*i.e.*, >60%) that follow pulse iron therapy (*i.e.*, 10 weekly doses of 100 mg) or large single total dose infusions (Figure 5) are superfluous (32). We believe that the initial period during which TSAT may exceed 50% does not offset the latter intervals of iron-limited erythropoiesis. Achieving a sustained but lower level of TSAT of 30 to 50% requires weekly or biweekly iron administration and ensures that erythropoiesis is not restrained by limitations of iron delivery, except in the rare circumstance of severe depression of TIBC to <150 ng/ml. Recent trends suggest that the "epidemic" of iron deficiency of HD patients in the United States reported by the Core Indicator Project has decreased recently. Between 1993 and 1996, the proportion of patients receiving parenteral iron has doubled to 51% while the fraction of those with TSAT >20% has increased from 44 to 63%. In addition, the proportion of patients with a ferritin level >100 ng/ml has increased from 63 to 73% (75).

Safety

In the United States, parenteral iron is administered as an iron dextran complex, while ferric sodium gluconate and saccharate are widely used in Europe and other countries. The most effective dosing strategies remain undefined. Some regimens deliver iron alone during each HD session, whereas others coadminister iron with heparin (60,76,77). Iron dextran preparations can be given slowly as 25- to 200-mg boluses, or alternatively, infused in 0.5- to 1.0-g quantities. A 25-mg test dose is recommended before administration of the remaining dose. Adverse reactions include wheezing, dyspnea, and hypotension. Other side effects include myalgias and arthralgias (41,54,78,79). Life-threatening reactions are rare, occurring in only 0.7% of patients, many of whom received multiple doses (78). In the Veterans Administration EPO trial, Kaufmann and

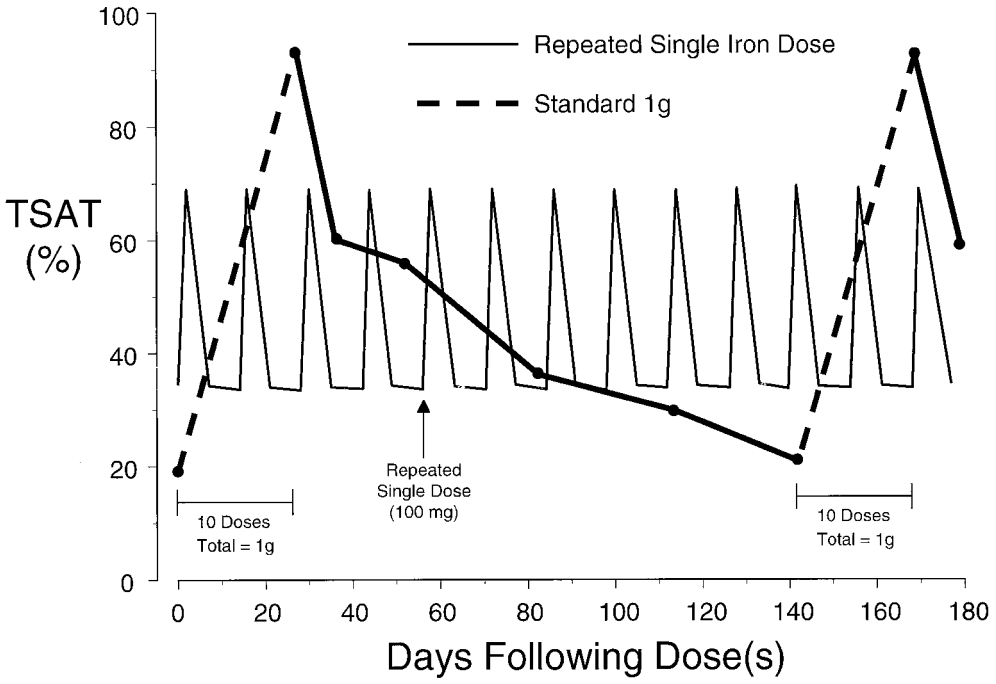

Figure 5. Temporal profiles of TSAT achieved by intermittent on-demand iron doses (dashed bold line) in response to decreased TSAT or ferritin (solid bold line) differ from those achieved by repeated 100-mg doses of iron administered intravenously every 2 wk as maintenance protocol (solid line). Based on data in reference (32).

