

# Le Bulletin de la Dialyse à Domicile

## Hepatic iron load differs strikingly between peritoneal dialysis and hemodialysis patients

Le contenu hépatique en fer diffère de façon significative entre les patients en dialyse péritonéale et les patients en hémodialyse

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### Résumé

#### Introduction

La surcharge martiale est l'un des sujets les plus controversés dans la prise en charge de l'anémie des patients dialysés. La supplémentation parentérale (IV) en fer est couramment prescrite aux patients en hémodialyse (HD), mais moins fréquemment aux patients traités par dialyse péritonéale (DP). De plus les cibles de ferritine sérique sont beaucoup plus faibles et physiologiques en DP qu'en HD.

#### Méthodes

Nous avons comparé la concentration hépatique en fer (CHF), mesurée par imagerie par résonance magnétique (IRM), à l'aide de la méthode du rapport signal-intensité (SIR) selon l'Université de Rennes, dans une cohorte de 32 patients en DP résidant en région parisienne (publiée en 2017), avec deux cohortes de patients hémodialysés français, étudiés de la même manière (119 patients publiés en 2012 et 80 patients supplémentaires publiés en 2014).

#### Résultats

Une charge hépatique normale en fer ( $CHF \leq 50 \mu\text{mol/g}$  de poids sec) a été observée chez 81,3% des 32 patients de DP (IC: 64,3-91,5%), comparativement à seulement 16% (IC: 10,4-23,7%) dans la première cohorte HD et 35% (IC: 25,4-45,9%) dans la deuxième cohorte HD ( $p < 0,0001$  dans les deux cas ; test  $X^2$ ). Une surcharge légère en fer ( $50 < CHF \leq 100 \mu\text{mol/g}$ ) a été observée chez 5 patients de DP et une surcharge importante ( $CHF > 200 \mu\text{mol/g}$ ) chez un seul patient de DP (qui avait reçu du fer intraveineux (IV)) (3,1% ; IC: 0-17,1%). Inversement, une surcharge en fer importante a été observée chez 30,3% des patients de la première cohorte HD (IC: 22,7-39%) et 11,3% de ceux de la deuxième cohorte HD (IC: 5,8-20,2%) ( $p = 0,0033$  par rapport à la première cohorte ; test  $X^2$ ).

#### Conclusion

Contrairement à l'hémodialyse, la surcharge en fer est rare et généralement légère chez les patients en dialyse péritonéale.

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Mots clés : Concentration hépatique en fer; dialyse péritonéale; hémodialyse; IRM hépatique; surcharge martiale.

### Summary

#### Introduction

Iron overload is one of the most controversial topics in the management of anemic dialysis patients. Parenteral iron supplementation is commonly prescribed to hemodialysis (HD) patients but less frequently to peritoneal dialysis (PD) patients. Moreover, ferritin targets are far lower and more physiological in PD than in HD.

#### Methods

We compared the liver iron concentration (LIC) measured by means of Signal-Intensity ratio (SIR) magnetic resonance imaging (MRI) according to Rennes University method in a cohort of 32 PD patients living in the Paris region published in 2017, with two cohorts of French HD patients studied in the same way (119 patients reported in 2012 and 80 further patients reported in 2014).

#### Results

Normal hepatic iron load ( $LIC \leq 50 \mu\text{mol/g}$  of dry weight) was observed in 81.3% of the 32 PD patients (CI: 64.3-91.5%), as compared to only 16% (CI: 10.4-23.7%) in the first HD cohort and 35% (CI: 25.4-45.9%) in the second HD cohort ( $p < 0.0001$  for both comparisons;  $X^2$  test). Mild iron overload ( $50 < LIC \leq 100 \mu\text{mol/g}$ ) was found in 5 PD patients and severe overload ( $LIC > 200 \mu\text{mol/g}$ ) in only one PD patient (who had received IV iron) (3.1%; CI: 0-17.1%). Conversely, severe iron overload was found in 30.3% of patients in the first HD cohort (CI: 22.7-39%) and 11.3% of those in the second HD cohort (CI: 5.8-20.2%) ( $p = 0.0033$  versus the first HD cohort,  $X^2$  test).

#### Conclusion

Contrary to hemodialysis patients, iron overload is rare and mostly mild in peritoneal dialysis patients.

Key words : Hemodialysis; hepatic MRI; iron overload; liver iron concentration; peritoneal dialysis.

## INTRODUCTION

The discovery of epoetin in the eighties has represented for end-stage kidney disease (ESKD) patients and nephrologists a therapeutic revolution, enabling anemia to be partially corrected in most patients, thereby markedly improving their quality of life, reducing the need for blood transfusion and finally the risk of HLA (Human Leucocyte Antigen) sensitization [1]. Parenteral iron is required to ensure erythropoiesis-stimulating agents (ESA) full therapeutic efficacy since iron deficiency is common in hemodialysis patients, due to massive transfer of stored iron to erythroid progenitor cells during ESA therapy, together with inadequate iron mobilization from storage sites (due to high hepcidin levels observed in ESKD), and important blood losses due to the hemodialysis (HD) technique, aggravated by iterative routine blood sampling for follow-up of uremic state, and also to occult fecal bleeding related to uremic enteropathy [2-5]. This latter blood loss is increased by the mandatory use of anticoagulation (unfractionated or low-molecular-weight heparin) to avoid clotting in the extracorporeal circuit during HD sessions [5, 6].

