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Iatrogenic iron overload and its potential consequences in patients on hemodialysis

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In this issue

■ Summary

Iron overload was considered rare in hemodialysis patients until recently, but its clinical frequency is now increasingly recognized. The liver is the main site of iron storage and the liver iron concentration (LIC) is closely correlated with total iron stores in patients with secondary hemosiderosis and genetic hemochromatosis. Magnetic resonance imaging (MRI) is now the gold standard method for estimating and monitoring LIC. Studies of LIC in hemodialysis patients by magnetic susceptometry thirteen years ago and recently by quantitative MRI have demonstrated a relation between the risk of iron overload and the use of intravenous (IV) iron products prescribed at doses determined by the iron biomarker cutoffs contained in current anemia management guidelines. These findings have challenged the validity of both iron biomarker cutoffs and current clinical guidelines, especially with respect to recommended IV iron doses. Moreover, three recent long-term observational studies suggested that excessive IV iron doses might be associated with an increased risk of cardiovascular events and death in hemodialysis patients. It has been hypothesized that iatrogenic iron overload in the era of erythropoiesis-stimulating agents might silently increase complications in dialysis patients without creating obvious, clinical signs and symptoms. High hepcidin-25 levels were recently linked to fatal and nonfatal cardiovascular events in dialysis patients. It has been postulated that the main pathophysiological pathway leading to these events might involve the pleiotropic master hormone hepcidin, which regulates iron metabolism, leading to activation of macrophages in atherosclerotic plaques and then to clinical cardiovascular events. Thus, the potential iron overload toxicity linked to chronic administration of IV iron therapy is now becoming one of the most controversial topics in the management of anemia in hemodialysis patients.

Introduction

Routine use of recombinant erythropoeisis-stimulating agents (ESA) over the past three decades has enabled anemia to be partially corrected in most patients with end-stage renal disease (ESRD), thereby improving their quality of life and reducing the need for blood transfusion and morbidities related to anemia [1]. ESA use frequently leads to iron deficiency, due to massive transfer of stored

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iron to erythroid progenitor cells [1], inadequate iron mobilization from repleted storage sites resulting in functional iron deficiency, together with blood loss related to the hemodialysis procedure itself and also to routine blood sampling for laboratory tests as well as occult gastrointestinal bleeding due to uremic enteropathy aggravated by uremia-induced platelet dysfunction and anticoagulation with either unfractionated heparin or low-molecular-weight heparin during the dialysis session [1–3]. Almost all ESA-treated hemodialysis patients receive parenteral iron to ensure sufficient available iron before and during ESA therapy [3,4]. Therefore, the twin risks of iron deficiency and iron overload must be stringently controlled in dialysis patients on iron therapy. Significantly, most studies published in the last two decades have focused on the detection and treatment of iron deficiency in dialysis patients, while few have dealt with iron overload [3,5]. Thus, until recently, iron overload among dialysis patients was widely considered to be more prevalent during the pre-ESA era, when blood transfusion was often used to treat anemia and intravenous iron was given without concomitant ESA. As a result, iron overload was considered rare or even exceptional in the ESA era, whereas it is now increasingly recognized as a potentially problematic clinical issue [3,6–9]. The liver is the main site of iron storage, and the liver iron

concentration (LIC) is closely correlated with total body iron stores in patients with secondary forms of hemosiderosis such as thalassemia major, sickle cell disease and genetic hemochromatosis [10]. Hepatic magnetic resonance imaging (MRI) is now the gold standard for iron store estimation and monitoring in patients with secondary hemosiderosis and genetic hemochromatosis [10]. Recent quantitative magnetic susceptometry and MRI studies of dialysis patients have strongly suggested a link between the cumulative dose of IV iron and the risk of excess liver iron stores, and also challenged both iron biomarker cutoffs and clinical guidelines, especially with respect to recommended iron doses [8,11]. Three epidemiological studies recently suggested that higher IV iron doses might be associated with increased mortality and cardiovascular events in hemodialysis patients [12–14]. These findings have led to several editorials and position articles highlighting the potential dangers of excessive use of IV iron products [9,15,16] as well as the inadequacy of the guidelines proposed by KDIGO-2012 (Kidney Disease Improving Global Outcomes) and the iron biomarker targets set by KDOQI-2006 (Kidney Disease Outcomes Quality Initiative) and the older ERA-EDTA-2009 position paper (European Renal Association–European Dialysis and Transplant Association), by opposition to the newer ERA-EDTA-2013 position paper, with a view to protect end-stage renal disease (ESRD) patients from iron overload [4,17,18]. They also contributed to the organization of the KDIGO Controversies Conference on iron management in chronic kidney disease, which took place in San Francisco on March 27–30, 2014 [19]. This conference was attended by nephrologists, hematologists, hepatologists and specialists in iron metabolism. Its consensus statements recognized the "iron overload" entity in hemodialysis patients and called for a specific research agenda [19]. Finally, in June 2015 the Dialysis Advisory Group of the American Society of Nephrology published an updated recommendation on uncertainties of usage of high-dose of intravenous iron in hemodialysis patients [20]. It is noteworthy that the Japanese Society for Dialysis had already proposed, some years ago, that dialysis patients should receive a minimal amount of IV iron, only if they had true iron deficiency (ferritin < 100 μg/L), and had also warned against maintenance intravenous iron therapy for fear of toxicity [21].

Glossary

AUC	area under the curve
AUDIT	Alcohol Use Disorders Test
CHAID	CHi-squared Automatic Interaction Detection
CI	confidence Interval
CKD	chronic kidney disease
DOPPS	Dialysis Outcomes and Practice Patterns Study
EMA	European Medicines Agency
ERA-EDTA	European Renal Association–European Dialysis and Transplant Association
ERBP	European Renal Best Practice
ESA	erythropoiesis-stimulating agents
ESRD	end-stage renal disease
FDA	Food and Drug Administration
HCV	hepatitis C virus
HD	hemodialysis
HFE	hereditary hemochromatosis gene
HIF	hypoxia-inducible factor
HIF-PH	hypoxia-inducible factor prolyl hydroxylase
HR	hazard ratio
IRIDA	iron refractory deficiency anemia
IV	intravenous
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LIC	liver iron concentration
MRI	magnetic resonance imaging
NASH	non-alcoholic steatohepatitis
PD	peritoneal dialysis
PRAC	Pharmacovigilance Risk Assessment Committee
RNA	ribonucleic acid
RR	relative risk
SQUID	superconducting quantum interference device
USRDS	United States Renal Data System

Blood losses in hemodialysis patients

Blood losses are a major factor in causing iron deficiency in hemodialysis patients. There are three cumulative sources of blood loss in hemodialysis patients:
- the dialysis technique itself;
- regular blood sampling for laboratory tests;
- occult intestinal bleeding due to uremic enteropathy and platelet dysfunction.

Moreover, the vascular access and comorbidities strongly influence the sources and amount of blood loss.

Blood losses in this setting have traditionally been estimated at between 4 and 12 liters per year (2 to 6 g of iron per year, one litre of blood containing about 500 mg of iron), but this approximation clearly overestimates modern dialysis-related blood losses [3,22]. Of note, considering that one liter of blood contains about 500 mg of iron may also be an over-estimation because of the lower hematocrit of dialysis patients, resulting in a lower iron content [3].

Blood loss has been estimated at 0.3 mL/session [23] and 0.9 mL/session [24] with modern dialysis membranes, and bloodline losses at 0.2 mL/session [23]. Thus, assuming losses of 1.1 mL per session, annual losses due to the hemodialysis technique itself during conventional hemodialysis (3 sessions/week, 150 sessions/year) represent about 165 mL (*table I*) [3]. Japanese researchers recently reported similar volumes: residual blood in the tubing set and dialyser (measured by atomic spectrometry in 238 patients) represented an average loss of 1245 µg of iron per dialysis session [25].

