Hepatic Iron Load at Magnetic Resonance Imaging Is Normal in Most Patients Receiving Peritoneal Dialysis

To the Editor: Over the past 3 decades, the routine use of erythropoeisis-stimulating agents (ESA) has enabled the correction of anemia in most patients with end-stage renal disease (ESRD), reducing the need for blood transfusions and improving the quality of life of severely anemic patients.[1] Almost all ESA-treated hemodialysis patients receive parenteral iron to ensure sufficient available iron for ESA therapy.[1–4] Iron deficiency is common in hemodialysis patients due to inadequate iron mobilization from repleted storage sites (functional iron deficiency) and blood loss related to the hemodialysis procedure itself, to routine blood sampling for laboratory tests (especially for monitoring of uremia), and to occult fecal bleeding due to uremic enteropathy.[5,6]

Until recently, iron overload was considered to be very rare among hemodialysis patients, but it is now an increasingly recognized clinical problem.[7–11] The liver is the main site of iron storage, and the liver iron concentration (LIC) correlates closely with total iron stores in patients with genetic hemochromatosis and hemosiderosis secondary to hematological disorders.[12] Magnetic resonance imaging (MRI) is now the gold standard method for LIC estimation in nonrenal patients with iron-overload disorders.[12] A recent study of LIC in hemodialysis patients using quantitative MRI, and another study based on magnetic susceptometry a few years ago, demonstrated a strong link between infused iron dose and liver iron load in this setting.[7,9]

Compared to hemodialysis patients, patients undergoing peritoneal dialysis (PD) have fewer sources of blood loss,[5,6,11] and guidelines therefore advocate oral iron as first-line therapy. Furthermore, the ferritin targets recommended in current guidelines are far lower and more physiological in PD than in hemodialysis patients.[2–4,13] Thus, almost all hemodialysis patients, but few PD patients, receive parenteral iron. In contrast to the situation regarding hemodialysis patients, there are no published data on liver iron content in PD patients. Moreover, given the major difference in iron therapy between hemodialysis and PD patients, an analysis of this specific population of patients with ESRD may give useful information on the influence of ESRD itself on liver iron load. The aim of this study was therefore to determine LIC in PD patients by MRI.

METHODS

Patients and Dialysis

This observational study was carried out between 17 June 2014 and 17 November 2015. A total of 32 adult patients receiving PD were recruited, and their LICs were analysed by MRI. The patients had been treated for at least 2 months in a PD unit belonging to 1 of 4 nephrology divisions in the Paris region (Hôpital Pitié-Salpêtrière; CHU Bicêtre, Kremlin-Bicêtre; CH Marc Jacquet, Melun; and HP Claude Galien, Quincy-sous-Sénart). The inclusion and exclusion criteria have been described elsewhere.[7]

All participants gave their written informed consent after receiving a verbal explanation from their nephrologist of the reasons for the extra blood sampling, genetic testing in case of iron overload, and MRI scans. Ethical approval for the study was granted by the Drug, Devices and Clinical Trials Committee of Claude Galien hospital (COMEDIMS Claude Galien, 9 December 2004[7]; in France, COMEDIMS follows the use of drugs and devices in hospitals and has the role of an institutional review board).

The treatment of anemia in these patients was carried out according to usual practice and remained unchanged during the study; it followed European Renal Best Practice (ERBP) guidelines and comprised, if required, ESA, and iron.[13] In France, the first step in iron therapy is to advise patients to eat red meat. Oral iron therapy is prescribed only if dietary measures fail or if iron deficiency is substantial. We used i.v. iron only if oral iron was ineffective or poorly tolerated.

Quantitative MRI of Hepatic Iron Stores

A signal-intensity ratio method was used for MRI based on T1 and T2* contrast imaging without gadolinium, as established by Gandon *et al.* at Rennes University.[14] Patients on iron therapy (i.v. or oral) received their iron dose at least 1 week before MRI. The MRI measurements were performed centrally at the Division of Radiology of Claude Galien hospital by the same senior radiologist (Y.C.).