colleagues cited two "possible" severe reactions in their study involving 2400 doses of epoetin (41). The anaphylactoid reactions are not dose-dependent and may occur after the test dose or after many previous doses. The mechanisms mediating hypersensitivity to iron dextran remain unclear, but may involve mast cell degranulation without immune complex involvement (80). However, the symptoms of arthralgias, myalgias, and hypotension are rate-related. In our experience, anaphylactoid reactions are extremely uncommon. The few patients with documented severe reactions have received iron dextran without incident, after pretreatment with prednisone, diphenhydramine, and a type-2 antihistaminic. It is our policy to administer iron dextran at a rate that does not exceed 5 mg/min. There is no substantial difference in the adverse reaction profiles of the two available United States iron dextran preparations (81).

The safety profile of nondextran iron preparations is equivalent to and occasionally superior to that of iron dextran. Faich and Strobos (82) estimated an overall adverse event rate for iron dextran of 1.2 adverse reactions per million doses. For iron gluconate, the overall frequency was 0.6 adverse reactions per million doses. More fatalities occurred over a 21-yr period (1976–1996) from iron dextran than from iron gluconate (46 *versus* 0). However, one should note that the types of iron dextran preparations differed during this period and that the reporting monitors for iron gluconate may have been less complete than for iron dextran. More recently, Nissenson and colleagues (83) reported that iron gluconate administration was a safe alternative for patients with iron dextran hypersensitivity.

The European experience with iron saccharate is based on data from Sunder-Plassman and Hörl (84), who administered single doses from 10 to 100 mg to their HD patients. TSAT increased in a dose-dependent manner, but decreased rapidly within 1 min after the dose. Doses of 40 to 100 mg increased serum iron when measured 30 min after the dose. The serum ferritin remained elevated for the entire interdialytic period only in those who had received a 100-mg dose. "Oversaturation" of transferrin by iron (*i.e.*, TSAT $>100\%$) did not occur when transferrin levels exceeded 180 mg/ml. In patients with very low transferrin levels, TSAT exceeded 100%, but the absence or presence of adverse reactions was not commented on. Using iron gluconate, administered over either 30 or 240 min, Zanen *et al.* (85) detected oversaturation in those who were rapidly infused with iron. Some of these patients exhibited reactions, including hypotension. The authors attributed these symptoms to the presence of free iron in plasma, resulting from delivery of a quantity of iron that transiently exceeded the iron-binding capacity of all iron-binding plasma proteins, including transferrin. It has also been speculated that dissociation of iron from gluconate and saccharate complexes proceeds more rapidly than for dextran congeners.

More recently, the issue of the appearance of plasma-free iron during rapid iron infusion has been studied by the bleomycin iron assay (86). In general, bleomycin-detectable iron is not present when iron sucrose infusions contain <50 mg of elemental iron. However, bleomycin-detectable iron is consistently present after rapid infusions that contain more than 100 mg of iron. The significance of the bleomycin-detectable iron is currently unclear. However, adverse reactions are nearly always obviated by low dose or slow iron infusion. Finally, the concept of transferrin oversaturation with iron may be misleading. We have noted that iron oversaturation frequently occurs with high single dose iron or multiple dose iron-dextran infusions (*i.e.*, 10 weekly 100-mg doses) if TSAT and transferrin measurements are obtained within 2 to 3 d of infusion (32). Essentially, during oversaturation, serum iron—the numerator of transferrin saturation calculation (serum iron divided by TIBC)—is spuriously increased, thereby elevating TSAT. Current calorimetric methods cannot separately determine the fractions of iron resident on dextran and transferrin (87).

Clinical Risks of Iron Therapy

The major biologic functions of iron, aside from its incorporation into heme, are its participation in a variety of oxidation-reduction reactions. Normally, iron on transferrin or ferritin is shielded from participation in unwanted redox reactions (88). However, if iron is released from its ferritin core, it can catalyze a variety of deleterious reactions. Iron, in the presence of superoxide and its dismutation product hydrogen peroxide, can induce chain reaction formation of highly reactive hydroxyl radicals by the Haber-Weiss reaction that may depolymerize polysaccharides, fracture DNA, inactivate enzymes, and initiate peroxidation of the cell membrane lipid bilayer. To counteract rogue free radicals, cells use a primary line of defense (Table 2) involving superoxide dismutase, catalase, and glutathione peroxidase. Phospholipid hydroperoxide glutathione peroxidase provides a secondary line of defense, limiting membrane lipoperoxidation. Antioxidants such as vitamins E and C may, in part, limit chain reaction formation of free radicals.