The use of intravenous (IV) iron therapy in HD patients has increased massively worldwide over the last fifteen years, because of its convenience and superiority over oral preparations for treating true iron deficiency, and its ability to overcome functional iron deficiency, often encountered in ESKD [1-6]. Moreover, IV iron products enable cost savings of about 20-30% on expensive ESAs [5-6]. The Kidney Disease Outcomes Quality Initiative (KDOQI)'s guideline in the USA, issued in 2006 and endorsed by the European Renal Best Practice (ERBP) statement of the European Renal Association (ERA-EDTA) in 2009 tightened the definition of iron deficiency in ESKD (ferritin < 100  $\mu\text{g/L}$  instead of 20  $\mu\text{g/L}$ ) and adopted higher iron-store repletion criteria for hemodialysis patients (250 < ferritin target < 500  $\mu\text{g/L}$ ) [2, 3]. The KDIGO (Kidney Disease Improving Global Outcomes) 2012 guideline set the upper ferritin limit at 500  $\mu\text{g/L}$  for hemodialysis patients, underlining the risk of functional iron deficiency during ESA treatment, as well as the ability of IV iron to avoid the use (and adverse effects) of ESAs [4]. These clinical guidelines, which are largely followed by nephrologists worldwide, have clearly contributed to the increased use of parenteral iron in hemodialysis patients over the last decade [5, 6].

Liver is the main site of iron storage in human health and disease, and liver iron concentration (LIC) has been shown to correlate closely with total body iron stores in patients with iron-overload disorders [7, 8]. Magne-

tic resonance imaging (MRI) has become in the recent years the gold-standard method for non-invasive liver iron load estimation and therefore for diagnosing iron overload and finally for monitoring non-renal patients with iron-overload disorders especially under phlebotomy or iron-chelating agents [7, 8].

Recent radiological studies in hemodialysis patients have shown a high frequency of iron overload and also demonstrated a strong link between the infused iron dose and the risk of iron overload in this setting, thus challenging current guidelines with respect to the safety of IV iron at high repeated doses, as well as the reliability of iron biomarker cutoffs and methods for monitoring iron stores in dialysis patients [9-12]. These findings led to calls for a revision of iron therapy guidelines in ESKD patients [10, 12-15]. Iron overload which was thought, few years ago, to be very rare in hemodialysis patients in the actual ESAs era, is now increasingly recognized and considered to be one of the most controversial topics in anemia management of ESKD patients [9-14]. Hemodialysis-associated hemosiderosis was recently shown in a pool-analysis to be encountered in up to 66% of 500 patients studied by non-invasive radiological methods (Magnetic Susceptometry study, n=1; MRI studies; n=10) [16].

Compared to hemodialysis patients, peritoneal dialysis patients have less blood losses [5, 13]; moreover, ferritin targets advocated by current guidelines are far lower and more physiological in PD than in HD [2-4, 17]. Finally, while almost all hemodialysis patients receive intravenous iron, only few peritoneal dialysis patients are treated by parenteral iron, generally as second line.

We hypothesized as rationale of this study, that a comparison of liver iron content by MRI between peritoneal dialysis and hemodialysis patients would give an unique insight on the influence of ESKD status itself on liver iron metabolism and iron overload.

## MATERIAL AND METHODS

### *Patients and dialysis*

With the patients' written informed consent and approval from the Drug, Devices and Clinical Trials Committee of Claude Galien hospital (COMEDIMS Claude Galien, 9 December 2004 and 15 February 2013 [12]), we enrolled between 17 June 2014 and 17 November 2015, 32 adult patients treated at least for 2 months with peritoneal dialysis (in one of the four following nephrology divisions in the Paris region: Groupe Hospitalier

Pitié-Salpêtrière, Paris; Centre Hospitalier Universitaire Bicêtre, Kremlin-Bicêtre; Centre Hospitalier Marc Jacquet, Melun ; Hôpital Privé Claude Galien, Quincy-sous-Sénart) and analyzed their liver iron content by means of quantitative MRI without gadolinium. Patients characteristics have been previously described in depth [18]. The inclusion and exclusion criteria of this study have also been previously published and described in depth [12, 18].

Anemia treatment of the PD patients followed ERBP guideline and comprised, if required, ESA and iron [18]. The ferritin target was set at 100  $\mu\text{g/L}$ . As the first step of iron therapy, patients were advised to eat red meat. Oral iron therapy was only prescribed if dietary measures failed or if the iron deficiency was severe. IV iron was only used if oral iron was ineffective or poorly tolerated [18].