Biological Markers of Iron Metabolism

The efficacy of anemia treatment was determined using a 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). The blood samples for measurement of biological markers of iron metabolism were obtained at least 7 days after the last iron infusion (in patients treated with i.v. iron) or 1 week after the last iron tablet. The closest biological markers of iron metabolism to MRI were analyzed.

Search for C282Y HFE Gene Mutation

PD patients with abnormal iron load on MRI were screened for the C282Y HFE gene mutation (BIOMNIS, Lyon, France; and CERBA, Saint Ouen l'Aumone, France).[7]

Statistical Analyses

As values did not conform to a Gaussian distribution (Shapiro–Wilk normality test), according to Sheskin, all data are expressed as median and range.[15] Prism 6 software (GraphPad, San Diego, CA) was used for all statistical tests.

RESULTS

Study Population

The PD study cohort consisted of 32 French adult patients treated in the Paris region. Twelve other PD patients refused to participate in the study. Demographic, clinical, and biological characteristics of the patients are summarized in Tables 1 and 2. A total of 22 patients received automated PD, whereas the remaining 10 received continuous ambulatory peritoneal dialysis (CAPD) (nurse-assisted CAPD, n = 6; self-CAPD, n = 4). As we had no access to their medical records, before the initiation of dialysis, we were unable to analyze their exposure to therapeutic iron and blood transfusions before ESRD. The oral route was the preferred method of iron administration in these PD patients (8 of 32) (Table 1).

Table 1. Demographic and clinical characteristics of 32 patients treated by peritoneal dialysis and studied by MRI to determine liver iron content

Variable	Peritoneal dialysis patients (N = 32)
Age (yr)	64.5 (34–92)
Sex, female (%)	46.9
Duration of dialysis (mo)	12.5 (2–52)
ESA therapy (%)	71.9
Darbepoetin dose (μg/mo)	59.1 (0–150)
Iron therapy (i.v. or oral) (%)	37.5
Parenteral iron therapy (%)	12.5
Parenteral iron therapy (mg/PD mo)	0 (0–112.5)
Oral iron therapy (%)	25
Oral iron therapy ingested (mg/PD mo)	0 (0–2560)
Charlson Comorbidity Index	5 (2–15)
Diabetes (%)	34.4
Normal LIC at MRI (≤ 50 μmol/g), n	26
Abnormal LIC at MRI (> 50 μmol/g), n	6
Mild hepatic iron overload at MRI (51–100 μmol/g), n	5
Moderate hepatic iron overload (101–200 μmol/g), n	0
Severe hepatic iron overload (> 200 μmol/g), n	1

LIC, liver iron concentration; MRI, magnetic resonance imaging.
Values shown are median (range), percentage (%) of patients, or number (n) of patients.

Table 2. Biochemical markers of iron metabolism in 32 patients treated by peritoneal dialysis and studied by MRI to determine liver iron content

Variable	Patients treated by peritoneal dialysis (N = 32)
Hemoglobin (g/dl)	11.5 (8.7–16.2)
Serum ferritin (μg/l)	144 (11–885)
Serum iron (μmol/l)	13.2 (5.5–24.3)
Serum transferrin (g/l)	2.3 (1.5–3.6)
Transferrin saturation (TSAT) (%)	23.2 (1.1–50.0)
Serum transferrin soluble receptors (sTfR) (mg/l)	3.3 (2.3–7.9)
C-reactive protein (mg/l)	6.7 (1.3–67.6)

MRI, magnetic resonance imaging.
Values shown are median (range).

Hepatic Iron Load on MRI

The LIC on MRI was normal (≤50 μmol/g) in 26 of 32 patients (Table 1, Figure 1). Iron overload on MRI was mild (50 < LIC ≤ 100 μmol/g) in 5 of 6 PD patients with hemosiderosis (Table 3). Only 1 PD patient had severe iron overload on MRI (> 200 μmol/g) and had received i.v. iron (Table 3). None of the PD patients had moderate iron overload (100 < LIC ≤ 200 μmol/g). Iron overload on MRI was not associated with the C282Y HFE gene mutation (homozygous or heterozygous) in these patients (Table 3).

