Chapter 4

Iatrogenic Iron Overload in Dialysis Patients

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Additional information is available at the end of the chapter

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1. Introduction

During the past two decades, routine use of recombinant erythropoeisis-stimulating agents (ESA) has enabled anemia to be corrected in most patients with end-stage renal disease, permitting better outcomes and improving quality of life [1]. The use of ESA is frequently associated with iron deficiency, resulting primarily from massive transfer of stored iron to erythroid progenitor cells [2]. Mobilization of iron from repleted storage sites may also be inadequate, resulting in functional iron deficiency [3]. Moreover, blood loss related to hemodialysis itself and to occult intestinal bleeding due to uremic enteropathy can markedly aggravate iron deficiency in this setting [1]. As successful use of ESA requires sufficient available iron before and during therapy, almost all dialysis patients on ESA currently receive parenteral iron therapy [3]. The dual risk of iron deficiency and iron overload must therefore be closely monitored in dialysis patients. Interestingly, most relevant studies published in the last two decades have focused chiefly on the detection and treatment of iron deficiency in dialysis patients, while very few have examined iron overload [3-4].

Until recently it was widely considered that iron overload among dialysis patients was more prevalent during the pre-ESA era, when blood transfusion was frequently used to treat anemia and when intravenous iron therapy was given without concomitant ESA administration; iron overload was therefore considered rare, or even exceptional, among dialysis patients in the ESA era but is now an increasingly recognized clinical situation [3-7].

The only laboratory parameter available to screen for iron overload in dialysis patients is serum ferritin, but confirmation necessitates liver or bone biopsy, and few data were available on patients with end-stage renal disease until now, owing to the aggressiveness of these histological examinations [4]. Moreover, serum ferritin is an acute-phase reactant, and these patients' frequent systemic inflammation may inhibit both iron mobilization from reticuloendothelial stores and intestinal iron absorption via hepcidin modulation; the relationship between ferritin and iron stores may therefore be blunted or skewed [4, 8].

American and European clinical practice guidelines (KDOQI-2006 and European Best Practice Guideline-2009) warned against regular iron administration when the ferritin concentration exceeds 500 µg/L, although the former guideline allowed clinicians to make a decision on IV iron administration above this level after carefully weighing up ESA responsiveness, hemoglobin and transferrin saturation, and the patient's clinical status [1, 9]. It is also worthy of note that the recent KDIGO-2012 guideline proposed a trial of IV iron in dialysis patients prior to ESA use, with the aims of sparing these expensive drugs and of reaching high TSAT (30%) and ferritin (500 µg/L) target values [10]; however, these new KDIGO target values for iron biomarkers were not fully endorsed by EDTA-ERA because of the potential risk of iron overload [11]. Likewise, the Japanese Society for Dialysis recently proposed that a minimal amount of IV iron (up to 650 mg in the induction phase) should be given to dialysis patients, and only in case of true iron deficiency (ferritin <100 µg/L), while also warning against maintenance intravenous iron therapy because of the risk of iron toxicity [12].

2. Normal iron metabolism

Iron stores in healthy humans average 3 to 4 g in men and 2.2 to 3.5 g in women [13, 14]. About 60% of iron is located within the hemoglobin protein of circulating erythrocytes and, to a lesser degree, in medullary erythrocytes; 20% of iron stores are located in the liver (hepatocytes and Kupffer cells) and in the reticulo-endothelial system (mainly in spleen macrophages), in the form of the iron-storage protein ferritin (marginally in haemosiderin) whereas muscle myoglobin accounts for about 10% of body iron [8, 13, 14]. Iron-containing enzymes represent only 1% of iron stores, while plasma transferrin-bound iron represents only a small fraction (0.2%=3 mg) of total body iron [13, 14]. Each day, macrophages of the reticulo-endothelial system recycle about 30 mg of iron from senescent erythrocytes, thus providing the 20-30 mg of iron required for normal erythropoïesis [8, 13, 14]. Physiological iron losses are estimated at about 1 mg/day (urinary loss: 0.1 mg/day; gut loss secondary to enterocyte desquamation: 0.6 mg/day; skin loss: 0.3 mg/day) but are increased in women by menstruation (the main cause of iron-deficiency anemia worldwide), pregnancy and breast-feeding [14]. Therefore, recommended daily dietary iron intake to compensate for iron losses is 10 mg/day generally (because of an absorption rate of only 10%) and 30 mg/day in pregnant women and nursing mothers [14]. Hepcidin-25, a hormone synthesized in the liver, is the master regulator of iron metabolism, acting negatively on both intestinal iron absorption and iron release from reticulo-endothelial macrophages and liver cells by decreasing the expression of ferroportin, a protein that regulates iron export from these cells [8]. Hepcidin-25 synthesis is increased by iron itself and by inflammation (via IL6), and decreased by anemia, hypoxia, iron deficiency, haemorrhage, erythropoïetin, and increased medullary erythropoïesis [8]. The mechanism by which this latter situation down-regulates hepcidin synthesis was recently linked to a new peptide hormone, erythroferrone, secreted by erythroblasts and acting directly on the liver [15]. Defective hepcidin-25 synthesis plays a paramount pathophysiological role in genetic hemochromatoses, whereas excessive, unregulated hepcidin synthesis is the mainstay of a newly discovered genetic (autosomal recessive) form of iron-deficiency anemia called IRIDA (iron refractory iron deficiency anemia) related to mutation of the *TMPRSS6* gene (encoding matriptase-2); IRIDA is refractory to oral iron but partially responsive to IV iron products [16].

3. Blood loss in hemodialysis patients

With the ready availability of ESA and IV iron, iatrogenic blood losses, which are major contributors to iron deficiency in dialysis patients, have often been neglected. There are three distinct and cumulative sources of blood loss in this setting: 1) the dialytic technique itself; 2) regular blood sampling for patient monitoring, and 3) occult intestinal blood loss. Traditionally estimated to be between 4 and 12 liters/year, these blood losses classically represent 2 to 6 g of iron lost per year (1 L of blood contains about 500 mg of iron, although the value may be lower in dialysis patients because of a lower hematocrit) [17]. These classical approximations clearly overestimate dialysis-related blood loss. In addition, the type of vascular access and comorbidities may strongly influence both the type and magnitude of blood loss.