This PD cohort was compared to two historical cohorts of hemodialysis (HD) patients studied at Claude Galien hospital [12, 19]. The first HD cohort comprised 119 fit hemodialysis patients free of overt inflammation or malnutrition and undergoing chronic intermittent bipuncture bicarbonate hemodialysis three times a week (at the Claude Galien dialysis unit) with ultrapure dialysate and single-use biocompatible membranes. They were enrolled in a 60-month prospective cross-sectional study from 31 January 2005 to 31 January 2010 [12]. These 119 patients were the subjects of a 2012 publication highlighting the risk of iron overload in hemodialysis patients [12]. The second cohort comprised a further 80 fit hemodialysis patients studied in the same way and recruited from 1 February 2010 to 31 August 2013 at Claude Galien hospital [19]. These 80 patients, together with the 119 patients of the first HD cohort, were the subject of two publications in 2014 and 2015, focusing on the monthly potential toxic dose of IV iron in HD patients and on the predictive value of iron biomarkers for diagnosing iron overload in this setting [19, 20]. Of note, the results of our first HD cohort study led us to call for a revision of guidelines in this area and to anticipate the new European guideline which sets the upper ferritin target at 300  $\mu\text{g/L}$  and the TSAT at 30%, with the same hemoglobin target of 10-12 g/dL [12, 17, 19]. This study is registered under International Standard Randomized Controlled Trial Number (ISRCTN) 80100088 [12, 18-20]. This study is also declared to the French Institute of Health Data (INSD: Institut National des Données de Santé) as an observational study (category MR-4 of Jardé law), and its database is declared to the devoted French commission (CNIL) under the successive numbers 1875675 (until year 2018) and 2214279

(since year 2019).

### *Quantitative magnetic resonance imaging of hepatic iron stores*

We used a signal-intensity ratio method for quantitative magnetic MRI based on T1 and T2\* contrast imaging without gadolinium, as established by Gandon and coworkers at Rennes University in 2004 [21]. Wherever possible, patients received their last iron dose (IV or oral) at least one week before MRI. MRI measurements were done centrally at the Division of Radiology of Claude Galien hospital by the same senior radiologist (YC), who was unaware of the patients' medical history (with the exception of the dialysis technique) and biochemical results. As the upper 95th percentile of LIC in healthy adults is 32  $\mu\text{mol/g}$  of dry liver, but as hepatic MRI accurately detects liver iron overload exceeding 50  $\mu\text{mol/g}$  of dry liver, the upper limit of normal iron load was set at 50  $\mu\text{mol/g}$  for these studies of dialysis patients [12,18-20]. Mild iron overload is considered by  $50 < \text{LIC} \leq 100 \mu\text{mol/g}$  of dry liver, values  $100 < \text{LIC} \leq 200 \mu\text{mol/g}$  is moderate iron overload and LIC values  $> 200 \mu\text{mol/g}$  severe iron overload [21]. These LIC cut-offs are based on previous and current liver biopsy data and correspond to an increasing risk of complications in iron-overload disorders such as genetic hemochromatosis and secondary hemosiderosis [7, 8]. Of note, the MRI method was done similarly for these three cohorts on the same apparatus, an Optima™ MR450w MRI machine (GE Medical Systems, Milwaukee, Wisconsin, USA) operating at a field strength of 1.5 Tesla, by the same radiologist (YC) helped by the same technician team, using for LIC calculation the same free analytical software available on the Rennes University website.

### *Biological markers of iron metabolism*

Anemia treatment efficacy was estimated by hemoglobin assay and reticulocyte counts every month, as well as monthly or quarterly measurements (depending on local policy) of iron biomarkers (ferritin, transferrin, serum iron and transferrin saturation (TSAT), soluble transferrin receptors (sTfR)) and C-reactive protein. All the blood samples used to measure biological markers of iron metabolism in hemodialysis patients were obtained at the outset of the midweek dialysis session and wherever possible, patients received their last iron dose at least one week before blood sampling [12, 19, 20]. For PD patients, the blood samples for measurement of biological markers of iron metabolism were obtained at least seven days after the last iron infusion (in the few patients treated with IV iron) or one week after the inges-

tion of the last iron pill [18]. Statistical analyses used the mean of three values for each iron biomarker, obtained the same month as hepatic MRI and one month before and one month after MRI for hemodialysis patients and, if available, for PD patients [12, 18-20].

#### *Search for HFE gene mutation*

To exclude a pathophysiological role of hemochromatosis genes, the PD patients as the HD patients with abnormal iron load on MRI were screened for the major C282Y HFE gene mutation and minor gene mutations H63D and S65C after obtaining specific written informed consent for genetic analysis, in keeping with French law. Testing was performed by BIOMNIS (Lyon, France) and CERBA (Saint-Ouen-l'Aumône, France), based on allelic discrimination, using real-time Polymerase Chain Reaction (PCR)(Chimie TaqMan® ABI PRISM 7000, Roche, France) and a standardized kit [12, 18, 19].

#### *Statistical analyses*

As values did not conform to a Gaussian distribution (at Shapiro-Wilk normality test), all data are expressed as medians and ranges; percentages are given with their 95% confidence intervals calculated with the modified Wald method [22].

The different groups of patients (PD patients, first HD cohort, second HD cohort) were compared by using non-parametric analysis of variance (Kruskal-Wallis test) for continuous variables, followed by post-tests using the non-parametric Dunn test and the chi-square test for categorical variables [22].

Prism 7 software (Graphpad, San Diego, USA) was used for all tests, and p values < 0.05 were considered to denote statistical significance [22].

## **RESULTS**

#### *Characteristics of the patients*

The PD study cohort consisted of 32 french adults treated in the Paris region; details results for this PD cohort and for the two hemodialysis cohorts have been previously published elsewhere [12, 18, 19].

