ASSESSMENT OF LIVER IRON CONTENT BY MAGNETIC RESONANCE IN CHRONIC KIDNEY DISEASE AT THE START OF MAINTENANCE HEMODIALYSIS AND 12 MONTHS LATER

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INTRODUCTION AND AIMS:

Intravenous iron therapy is increasingly used as part of the treatment of anemia in chronic kidney disease (CKD) and hemodialysis patients[1,2]. Recent Magnetic Resonance Imaging (MRI) studies have shown that most maintenance hemodialysis patients receiving intravenous (IV) iron supplementation have moderate to severe hepatic iron overload[3,4,5,6], considered a reason for concern.
The present study developed around 3 questions:

-Is iron overload already present at the time of dialysis initiation?
-How fast is the progression of hepatic iron overload in hemodialysis patients with current anemia treatment?
-Would it be possible to identify at the start biomarkers that would enable to follow closely some patients at greater risk of developing iron overload?

To clarify these questions we analysed liver iron content (LIC) by MRI in a sample of patients at the start of maintenance hemodialysis, repeated LIC measurement 12 months later and explored the determinants of iron overload.

MATERIAL AND METHODS:

After approval by the Hospital's Ethical Committee, a prospective, observational study was conducted including adult patients starting maintenance hemodialysis.

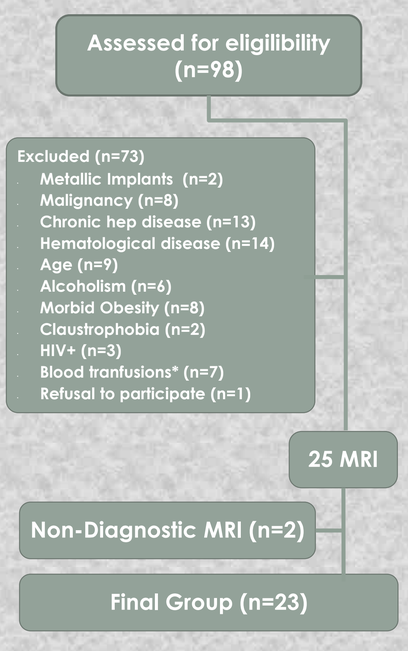
MRI without gadolinium was performed to calculate LIC based on the signal intensity ratio method developed and validated by Gandon at Rennes University[7].

Criteria for exclusion were age (younger than 18 or older than 85 years old), more than 4 packed red blood cell transfusions (PBRC) in the last 12 months or any PBRC administration in the last 2 weeks, haematological or oncological disease, known genetic hemochromatosis, alcoholism, hepatic disease or infection with Human Immunodeficiency Virus (HIV). Patients with morbid obesity, metallic devices or claustrophobia precluding MRI were also excluded.

After informed consent, 25 patients were enrolled in a prospective observational study consisting of hepatic MRI to measure LIC, retrieval of clinical data and biochemical blood analysis at the initiation of maintenance hemodialysis and 12 months later.

Two patients were not included because of non-diagnostic MRI images due to respiration-induced artefacts, leaving 23 eligible patients.

MRI was postponed if IV iron therapy was administered in the previous week to minimize interference with MRI results[8].



Statistical analysis: Categorical data were presented as frequencies (percentages), and continuous variables as median and inter-quartile range. Continuous variables were compared using the Mann-Whitney test given normality was not verified (Shapiro-Wilks test); categorical variables were compared using Fisher's exact test. The association between the different variables and LIC on MRI was analysed using the Spearman correlation coefficient. To compare initial and 12 months LIC values, Wilcoxon signed rank test was used.

The level of significance α=0.05 was considered. Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows 21.0

RESULTS: At the start of Hemodialysis

Characterization of patients Patients' age was 66 years (IQR: 55-73), 12 were male (52%). Seventeen were Caucasian (74%) and 6 were of African descent. The causes of kidney disease were diabetes (n=6; 26%), hypertension (n=5; 22%), glomerulonephritis (n=7; 30%), interstitial kidney disease (n=3; 13%) and unknown (n=2; 9%). Demographic and biochemical parameters at the start of HD are shown in Table 1.