The potential toxicity of chronic iron exposure warrants concern for dialysis patients. This concern relates to the fol-

Table 2. Mechanisms used to minimize toxic effects of iron

Primary prevention—Iron is chaperoned and shielded
extracellular Fe: transferrin
extracellular heme: haptoglobin, albumin, and hemopexin
intracellular iron: ferritin (normal) and hemosiderin (tissue accumulation)
transcellularly: carrier proteins (mobilferritin, transferritin, apoferritin) and chelators (pyrophosphate).
Secondary prevention—Cellular defenses against free radical formation
enzyme systems within cells
superoxide dysmutase, catalase, glutathione peroxidase
specific enzyme at lipid membranes
phospholipid hydroperoxide glutathione peroxidase
antioxidants
vitamin E, vitamin C, vitamin A
cellular chelators of iron
citrate, ADP, pyrophosphates

lowing potential complications: (*1*) parenchymal iron infiltration; (*2*) permanent organ damage, including complications of cirrhosis, pancreatic fibrosis, cancer, and myocardial infarction; (*3*) an increased risk of infection; and (*4*) free iron-mediated oxidant tissue injury. During inflammation or ischemia, the presence of iron in tissues may perniciously potentiate oxidative injury. This is particularly relevant because chronic inflammatory states are often concomitants in the chronically iron-exposed ESRD population.

Tissue Iron Accumulation/Damage

In ESRD, the major risk for iron accumulation stems from either excessive red cell transfusions or excessive parenteral iron administration. Bodily iron stores are generally <1 g and the storage limit of the RES is exceeded at approximately 5 g of iron with overflow into parenchymal cells (89). Before the advent of epoetin, iron overload in HD patients was common and represented the consequence of repeated blood transfusions that offset blood losses (Figure 2B). In the anemia associated with CRF, red cell iron is shifted into RES storage deposits. Iron was deposited principally in hepatocytes and Kupffer cells during concomitantly depressed periods of erythropoiesis (90). Further iron uptake by nonerythroid tissues was fostered by downregulation of surface transferrin receptors during erythropoietin deficiency. Ferrokinetic studies of such untreated HD patients demonstrated direct correlations between nonerythroid iron turnover, serum iron levels, and transferrin saturation. Ultimately, iron overload was demonstrated in biopsies of marrow and liver (90–93). Elevated serum ferritin levels were seen even in those patients who had never received exogenous iron (93).

A variety of methods are available for diagnosing iron overload. The "gold standard" remains the assessment of the hepatic iron index in a liver biopsy specimen (94). Noninvasive means include computed tomography, magnetic resonance imaging, and magnetic susceptibility measurement (95). The assessment of iron overload in ESRD patients is confounded by the normal age-associated increment in iron. If one accepts the following three suppositions: (*1*) tissue iron overload results from red blood cell transfusion or excessive parenteral iron, (*2*) RES storage limits are not exceeded until 5 g of iron have accumulated (96,97), and (*3*) each nanogram of ferritin per milliliter corresponds to approximately 8 mg of storage iron (97), then spillover into parenchymal cells should not occur in healthy subjects until ferritin levels exceed 625 ng/ml. However, ferritin levels are affected by inflammation. CRP, serum amyloid-A, and circulating cytokines are increased in ESRD patients. Because of the acute phase reactivity of ferritin, the relationship of tissue iron to serum ferritin is altered such that ESRD patients probably have lower levels of tissue iron at any given level of ferritin, compared to age- and gender-matched healthy individuals. If so, tissue iron deposition in CRF patients is unlikely at ferritin levels <625 to 800 ng/ml. However, there are no contemporary studies that specifically examine the relationship of ferritin to tissue iron in patients who are already on or are being initiated into a maintenance hemodialysis program.