Two recent publications have quantified blood loss associated with modern dialysis membranes at respectively 0.3 ml/session [18] and 0.9 ml/session [19], while blood-line losses have been calculated to be about 0.2 ml/session [18]. Thus, taking a value of 1.1 ml/session, annual blood losses due to conventional hemodialysis *per se* (3 sessions/week, 150 sessions/year) would be about 165 ml/year. But the major source of blood loss in dialysis units stems from the care of tunnelized double-lumen catheters, when nurses apply the universal protocol of purging 7 to 10 ml of blood in each branch at the outset of the hemodialysis session, leading to a yearly blood loss of 2.4 L, to which should be added 288 ml for routine monthly bacterial cultures of the anticoagulant locks. Thus, the total annual blood loss related to catheter care is about 2.68 L [20]. Use of a recent protocol proposed by Prof. Bernard Canaud, based on the purge of only 2 ml of blood instead of 7-10 ml/branch, would lessen catheter-related blood loss to only 888 ml/year, representing a net 77% reduction [20].

In a recent survey in France, blood samples for regular patient monitoring were quantified in 10 dialysis centers run by the healthcare provider Générale de Santé at between 350 ml and 450 ml/year [20], a volume close to the 368 ml found by Sargent and Acchiardo in patients dialysed at the University of Tennessee in Memphis in 2004 [17]. Note that blood sampling may be far more abundant in academic hospitals conducting clinical trials or pathophysiological studies.

The third source of blood losses in hemodialysis patients is the gut. These losses are occult, being below the detection limit of stool tests. They are favoured by uremic enteropathy and thrombopathy, anticoagulation of the extracorporeal circuit during dialysis sessions, and also antiplatelet and antivitamin K drugs [21, 22]. Rosenblatt and coworkers, in a study performed in the 1980s using chromium 51-labelled erythrocytes, quantified faecal blood loss at 0.83 ml/day in healthy controls, 3.15 ml/day in non dialysis chronic kidney disease (CKD) patients and 6.27 ml/day (2.2 L/year) in hemodialysis patients [21]. These occult faecal blood losses are increased by antiplatelet and antivitamin K drugs: dialysis patients thus treated require higher IV iron dosages to replenish their iron stores (e.g 703 to 961 mg/year) [22, 23]. Thus, total blood losses in a hemodialysis patient with a native arteriovenous fistulae treated in a non academic center and not receiving antiplatelet or antivitamin K drugs can be estimated at 2.85 L/year (1.425 g of iron/year), whereas a patient with the same clinical profile but a double-lumen tunnelized catheter will lose 5.5 L/year (2.765 g of iron); note that both values are far lower than the classical estimates of 2 to 6 g/year [20].

4. Evolving concept of iron as an adjuvant of erythropoiesis —Stimulating agent therapy over the last two decades

With the advent of erythropoietin replacement therapy in the eighties, the goal of iron therapy was to maintain iron stores and thereby prevent true iron deficiency, mainly with oral iron supplements when the serum ferritin level was less than 50 μg/L; IV iron was advocated at that time as a second-line option in case of severe iron deficiency, poor tolerance or inefficacy of oral iron salts [24, 25]. Parenteral iron therapy has gained popularity in the nephrology community in the last fifteen years because of its convenience (infusion during dialysis sessions), its superiority over oral preparations for treating true iron deficiency, and its ability to overcome functional iron deficiency, a very common clinical situation in hemodialysis patients; in addition, this treatment enabled cost savings of about 20%-30% on expensive ESA drugs [1, 9].

Based solely on bone marrow studies and the lack of known long-term adverse effects, recent guidelines have redefined iron deficiency and adjusted iron-store repletion criteria to even higher levels (the KDIGO 2012 target for “upper normal” ferritin in hemodialysis patients is now 500 μg/L), underlining the risk of functional iron deficiency during ESA treatment and the ability of IV iron to spare ESA use, and even going so far as to advocate a trial of IV iron prior to ESA initiation. All these changes have amplified the use of parenteral iron products [7, 10, 26].

5. Increased use of IV iron in dialysis patients worldwide in the last two decades

A recent epidemiological analysis of the management of anemia in hemodialysis patients in the USA, based on USRDS data, showed an increase in the use of IV iron from 64% of patients in 2002 to 76% in 2008, together with an increase in the infused dose from 166 mg/month to 216 mg/month [27]. In addition, during the first year of hemodialysis, the usual monthly infused dose of iron was shown to be far higher, ranging from 270 mg to 305 mg [27]. The change made to the ESA label by the Food and Drug Administration in June 2010 also led to an increase in the percentage of US patients receiving IV iron, from 57% (August 2010) to 71% (August 2011), together with a significant decline in the ESA dosage and an increase in the median ferritin level from 556 to 650 µg/L, with values exceeding 800 µg/L in 34% of patients [28]. While the median dose of IV iron remained largely stable at 190 mg/month, it is noteworthy that 18% of patients received more than 500 mg/month during this period [28].

Very similar trends in the use of IV iron were recently observed in other industrialised countries, with the exception of Japan: the percentage of patients treated with IV iron rose between 1999 and 2010 from 50% to 71% overall, from 65% to 80% in Canada, from 55% to 70% in France, from 65% to 80% in Germany, and from 60% to 80% in the UK; during the same period (1999-2010), the mean ferritin level rose from 380 to 450 µg/L in Canada, from 420 to 580 µg/L in Germany and from 400 to 500 µg/L in the UK, while it remained stable in France at around 400 µg/L [29]. In Japan, the percentage of patients receiving IV iron rose only from 25% to 36% and the mean ferritin level rose only from 280 to 320 µg/L [29]. The overall mean monthly iron dose administered in industrialized countries other than the U.S. rose by 21%, from 232 mg/month in 1992 to 281 mg/month in 2010 [29].