DISCUSSION

In this study, LIC was measured by MRI in a cohort of 32 adult patients receiving PD. By comparison with 2 cohorts of French patients receiving hemodialysis and studied in 2012 and 2014 by the same centralized radiological method and same radiology team,[7,16] we observed striking differences in LIC between our PD patients and the historic hemodialysis cohorts. LIC was normal in most PD patients (26/32; 81.3%) compared to few hemodialysis patients (~16% in the first hemodialysis cohort and 35% in the second hemodialysis cohort (which had a lower ferritin target of anemia treatment)). Only one PD

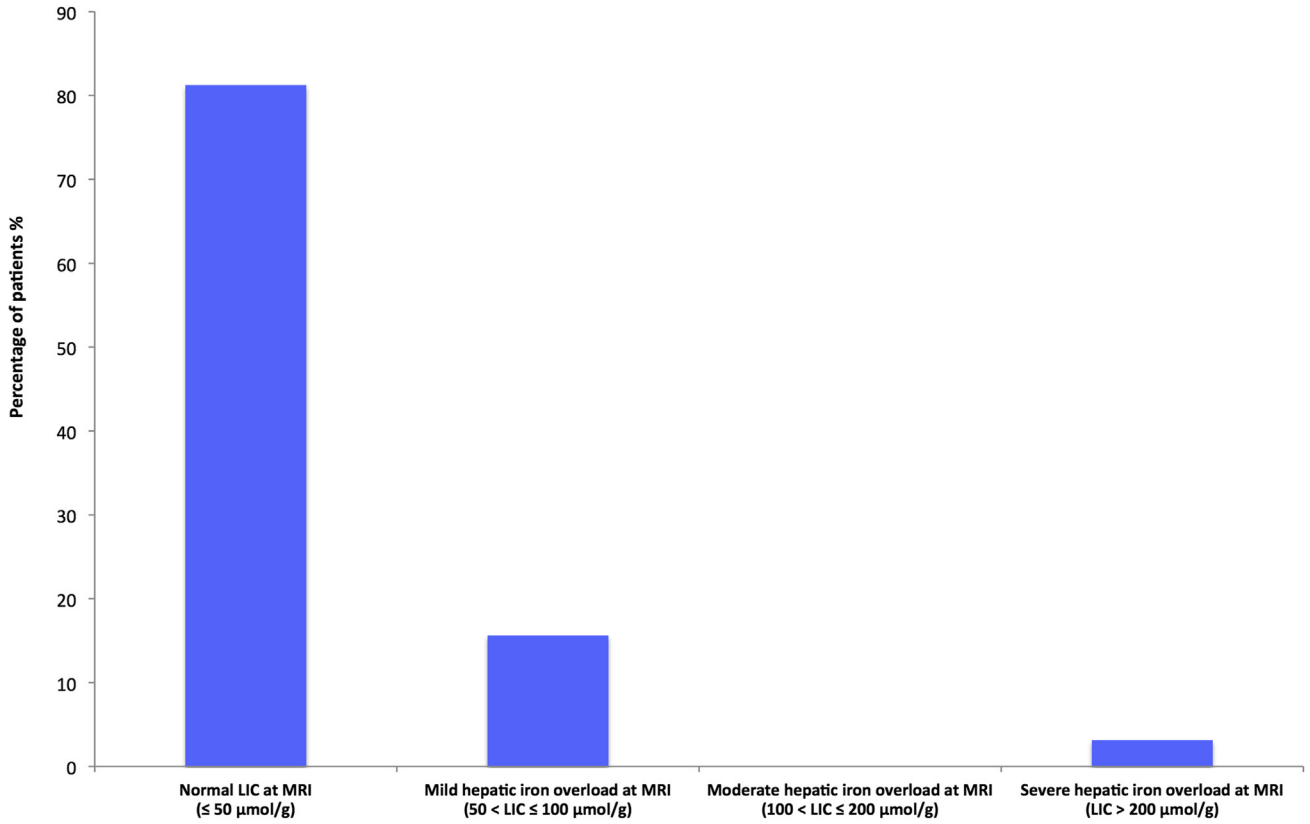

Figure 1. Histogram of repartition of liver iron content measured by quantitative MRI in a cohort of 32 patients treated by peritoneal dialysis. LIC, liver iron concentration; MRI, magnetic resonance imaging.