There were striking differences in anemia therapy between the peritoneal dialysis and hemodialysis patients: 71.9% of the PD patients received ESA, versus 99.2% of the first HD cohort and 95% of the second HD cohort (p < 0.0001 for PD cohort and cohort n°1 and p = 0.0018 for PD cohort and cohort n°2; X<sup>2</sup> test) (Table I). Likewise, only 12.5% of the PD patients received IV iron, versus 95% of the first HD cohort and 85% of the second HD cohort (p < 0.0001 versus each HD cohort;

X<sup>2</sup> test) (Table I). The oral route was the preferred method of iron administration for PD patients (25%; CI: 13-42.3%), but was used in none of the HD patients in either cohort (Table I). Despite these differences in the use of ESA and IV iron, hemoglobin levels were similar in the PD patients and the HD patients of both cohorts (Table II).

#### *Hepatic iron load by MRI differs strikingly between peritoneal dialysis and hemodialysis patients*

The LIC differed between the 3 cohorts (p < 0.0001 at kruskal-Wallis test) (Table I) (Figures 1 and 2). Hepatic iron load by MRI was normal ( $\leq 50 \mu\text{mol/g}$ ) in 81.3% of the 32 PD patients (CI: 64.3-91.5%), as compared to only 16% (CI: 10.4-23.7%) of the first HD cohort and 35% (CI: 25.4-45.9%) of the second HD cohort (p < 0.0001 versus each HD cohort; X<sup>2</sup> test).

Iron overload by MRI was mild ( $50 < \text{LIC} \leq 100 \mu\text{mol/g}$ ) in 5 of the 6 PD patients with hemosiderosis (Figures 1 and 2). The sole remaining PD patient (3.1%; CI: 0-17.1%) had severe iron overload on MRI ( $> 200 \mu\text{mol/g}$ ) (Figures 1 and 2). By comparison, MRI showed severe iron overload ( $> 200 \mu\text{mol/g}$ ) in 30.3% of patients in the first HD cohort (CI: 22.7-39%) and 11.3% of those in the second HD cohort (CI: 5.8-20.2%) (p = 0.0033 versus the first HD cohort; X<sup>2</sup> test) (Figure 2). None of the PD patients had moderate iron overload ( $100 < \text{LIC} \leq 200 \mu\text{mol/g}$ ). Interestingly, the only PD patient with severe iron overload had received IV iron (Figure 3).

Iron overload by MRI was not associated with the C282Y, H63D and S65C HFE gene mutations (either homozygous or heterozygous), either in the PD patients, or in the hemodialysis patients. None of the six PD patients with liver iron overload had any mutation of the HFE gene, whereas the frequency of any mutation was found low and identical in HD patients with iron overload as compared to those with normal LIC [12, 18, 23].

Of note, the lower ferritin and TSAT targets applied to the second HD cohort relative to the first HD cohort had a substantial impact on the risk of iron overload by MRI: the proportion of patients with liver iron overload ( $\text{LIC} > 50 \mu\text{mol/g}$ ) fell from 84% in the first HD cohort to 65% in the second HD cohort (p < 0.005, X<sup>2</sup> test) [12, 19]. Severe iron overload with potential clinical consequences ( $\text{LIC} > 200 \mu\text{mol/g}$ ) also fell markedly, from 30.3% to 11.3% (p < 0.005, X<sup>2</sup> test [12, 19]).

Table I: Characteristics and findings in 2 cohorts of hemodialysis patients and a cohort of 32 peritoneal dialysis patients

Variables	Original Cohort (HD cohort n°1) n= 119	Second Cohort (HD cohort n°2) n= 80	PD patients (PD cohort n°3) n= 32	p value at Kruskal-Wallis test with Dunn's post-test or at Chi2 test (comparison of cohorts 1, 2 and 3)
Age (years)	60 [19 - 87]	70.5 [23 - 91]	64.5 [34 - 92]	p = 0.0020; 1/3: p = 0.6201; 2/3: p = 0.6602; 1/2: p = 0.0013
Female sex, Percentage of patients (%)	38.7 [30.4 - 47.6]	38.8 [28.8 - 49.7]	46.9 [30.9 - 63.6]	1/3: p = 0.5233 at X <sup>2</sup> test; 2/3: p = 0.5639; 1/2: p = 0.8926
Dialysis vintage (months)	16 [2 - 95]	8.5 [2 - 66]	12.5 [2 - 52]	p = 0.0015; 1/3: p = 0.3435; 2/3: p > 0.9999; 1/2: p = 0.0011
ESA therapy, Percentage of patients (%)	99.2 [94.9 - 100]	95 [87.5 - 98.4]	71.9 [54.5 - 84.6]	1/3: p < 0.0001 at X <sup>2</sup> test; 2/3: p = 0.0018; 1/2: p = 0.1687
ESA dose (µg/month)	130 [0 - 566]	157.8 [0 - 775]	59.1 [0 - 150]	p < 0.0001; 1/3: p < 0.0001; 2/3: p < 0.0001; 1/2: p = 0.0362
Iron therapy (IV or oral), Percentage of patients (%)	95 [89.2 - 97.9]	85 [75.4 - 91.4]	37.5 [22.9 - 54.8]	1/3: p < 0.0001 at X <sup>2</sup> test; 2/3: p < 0.0001; 1/2: p = 0.0316
IV iron therapy, Percentage of patients (%)	95 [89.2 - 97.9]	85 [75.4 - 91.4]	12.5 [4.4 - 28.7]	1/3: p < 0.0001 at X <sup>2</sup> test; 2/3: p < 0.0001; 1/2: p = 0.0316
Oral iron, Percentage of patients (%)	0	0	25 [13 - 42.3]	1/3: p < 0.0001 at X <sup>2</sup> test; 2/3: p < 0.0001
Charlson's comorbidity index	6 [2 - 16]	7 [2 - 16]	5 [2 - 15]	p = 0.0186; 1/3: p > 0.9999; 2/3: p = 0.0652; 1/2: p = 0.0435
Diabetes, Percentage of patients (%)	22.7 [16 - 31.1]	38.8 [28.8 - 49.7]	34.4 [20.3 - 51.8]	1/3: p = 0.2615 at X <sup>2</sup> test; 2/3: p = 0.8290; 1/2: p = 0.0223
LIC at MRI (µmol/g)	100 [5 - 340]	65 [5 - 320]	20 [5 - 230]	p < 0.0001; 1/3: p < 0.0001; 2/3: p < 0.0001; 1/2: p = 0.0005