6. Hemodialysis-associated hemosiderosis in the pre-ESA era

Post-mortem studies performed at the end of the 1970s and early 1980s showed that iron deposits were abundant in the adrenal glands, lymph nodes and lungs of dialysis patients with severe hepatosplenic siderosis, and generally sparser in the heart, kidney and pancreas [30-32]. In the liver, the earliest detectable iron deposits were observed within cells lining the sinusoids and in Kupffer cells; as hepatic siderosis progressed, iron appeared within hepatocytes, first in the peripheral zones of the hepatic lobules in the vicinity of portal triads and subsequently throughout the lobules [30]. In the spleen, the principal site of iron storage was also the cells lining the splenic sinusoids, while the white pulp was generally spared [30]. Even in case of massive hepatic siderosis there was no cytological evidence of cell damage, but reticulin and trichrome stains showed an increase in the hepatic fibroconjunctive network, together with loss of liver cells [30-32]. Similarly, most patients who had marked hemosiderosis and underwent liver biopsy had focal portal fibrosis [33]. These post-mortem studies also showed a strong link between iron overload and both blood transfusions and intravenous high-molecular-weight iron dextran (IMFERON®); interestingly, the closest relationship was between hepatic siderosis and IV iron [5][31-32]. Iron overload was usually absent in patients who had received little or no IV iron [31], whereas massive hepatosplenic siderosis was only seen in patients with a dialysis vintage of more than 3 years [5][32]. Adrenal involvement was observed in 11/24 unselected patients in the work of Pitts and coworkers [32] but in 17/18 patients with severe hepatosplenic siderosis studied by Ali [30]. Pancreatic involvement was less frequent, affecting 7/24 patients studied by Pitts and coworkers and 5/18 patients with severe hepatoplenic siderosis studied by Ali [30]. Interestingly, significant cardiac iron deposits were found in respectively 16.6% (4/24) and 22% (5/22) of unselected patients in the autopsy studies of Pitts [31] and Gokal [32], whereas cardiac involvement was found in 44% (8/18) of the patients with severe hepatosplenic siderosis studied post-mortem by Ali [30].

In the pre-ESA era, one strategy to avoid blood transfusion-related iron overload in dialysis patients with transfusion-dependent anemia was to use young instead of mature erythrocytes for transfusions [33]. Tissue iron depletion with the chelator desferrioxamine was advocated to prevent hemosiderosis or to cure organ dysfunction due to iron overload [33].

At the beginning of the 1990s, the advent of recombinant human erythropoïetin allowed simultaneous treatment of anemia and iron overload by allowing massive mobilization of iron stores and effective phlebotomy (by partial letting of the extracorporeal circuit) at the end of dialysis sessions in patients rendered non anemic [34], together with the first successful use of non invasive radiological tools (liver quantitative computer tomography) to diagnose hemodialysis-associated hemosiderosis and to monitor iron stores [35].

7. Liver iron content and modern non invasive imaging of iron stores

The liver is the main iron storage site in humans, and the liver iron concentration (LIC) correlates closely with total body iron stores in patients with secondary hemosideroses such as thalassemia major, sickle cell disease and genetic hemochromatosis [36, 37]. In order to avoid liver biopsy, a number of non invasive techniques have been developed to estimate liver iron stores, including the superconducting quantum interference device (SQUID), liver quantitative computer tomography (qCT), and magnetic resonance imaging (MRI) [38-39]. MRI has became the dominant technique, because of its sensitivity, reproducibility, availability and ability to image multiple organs in a single session [39]. Hepatic MRI is now considered the gold standard method for estimating and monitoring iron stores in secondary hemosideroses and genetic hemochromatoses ("iterative radiological biopsy"), and has been a major contributor to knowledge and care in this field during the last decade [37, 40].

As one specific feature of hemodialysis patients receiving intravenous iron in the pre-ESA era was that their bone marrow iron content was paradoxically low in up to one-third of cases despite severe hepatosplenic siderosis; thus LIC seems to be the best indicator of iron overload in hemodialysis patients, given that bone marrow analysis may be misleading even in the ESA era [5].

SQUID (also called magnetic susceptometry) is based on the determination of the magnetic volume susceptibility of paramagnetic ferritin/haemosiderin iron in the liver and has been validated by comparison with percutaneous biopsy; it does not distinguish ferritin from haemosiderin iron [38-39]. The limitations of this method relate to its scarcity (only 5 devices worldwide), its very high cost (about 1000 euros/exam) and the lack of calibration homogeneity (risk of underestimating LIC) [38-39].

Liver quantitative computer tomography (qCT) was superseded by MRI at the beginning of the 21st century [38-39]. Quantitative MRI for LIC estimation is based on the paramagnetic properties of iron, leading to a reduction in the magnetic resonance signal as the liver iron concentration increases; it does not distinguish ferritin from haemosiderin iron [39]. It is a low-cost (about 300 euros/exam), non irradiating technique that does not require gadolinium (therefore safe in CKD patients) and is available everywhere [39].

There are three valuable hepatic MRI methods for determining LIC: the signal-intensitity ratio, R2 relaxometry, and R2* relaxometry [39]. The signal-intensity ratio is the reference method. It was established at Rennes University in France on a 1.5 Tesla apparatus in 2004, and is predominantly used in Europe [41]. It was validated in a cohort of 191 patients with secondary hemosiderosis, genetic hemochromatosis and hepatic diseases who underwent liver biopsy for biochemical iron assay [41]; the results were successfully replicated in 3 prospective cohorts studied by independent teams in France, the Netherlands and Spain [42-44]. Two of these studies were performed by comparison with liver biopsy [42-44]. This approach is based on a comparison between liver and muscle intensity on various sequences (T1, PD, T2, T2+, T2++) and requires a specific algorithm to analyse the results (free software available on the website of Rennes University) (figure 1)[41]. It has a sensitivity of 89% and a specificity of 80% for the diagnosis of iron overload disease, and values are linear up to 350 µmol/g of dry liver [41]; a complementary algorithm established by a Spanish team is required for higher values [39].