Table 1: Patient demographics, biochemical parameters and LIC at the start of hemodialysis

Gender / Age	Diagnosis	Hb (g/dL)	Ferritin (ng/dl)	TSAT (%)	CHr (pg)	LIC (µmol/g)	IV Iron	Oral Iron	PBRC	ESA	
M /64	HTN	9,5	7	8	23	5	-	+	-	+	normal
F/54	DM	11,5	77	16	32	25	-	-	+	+	
F/72	IKD	8,2	321	25	30,6	25	-	-	-	+	
M/76	GN	8,6	461	48,4	34	35	-	-	-	-	
M/66	IKD	9,7	247	12,9	31,6	35	-	-	-	-	
F/71	DM	7,9	344	14,2	27,4	35	+	-	-	+	
F/41	GN	10,5	104	39,5	32,7	40	+	-	-	+	mild
M/68	GN	10,9	181	11,2	29,8	40	-	-	-	-	
M/73	GN	7,5	602	13,2	28,7	45	+	-	+	+	
M/27	GN	10,4	312	33,4	37,6	45	-	-	-	+	
F/58	GN	8,2	139	10,1	32,2	50	-	-	-	+	
F/55	UK	10,1	179	19,7	35	55	-	-	-	+	
F/66	DM	10,5	56	13,4	33,2	60	-	+	-	-	
M /49	DM	8,8	446	39	35	65	+	+	+	+	
M/71	HTN	10,3	407	9	33,8	65	-	-	+	-	
F/76	UK	8	140	17,3	28,4	75	-	-	-	-	
F/78	IKD	8,4	167	10,2	27,7	80	+	+	+	+	
M/83	HTN	9,7	156	26,8	31,2	80	-	+	-	+	
M/69	HTN	9	199	10,9	33,2	85	-	-	-	+	
F/54	HTN	10,5	216	35	33	100	+	+	+	+	
F /56	DM	9,8	245	31	30	110	+	-	-	+	moderate
M/64	DM	10,5	579	31	34,7	160	-	-	-	-	
M/76	GN	10,8	338	13	34,9	180	-	-	-	-	

Gender: M-Male, F-Female; Age: years, HTN- Hypertension; DM- Diabetes mellitus, IKD- Interstitial kidney disease; GN- Glomerulonephritis; UK- Unknown; Hb- Hemoglobin; TSAT- Transferrin saturation; LIC- Liver iron content; IV- Intravenous; PBRC- Packed Blood Red Cell transfusions; Normal values: serum ferritin 22-322 ng/ml; TSAT 20-50%

Table 2: Baseline Demographic and Clinical parameters in all patients and by LIC subgroups

	All patients (n=23)	Normal LIC (n=6) < 40 µmol/g	Mild to moderate LIC (n=17) ≥40 µmol/g	p-value
LIC (µmol/g)	55.0 (35.0-80.0)	30.0 (20.0-35.0)	65.0 (47.5-92.5)	<0.001
Age (years)	66.0 (55.0-73.0)	68.5 (61.5-73.0)	66.0 (54.5-74.5)	0.695
Male gender n (%)	12 (52)	3 (50)	9 (53)	1.000*
Caucasian n (%)	17 (74)	3 (30)	14 (82)	0.279*
Diabetes n (%)	6 (26)	2 (33.3)	4 (24)	0.632*
BMI (Kg/m^2)	28.0 (24.0-29.0)	26.2 (24.0-36.0)	28.0 (24.5-29.0)	0.932
CCI	5.0 (4.0-8.0)	5.0 (4.0-7.5)	6.0 (4.0-8.0)	0.912

LIC- Liver iron content; Gender: M-male, F- female; Y- yes; N- no; BMI - Body mass index; CCI - Charlson comorbidity index; Values are expressed as median and interquartile range (IQR); Gender, ethnicity and diabetes expressed as raw data
*Fisher's Exact Test; remaining p-values are obtained by Mann-Whitney test.