However, one of the main sources of blood loss in dialysis units is related to the care of (tunnelized) double-lumen catheters by nurses applying a universal purge protocol (7 to 10 mL of blood in each catheter branch at the outset of the session), which leads to an annual blood loss of 2.4 liters. An additional 288 mL should be added for routine monthly bacterial culture of anticoagulant locks when this practice is employed. Thus, total annual blood loss linked to the use of a double-lumen catheter is about 2.7 liters (*table I*) [26]. Note that the use of a recent protocol proposed by Professor Canaud, based on a purge of only 2 mL per branch, would reduce catheter-related blood loss to only 888 mL/year (−77%) [26]. Finally, sudden accidental bleeding due to insufficient compression or high internal pressure of a native fistula may cause additional, severe blood loss [26].

TABLE I

Blood losses in hemodialysis patients

Related to the dialytic technique (membrane + blood-lines)	165 mL of blood/year
Occult gut (micro-bleeding)	2257 mL of blood/year
Regular blood sampling for biological follow-up	428 mL of blood/year
Care of double-lumen catheters	2680 mL of blood/year
In Summary	
Patient with a native fistula	2680 mL of blood/year (1340 mg of iron)
Patient with a long-lasting double-lumen catheter	5320 mL of blood/year (2765 mg of iron)

According to Rottembourg J, Rostoker G. Use of intravenous iron supplementation in chronic kidney disease: interests, limits, and recommendations for a better practice. Neprol Therap 2015;11(7):531–42. doi:10.1016/j.nephro.2015.04.009. [Epub 2015 Oct 20].

Regular blood sampling is the second major source of blood loss in this setting. In a recent French survey, routine blood sampling was quantified at between 350 mL to 450 mL/year in 10 dialysis centers run by the RAMSAY-Générale de Santé healthcare provider [26], a volume close to that found by Sargent and Acchiardo (368 mL) at the University of Tennessee in Memphis in 2004 (*table I*) [22,26]. Blood sampling for routine follow-up has been recently estimated at 600 mL/year in Japan [25]. Note that blood sampling can be markedly increased by participation in clinical trials and pathophysiological studies.

The third source of blood loss is occult gut bleeding, which is below the detection limit of classical stool tests. This is favoured by uremic enteropathy, uremic platelet dysfunction, and anticoagulation of the extracorporeal circuit by unfractionated heparin or low-molecular-weight heparin [27]. In the 1980s, Rosenblatt et al., using chromium 51-labelled erythrocytes, quantified fecal blood loss at 0.83 mL/day in healthy controls, 3.15 mL/day in non-dialysed chronic kidney disease (CKD) patients and 6.27 mL/day (2.2 L/year) in hemodialysis patients [27] (*table I*). These losses are increased by antiplatelet drugs and vitamin K antagonists, which are frequently used in dialysis patients; these additional losses related to antiplatelet drugs and vitamin K antagonists necessitate the use of higher IV iron dosages to replenish iron stores (e.g. 703 to 961 mg of additional IV iron per year) [28,29].

Intravenous iron products in dialysis patients

Iron deficiency is an important clinical concern in CKD patients, especially hemodialysis patients, as it gives rise to superimposed iron-deficiency anemia and impairs various cellular functions. Oral supplementation, in particular with ferrous salts, is associated with a high rate of gastrointestinal side effects in this setting and is poorly absorbed, a problem that is avoided with intravenous (IV) iron products [26]. Recently, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use took measures to minimize the risk of rare allergic reactions to intravenous iron products by modifying the summaries of product characteristics, allowing IV iron infusions to take place only in public or private hospitals and dialysis facilities, and imposing clinical monitoring for at least 30 minutes after the infusions [26]. Seven different IV iron pharmaceuticals are available today in the USA and Europe and in other industrialized countries: their main physicochemical and pharmacokinetic characteristics are summarized in *table II*. The most recent and stable intravenous iron complexes (low-molecular-weight iron dextran, ferric carboxymaltose, iron isomaltoside 1000 and ferumoxytol) can be given at higher single doses and more rapidly than older preparations such as iron sucrose (*table II*) [26,30]. The larger size of the carbohydrate shell of some recent intravenous iron pharmaceuticals (low-molecular weight dextran and ferumoxytol) might increase the risk of anaphylaxis,

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TABLE II

Physicochemical characteristics and pharmacokinetics of intravenous iron products

Commercial name	Venofer®	Ferrlecit®	DexFerrum®	Cosmofer®/ Ferrisat® (Europe) and INFeD® (USA)	Ferinject® (Europe) and Injectafer® (USA)	Monofer®/ Monover®	Rienso® (Europe) and Feraheme® (USA)
Carbohydrate composition	Iron sucrose	Iron gluconate	Iron dextran of high-molecular-weight	Iron dextran of low-molecular-weight	Iron carboxymaltose	Iron isomaltoside	Ferumoxytol (polyglucose sorbitol carboxy methyl ether iron)
Molecular weight measured by manufacturer (Dalton) and (KDalton according the USP method of Geisser)	34,000 to 60,000 (44)	289,000 to 440,000 (37)	265,000	165,000 (165)	150,000 (150)	150,000 (69)	750,000 (185)
Reactivity	Moderate	High	Low	Low	Low	Low	Low
Half life in plasma (hours)	5.3–6	1.4	9.4 to 87.4	20	7 to 12	23.2	14.7
Cmax, mg Fe/L	35.3	20.6	–	120	37	37.3	130
Area under the curve (mg Fe/L × hours)	83.3	35	–	1371	333	1010	922
Clearance (L/hour)	1.23	2.99	–	–	0.26	0.10	0.11
Maximal infused dose	300 mg	125 mg	100 mg	20 mg/kg	20 mg/kg	20 mg/kg	510 mg
Minimal time of infusion	90 minutes	60 minutes	60 minutes	240 minutes	15 minutes	60 minutes	15 minutes

According to Rottembourg J, Rostoker G. Use of intravenous iron supplementation in chronic kidney disease: interests, limits, and recommendations for a better practice. Neprol Therap 2015;11(7):531–42. doi:10.1016/j.nephro.2015.04.009. [Epub 2015 Oct 20].

although this remains rare and is a subject of active debate [31]. Test doses are no longer mandatory [26,30]. Iron supplementation is recommended for all CKD patients with iron-deficiency anemia and those who receive erythropoiesis-stimulating agents, whether or not they require dialysis [4,17,18]. Parenteral iron therapy has gained popularity in the nephrology community in the last 15 years and the intravenous route has for many years been the preferred route of administration to hemodialysis patients because of its convenience (infusion during dialysis sessions), its superior efficacy over oral preparations for treating true iron deficiency, and its ability to overcome functional iron deficiency, a very common clinical situation in dialysis-dependent CKD patients [1,4,17,18]. Indeed, randomized trials in hemodialysis patients showed significantly greater increases in hemoglobin levels with intravenous iron as compared to oral iron, and a low rate of treatment-related adverse events during these albeit short trials [1,17]. In addition, IV iron products enable cost savings of about 30% by reducing ESA dose requirements [32]. It is also noteworthy that the recent meta-analysis performed by the Cochrane network comparing parenteral versus oral iron concluded that the 28 included studies (2098 participants) provided strong evidence for larger increases in ferritin [mean difference: 243 µg/L, 95% confidence Interval (CI): 188–297 µg/L] and transferrin saturation (mean difference: 10.2%; 95% CI: 5.5–14.8%), together with a moderate increase in hemoglobin (mean difference: 0.9 g/dL; 95% CI: 0.44–1.37 g/dL) in the IV iron-treated groups [33]. With the exception of iron gluconate and ferumoxytol, which are particularly indicated in CKD patients with iron deficiency, IV iron pharmaceuticals are only indicated for use in general cases of iron deficiency anemia (whatever the underlying disease) when oral iron is unavailable, ineffective or poorly tolerated, or as first-line treatment when there is a clinical need to rapidly replenish iron stores (iron sucrose and low-molecular-weight iron dextran) [34]. It is also noteworthy, that iron overload represents a formal contraindication to beginning or pursuing therapy with these IV iron products, as stressed in the *Contraindications* or *Precautions* section of the summaries of product characteristics [34]. Moreover, the Committee for Medicinal Products for Human Use of EMA in its reflection *paper on the data requirements for intravenous iron-based nano-colloidal products* published *on 26 March 2015* stated that the risk of iron overload leading to organ damage is inherent to all IV iron products and that this risk can be substantially mitigated through strict adherence to

therapeutic indications/contraindications and by avoiding off-label use or medication error [35]. Of note, in contrast, our review of the literature and clinical experience suggest that while iron loading of organs may be substantial, there is little evidence of related organ damage. The off-label use relates mainly to illicit use of IV iron products by athletes to improve performance and to the lack of initial trials of the oral route in the general population (in the absence of severe iron depletion, need for rapid reconstitution of iron stores, or known intolerance of the oral route); thus, it seems (from a judicial point of view) that European nephrologists might be concerned in CKD by adherence to label posology and monitoring for iron overload.