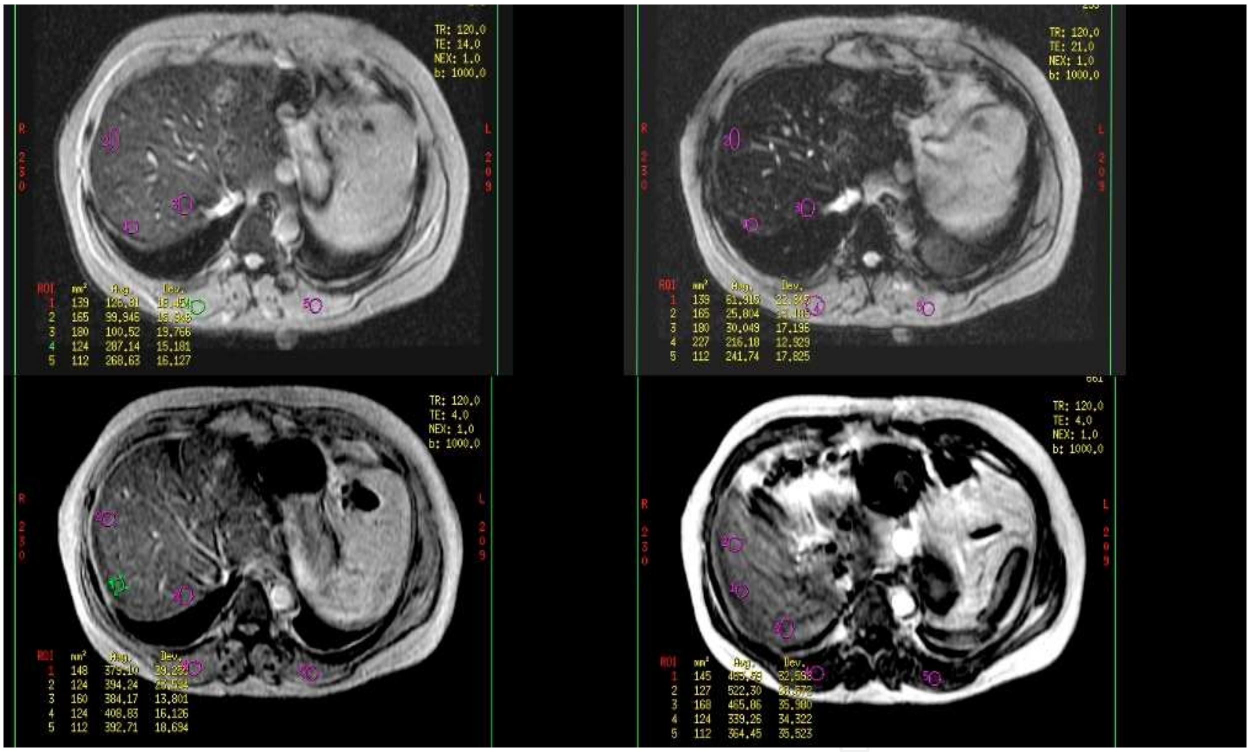


Figure 1. Magnetic resonance imaging quantification of hepatic iron stores according to the method of Rennes University

The second MRI technique for iron store quantification was established in Australia in 2005 on a 1.5 Tesla apparatus and is based on R2 relaxometry; it was validated in a cohort of 105 patients with thalassemia, genetic hemochromatosis and hepatic diseases who underwent liver biopsy for biochemical iron assay, and was also compared to SQUID in 23 patients [45]. It is based on R2/T2 sequences. It has a sensitivity of 86% and a specificity of 88% for the diagnosis of iron overload disease, and is linear up to 700 µmol/g of dry liver; however, it requires calibration of the apparatus with phantoms and also a specific configuration of the machine [45]. It is mainly used (and called Ferriscan) in Australia, New Zealand and North America.

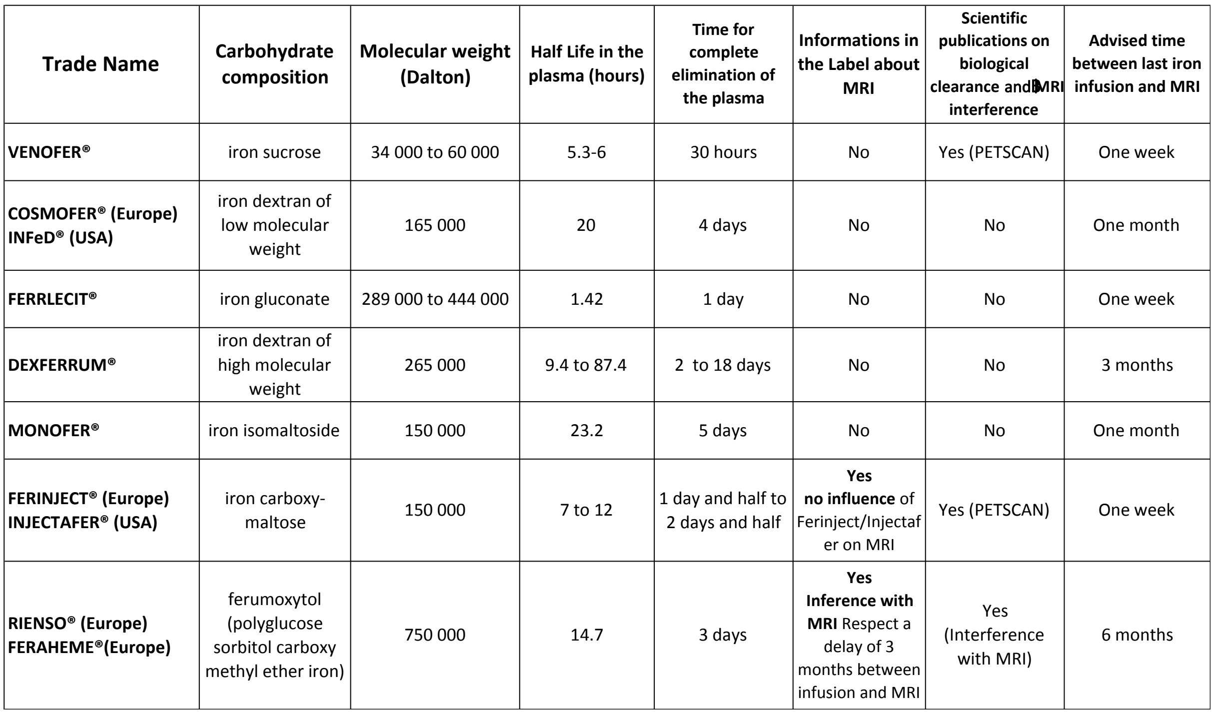
The third MRI technique for iron store quantification is based on R2* relaxometry: it is the most promising tool and can be used on a 1.5 Tesla apparatus with specific software; it not only quantifies iron in liver but also detects (in the same session lasting about 20 minutes) iron overload in heart, spleen and pancreas [46]. Its main limitation for LIC determination is its validation on only a small number of liver biopsies [38-39, 46].