ESA: erythropoiesis-stimulating agents; IV: intravenous; MRI: Magnetic Resonance Imaging; LIC: Liver Iron Content;  
 Values are given as median and [range]

Table II: Biochemical markers of iron metabolism in two cohorts of hemodialysis patients and a cohort of 32 patients treated by peritoneal dialysis

Variables	Original Cohort (HD cohort n°1) n= 119	Second Cohort (HD cohort n°2) n= 80	PD patients (PD cohort n°3) n= 32	p value at Kruskal-Wallis test with Dunn's post-test
Hemoglobin (g/dL)	12 [8.4 - 15.1]	11.1 [8.4 - 14.7]	11.5 [8.7 - 16.2]	p = 0.0113; 1/3: p > 0.9999, 2/3: p = 0.2496, 1/2: p = 0.0099
Serum ferritin (µg/L)	265.5 [15 - 1383]	145.3 [12 - 2229]	144 [11 - 885]	p = 0.0008; 1/3: p = 0.0225, 2/3: p > 0.9999, 1/2: p = 0.0024
Serum iron (µmol/L)	9.7 [3.6 - 26.3]	10.6 [4.2 - 26.3]	13.2 [5.5 - 24.3]	p = 0.0172; 1/3: p = 0.0141, 2/3: p = 0.1094, 1/2: p = 0.8732
Serum transferrin (g/L)	1.7 [1.1 - 2.8]	2 [1.2 - 4.5]	2.3 [1.5 - 3.6]	p < 0.0001; 1/3: p < 0.0001, 2/3: p = 0.1266, 1/2: p < 0.0001
Transferrin saturation (TSAT)(%)	23.1 [6.3 - 72.2]	21.6 [6.5 - 61.2]	23.2 [1.1 - 50]	p = 0.3558; 1/3: p > 0.9999, 2/3: p > 0.9999, 1/2: p = 0.4743
Serum transferrin soluble receptors (sTfR)(mg/L)	4.3 [1.4 - 13]	5.4 [0.5 - 12.8]	3.3 [2.3 - 7.9]	p = 0.0019; 1/3: p = 0.3983, 2/3: p = 0.0236, 1/2: p = 0.0122
C-reactive protein (mg/L)	4.3 [0.3 - 75.9]	3.9 [1 - 107.3]	6.7 [1.3 - 67.6]	p = 0.1551; 1/3: p = 0.2610, 2/3: p = 0.1739, 1/2: p > 0.9999

Values are given as median and [range]