The changing conception of iron therapy in hemodialysis patients over the past two decades

When erythropoietin replacement therapy became possible in the late 1980s, the goal of iron therapy was to maintain iron stores, allowing true iron deficiency to be prevented, mainly with oral iron supplements (in patients with serum ferritin levels below 50 μg/L) [36,37]. At that time, IV iron was considered a second-line option when oral iron drugs were poorly tolerated or ineffective, or when severe iron deficiency was present [36–38].

Based solely on short-term tolerability in controlled trials of IV iron products and on bone marrow studies, the guidelines EBPG of the European Renal Association ERA-EDTA issued in 2004 and of the Kidney Disease Outcomes Quality Initiative (KDOQI) in the USA issued in 2006 redefined iron deficiency (ferritin < 100 μg/L instead of 50 μg/L) and adopted higher iron store repletion criteria (ferritin target > 200 μg/L and < 500 μg/L) [2,4]. More recently, the KDIGO 2012 guideline has underlined the risk of functional iron deficiency during ESA treatment, and emphasized the ability of IV iron to obviate or reduce the need for ESA by advocating a trial of IV iron up to 500 μg/L of ferritin [17]. These clinical guidelines and the older ERA-EDTA position statement, which are widely followed and often exceeded by nephrologists worldwide, have unintentionally contributed to the extensive use of parenteral iron in hemodialysis patients in the last decade [3,4,17,18]. Indeed, an epidemiological study of anemia management in United States hemodialysis patients, based on the United States Renal Data System (USRDS) register, showed that the use of IV iron rose from 64% of patients in 2002 to 76% in 2008, while the infused dose rose from 166 mg/month to 216 mg/month over the same period [39]. Nevertheless, the usual monthly dose of IV iron during the first year of hemodialysis was even higher, ranging from 270 mg to 305 mg/month [39]. Furthermore, the US Food and Drug Administration modified the ESA label in June 2010, leading to a rise in the proportion of US patients receiving IV iron from 57% in August 2010 to 71% in August 2011, and to a significant decline in ESA dosages [40]. The median ferritin level rose from 556 to 650 μg/L, and 34% of patients had values exceeding 800 μg/L [40]. Moreover, nearly one in five dialysis patients received more than 500 mg IV iron/month during this period [40].

Similar trends in the use of IV iron in other industrialised countries were recently reported, with the sole exception of Japan [41]. Overall, the percentage of patients who received IV iron rose between 1999 and 2010 from 50% to 71% (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) [41]. Between 1999 and 2010, the mean ferritin level increased in most countries (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) but remained stable in France at around 400 μg/L [41]. In Japan, the proportion of patients receiving IV iron rose from 25% to 36%, while the mean ferritin level increased only from 280 to 320 μg/L [41]. Overall, in industrialized countries outside the USA, the average monthly dose of IV iron infused during hemodialysis sessions rose by 21%, from 232 mg/month in 1992 to 281 mg/month in 2010 [41].

Of note, the Dialysis Outcomes and Practice Patterns Study (DOPPS) Monitor study (9735 patients in 91 US facilities) showed a recent decrease in the amount of IV iron infused in the US, from 280 mg/month in 2011 to 200 mg/month in 2012, with a similar value in 2013 [42].

Historical features of hemodialysis-associated hemosiderosis before the erythropoietin era

Full-blown clinical iron overload due to transfusions and sole use of IV iron products in the pre-ESA era may provide some valuable lessons on the excessive use of iron supplements, mainly based on autopsy studies [3]. Indeed, post-mortem studies of dialysis patients with severe hepatosplenic sideroses in the late 1970s and early 1980s showed abundant iron deposits in the liver, spleen, adrenal glands, lymph nodes and lungs, with generally smaller amounts in the kidneys, pancreas and heart [43–45]. The earliest detectable hepatic iron deposits were found in cells lining the sinusoids and in Kupffer cells [43]. As hepatic siderosis progressed, iron started to appear in hepatocytes, initially at the periphery of hepatic lobules close to portal triads and then throughout the lobule [43]. The main iron storage site in the spleen was in the cells lining the splenic sinusoids, whereas the white pulp was usually spared [43]. Even massive hepatic siderosis was not apparently associated with cell damage, although reticulin and trichrome staining showed a more abundant fibro-connective framework, a loss of liver cells, and fatty changes in hepatocytes [43–45]. Of note, liver enzymes were seldom increased in patients with hepatic siderosis [44] and cirrhosis was a rare event [43–45].

Importantly, post-mortem studies showed that iron overload was strongly linked to both blood transfusion and also to the

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IV administration of high-molecular-weight iron dextran (IMFERON®); the closest relationship was between hepatic siderosis and the use of IV iron [6,44,45]. Patients who received little or no IV iron were usually free of iron overload, and massive hepatosplenic siderosis was only seen in patients who had been on dialysis for more than 3 years [3,6,44,45]. Adrenal involvement was observed in 45.8% (11/24) of unselected patients studied by Pitts and Barbour [44], compared to 94.4% (17/18) of patients with severe hepatosplenic siderosis studied by Ali et al. [43]. Pancreas involvement was found in only 7/24 patients (29.2%) in the study by Pitts and Barbour. and in 5/18 patients (27.8%) with severe hepatosplenic siderosis in the study by Ali et al. [43,44]. Significant iron deposits were found in the heart of respectively 16.7% (4/24) and 22.7% (5/22) of unselected patients in the autopsy studies of Pitts and Barbour [44] and Gokal et al. [45], but more frequently, in 44.4% (8/18) of patients with severe hepatosplenic siderosis in a post-mortem study by Ali et al. [43].

One strategy implemented at that time to avoid transfusion-related iron overload in dialysis patients with transfusion-dependent anemia was to transfuse young rather than mature erythrocytes [46]. The only available iron chelator deferoxamine (DESFERAL®) was advocated to prevent hemosiderosis and to treat organ dysfunction (cardiac insufficiency, multiple endocrine disturbances, skin pigmentation and hepatic fibrosis) due to iron overload but patients were prone to possible multiple side effects of deferoxamine, which include hepatic, ocular and hearing disorders, as well as fever and allergic reactions during the infusions [46].

The advent of recombinant human erythropoietin in the early 1990s represented a therapeutic revolution which allowed anemia and iron overload to be treated simultaneously by inducing both massive mobilization of iron stores and effective phlebotomy by partial letting of the extracorporeal circuit at the end of the dialysis sessions in patients who had been rendered non-anemic [47]. The same period saw the first successful use of quantitative computed tomography, the first noninvasive radiological tool, for the diagnosis of hemodialysis-associated hemosiderosis and for monitoring liver iron stores [48]. The full-blown clinical picture of hemodialysis-associated hemosiderosis disappeared from dialysis centers in industrialized countries at least 3 decades ago but may still occur in emerging countries where ESAs are not available [3].