Normal hepatic iron stores on MRI have been established on the basis of liver biopsy findings, together with categories of gradually increasing iron overload reflecting the risk of complications; moreover, as the upper 95% of LIC in healthy adults is 32 μmol/g of dry liver and hepatic MRI accurately detects liver iron overload exceeding 50 μmol/g of dry liver, the upper limit of normal was set at 50 μmol/g in many studies [6][41][45]. According to Rennes University, LIC values between 51 and 100 μmol/g represent mild iron overload, values between 101 and 200 μmol/g moderate iron overload, and values ≥ 201 μmol/g severe iron overload [41]. Management modalities for different clinically relevant thresholds of MRI-determined LIC have been forwarded by hepatologists and haematologists (e.g chelation in hemosiderosis, phlebotomy in genetic hemochromatosis, and specific follow-up of target organs)(Table 1) [37-41][45].

Liver Iron content (μmol/g)	Clinical thresholds of LIC in secondary hemosiderosis and genetic hemochromatosis
125 μmol/g (7 mg/g)	threshold for increased risk of iron induced complications and level of decision for chelation therapy or phlebotomy
143 μmol/g (8 mg/g)	threshold of saturation of reticulo-endothelial system in sickle-cell disease
160 μmol/g (9 mg/g)	threshold of hepatic fibrosis in sickle cell disease
269 μmol/g (15 mg/g)	threshold of risk of hepatic fibrosis and cardiac disease in thalassemia major
331 μmol/g (18 mg/g)	threshold of risk of hepatic fibrosis or cirrhosis in patients with genetic hemochromatosis

Table 1. Clinicaly relevant LIC thresholds in secondary hemosiderosis and genetic hemochromatosis

It is very likely that radiologists will be heavily solicited in the near future by nephrology teams requesting quantitative hepatic MRI for dialysis patients, both for research purposes and for diagnosis and follow-up of iron overload. Radiologists and nephrologists should also be aware of the marked differences in the pharmacological properties of available intravenous iron products, and their potential interference with MRI (summarized in table 2) [47].



Trade Name	Carbohydrate composition	Molecular weight (Dalton)	Half Life in the plasma (hours)	Time for complete elimination of the plasma	Informations in the Label about MRI	Scientific publications on biological clearance and MRI interference	Advised time between last iron infusion and MRI
VENOFER®	iron sucrose	34 000 to 60 000	5.3-6	30 hours	No	Yes (PETSCAN)	One week
COSMOFER® (Europe) **INFeD® (USA)**	iron dextran of low molecular weight	165 000	20	4 days	No	No	One month
FERRLECIT®	iron gluconate	289 000 to 444 000	1.42	1 day	No	No	One week
DEXFERRUM®	iron dextran of high molecular weight	265 000	9.4 to 87.4	2 to 18 days	No	No	3 months
MONOFER®	iron isomaltoside	150 000	23.2	5 days	No	No	One month
FERINJECT® (Europe) **INJECTAFER® (USA)**	iron carboxy-maltose	150 000	7 to 12	1 day and half to 2 days and half	**Yes** **no influence** of Ferinject/Injectafer on MRI	Yes (PETSCAN)	One week
RIENSO® (Europe) **FERAHEME®(Europe)**	ferumoxytol (polyglucose sorbitol carboxy methyl ether iron)	750 000	14.7	3 days	**Yes** **Inference with MRI** Respect a delay of 3 months between infusion and MRI	Yes (Interference with MRI)	6 months

(according to Rostoker G and Cohen Y. *Magnetic resonance imaging repercussions of intravenous iron products used for iron-deficiency anemia and dialysis associated anemia*. J Comp Assist Tomogr 2014: Sept 16)

Table 2. IV iron preparations: Physicochemical and pharmacokinetic parameters and influence on MRI