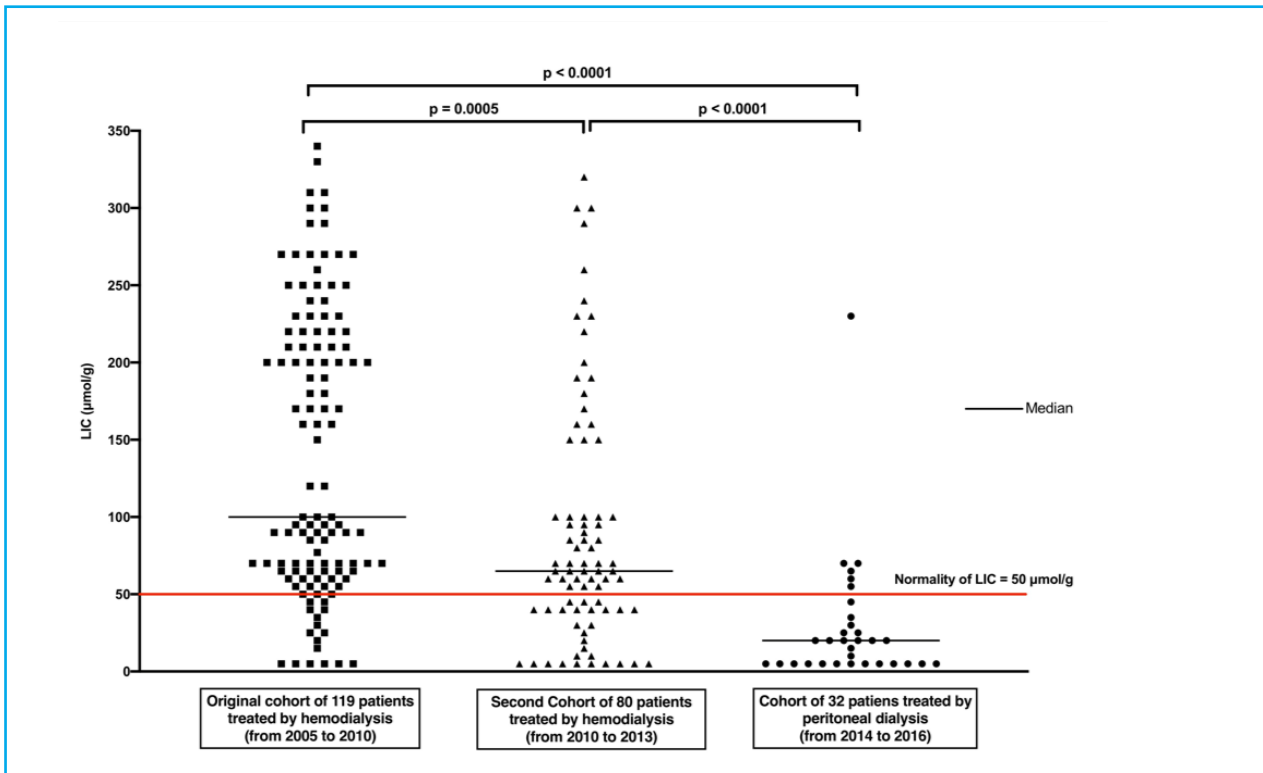


Figure 1: Liver iron concentration measured by MRI in three dialysis cohorts

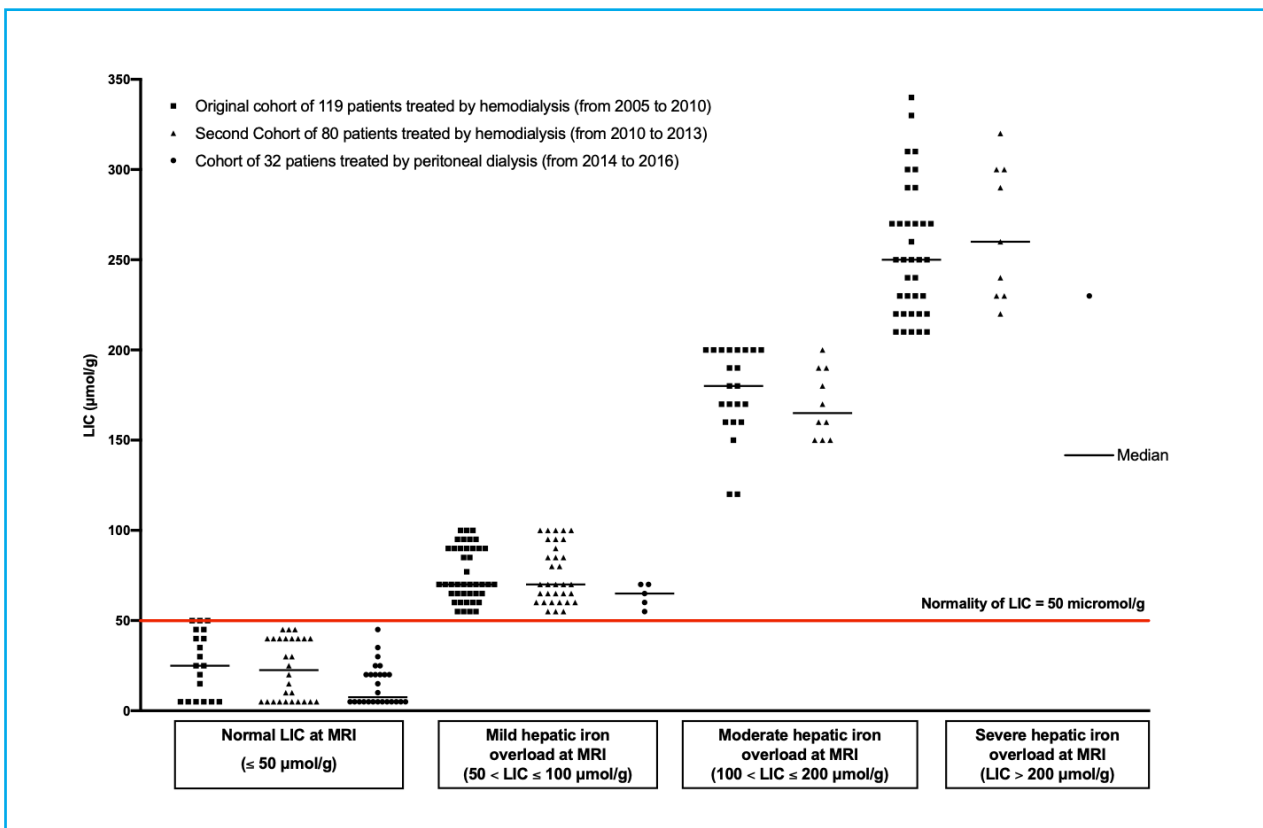


Figure 2: Distribution of liver iron concentration at MRI in three dialysis cohorts