Noninvasive imaging of liver iron stores by MRI: specific features in dialysis patients

The liver is the main iron storage site and the liver iron concentration (LIC) gives a very accurate picture of total body iron stores in patients with secondary hemosideroses such as thalassemia major, sickle cell disease and genetic hemochromatosis [49,50]. MRI is now the preferred technique for estimating and monitoring iron stores in patients without kidney disease because of its reproducibility, sensitivity, availability and ability to scan multiple organs in the same session [51,52]. There are three MRI modalities for liver iron assay: the signal-intensity ratio, R2 relaxometry, and R2* relaxometry [53–55] (see the article by Professor Gandon et al.). In addition, in renal patients, quantitative MRI does not require gadolinium and thus preventing the risk of gadolinium-associated nephrogenic fibrosis in CKD patients (a clinical situation mimicking scleroderma) [3]. It seems that the liver iron concentration could be the best marker of iron overload in ESRD: indeed, hemodialysis patients receiving IV iron in the pre-ESA era had paradoxically low bone marrow iron content in up to one-third of cases, despite severe hepatosplenic siderosis [6], suggesting that bone marrow analysis may not accurately quantify iron stores in dialysis patients, even in the ESA era [3,6]. As the upper 95% of LIC in healthy adults is 32 µmol/g but hepatic MRI accurately detects liver iron load exceeding 50 µmol/g, the upper limit of normality has been set at 50 µmol/g in most studies for dialysis patients [8].

Specific MRI protocols have been shown to provide a reliable estimation of tissue iron content in non-renal patient populations but have not yet been validated in dialysis patients [53–55]. Thus, there is currently a need to validate these MRI techniques for quantifying liver iron content, specifically in dialysis patients, notably by comparison with liver biopsy [3]. However, liver biopsy is an invasive and risky procedure, especially in frail end-stage renal disease patients, and such studies therefore raise ethical concerns [3]. Consequently, last year we proposed a prospective MRI study of dialysis patients requiring liver biopsy or liver surgery for their usual medical care, with the hope that it could help to fill this knowledge gap pointed out by the KDIGO conference on the controversies related to iron management in CKD [3,19].

In a recent pilot study, Rostoker et al. compared Scheuer's histological classification and Deugnier and Turlin's histological classification of iron overload (Perls staining) with signal-intensity-ratio MRI values obtained with the Rennes University algorithm in 11 hemodialysis patients in whom liver biopsy was formally indicated for their medical follow-up [53,56]. For Scheuer's histological classification, the Wilcoxon non-parametric matched-pairs test showed no significant difference in the ranking of iron overload by the two methods, i.e. histology and MRI (summary of ranks = 1.5; P = 1) [56]. The MRI and Scheuer's histological classifications were closely correlated (rho = 0.866, P = 0.0035, Spearman's coefficient), as were the absolute liver iron concentrations (LIC) at MRI (rho = 0.860, P = 0.0013, Spearman's coefficient) [56]. The absolute liver iron concentrations at MRI were also highly correlated with Deugnier and Turlin's histological scoring (rho = 0.841, P = 0.0033, Spearman's coefficient) [56]. Thus, this pilot study shows that liver iron determination based on signal-intensity-ratio MRI with

the Rennes University algorithm, very accurately identifies iron load in hemodialysis patients, by comparison with liver histology [56].

Radiologists may be solicited in the near future by nephrology teams requesting quantitative hepatic MRI for research purposes, and also for diagnosis and follow-up of iron overload in dialysis patients. Radiologists and nephrologists should realize that there are marked differences in the pharmacokinetics of IV iron products, and that these can interfere with MRI (*tables II and III*) [57]. The required time interval between the last IV iron infusion and MRI should range from one week (iron sucrose, iron gluconate, iron carboxymaltose) to one month (low-molecular-weight iron dextran and iron isomaltoside), 3 months (high-molecular-weight iron dextran) or even 6 months (ferumoxytol) if spurious results due to magnetic interference are to be avoided (*table III*) [57]. Of note, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency has recently modified the summary of product characteristics for ferumoxytol (RIENSO®/FERAHEME®) in 2015 in the wake of the literature review performed by Rostoker and Cohen, making a 6 month interval mandatory instead of the previous 3 months [57,58].

Iron overload in dialysis patients in the ESA era

Studies using superconducting quantum interference device (SQUID) thirteen years ago [11] and more recent studies employing quantitative MRI [8,59,60] to estimate LIC in hemodialysis patients, have provided new information on iron metabolism in ESRD and have underlined the risk of hemosiderosis. These studies also strongly suggest a link between the IV iron dose and the risk of iron overload in this setting, challenging current guidelines with respect to the influence on LIC of IV iron products at high repeated doses [4,8,17,18,59,60], as well as the reliability of iron biomarker cutoffs, and methods for monitoring iron stores in dialysis patients [8,9,15,16].

Two recent MRI studies have focused on iron overload in hemodialysis patients with serum ferritin levels far above 500 µg/L (the upper limit advocated by KDOQI-2006 and by the ERA-EDTA-ERBP 2009 position statement): Ferrari et al. used R2 relaxometry to study 15 Australian patients with a median ferritin of 782 µg/L and found hepatic iron overload in two-thirds of cases [59]. Ghoti et al. used T2*MRI to measure liver and spleen iron content, and to search for pancreatic and cardiac iron deposits in 21 iron-overloaded Israeli hemodialysis patients with serum

TABLE III
IV iron preparations: interference with MRI

Trade name	Time for complete plasma elimination	MRI information in the summary of product characteristics (SPC)	Studies of biological clearance and MRI interference	Recommended time between last iron infusion and MRI
VENOFER® (iron sucrose)	30 hours (1 day and 6 hours)	No	Yes (PETSCAN)	One week
COSMOFER® (Europe) INFeD® (USA) (iron dextran of low-molecular-weight)	4 days	No	No	One month
FERRLECIT® (iron gluconate)	1 day	No	No	One week
DEXFERRUM® (iron dextran of high-molecular-weight)	2 to 18 days	No	No	3 months
MONOFER®/MONOVER® (iron isomaltoside)	5 days	No	No	One month
FERINJECT® (Europe) INJECTAFER® (USA) (iron carboxymaltose)	1.5 to 2.5 days	Yes lack of influence of Ferinject/Injectafer on MRI	Yes (PETSCAN)	One week
RIENSO® (Europe) FERAHEME®(USA) [ferumoxytol (polyglucose sorbitol carboxy methyl ether iron)]	3 days	Yes Inference with MRI 1 – SPCs in USA and Europe (until 2015): respect an interval of 3 months between infusion and MRI 2 – New SPC in Europe (2015): respect an interval of 6 months between infusion and MRI	Yes (interference with MRI)	6 months

According to Rostoker G, Cohen Y. Magnetic resonance imaging repercussions of intravenous iron products used for iron-deficiency anemia and dialysis-associated anemia. J Comput Assist Tomogr 2014;38(6):843–844. doi:10.1097/RCT.0000000000000146.

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ferritin levels over 1000 µg/L [60]. They found hepatic siderosis in 19/21 patients (90%) and spleen involvement in all 21 patients (100%) [60]. Pancreatic involvement was sought in only 8 most overloaded patients and was found in 3 cases (37%) [60]. None of the patients had an abnormal cardiac R2* but few patients were studied and no definitive conclusions can thus be drawn on the risk of cardiac iron deposits in patients with very high ferritin levels (above 1000 µg/L) [60].

Two studies have analyzed liver iron stores, one using SQUID in 2004 [11] and the other in 2012 with the Rennes University MRI protocol [8] in cohorts of hemodialysis patients treated according to the KDOQI-2006 guideline [4] and the ERA-EDTA-ERBP-2009 position statement [18] and with optimal ferritin levels (between 200 and 500 µg/L). Canavese et al. used SQUID to study liver iron stores in 40 Italian patients and found normal values in 30% of cases (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) [11].