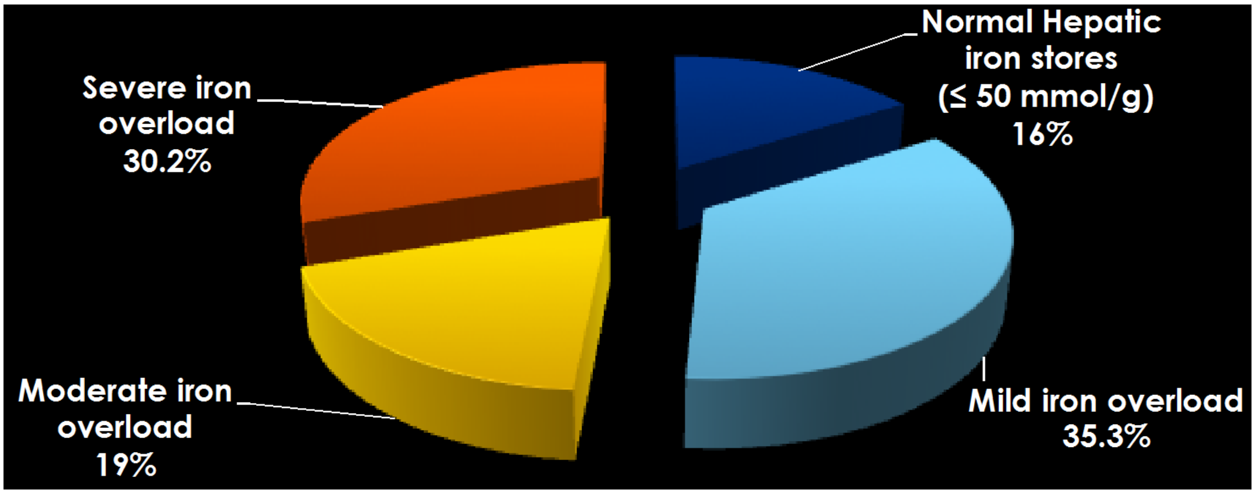
8. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents

Recent studies using SQUID and quantitative MRI to estimate liver iron stores in hemodialysis patients suggest a strong link between the infused iron dose and the risk of iron overload. They also strongly challenge the assumed safety of IV iron products, the reliability of current iron biomarker cutoffs, and current monitoring of iron stores in dialysis patients.

Two recent studies have focused on iron overload in hemodialysis patients with serum ferritin levels well above 500 μg/L: Ferrari et al measured hepatic iron content by magnetic resonance relaxometry R2 in 15 Australian patients with a median ferritin of 782 μg/L and found iron overload in 60% of them [48], whereas Ghoti et al [49] more recently analyzed LIC by T2*MRI, along with spleen, pancreas and heart iron deposits, in 21 iron-overloaded hemodialysis patients with serum ferritin levels above 1000 μg/L; they found hepatic siderosis in 19 patients (90%)(mild in 8, moderate in 5 and severe in 6), and spleen involvement in every case (21/21); pancreas involvement was sought in only 8 patients (because of poor compliance with the exam) and was found in 3 patients (37%); none of the patients had an abnormal cardiac R2*[49].

Two modern studies have analyzed hepatic iron stores by SQUID, one in 2004 [50] and the other in 2012 with quantitative MRI based on the Rennes University protocol [6], in cohorts of hemodialysis patients treated according to KDOQI and EDTA-ERBP guidelines with ferritin levels within the target range. Canavese et al used the SQUID technique to study 40 Italian patients and found normal LIC in 30% of them (median ferritin 245 μg/L), mild iron overload in 32.5% (median ferritin 329 μg/L) and moderate iron overload in 37.5% (median ferritin 482 μg/L) [50]. It was subsequently claimed that these findings could not be extrapolated to the general hemodialysis population, owing to possible biased selection of an iron-overloaded population [51].

We recently showed that 84% of a cohort of 119 fit hemodialysis patients treated according to contemporary guidelines had hepatic iron overload on MRI (≥ 51 μmol/g dry weight); mild iron overload was seen in 42 patients (35.3%) and moderate iron overload in 22 patients (18.5%), while 36 of these 119 patients (30%) had severe iron overload (≥ 201 μmol/g dry weight) at levels usually seen in genetic hemochromatosis; MRI also revealed spleen anomalies (a sign of secondary hemosiderosis) in several patients [6].



(according Rostoker G, Griuncelli M, Loridon C et al. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. Am J Med 2012; 125: 991-999)

Figure 2. Results of a cross-sectional study of 119 hemodialysis patients

In our cross-sectional study, infused iron, hepcidin and C-reactive protein values correlated with hepatic iron stores in both univariate analysis ($p<0.05$, Spearman test) and binary logistic regression ($p<0.05$). We found no relationship between the LIC of hemodialysis patients and alcohol consumption (assessed by the AUDIT score) or the major HFE mutation C282Y [6]. Like Canavese et al [50], we found an increased relative risk of iron overload in female patients (relative risk for females: 3.36 (95% CI: 1.03-10.9))[6]. In 11 patients who were monitored closely during parenteral iron therapy, the iron dose infused per month correlated strongly with both the overall increase and the monthly increase in the liver iron concentration (respectively rho=0.66, p=0.0306 and rho=0.85, p=0.0015, Spearman test)(figures 3 and 4)[6].