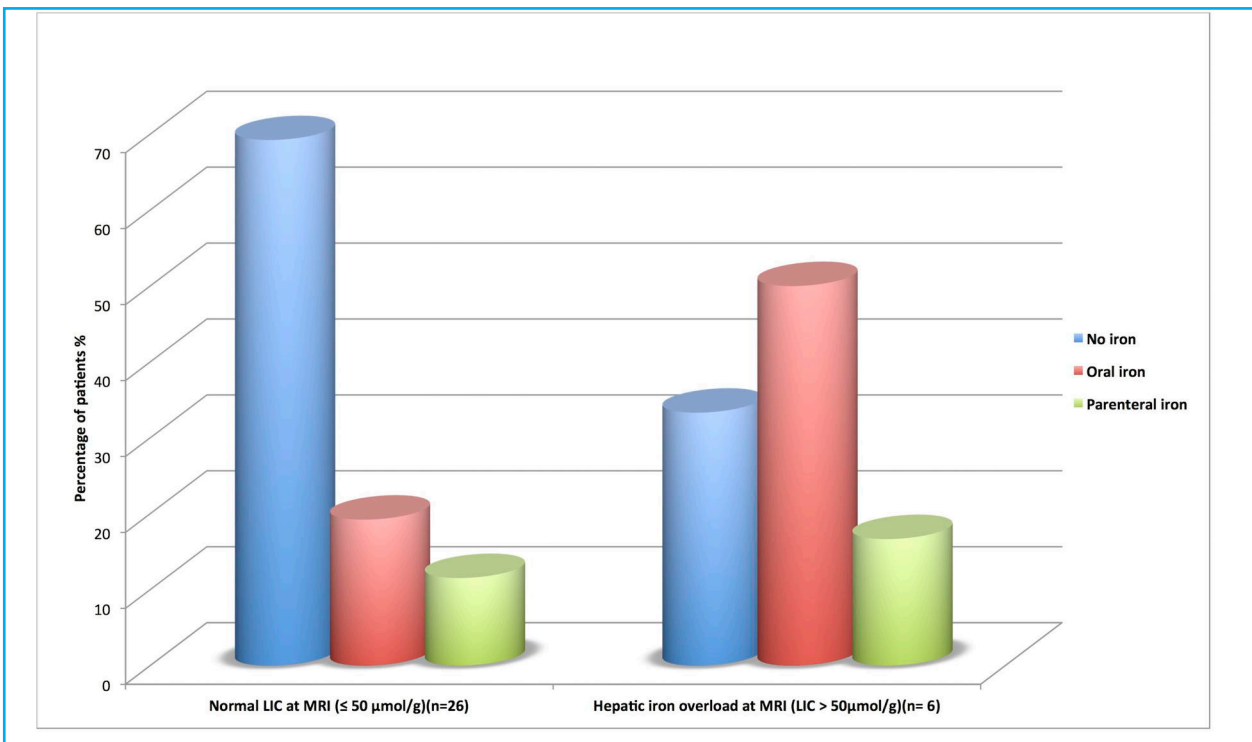


Figure 3: Histogram of distribution of liver iron concentration at MRI in 32 patients treated by peritoneal dialysis according to the modality of iron therapy

### *Differences in biological markers of iron metabolism between PD and HD patients*

As suspected, the patients in the second HD cohort had lower ferritin levels, similar to those of the PD patients (Table II). The most striking differences in biological iron markers between PD and HD patients of the first cohort involved serum iron ( $p = 0.0141$ ) and transferrin ( $p < 0.0001$ ), despite similar levels of C-reactive protein (Table II).

## DISCUSSION

We measured liver iron concentration non-invasively, by means of a validated MRI method (Signal Intensity Ratio with Rennes algorithm) [8, 21], in a cohort of 32 French PD patients, by comparison with two cohorts of French HD patients (published in 2012 and 2014). These patients were studied with the same centralized radiological method and by the same radiology team [12, 18, 19].

We observed striking differences in liver iron load between the PD and HD patients. Hepatic iron load was normal in most PD patients (81.3%) but in few HD patients (16% in the first HD cohort and 35% in the second HD cohort, which had a lower ferritin target) [12, 18, 19]. Furthermore, iron overload by MRI was mild in 5

of the 6 PD patients with hemosiderosis; only one PD patient (3.1%) had severe iron overload, compared to 30.3% of patients in the first HD cohort and 11.3% of those in the second HD cohort. None of the PD patients had moderate hepatic iron overload [12, 18, 19].

MRI has made a major contribution to knowledge of iron overload disorders and to the care of non-renal patients in this setting, especially by allowing “serial radiological biopsy” [7, 8, 24]. Quantitative MRI has also recently provided new insights into iron metabolism in hemodialysis patients, and the risk of iron overload [10-13, 16]. Liver iron determination based on signal-intensity-ratio MRI and the Rennes University algorithm was recently shown to accurately identify iron load in hemodialysis patients by comparison with liver histology, as in non-renal patients [25].

Of note, MRI has been advocated by some authors for follow-up of iron stores of dialysis patients in countries where it is fully reimbursed for diagnosis and follow-up of iron-overload disorders by the national health system such as France and many other European countries; it cost varies around 300 to 350 euros which represents about the cost of one and half dialysis session in a centre [5, 12, 13]. The case of US is more complex since the price of an MRI exam with radiologist fees is about 3000-3500 US dollars and usually not reimbursed by

Medicare or Medicaid [16].