Figure 6 summarizes the results of one study, conducted before epoetin was routinely used, that correlated ferritin with RES stores in liver and spleen (44). These tissue stores did not correlate with those in the bone marrow (44). Most studies of iron overloaded dialysis patients have included patients who received parenteral iron and blood transfusions (44,92,93,98,99). Gokal *et al.*, in the pre-epoetin era, reported the distribution of serum ferritin levels in 120 maintenance HD patients who had received periodic blood transfusions and parenteral iron dextran (99). In nearly 71% of subjects, ferritin levels exceeded 800 ng/ml. More than half of the study population had ferritin levels exceeding 1000 ng/ml, a level generally reflecting iron overload. Hepatic and splenic iron was detected post mortem in 16 of 22 individuals who had elevated iron burden that averaged 8.8 g. However, hepatic fibrosis was present in a single patient. Iron was present in the cardiac myocytes of five patients, but there was no evidence of fibrosis. One investigation has attempted to isolate differences in the degree of iron overload of HD patients treated for anemia exclusively by either intravenous iron or blood transfusion (93). In both groups, ferritin levels ranged from normal to >1000 ng/ml. Serum ferritin levels were 3- to fivefold greater in iron-treated individuals. More than half of these maintained values >1000 ng/ml. Iron was present in hepatocytes and Kupffer cells in some patients from both groups. The degree of fibrosis was mild, but the presence of cirrhosis was not specifically reported. The absence of cirrhosis by liver biopsy was demonstrated even when ferritin levels approached 3000 ng/ml after repeated intravenous iron administration. Finally, and concordant with the above data, parenchymal injury from iron overloading is exceedingly difficult to achieve in the experimental setting (100,101).

Distinguishing among mechanisms that promote parenchymal iron deposition is important. Hepatic fibrogenesis occurs after a critical mass of iron has accumulated, approximately 20 to 30 mg iron/g dry wt. Hemosiderosis from iron overload secondary to red cell transfusions is often complicated by the acquisition of transfusion-related hepatitis (102), which, in

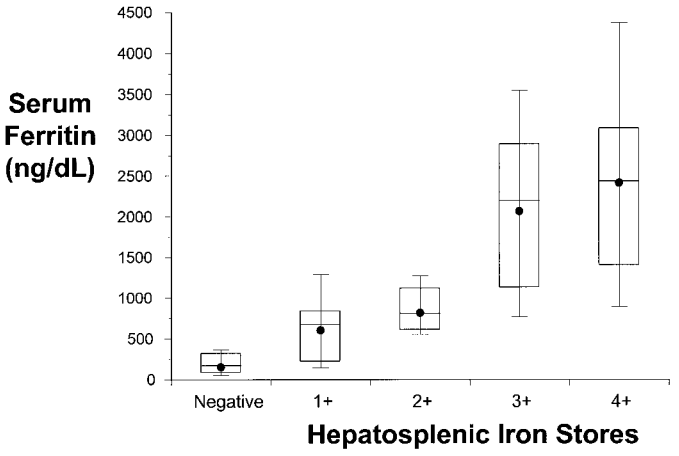

Figure 6. Relationship of hepatosplenic iron stores to serum ferritin. Adapted from *Lancet* 1: 652–656, 1982.

turn, facilitates the deposition of iron into the hepatic parenchyma (103). Ethanol-induced or viral hepatic injury may significantly lower the ferruginous threshold that predisposes to the development of cirrhosis. There is little direct evidence that persuasively links parenchymal damage to an iron overloaded state in HD patients. Since a diverse group of disorders can produce histologic and functional changes in liver (hepatitis B or C), pancreas (diabetes), and heart (hypertension, anemia, coronary artery disease [CAD]), and these disorders frequently complicate the clinical course of the dialytic patient, the issue is confounded further.