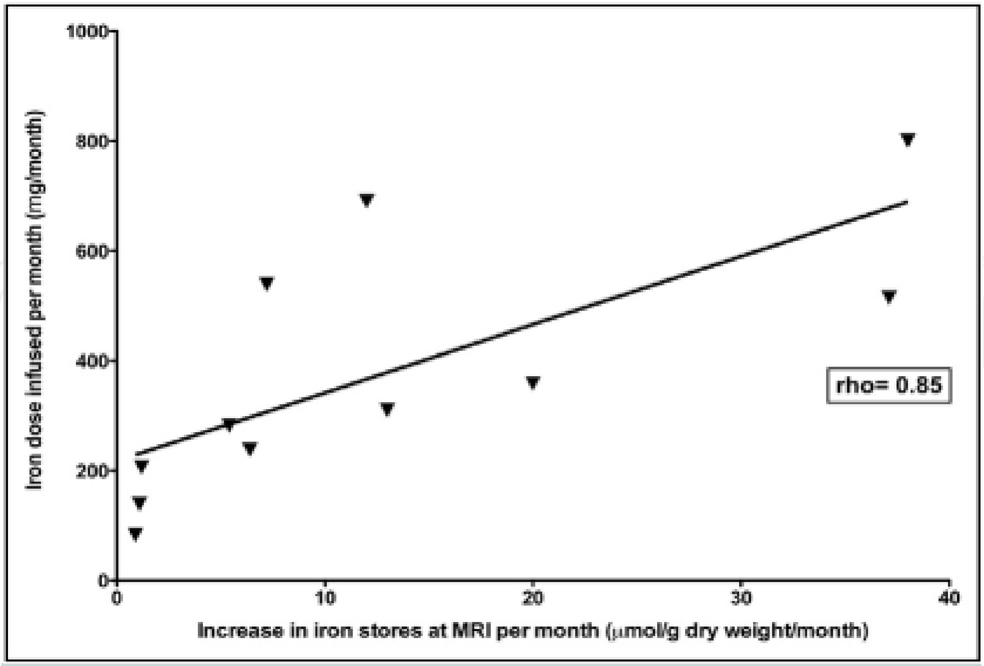


Figure 3. Correlation between the infused iron dose and iron stores in 11 hemodialysis patients. Relationship between the monthly infused dose of iron and the monthly increase in iron stores evaluated by magnetic resonance imaging (MRI) in 11 hemodialysis patients. The relationship was studied with the Spearman test, which showed a very strong correlation (rho=0.854; *P*=0.0015).

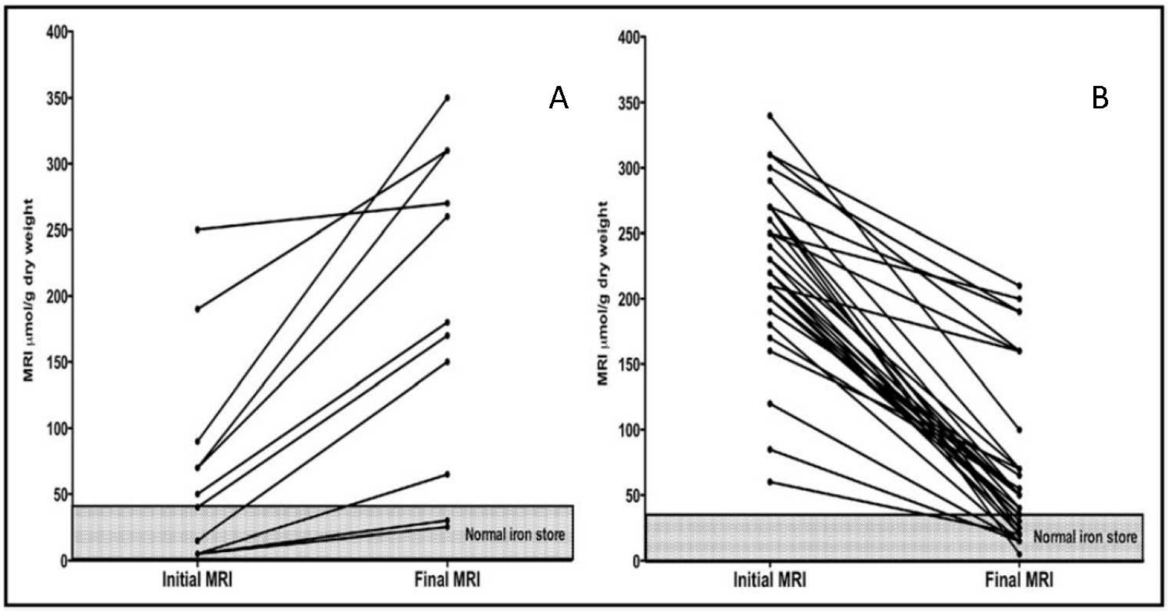


Figure 4. Time course of hepatic iron stores studied by magnetic resonance imaging in hemodialysis patients. (A) Initial and final hepatic iron concentrations on MRI in 11 patients during iron therapy. (B) Initial and final hepatic iron concentrations on MRI in 33 patients with hepatic iron overload after iron withdrawal (n=19) or after a major iron dose reduction (n=14) (according Rostoker G, Griuncelli M, Loridon C et al. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. Am J Med 2012; 125: 991-999).

In the 33 patients with iron overload, iron stores fell significantly after iron withdrawal or after a major reduction in the iron dose (first MRI: 220 μmol/g (CI: 60-340); last MRI: 50 μmol/g (CI: 5-210); $p < 0.0001$, Wilcoxon's paired test)(figure 4)[6]. The slope of the decline in hepatic iron was not significantly different after iron withdrawal (17.9 μmol/g dry weight/month), iron dose reduction (12.8 μmol/g dry weight/month), and renal transplantation (11.9 μmol/g dry weight/month)($p > 0.05$, Kruskal-Wallis test) [6]. Thus, the frequency of iron overload appears to be markedly underestimated in hemodialysis patients receiving both erythropoeisis-stimulating agents and parenteral iron [6,7]. We concluded that most hemodialysis patients receiving ESA and intravenous iron supplementation likely have hepatic iron overload on MRI and called for a revision of guidelines on iron therapy in this setting, especially regarding the amount of iron infused and the use of non invasive methods for monitoring iron stores [6,7].

9. Detrimental effects of iron overload in dialysis patients

The classical (although rare) clinical picture of hemodialysis-associated hemosiderosis in the pre-ESA era (pigmented skin, cirrhosis and cardiac failure associated with multiple endocrine disorders) has totally disappeared from dialysis centers for at least 3 decades [5]. It is also noteworthy that genetic hemochromatosis and secondary hemosiderosis related to hematological disorders are now diagnosed very early, long before any organ dysfunction is detected [37,40]. Therefore, iron overload in dialysis patients in the ESA era is more likely to silently increase the burden of complications of dialysed CKD than to have obvious clinical effects.