Table 3: Baseline biochemical parameters at the start of Hemodialysis and association with LIC

	All patients (n=23)	Rho	p-value	Normal LIC (n=6) < 40 µmol/g	Mild to moderate LIC (n=17) ≥40 µmol/g	p-value*
Hemoglobin (g/dL)	9.7 (8.4-10.5)	0.183	0.403	9.1 (8.1-10.2)	10.1 (8.6-10.5)	0.342
Ferritin (ng/dL)	216.0 (140.0-344.0)	0.176	0.422	284.0 (59.5-373.3)	199.0 (148.0-372.5)	0.973
TSAT (%)	16.0 (11.2-31.0)	0.091	0.681	15.1 (11.7-30.9)	17.3 (11.1-32.2)	0.854
CHr (pg)	32.2 (29.8-34.0)	0.315	0.143	31.1 (26.3-32.5)	33.0 (29.9-34.8)	0.131
CRP (mg/dL)	0.80 (0.00-3.00)	-0.191	0.407	2.32 (0.96-8.22)	0.66 (0.00-2.33)	0.122
PTHi (pg/ml)	232.0 (137.0-343.8)	-0.277	0.212	262.5 (205.0-3-384.7)	195.5 (102.5-321.3)	0.198
Albumin (g/dL)	3.1 (2.5-3.3)	0.206	0.346	3.0 (2.5-3.4)	3.1 (2.4-3.3)	0.962

LIC- Liver iron content; Hb- Hemoglobin; TSAT- Transferrin saturation; CHr- Reticulocyte hemoglobin content; CRP- C-reactive protein; PTHi- Intact parathyroid hormone; Values are expressed as median and interquartile range (IQR); Rho and p-value were obtained with Spearman's correlation; p-value* was obtained with Mann-Whitney

At the start of hemodialysis, only 6 out of 23 patients (26%) had normal LIC (<40µmol/g) estimated by MRI.

Of the remaining 17 patients, 14 (61%) had LIC values between 40 and 100 (mild overload) and 3 (13%) had LIC values between 101-200 µmol/g, representing moderate overload.

Two patients already had LIC values of 160 and 170µmol/g, without any iron supplementation.

HFE gene mutation (H63D and C282Y) was not detected, so Hereditary Hemochromatosis associated to HFE gene was not confirmed in these patients.

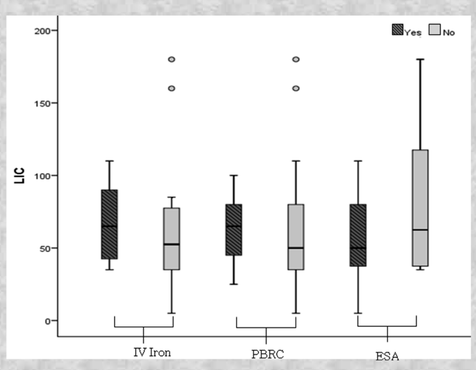


Figure 1: LIC was higher for those patients with previous iron or PBRC transfusions, and lower in patients already on ESA, but the difference was not statistically significant.
LIC (µmol/g) of patients who received (Yes) or did not receive (No) IV Iron: 65.0 (40.0-100.0) vs 52.5 (35.0-78.8), p=0.461; PBRC transfusions 65.0 (40.0-85.0) vs 50.0 (35.0-82.5), p=0.648; ESA 50.0 (35.0-80.0) vs 62.5 (36.3-138.8), p=0.518 ; LIC- Liver iron content; IV- intravenous; PBRC- packed red blood cells, ESA- Erythropoiesis stimulating agents

RESULTS: 12 months later

After 12 months in routine hemodialysis, determination of LIC by MRI was repeated in 7 consecutive patients.
The repetition of MRI at 12 months showed a significant increase in LIC in all 7 patients (p=0.018).