Erythropoiesis is stimulated in the anemic patient treated with epoetin (Figure 2C). Epoetin induces synthesis and expression of transferrin receptors on the cell surface by activating iron regulatory protein-1 (IRP-1). IRP-1 stabilizes the messenger RNA of the transferrin receptor for its subsequent translation to receptor protein (104). Consequently, the preferential uptake of iron by the erythron reduces the likelihood of iron deposition in nonerythroid tissues. Serum ferritin levels decrease abruptly after initiation of epoetin in CRF patients (3,105), and in healthy subjects (2,39). In fact, stored iron is mobilized to support new hemoglobin synthesis. Hence, parenchymal iron deposition should no longer constitute a problem because most patients deprived of iron while receiving EPO quickly deplete their iron stores (2,39,105). Moreover, further depletion of iron stores occurs in the HD patient due to ongoing treatment- and dialyzer-related blood losses. Iron overload described in the early epoetin era was in fact treated rapidly by periodic phlebotomy and escalating doses of epoetin (106,107). Today, very few dialysis patients are iron overloaded to the extent seen before availability of epoetin; however, iron overload may still occur when one of several specific circumstances occurs. These are a continued requirement for blood transfusions, an inability to be successfully treated with epoetin, and the presence of the hemochromatosis gene (108). Penetrance of the abnormal allele is high; 1 in 300 Caucasians is a homozygote and 1 in 10 people is a heterozygote.

Increased Free Radical Generation from Free Iron

The potentially noxious effects of increased iron burden in the CRF patients cannot be dismissed. The dialytic procedure itself induces free radical formation (109,110). Free radicals are difficult to quantify, and indirect methods have been used to assess free radical formation. The most direct assays quantify changes in polyunsaturated fatty acids or advanced oxidation protein products. Less direct methods measure cellular malondialdehyde (MDA) content or carbonyl-containing compounds. The least specific method measures thiobarbituric acid-reactive substances (TBAR). Peroxidation can also be assessed by the consumption of antioxidants such as vitamins E, C, A, and substance Q (ubiquinone). Finally, changes in antioxidant enzyme systems, including catalase, glutathione peroxidase, and superoxide dismutase, are also used to infer the *de novo* generation of reactive oxygen species.

During periods of oxidative stress, an increased bodily iron content may represent increased liability for the ill dialysis patient. Leukocytes are known to migrate into areas of tissue injury where they can generate superoxide, which can reduce ferritin-bound Fe^{3+} (ferric iron) to Fe^{2+} (ferrous iron) and generate free radicals. In experimental models, increased tissue iron content amplifies free radical-mediated oxidative tissue damage (111). In addition, iron has been linked to mutagenesis and carcinogenesis (112). Chronic inflammation, a frequent concomitant of dialysis patients, can conceivably prompt the emigration of activated circulating leukocytes from the circulation into iron-rich tissues, and their presence within inflammatory loci could potentiate ongoing cellular injury. However, these unfavorable circumstances are mitigated, in part, by upregulation of antioxidant systems that protect cells against lipoperoxidation (113). Overall, the contributory role of iron to such pathogenic events in dialysis patients is controversial.

Iron-induced lipoperoxidation and reactive oxygen species formation in HD patients have been ascribed to infusions of iron dextran and gluconate after their administration as 40- to 60-mg doses over 15 min (114). Both preparations increased 4-hydroxinonenal, a marker of lipid peroxidation, by nearly 25% within 2 to 4 h after the dose. These increases are modest and their significance is unclear, since healthy control subjects have not been studied. The study by Banyai *et al.* (86) indicates that a rapid 100-mg infusion of iron sucrose is associated with bleomycin-detectable free iron for up to 3 h after the dose. However, the authors reported no evidence of acute or chronic toxicity in their study patients. Other studies have shown that the oxidative stress that succeeds an iron hydroxide sucrose infusion is of minor degree and attenuated by a single 1200 U dose of vitamin E (115).

When levels of oxygen free radicals and markers of peroxidation (MDA, advanced oxidation protein products, carbonyl content) are examined in HD, the latter are increased, whereas the levels of intrinsic antioxidants (vitamins C, E, and Q) decrease. However, long-term epoetin treatment of anemia, regardless of intravenous iron therapy, does not alter these parameters, despite marked differences in ferritin levels (116). The latter studies are in keeping with those performed by Delmas-Beauvieux *et al.* (113), who could not demonstrate significant erythrocyte membrane lipoperoxidation or changes in antioxidant enzyme levels unless anemia was managed solely with parenteral iron. Then, MDA increased and antioxidant enzymes decreased. Taken collectively, the data suggest that there may be some risk from free radical formation associated with solitary iron therapy in anemia management, but not when iron is chronically used ($<$200 mg/mo) in combination with epoetin.