patient (3.13%) had severe iron overload, compared to 30.3% of patients in the first hemodialysis cohort and 11.3% of those in the second cohort.[7,16] We conclude that, in contrast to hemodialysis patients, iron overload on MRI is rare and mostly mild in patients receiving PD.

Table 3. Characteristics of 9 peritoneal dialysis patients with either high LIC at MRI or having been treated by i.v. iron

Patient	Sex	Age at MRI (yr)	LIC at MRI (µmol/g)	Duration of PD before MRI (mo)	Iron (i.v./oral) cumulative dose since initiation of PD (mg)	Duration of iron exposure (d or mo)	Time between iron oral tablet ingestion or i.v. iron infusion and MRI (d or mo)	Blood transfusion since initiation of PD (mo)	Serum ferritin (µg/l)	Transferrin saturation (TSAT) (%)	Genetic test HFE
1	F	34	230	10	i.v. 300 mg	3 mo	6 mo	0	100	15	Negative
2	F	75	65	21	No iron	0	N/A (no iron therapy)	0	885	28	Negative
3	M	63	70	14	Oral 14,480 mg	7 mo	8 mo	0	150	35	Heterozygous CYS282-Tyr
4	M	78	60	28	No iron	0	N/A (no iron therapy)	0	487	32	Negative
5	M	73	55	3	Oral 7680 mg	3 mo	7 d	0	124	29.9	Negative
6	M	73	70	4	Oral 3672.5 mg	4 mo	7 d	0	159	50	Negative
7	F	47	20	35	i.v. 2000 mg	2 mo	30.5 mo	0	111	24	Not done
8	F	56	5	42	i.v. 2000 mg	21 d	10 mo	0	201	28	Not done
9	M	40	5	8	i.v. 900 mg	8 mo	7 d	0	57	17	Not done

F, female; LIC, liver iron concentration; M, male; MRI, magnetic resonance imaging; N/A, not applicable; PD, peritoneal dialysis.

Belkacem Issad[1], Nasredine Ghali[2], Séverine Beaudreuil[3], Mireille Griuncelli[5], Yves Cohen[4] and Guy Rostoker[5]

[1]Division of Nephrology and Dialysis, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; [2]Division of Nephrology and Dialysis, Centre Hospitalier Marc Jacquet, Melun, France; [3]Division of Nephrology, Dialysis and Transplantation, Centre Hospitalier Universitaire Bicêtre, Kremlin-Bicêtre, France; [4]Division of Radiology, RAMSAY-Générale de Santé, Hôpital Privé Claude Galien, Quincy-sous-Sénart, France; and [5]Division of Nephrology and Dialysis, RAMSAY-Générale de Santé, Hôpital Privé Claude Galien, Quincy-sous-Sénart, France

Correspondence: Guy Rostoker, Division of Nephrology and Dialysis, RAMSAY-Générale de Santé, Hôpital Privé Claude Galien, Quincy-sous-Sénart, France. E-mail: rostotom@orange.fr

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

BI 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 Division of Nephrology and Dialysis, Département d'Urologie et de Néphrologie, Groupe Hospitalier Pitié-Salpétrière. He also participated in the writing of the article. NG 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. SB 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. MG contributed to data acquisition, analysis, and interpretation, and to the statistical analysis, and prepared the tables and figure. YC contributed to the acquisition and analysis of centralized MRI examinations. GR 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 wrote the article.

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