The French study published in 2012, showed hepatic iron overload on MRI (> 50 µmol/g dry weight) in 84% of 119 stable hemodialysis patients treated according to current guidelines; iron overload was mild in 42 patients (35.3%), moderate in 22 (18.5%) and severe (> 200 µmol/g dry weight) in 36 (30%), at levels usually observed in genetic hemochromatosis (*figure 1*) [8]. MRI also showed spleen anomalies (a feature of secondary hemosiderosis) in several patients [8].

In the French cross-sectional study, LIC correlated with infused iron, hepcidin and C-reactive protein values in univariate analysis (*P* < 0.05, Spearman test) and in binary logistic regression (*P* < 0.05) [8]. No link was found between the LIC of hemodialysis patients with excessive alcohol consumption [Alcohol Use Disorders Test score (AUDIT)] and the major *HFE* mutation C282Y [8]. As in the SQUID study by Canavese et al. [11], females had an increased relative risk of iron overload [RR: 3.36 (95% CI: 1.03–10.9)] [8]. Eleven patients were closely monitored during parenteral iron therapy, showing that the monthly IV iron dose correlated strongly with both the overall and monthly increases in LIC (rho = 0.66, *P* = 0.0306 and rho = 0.85, *P* = 0.0015, respectively; Spearman's test) (*figures 2 and 3*) [8].

Finally, in the 33 longitudinally studied 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 3*) [8]. The slope of the decline in hepatic iron was −17.9 µmol/g dry weight/month after iron withdrawal, −12.8 µmol/g dry weight/month after a major iron dose reduction, and 11.9 µmol/g dry weight/month after renal transplantation [8].

Two recent replication studies, with small number of hemodialysis patients one in the USA (*n* = 17; median ferritin 596 ng/mL) and one in Australia (*n* = 10; median ferritin: 371 ng/mL) have similarly observed a high frequency of iron overload at quantitative MRI (50% with T2* in US patients [61] and 80% in Australian patients with Ferriscan T2/R2 [62]). Of note, no cardiac iron deposits were observed by T2* in either study [61,62].
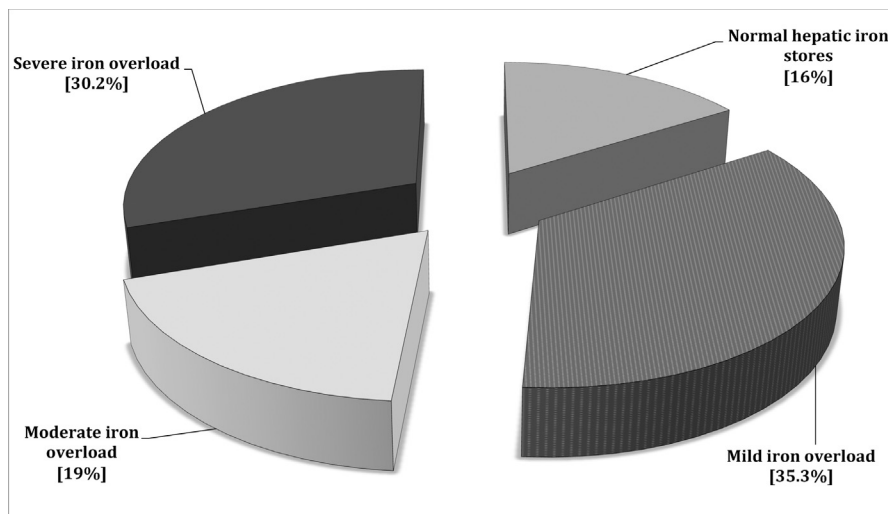

FIGURE 1

Results of a cross-sectional quantitative MRI study of 119 hemodialysis patients. According to 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 (10):991–999. doi:10.1016/j.amjmed.2012.01.015. [e1]. And Rostoker G, Griuncelli M, Loridon C, Cohen Y. Iatrogenic iron overload in dialysis patients. Chapter of the book: *Updates in Hemodialysis*. Book edited by Hiromichi Suzuki, ISBN 978-953-51-2162-6, Published: September 9, 2015 under CC BY 3.0 license. © The Author(s). Intech, New York, Rijeka and Shangai. doi:10.5772/59316.
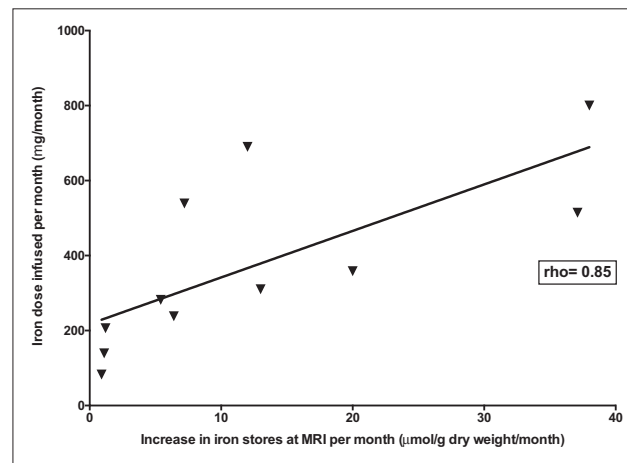
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FIGURE 2

Correlation between the infused iron dose and hepatic iron stores in 11 hemodialysis patients studied by quantitative MRI. According to 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(10):991–999. doi:10.1016/j.amjmed.2012.01.015. [e1].

Thus, most hemodialysis patients receiving ESA and IV iron supplementation according to current guidelines appear to have hepatic iron overload in these recent LIC imaging studies [8,11,59–62].

Whereas the potential iron overload toxicity is now one of the most controversial topics in the management of anemia in hemodialysis patients, data on this topic are lacking in peritoneal dialysis patients. While most hemodialysis patients receive parenteral iron supplementation, a much smaller number of peritoneal dialysis (PD) patients are treated with IV iron; moreover, the ferritin target is far lower and more physiological in PD than in hemodialysis (HD) population. A prospective
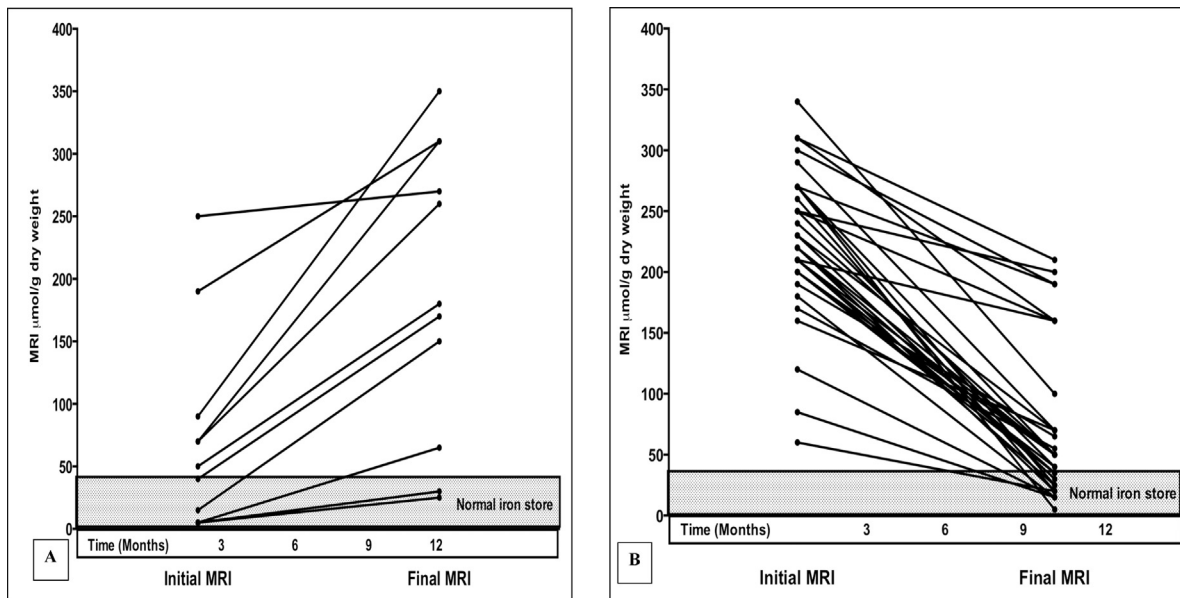

FIGURE 3

Time course of hepatic iron stores studied by magnetic resonance imaging in hemodialysis patients.
A. Initial and final hepatic iron concentrations on magnetic resonance imaging (MRI) in 11 patients receiving iron therapy. B. Initial and final hepatic iron concentrations on MRI in 33 patients with hepatic iron overload, after iron withdrawal (_n_ = 19) or a major iron dose reduction (_n_ = 14). Modified according to 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(10):991–999. doi:10.1016/j.amjmed.2012.01.015. [e1].