Three recent epidemiological studies convergently show that excessive IV iron administration can adversely affect the prognosis of hemodialysis patients by increasing mortality and cardiovascular events [52-54]. In a prospective cohort study conducted in Taiwan, 1239 hemodialysis patients were followed for one year: 583 patients not receiving iron therapy were compared to 656 patients treated with IV ferric chloride hexahydrate, the latter patients being divided into 3 subgroups according the cumulative dose of IV iron: 40-800 mg/6 months, 840-1600 mg/6 months and 1640-2400 mg/6 month [52]. Patients in the 2 subgroups with the largest cumulative iron dose had higher adjusted mortality (Hazard ratio (HR) 3.1 and 3.7) and more cardiovascular events (HR 3.5 and 5.1) than those not receiving IV iron and those having received less than 820 mg/6 months (136 mg/month) [52]. Similarly, Kuragano and coworkers prospectively followed 1086 Japanese hemodialysis patients during 2 years and compared 4 subgroups of patients: an oral iron group, an oral iron+very low IV iron group, a low IV iron group (< 200 mg/month), and a high IV iron group (> 200 mg/month) [53]. They observed more acute cardiocerebral vascular disease (hazard ratio 6.02) and hospitalizations (hazard ratio 2.77) in the high IV iron group, whereas both low (hazard ratio 1.78) and high (hazard ratio 5.22) IV iron regimens increased the frequency of infections but at different rates [53]. High ferritin levels (consistently above 100 μg/L) were associated with an increase risk of acute cardiocerebral vascular disease (hazard ratio 2.22), infections (hazard ratio 1.76) and death (hazard ratio 2.28) [53]. Similarly, a jump in the ferritin level from low to high (from less to more than 100 μg/L) was associated with an increased risk of acute cardiocerebral vascular disease (hazard ratio 1.59) and death (hazard ratio 6.18) [53]. More recently, the DOPPS study, using Cox regression models with multiple adjustments, analyzed associations between IV iron and outcomes in 32 435 hemodialysis patients followed in 12 countries from 2002 to 2011 and found an increased adjusted mortality rate among patients receiving 300-399 mg/month (HR: 1.13) and 400 mg/month or more (HR: 1.18) as compared with those receiving no iron and those receiving 1-99, 100-199 and 200-299 mg of IV iron per month [54]. Similarly, the risk of hospitalization was elevated (HR: 1.12) in patients receiving 300 mg/month or more of IV iron as compared to those receiving 100-199 mg/month [54]. The results of the Japanese study on the risk of infection are convergent with recent results fom an American study showing that iron maintenance therapy at 200 mg/month is not associated with an increased short-term risk of infections, as encountered with bolus characterized by monthly iron exposure of 700 mg [55].

Three mechanisms may act synergystically to increase mortality and cardiovascular events in iron-overloaded dialysis patients, namely increased levels of hepcidin and oxidative stress, and arterial structural changes.

Some authors recently advocated critical re-evaluation of hepcidin levels in renal failure patients, postulating that hepcidin is not intrinsically elevated in hemodialysis patients but rather reflects poor matching with healthy subjects and frequently excessive iron stores in these patients [56]. It thus seems that hepcidin elevation in fact represents a physiologic defense mechanism against iron overload that is preserved in CKD, even during dialysis [56]. Moreover, increased levels of hepcidin-25 in patients with severe iron overload on MRI have been shown to normalize in parallel with LIC normalization [6]. As high levels of hepcidin-25 in dialysis patients have recently been linked to fatal and nonfatal cardiovascular events, it is tempting to postulate that the main pathophysiological pathway between iron overload and these events involves pleiotropic effects of hepcidin-25 [57]. The worsening of oxidative stress usually encountered in end-stage renal disease by IV iron infusions and iron overload (mediated by the release of labile, non transferrin-bound iron) may also adversely affect the vascular bed and act as a "second hit" [58, 59]. Finally, in the hemodialysis population, excess iron may also play a direct role in the high burden of cardiovascular complications by impairing endothelial function, as shown in patients with hereditary hemochromatosis [60], and also by favoring atherosclerosis [61, 62].

Given data on heterozygotous genetic hemochromatosis and secondary hemosideroses, the risk/benefit ratio of iron therapy may remain favorable in hemodialysis patients with mild iron overload (LIC < 100 μmol/g), whereas the risk in patients with moderate iron overload (LIC > 100 μmol/g and < LIC < 200 μmol/g) needs to be ascertained [6,7]. It is also tempting to postulate that hemodialysis patients with severe hepatic iron overload (e.g. > 200 μmol/g) are at risk of silent and gradual multiple organ dysfunctions due to hemosiderosis, together with a higher burden of cardiovascular complications [6,7].

10. Future directions

Iron overload in hemodialysis patients may be favored by reimbursement policies in the USA and many other developed countries, which have led to a dramatic increase in the use of intravenous iron preparations in order to offset the cost of ESA therapy; the situation may also be aggravated by excessive advocated doses of intravenous iron and erroneous iron biomarker targets aimed at “repleting exaggerately” iron stores [6,7]. A new pharmacometric and economic approach to iron therapy has recently been advocated [6,7,26,58]. Moreover, the KDIGO Controversies Conference on Iron Management in Chronic Kidney Disease, which took place in San Francisco on March 27-30, 2014 and was attended by nephrologists, hematologists, hepatologists and specialists in iron metabolism, recognized the entity of iron overload in hemodialysis patients and called for an agenda of research on this topic, especially by means of MRI [63]. Analysis of liver iron content in dialysis patients by means of quantitative MRI, a new research tool that overcomes a major hypothetical limitation in hemodialysis patients, namely bone marrow iron depletion despite severe hepatosplenic siderosis, and allows safe non aggressive iterative "radiological liver biopsy" might, in combination with data-mining statistical methods and classical statistical methods such as AUC determination and logistic regression, allow nephrologists to determine both a non toxic dose of infused iron and relevant target values for biological markers of iron metabolism, thereby improving the safety of parenteral iron products in dialysis patients [6,7,26,58, 63]. Finally, specific MRI protocols need to be established in radiology and nephrology divisions for each pharmaceutical iron product, in order to avoid spurious results [47].

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