CAD and Myocardial Infarction

Iron stores in nonazotemic men progressively increase with age (117). In nonazotemic women, the increase occurs after menopause. To explain the lower incidence of CAD in women (118), Sullivan formulated the “iron hypothesis,” which stated that the large gender differences in myocardial infarction rates among developed countries could be attributed to the gender-related differences in bodily iron stores. The generation of free radicals by iron and the consequent oxidation of LDL-cholesterol lent further credence to the theory. The adverse effects of

iron on CAD were first described in Finland, where it was shown that the risk of acute myocardial infarction increased twofold independently of LDL cholesterol as the ferritin level surpassed 200 ng/ml (119). However, other studies using case-control or prospective cohort designs have not confirmed an increased rate of risk of CAD attributable to iron (120–122). In fact, in the NHANES I study, greater iron intake was associated with decreased CAD risk (123). In the elderly nonazotemic population, mortality from cardiovascular disease and all-cause mortality is associated with lower iron levels (124). Nurko and Young (125) found no relationship between baseline ferritin levels and death attributable to cardiovascular disease in 2021 patients examined during WAVE I of the USRDS Mortality Morbidity Study. All-cause mortality over a 2-yr period was similarly independent of ferritin levels in this analysis. Significantly, multiple covariates were examined in this study, reflecting the prospective format of its data collection. Two recent reviews have examined the conflicting epidemiologic observations relating iron to CAD and suggest that only future clinical trials can resolve this issue (126,127).

Findings in nonazotemic patients are difficult to extrapolate to patients with ESRD. For instance, repeated phlebotomy in nonazotemic male subjects with ferritin levels >200 ng/ml reduces the extent of free radical generation as assayed by TBAR (128). To the extent that declines in TBAR reflect diminished oxidative stress, reducing iron stores might reduce the rate of myocardial infarction if carried out over a sufficient time period. However, there is no existing long-term study that confirms this hypothesis even in nondialysis patients.

Two studies have impugned an increased risk for cardiac death associated with the repetitive administration of iron dextran over 5 to 6 mo (21,129). Collins and coworkers found a relative risk (RR) for cardiac death of 1.11 in HD patients who received at least 1.7 g of iron dextran in a 3- to 6-mo period, compared to individuals who did not receive any iron during a preceding 6-mo entry period (21). Besarab *et al.* (129) reported, in a *post hoc* analysis, an increased risk for all-cause mortality in the "normal hematocrit" subgroup of the Normal Hematocrit Trial in patients with cardiac disease. Within the normal hematocrit subgroup, the average cumulative iron dextran dose over 6 mo was 372 mg greater in subjects who died than in survivors. The odds ratio (OR) for death was 2.4 for patients who received *any amount of iron compared to none* during the 6 mo preceding death or censoring. However, multivariate analysis was not performed with respect to the hematocrit finally achieved, loss of vascular access and its effect on Kt/V, or four other important baseline covariates: age, NYHA III cardiac disability, presence of peripheral vascular disease, and absence of hypertension. In *post hoc* analyses and epidemiologic studies, it is difficult to separate cause from effect. As a group, the normal hematocrit patients had lower, not higher, ferritin levels. Kalantar-Zadeh and Don (130) recently documented that ferritin levels >600 ng/ml reflected increased morbidity, manifested by increased duration of hospitalization, more than they reflected iron excess in ESRD patients.

Certainly, a patient who demonstrates a progressive increase in ferritin during iron therapy without a hematopoietic response should not continue to receive iron. Increased iron administration may be a marker for patients who are refractory to epoetin regardless of whether a hemoglobin of 11 to 12 g/dl (NKF-DOQI guidelines) or 13 to 15 g/dl (Normal Hematocrit Trial) is targeted. The reason for refractoriness may not always be obvious, but includes infection, inflammation, malignancies, and chronic blood loss. It is currently not possible to optimize erythropoiesis by establishing a level of iron depletion that does not impair one's ability to manage anemia. Clearly, new and improved indicators of iron availability that more precisely reflect iron storage than that currently provided by conventional iron indices are required. In summary, the available evidence does not suggest that any additional cardiovascular risk accrues in ESRD patients when ferritin levels are maintained within the range recommended by NKF-DOQI guidelines.