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observational study recently measured liver iron concentration by means of T1 and T2* contrast magnetic resonance imaging without gadolinium, in a cohort of 32 peritoneal dialysis patients in the Greater Paris Area and compared them with two cohorts of French HD patients (respectively n = 119 published in 2012 and n = 80 published in 2014) using similar methods [63]. Normal hepatic iron load (LIC $\leq$ 50 µmol/g of dry weight) was observed in 81.25% of PD patients (CI: 64.32%–91.48%), as compared to only 15.97% (CI: 10.38%–23.68%) in the first HD cohort and 35% (CI: 25.43%–45.94%) in the second HD cohort (P < 0.0001 at X^2 test by comparison with each cohort) [63]. Mild iron overload (50 < LIC $\leq$ 100 µmol/g) was observed in most PD cases (5 out of 6) and only 1 PD patient previously treated by IV iron infusions (3.13%; CI 0%–17.11%) had severe iron overload at MRI (> 200 µmol/g) as compared to 36% (CI: 27%–46%) in the first HD cohort and 11.25% in the second HD cohort (CI: 5.82%–20.23%) (P = 0.0033 at X^2 test by comparison with the first HD cohort) [63]. It seems, therefore, that iron overload is rare and mostly mild in PD patients. 50 < LIC $\leq$ 100 µmol/g Finally, a recent MRI study of LIC at initiation of dialysis in Portugal (n = 23 patients), showed that a substantial proportion of patients (74%) had iron overload due either to previous infusions of IV iron products or to dysmetabolic iron overload syndrome; LIC of these patients increased significantly during the hemodialysis period due to IV iron products infusions [64].

Potential morbidity and mortality related to iron overuse in hemodialysis patients

Data from epidemiological studies

Three short-term observational studies showed no detrimental impact of high-dose IV iron on morbidity or mortality in dialysis patients (observation time after exposure of 1 month (with iterative rolling periods) in Feldman et al.'s study, two months in Miskulin et al.'s study, and 3 months in Kshirsagar et al.'s study) [65–68]. On the contrary, three other epidemiological studies with longer follow-up (1 to 2 years) showed that excessive IV iron might be associated with increased mortality and cardiovascular events in hemodialysis patients [12–14]. It is likely that the longer follow-up of the latter studies could explain these discrepancies, and suggests that excess therapeutic iron could cause chronic, cumulative toxicity if given for long periods in vulnerable dialysis patients [3].

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 [12]. The patients receiving IV iron were divided into 3 subgroups according to the cumulative dose: 40–800 mg/6 months, 840–1600 mg/6 months and 1640–2400 mg/6 months [12]. The two subgroups with the higher cumulative iron doses had higher adjusted mortality [respective hazard ratios (HR): 3.1 and 3.7] and more cardiovascular events (respective HRs: 3.5 and 5.1) than those not

receiving IV iron and those who received less than 820 mg/6 months (or 136 mg/month) [12].

Kuragano et al. prospectively monitored 1086 Japanese hemodialysis patients for 2 years and compared those on oral iron with those treated with IV iron, divided into 3 groups: oral iron + very-low-dose IV iron, low-dose IV iron (< 200 mg/month) and high-dose IV iron ($\geq$ 200 mg/month) [13]. They observed more cases of acute cardiocerebrovascular disease (HR: 6.02) and hospitalization (HR: 2.77) in the high-dose IV iron group, and increased risk of infections in both the low (HR: 1.78) and high (HR: 5.22) IV iron-treated groups [13]. High ferritin levels (consistently above 100 µg/L, in accordance with Japanese guidelines [13]) were associated with a risk of acute cardiocerebrovascular disease (HR: 2.22), infections (HR: 1.76) and death (HR: 2.28) [13]. Moreover, a category switch from low to high ferritin (from less to more than 100 µg/L) was also associated with an increased risk of acute cardiocerebrovascular disease (HR: 1.59) and death (HR: 6.18) [13].

Finally, the DOPPS study, using Cox regression models with multiple adjustments, analyzed associations between IV iron and clinical outcomes in 32,435 hemodialysis patients followed for a median time of 1.7 years (range 1–2.4) in 12 industrialized countries [14]. The authors observed higher adjusted mortality in patients receiving 300–399 mg/month of IV iron (HR: 1.13) and 400 mg/month of IV iron or more (HR: 1.18) than in those receiving no iron or 1–99, 100–199 or 200–299 mg of IV iron/month [14]. Similarly, the risk of hospitalization was higher (HR: 1.12) in patients receiving 300 mg/month or more of IV iron as compared to those receiving 100–199 mg/month [14]. Of note, monthly iron doses found to be associated with morbidity and mortality events in the DOPPS study are very similar to those (400 mg/month) shown by Kalantar-Zadeh et al. to be associated with higher mortality among hemodialysis patients in the DaVita cohort published ten years ago [68].

The results of the Japanese study are in keeping with a recent US study showing that unlike monthly bolus doses of 700 mg, iron maintenance therapy at 200 mg/month is not associated with an increased short-term risk of infections [69]. The latter results are in line with the findings of a recent controlled trial of IV iron-sucrose versus oral iron in non-dialyzed CKD patients, showing increased serious cardiovascular and infectious events in IV iron-treated patients as compared to those receiving oral iron [70].

Influence of iron load on the liver as an organ of iron deposition and as an organ involved in iron absorption and metabolism

Influence of iron load on the liver as an organ of iron deposition

Genetic hemochromatosis and secondary hemosiderosis related to hematological disorders are now diagnosed very early in most patients, long before any organ dysfunction, and cirrhosis is now rarely encountered [10,49,50]. Despite the high

prevalence of iatrogenic iron overload in the pre-ESA era, hepatic cirrhosis was very rare in hemodialysis patients, and so were anomalies of liver enzymes [6,43–46]. Indeed, liver biopsy generally showed focal portal fibrosis in patients with marked hemosiderosis [46], strongly suggesting that the risk threshold for hepatic cirrhosis in iron-overloaded dialysis patients in the pre-ESA era was high in the absence of coexisting viral hepatitis or alcoholism [43–46]. This paucity of liver enzyme anomalies and cirrhosis also seems to hold true for dialysis patients with evidence of iron overload in noninvasive radiological methods (e.g. susceptometry and MRI) [8,11,60–62]. This not surprising since all forms of cirrhosis (hemosiderosis, alcoholic liver disease, viral hepatitis, NASH and genetic hemochromatosis) take many years to fully develop. Therefore, the short life span of ESRD patients may also account for scarcity of iron overload-induced cirrhosis in this population. Thus, considering the scarcity of cirrhosis and its slow onset, increased LIC in dialysis patients must rather be considered as a potential predictor of iron-mediated disruption of homeostasis of iron-regulating hormones in the liver and intensification of oxidative stress, inflammation, events which could possibly lead to accelerated morbidity, mortality and increased burden of complications in this population [3,15,16].