This study comparing LIC in PD and HD patients gives additional information on the respective role of ESKD and iron therapy in the pathophysiology of dialysis-associated hemosiderosis: the rarity of increased liver iron content observed here in PD where IV iron is used in second (or third line) of therapy and where ferritin target is physiological as compared to HD, strongly reinforce the hypothetical role of indiscriminate use of IV iron in this setting and the lack of influence of ESKD “per se” in this clinical complication. Indeed, previous binary logistic regression analyses in these two HD cohorts have shown that the main factor associated with LIC was the monthly infused iron dose (together with age, gender and hepcidin) which also represented about 33% to 37% of the variance of LIC at the Spearman correlation test (mathematically related to Pearson correlation test) [12, 19, 22]. Interestingly, in a combined statistical analysis of these two cohorts of fit HD patients devoted to iron biomarkers, ferritin was also shown to correlate to LIC (Rho = 0.52 at the Spearman correlation test) and had the best discriminatory capacity in ROC curves analysis to predict iron overload (AUC = 0.77) [20].

Moreover, in our original publication of the first HD cohort published in 2012, we could demonstrate the culprit role of IV iron in a longitudinal follow-up of 44 hemodialysis patients: 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 liver iron concentration by MRI (respectively rho = 0.66; p = 0.0306 and rho = 0.85; p = 0.0015; Spearman test). In the 33 patients with iron overload, iron stores fell significantly after iron withdrawal or after a major reduction in the iron dose (Median LIC at first MRI: 220  $\mu\text{mol/g}$  (CI: 60-340); Median LIC at last MRI: 50  $\mu\text{mol/g}$  (CI: 5-210); p < 0.0001, Wilcoxon’s paired test) [12]. Finally, the role of the high ferritin target in the onset of severe iron overload may also be strongly suspected in view of the reduction of occurrence of such cases in the second HD cohort where lower ferritin and TSAT targets were voluntarily applied [19].

Iron metabolism differs markedly between peritoneal dialysis and hemodialysis; in particular, PD is associated with fewer sources of iron deficiency, including blood losses directly related to the hemodialysis technique and occult gastrointestinal tract bleeding aggravated by anticoagulation of the hemodialysis circuits [5, 13]. This lower need for iron store replenishment explains the more conservative strategy advocated for PD patients in current guidelines, with a ferritin target of > 100  $\mu\text{g/L}$  and the use of oral iron for first-line therapy [2-4, 17].

Moreover, IV iron is not recommended by the KDIGO guideline and the ERBP position statement as an ESA-sparing agent for PD patients, contrary to HD patients, but is reserved for PD patients who do not tolerate or respond poorly to oral iron, and for PD patients with high iron requirements [4, 17]. This explains why only a small fraction of PD patients in France and many other countries receive IV iron despite its efficacy [26, 27, 28]. The rationale of this study was that a comparison of liver iron content by MRI between peritoneal dialysis and hemodialysis patients would reflect the reciprocal influence of uremic status itself and parenteral iron therapy on liver iron metabolism. The normal liver iron content observed here in most of our PD patients as compared to far fewer HD patients strongly supports and reinforces the role of excessive IV iron infusion and high ferritin targets in iatrogenic iron overload recently observed in a large proportion of hemodialysis patients (up to 66%) [9-14, 16].

The normal serum transferrin levels observed here in PD patients, versus the low levels seen in HD patients, despite similar levels of C-reactive protein, calls for further studies of the possible negative relationship between infused IV iron, excess iron stores and transferrinemia in ESKD patients, as suggested several years ago by Descombes and Fellay, who linked hypotransferrinemia to increased ferritin levels beside the classical role of inflammation and uremia per se on transferrin [29-31]. Finally, the few cases of mild iron overload in PD patients treated by oral iron suggest the possibility in ESKD of iron overload related to excessive ingestion of oral iron medication as encountered in healthy subjects [7], together with the ability of erythropoietin to increase iron intestinal absorption in ESKD patients as shown in a rat model of chronic renal failure [32]. This suggests the need of a cautious follow-up of LIC of ESKD patients treated by the new iron-derived phosphate binders some of which are absorbed [13].

## CONCLUSION

Contrary to HD patients, iron overload by MRI is rare and mostly mild in PD patients. The normal liver iron content observed here in most PD patients strongly reinforces the role of excessive IV iron infusion and high ferritin targets in the pathophysiology of iatrogenic iron overload recently observed in a large proportion of hemodialysis patients.

## DISCLOSURE

*The authors have no conflict of interest to declare.*



### Authors' contributions

*Guy Rostoker* contributed to the conception, design and supervision of the study; data acquisition, and planning and conduct of the study in the peritoneal dialysis unit of the Hôpital Privé Claude Galien, Division of Nephrology and Dialysis. He supervised the statistical analysis, data interpretation and reporting of the work, and write the article.

*Nasredine Ghali* contributed to the study design and data acquisition, and to the planning and conduct of the study in the peritoneal dialysis unit of the Centre Hospitalier Marc Jacquet, Division of Nephrology and Dialysis.

*Séverine Beaudreuil* contributed to data acquisition and to the planning and conduct of the study in the peritoneal dialysis unit of the Bicêtre Hospital, Division of Nephrology, Dialysis and Transplantation.

*Mireille Griuncelli* contributed to data acquisition, analysis and interpretation, and to the statistical analysis, and prepared the tables and figures.

*Yves Cohen* contributed to the acquisition and analysis of centralized MRI exams.

*Belkacem Issad* contributed to the conception, design and supervision of the study; data acquisition, and planning and conduct of the study in the peritoneal dialysis unit of the, Groupe Hospitalier Pitié-Salpêtrière, Division of Nephrology and Dialysis. He also participated in the writing of the article.

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