Infection

Microorganisms require iron for survival (131). Iron uptake by most follows the same steps as occur in the human gut. Iron is first chelated before its transit into the cell as ferric ion via a specific uptake system. Because of the interaction between iron and free radicals and the danger to the cell, microbial organisms, like higher species, have evolved regulatory mechanisms that partition iron from the cytosol and control its assimilation (132). Stored bodily iron is unlikely to render an organism more virulent. *In vitro,* the absence of free iron is crucial for proper phagocytosis and killing. Any putative effect of stored iron would likely proceed through mechanisms involving neutrophil dysfunction after release of free iron from storage.

In hereditary hemochromatosis, there is no convincing evidence for increased susceptibility to infections other than those due to Yersinia *spp.* (133), a susceptibility shared by HD patients (134). Approximately 12% of patients with idiopathic hemochromatosis die from pneumonia (135), usually those who have developed marked organ dysfunction. In animal models, massive iron excess must accrue to enhance virulence of microorganisms, but the clinical relevance of such models is highly doubtful.

Is the risk to ESRD patients significant in view of the fact that neutrophil function is impaired by uremia *per se*? An increased incidence of infection has been reported in dialysis patients with iron overload (136–140). The incidence of overall infections in ESRD patients in the United States in 1996, depending on age, was 16 to 24% (141). Many factors foster neutrophil dysfunction in HD patients, including malnutrition, increased intracellular calcium, the dialysis treatment *per se*, and low and high molecular weight circulating plasma factors (142). In HD patients (143,144) and healthy individuals (145), *in vitro* studies show suppression of phagocytosis by iron. It is this process that is invoked to explain the increased susceptibility to infection of HD patients.

Patruta *et al.* (143) reported that patients with functional iron deficiency demonstrated impaired neutrophil function after iron treatment. The functionally iron-deficient group had a mean TSAT of 16.5% and a mean ferritin of 911 ng/ml, a

profile more consistent with RES blockade. Moreover, the TSAT in the healthy control group was 19.5%, considerably lower than that seen in the general population (117). The study found that phagocytosis was diminished in these HD patients. Polymorphonuclear neutrophiles (PMN) from control patients ingested 90% of organisms, whereas those from HD patients ingested only 80% of organisms. Intracellular killing by PMN was significantly decreased from 70% in control patients to 50 to 52% in HD patients whose ferritin levels exceeded 650 ng/ml. The baseline oxidative burst capacity of PMN was increased in HD patients, but decreased to half-normal after stimulation by zymosan. The degree of neutrophil impairment in HD patients was similar to that seen in nonazotemic iron-overloaded patients. Taken together, the data attest that iron overload as reflected by a ferritin level >650 ng/ml can produce measurable decreases in neutrophil function *in vitro*. The clinical significance of these changes remains enigmatic.

Collins *et al.* (20) reported that frequent low-dose, but not high-dose, iron therapy produced a 35% increase in infection-related deaths. Their initial report analyzed the survival during the last 6 mo of 1994 of 33,120 Medicare recipients who had survived the first 6 mo. The actual dose of iron given and its schedule of administration, pulse, or maintenance was not described. Collins' group has since rendered a more detailed analysis, centered on a claims-based analysis of 309,219 prevalent patients and distributed as four, 6-mo survival cohorts from 1994 to 1995 with a 1-yr follow-up. Patients with catheters or previous admissions for sepsis (6.4%) were excluded (21,22). The categories of iron use were expanded to 12, stratified by frequency of administration and number of vials. Using a reference group that received no iron during a 6-mo period, the RR for infectious mortality was 1.14 to 1.20 in those who received high-dose, high-frequency intravenous iron (>17 vials over 3 to 6 mo). All-cause mortality was similarly increased. The RR for hospitalization from sepsis was 1.13. In both studies, the important clinical parameters of TSAT, ferritin level, and mean hematocrit were not available. It is therefore impossible to determine whether those who had been treated with more iron were more ill than those who had received less. Therefore, it is difficult to establish a physiologic link between iron and the observed results. This aspect should be addressed in future studies.