Influence of iron load on the liver as an organ involved in iron absorption and metabolism

Hepcidin-25 is now recognized as the master hormone of iron metabolism. It is synthesized in the liver and acts negatively on both intestinal iron absorption and iron release from reticuloendothelial macrophages and liver cells by reducing the expression of ferroportin, a protein that regulates iron export out of these cells [3]. Iron itself and inflammation (via IL6) enhance hepcidin-25 synthesis, while anemia, hypoxia, bleeding, iron deficiency, erythropoietin, and increased medullary erythropoïesis all down-regulate hepcidin-25 synthesis [3]. The mechanism by which erythropoietic stimulation after blood loss down-regulates hepcidin synthesis has recently been linked to a new peptide hormone called erythroferrone, which is secreted by erythroblasts and acts directly on the liver [3]. Hepcidin and erythroferrone can be seen as the iron metabolism counterparts of the glucose-regulating hormones insulin and glucagon. Deficient hepcidin-25 synthesis plays a central pathophysiological role in genetic hemochromatoses, whereas unregulated hepcidin synthesis is responsible for a newly discovered genetic (autosomal recessive) form of iron-deficiency anemia called iron refractory iron deficiency anemia (IRIDA), due to mutation of the *TMPRSS6* gene that encodes matriptase-2 [3]. IRIDA is refractory to oral iron but responds partially to IV iron [3]. Italian authors recently called for a critical re-evaluation of hepcidin levels in CKD patients, postulating that hepcidin is not intrinsically elevated in hemodialysis patients, but rather reflects poor matching with healthy subjects and frequently excessive iron stores [71]. These authors postulated that hepcidin elevation may in fact be a physiologic defence mechanism against iron overload, and that it is preserved in patients with renal failure, even in those maintained on dialysis [71]. Indeed, very high hepcidin-25 levels have been observed in dialysis patients with severe iron overload found on MRI [8,11] and have been further shown to normalize in parallel with liver iron stores [8], thus supporting the latter hypothesis. As high hepcidin-25 levels in hemodialysis patients were recently shown to be related to fatal and nonfatal cardiovascular events, the main physiopathological pathway linking these events to iron overload might involve the pleiotropic effects of hepcidin-25, secreted in excess by liver in case of iron overload, and able to activate macrophages in atherosclerotic plaque, rendering it unstable [72].

Other potential toxic mechanisms of iron overload

It is likely that, beside elevated hepcidin levels, two other mechanisms might act synergistically to increase mortality and cardiovascular events in iron-overloaded hemodialysis patients, namely increased oxidative stress, and arterial and cardiac structural changes [3].

Oxidative stress, usually encountered in end-stage renal disease [73] and provoked by IV iron infusions [16] and severe iron overload (and mediated by the release of labile, non-transferrin-bound iron in those dialysis patients with massive hepatic iron load mimicking untreated thalassemia and genetic hemochromatosis) [74], might also adversely affect the vascular bed and act as a "second hit''. In the dialysis population, excess iron might also play a direct role in cardiovascular complications by impairing endothelial function, as shown in patients with hereditary hemochromatosis [75], and also by directly favoring atherosclerosis [76,77]. Conversely, taking into account data from post-mortem studies in the pre-ESA era, we may suspect that myocardial iron deposits in heavily iron-overloaded dialysis patients might also play a role in dialysis-related cardiovascular morbidity and mortality, especially sudden death [3,6,43–45]. Thus, well-powered cardiac T2*MRI studies are needed in this subset of heavily-overloaded dialysis patients to search for ferric cardiomyopathy.

In addition to these hypothetical detrimental effects on the cardiovascular system and mortality, iron overload might affect several lineages of immune cells, leading to an increased risk of infection, as shown in some epidemiological studies: these effects could include CD4+ T cell depletion associated with shortened cell lifespan, CD8+CD28− T lymphocyte expansion, impaired phagocytic activity, and microbial killing of polymorphonuclear leukocytes and monocytes [78]. In addition, since iron is an essential element for bacterial multiplication and virulence, iron overload due to high doses of IV iron might increase the risk and severity of infections [19]. Iron overload might also affect glucose regulation by inducing apoptosis of insulin-secreting pancreatic beta cells [79]. Since 40% of dialysis

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patients worldwide are diabetic, and as it has been suggested that even a slight increase in iron stores may play a role in the progression of macrovascular and microvascular complications of diabetes [80], it is likely that diabetic dialysis patients might thus be at higher risk of complications from iron overload.

Prevention of iron overload in dialysis patients

Iron overload in hemodialysis patients has been inadvertently encouraged by reimbursement policies in the USA and many other industrialized countries, which have led to an increase in the use of IV iron in an attempt to reduce ESA dose requirements [9,20]. The situation has been compounded by excessively high recommended doses of IV iron and, possibly, by erroneous iron biomarker targets which lead to supraphysiological iron stores [8,9]. Also, nephrologists have come to fear the adverse effects of ESA whilst wrongly believing that iron IV products are non-toxic [20]. Major changes in the approach to iron therapy have occurred recently.

First, the 2013 European Renal Best Practice position statement on anemia management warned against excessive use of IV iron products and the potential risk of iatrogenic iron overload, beside other potential toxicities, based on studies published in 2011 and 2012 and analysing LIC in dialysis patients by MRI [8,59,60] and a SQUID study published in 2004 [11,81]. This ERBP-2013 position statement did not fully endorse the 2012 KDIGO guideline on iron therapy, because of the potential risk of iron toxicities, and advocated a more conservative and safer upper limit of ferritin at 300 ng/mL instead of 500 ng/mL for starting iron therapy [81].

Second, the KDIGO Controversies Conference on Iron Management in Chronic Kidney Disease, which took place in San Francisco in March 2014, recognized the entity of iron overload in hemodialysis patients (together with other adverse effects) and called for a research agenda on this topic [19]. Third, the Dialysis Advisory Group of the American Society of Nephrology proposed an *aggiornamento* on the policy of high "blind" usage of IV iron products in hemodialysis patients [20]. Recent reviews of anemia and iron therapy in CKD, published in hematology and nephrology journals, now give a more balanced view, emphasizing not only the benefits but also the potential risks of IV iron products, including the danger of iron overload [82–84].

Quantitative MRI, which allows safe, noninvasive, repeated "radiological liver biopsy" has recently been advocated by French [8,26,85] and Japanese authors [86] for routine monitoring of iron store in dialysis patients and non-renal patients on long-term treatment with IV iron products [85].

A recent cohort study of hemodialysis patients, combining quantitative MRI with data-mining yielded nontoxic doses of IV iron, thereby improving the safety of parenteral iron products in dialysis patients [87]. The aim of this study, based on decision

tree learning and on MRI determination of hepatic iron content, was to identify a noxious pattern of parenteral iron administration in a prospective cohort of 199 hemodialysis patients treated for anemia with parenteral iron-sucrose and an ESA, in keeping with current clinical guidelines [87]. Hepatic iron stores were measured blindly by T1 and T2* contrast MRI, without gadolinium, coupled with CHi-squared Automatic Interaction Detection analysis (CHAID) [87]. The CHAID algorithm splits the patients according to the monthly IV iron dose, with a single cutoff of 250 mg/month. The odds ratio for hepatic iron overload on MRI was 3.9 (95% CI: 1.81 to 8.4) with more than 250 mg of IV iron/month versus less than 250 mg/month [87]. This MRI study suggests that the standard maximal monthly IV iron dose should be lowered to 250 mg to lessen the risk of iron overload in dialysis patients and seems to be in good agreement with the 3 recently published long-term epidemiological studies [12–14,87].

The worldwide nephrology community is also rediscovering the ingenious, cautious Japanese strategy of iron therapy, which maintains optimal hemoglobin levels (somewhat lower than in western countries) with minimal use of IV iron products and lower ferritin levels [21,88].