During the 12 months in chronic hemodialysis, all patients did IV iron (total minimum 1830mg to maximum 5600mg).
Last IV iron administration was 9 to 34 days before MRI.
There were no major blood losses reported and none had PBRC transfusions during 12 months follow-up.
The increase in LIC did not correlate with the total dose of iron infused since the start of hemodialysis (p=0.702).
None of the demographic, clinical or biochemical parameters was associated with LIC at the start of hemodialysis or after 12 months (Table 2, 3, figure 1).

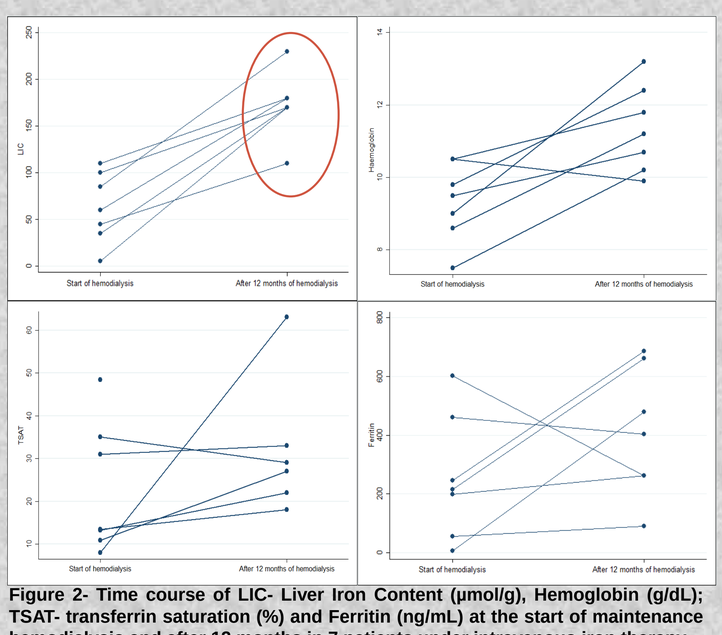


Figure 2- Time course of LIC- Liver Iron Content (µmol/g), Hemoglobin (g/dL); TSAT- transferrin saturation (%) and Ferritin (ng/mL) at the start of maintenance hemodialysis and after 12 months in 7 patients under intravenous iron therapy.

DISCUSSION:

Unexpectedly, at the time of dialysis start, the majority of CKD patients already showed some degree of hepatic iron overload, assessed by MRI. This finding questions KDIGO[9] recommendations of administering iron first rather than ESA in CKD, since most patients already have a surplus of iron accumulated.

Even those patients who did not receive significant amounts of iron or any iron at all, had some iron overload, suggesting that CKD patients have a propensity to store iron in the liver instead of using it efficiently in erythropoiesis.

The steep rise in LIC after 12 months in maintenance hemodialysis under intravenous iron therapy, suggests a severe mismatch between given and utilized iron for erythropoiesis, as much of the iron seems to be taken up by the liver and sequestered, not used in effective erythropoiesis.

In this observational single-center study with a small size sample, it was not possible to identify at the start biomarkers for increased risk of iron overload.

CONCLUSIONS:

The results indicate that the majority of CKD patients have liver iron overload before initiation of maintenance hemodialysis, increasing significantly to worrisome levels in all patients in the first 12 months in hemodialysis under intravenous iron.

These findings strengthen the view that iron administration to CKD patients should be done with caution, in line with the "plea for moderation" first put forward in an editorial of the American J Medicine in 2012[10].

In addition, it raises new questions regarding iron homeostasis in CKD and hemodialysis, outlining the need to find different therapeutic strategies in anemia of CKD, questioning actual guidelines that suggest iron first, rather than ESA in CKD.

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