Simple extrapolation of historical data before the epoetin era is inadequate to assess whether there is an increased risk of infection for HD patients. In view of the known immunosuppressive effects of red cell transfusions (146) and neutrophil dysfunction secondary to anemia (147), alternative explanations that are unrelated to iron administration may contribute to the increased rate of infection of HD patients. Approximately 40% of the infectious complications of HD patients are related to the type of vascular access as delineated by Hoen *et al.* (136). Lower pulmonary tract and urinary tract infections constitute the remainder of these, and the presence of a central venous catheter represents the strongest predictor of infection (OR, 31, compared to native fistulas) followed by a history of prior bacterial infection (OR, 3.9). A ferritin level >500 ng/ml, however, bears a much lower risk (OR, 1.7). Unexamined aspects of this investigation included the acquisition of ferritin levels relative to the time of infection and the effect(s) of covariates, such as the adequacy of dialysis and the type of hemodialyzer membrane used. Importantly, this study was conducted at a time when 14% of patients were receiving epoetin to correct anemia. A more recent report from Hoen *et al.* examined the risk factors for developing at least one bacteremic episode in a predominantly epoetin-treated population and reiterated that the dominant risk factors for infection were presence of a dialysis catheter and a previous episode of bacteremia (137). Significantly, epoetin-resistant anemia also appeared to be a risk factor. Patients with higher hemoglobin levels had a RR of 0.7. Neither parenteral iron administration nor serum ferritin possessed sufficient power to predict infection.

Ferritin levels of 500 ng/ml (138) and 1000 ng/ml (140) have been used as putative thresholds for increased infectious risk. During the epoetin era, there has been a marked change in the distribution of the ferritin levels that constitute an increased level of risk. Before the advent of epoetin, many more HD patients had ferritin levels that exceeded 1000 ng/ml than the 5% or less that do so today. Treatment of patients with ferritin levels greater than 2000 ng/ml with desferrioxamine decreased overall infectious risk (148). Chelation by desferrioxamine therapy (148) not only decreases the degree of iron overload, but also increases the degree of erythropoiesis by enhanced mobilization of iron to the erythron (149). This effect may be mediated by accelerated carriage of iron from ferritin across the erythroblast membrane, or, alternatively, from enhanced cell expression of surface transferrin receptors. Thus, increased erythropoiesis negates the infectious risk of iron overload. The reduction in risk for infection in iron-overloaded patients after epoetin therapy is conceivably attributable to improved granulocyte function after anemia correction (147,148). It is not only the degree of iron overload that is important, but also how the iron is utilized.

Summary

Recombinant epoetin therapy and correction of the chronic anemia of renal failure have greatly reduced the number of red cell transfusions and hence the propensity to iron overload. The majority of HD patients require intravenous iron therapy to achieve the hematocrit levels that correspond to improved outcome measures. Although the short-term benefits of intravenous iron have been clearly defined, the long-term risks of intravenous iron are less well-defined. Iron overload before the availability of epoetin constituted a serious problem; our review of the literature does not decisively conclude that these patients had more serious bacterial infections or increased mortality when compared with their non-iron overloaded counterparts, unless chronic transfusion-related hepatic disease was superimposed. Specifically, no data unequivocally confirm that iron overload from parenteral iron contributes to all-cause patient morbidity or mortality. Furthermore, therapy that maintains intravenous iron optimal iron stores and replaces iron losses associated with the dialytic procedure does not engender iron overload in the carefully monitored patient. Optimized

anemia therapy in ESRD requires individualized and specific application of epoetin and iron for each patient, and significant cost savings can result from such a strategy. Prospective studies are clearly necessary to define those parameters that reflect adequacy of iron storage in renal failure patients. We should develop alternative means of iron delivery and develop monitors that accurately discriminate between patients who will respond to additional iron therapy and those who will not. Whether ferritin should be supplanted by another parameter and whether iron itself poses an increased risk to those patients it has so beneficially served are issues that must be resolved. Until these answers are known, the importance of carefully crafted iron therapy cannot be overstated.

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