Rostoker et al. have recently speculated that the better overall survival of Japanese hemodialysis patients, as compared with US and European patients, might be, at least in part, related to lower use of IV iron products and, thus, less iron overload although these findings may also be related to less inflammation (partially) due to a very high quality of dialysis in Japan [3].

Major progress in the management of iron status in dialysis patients may soon come from investigational drugs that selectively inhibit hypoxia-inducible factor prolyl hydroxylases (HIF-PH) and stabilize hypoxia-inducible factor (HIF) [89]. HIF, a key regulatory protein which stimulates erythropoietin and transferrin production, reduces hepcidin production, and thereby modulates iron absorption and metabolism, although the direct or indirect influence (via erythropoietin) of HIF on hepcidin modulation is still an open question [89].

In addition to HIF stabilizers, iron administration via the dialysate ferric pyrophosphate citrate (Triferic®) and a ferric citrate-based phosphate binder (Auryxia®) are new therapeutic options for compensating iron deficiency related to blood loss in hemodialysis patients and for providing the iron required for erythropoiesis [90–93]. Ferric pyrophosphate citrate (Triferic®) rapidly delivers iron directly and safely to the bone marrow (5–7 mg iron) during hemodialysis sessions via the dialysate, efficiently matching the amount of iron required by ESA to generate red blood cells, without increasing ferritin levels [90]. The new phosphate binder composed of ferric citrate (Auryxia®), besides its ability to chelate intestinal phosphate, reduces the need for IV iron in dialysis patients, thus theoretically lowering the risk of iatrogenic iron overload and re-establishing oral iron as an

efficient iron source; alternatively it may cause intestinal side effects precluding its ability to reduce IV iron dose [91–93]. Moreover, the *Precautions* section of the summary of product characteristics for ferric citrate (Auryxia®) states that iron citrate may be absorbed (probably) via disrupted intestinal tight junctions in uremic patients, meaning that physiological regulation of iron absorption may be overstepped, resulting in iron overload [94–97]. Careful monitoring of iron stores in dialysis patients on ferric citrate (Auryxia®) is therefore recommended by the FDA [94].

The nephrology community is awaiting the results of the academic prospective randomized trial PIVOTAL which began in the UK in 2013 (with lead investigator Professor Macdougall). This trial is comparing two iron therapy strategies based on iron sucrose: the first is in keeping with KDOQI 2006 and ERBP 2009 and is aimed at maintaining ferritin > 200 µg/L and TSAT > 20%, while the second is more liberal, with larger replenishment of iron stores (ferritin up to 700 µg/L and TSAT up to 40%). A total of 2080 incident patients with a dialysis vintage of less than 1 year will be followed for 4 years in 55 UK dialysis centers [98]. The primary endpoint will be the time to all-cause death or a composite of nonfatal cardiovascular events comprising myocardial infarction, stroke and hospitalisation for heart failure [98]. Of note, this trial will not examine the possible benefits of more physiological targets of iron replenishment advocated by ourselves and others [8,9,15,16] and applied successfully in Japan for the past decade [21]. This clearly will require a specific trial.

Finally, hepatitis C infected-dialysis patients represent a population prone to ferrotoxicity. About 2.5% of the world's population, corresponding to about 177 million individuals, are infected by the hepatitis C virus (HCV), a small, single-stranded RNA virus [99]. The prevalence of HCV infection among dialysis patients in Japan, Europe and North America during the 2012–2015 period was found to be 8.7% in the DOPPS study and the propagation of nosocomial HCV in hemodialysis facilities still occurs [99]. Increased hepatic tissue iron has been shown to exert deleterious effects in the course of hepatitis C, favouring development of fibrosis and cirrhosis and possibly increasing the risk of liver cancer in the general population [99]. A deleterious influence of the hereditary hemochromatosis gene (HFE) mutations has also been shown in HCV infection. Moreover, serum hepcidin level is suppressed and iron absorption is enhanced by HCV infection [99]. Data on the effects of IV iron in hemodialysis patients with hepatitis C are scarce (only 2 studies) but strongly suggest that parenteral iron may contribute to hepatocellular injury [99]. Given the known impact of iron in promoting growth and virulence of HCV and the associated liver disease, it is mandatory to use iron therapy cautiously and closely monitor plasma markers of iron metabolism and liver iron stores noninvasively by means of MRI to avoid iron overload in this vulnerable dialysis population [99].

Reconsidering iron biomarkers for practical management of patients, with the aim of avoiding iron overload

Recent MRI studies of LIC in hemodialysis patients have attempted to find a correlation between iron biomarkers and the liver iron concentration, and to define thresholds of risk of iron overload based on these biomarkers [11,53,100]. Ferritin correlated with LIC in both the Italian and French studies, but not in the Australian study because of its small size (only 15 patients) [11,53,100].

A recent French study analyzed correlations between iron biomarkers (ferritin, iron, transferrin, TSAT, erythrocyte mean corpuscular volume and hepcidin) and liver iron concentrations measured blindly by quantitative MRI, and examined their accuracy for the diagnosis of iron overload in a prospective cohort of 212 hemodialysis patients treated with parenteral iron-sucrose and ESA, in keeping with ERBP anemia statements [18,81]. The relationships were analysed using Spearman's coefficient, logistic regression, and ROC curves [100]. Serum ferritin showed the strongest correlation with LIC (rho = 0.52). Weaker but significant correlations were also found between LIC and serum iron (rho = 0.22), serum transferrin (rho = −0.34), TSAT (rho = 0.36) and hepcidin-25 (rho = 0.42).

Likewise, in logistic analysis, only serum ferritin correctly classified the patients into those with normal liver iron stores (LIC ≤ 50 µmol/g) and those with elevated liver iron stores (LIC > 50 µmol/g) (odds ratio 1.007; 95% CI: 1.004–1.010) [100].

Serum ferritin was the most discriminatory iron biomarker in ROC curve analysis (AUC = 0.767; 95% CI: 0.698–0.835) as compared to hepcidin (AUC = 0.710; 95% CI: 0.631–0.789), transferrin (AUC = 0.703; 95% CI: 0.623–0.783) and TSAT (AUC = 0.634; 95% CI: 0.552–0.715). The optimal serum ferritin cut offs were 160 µg/L for LIC > 50 µmol/g (mild and moderate overload; diagnosis accuracy 69.30%; specificity 76.9%; sensitivity 66.9%) and 290 µg/L for LIC > 200 µmol/g (severe overload; diagnosis accuracy 75.9%; specificity 77%; sensitivity 72.3%) [100]. This latter ferritin cut off is close to that found in the Italian study performed by SQUID (340 µg/L); differences in the accuracy of LIC measurement between SQUID and MRI and on the size of the populations studied may explain these discrepancies [11,100]. Indeed, for the former point, the expert panel of the Italian Society of Hematology concluded that the consistency of the results from studies measuring the accuracy of LIC in thalassemia by SQUID was poor and underestimation of LIC was a critical factor [101].

These ferritin thresholds for the risk of iron overload are clearly lower in MRI and SQUID studies than in bone marrow smear studies (analysed in detail in clinical guidelines). This warrant studies to analyse further the reasons for these discrepancies between liver and bone marrow iron analyses and their

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potential consequences for the management of iron therapy in dialysis patients [3,8,9,100].

Conclusions

Iron overload was previously considered rare in hemodialysis patients but is now an increasingly recognized clinical situation. Recent studies based on quantitative MRI strongly suggest a link between the IV iron dose and the risk of iron overload, and challenge both current iron biomarker cutoffs and clinical guidelines, especially with respect to recommended iron doses. In addition, some recent long-term observational studies have suggested that excessive IV iron might increase mortality and cardiovascular events in hemodialysis patients. This recently rediscovered adverse effect of intravenous iron products has led to profound and ongoing changes in the concept of and clinical approach to IV iron therapy in dialysis patients.

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