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

Patricia Carrilho[1], Ines Santiago[2], Pedro Fidalgo[1], Marta Alves[3], [1]Hospital Prof Fernando Fonseca, Nephrology, Amadora, Portugal, [2]Hospital Prof Fernando Fonseca, Radiology, Amadora, Portugal, [3]Centro Hospitalar de Lisboa Central, Epidemiology and Statistics Office of the Research Unit, Lisboa, Portugal.

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]. Rostoker has recently described iron overload in 84% of a cohort of 119 stable patients on hemodialysis who were treated with ESA and iv iron preparations in compliance with the accepted guidelines[3].

Whether iron overload is present at the time of dialysis initiation is still unknown, however.

The present study aims to contribute to clarifying that question by analyzing liver iron content (LIC) by magnetic resonance imaging (MRI) in a small population of incident hemodialysis patients, and to explore the determinants of iron overload, especially the role of parenteral iron therapy and blood transfusions.

MATERIAL AND METHODS:

The study took place in Hospital Fernando da Fonseca after approval by its Ethical Review Board.

From March 2014 to November 2015, 19 consecutive patients who attended the nephrology outpatient clinic or were hospitalized and started maintenance hemodialysis (HD) were invited to participate in a prospective, observational, hospital-based study consisting of hepatic magnetic resonance, clinical data retrieval and biochemical blood analysis at the time of dialysis start. Of those, 17 accepted to participate and were enrolled after giving informed consent.

Criteria for inclusion were age: older than 18 and younger than 85 years old, anemia defined as hemoglobin lower than 11g/dL; or undergoing therapy with iron or erythropoiesis stimulating agents (ESA).

Criteria for exclusion were more than 4 packed red blood transfusions (PBRC) in the last 12 months, hematological or oncological disease, genetic hemochromatosis, alcoholism, hepatic disease, or PBRC transfusion in the last 2 weeks. MRI was postponed if intravenous iron therapy was administered in the last week to minimize interference with MRI results[4]. Patients with morbid obesity, metallic device or claustrophobia precluding magnetic resonance were also excluded.

Hemoglobin (Hb), reticulocyte Hb content (CHr), TSAT, ferritin and protein C reactive (PCR) were determined at hemodialysis start. Clinical data were collected, including demographic parameters and history of previous transfusion, iron and ESA therapy. Charlson comorbidity index (CCI)[5] and body mass index (BMI) were calculated.

Magnetic resonance imaging without gadolinium was performed at the time of dialysis start to calculate LIC in a 1T equipment (Signa, GE Medical Systems ®, Milwaukee, WI) and consisted of 4 gradient echo sequences with a slice thickness of 10 mm, a 128x256 matrix and a field of view adapted to patient´s abdominal diameter. Repetition time/echo time/flip angle parameters of 120/7/90º, 120/7/20º, 120/14/20º and 120/21/20º were applied. Oval regions of interest were placed in the resultant images in 3 liver regions and right and left paraspinous muscles, each with a minimum area of 50 mm^2. Mean signal intensity values were registered and used to calculate LIC based on Gandon's formula[6].

Statistical analysis:
Categorical data were presented as frequencies (percentages), and continuous variables as median and inter-quartile range (IQR: 25th percentile-75th percentile). Continuous variables were compared using the Mann-Whitney test since that 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 were analyzed with Spearman correlation coefficient. The level of significance α=0.05 was considered. The statistical analysis as performed using the Statistical Package for the Social Sciences for Windows 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.).

RESULTS:

Characterization of patients

Of the 17 patients included, 11 were males and 6 were females; 12 were Caucasians and 5 were of African origin. The median age was 66 (54,0-74,5) years. The etiology of kidney disease was diabetes (29%), hypertension (29%), glomerulonephritis (29%) and chronic interstitial nephritis (13%). Demographic and biochemical parameters at the start of hemodialysis are shown in Table 1. The median Charlson comorbidity index (CCI) was 5 (4-7,5). According to body mass index (BMI), 5 patients had normal weight, 9 were overweight and 3 were obese.

Table 1: Correlation between Liver Iron Content (LIC) and demographic, biochemical and total iv iron dose

	Median (IQR)	Spearman's rho correlation	p-value
Age (years)	66 (54-74,5)	0,211	0,416
CCI	5 (4-7,5)	0,549	0,022
BMI	28 (24-29)	0,115	0,661
Hb (g/dL)	9,8 (8,9-10,5)	0,147	0,573
Ferritin ng/mL	245 (130-426)	0,366	0,148
TSAT (%)	16 (11,9-34,2)	0,125	0,633
CHr (pg)	33 (30,6-34,4)	0,317	0,215
PCR (mg/dL)	0,65 (0,0-3,1)	0,095	0,725
Total dose IV iron (mg)	450 (87,5-1900)	0,058	0,913

Table 1: CCI: Charlson Comorbidity Index; BMI: Body Mass Index; TSAT: Transferrin saturation; CHr: Reticulocyte Hemoglobin Content; PCR: C-reactive Protein

Table 2. Summary of patient groups analyzed

Group	Patient ID	Sex/Age	IV Iron (Y/N)	PRBC (Y/N)	Oral iron (Y/N)	ESA (Y/N)	LIC (µmol/g)
1	2	M/64	N	N	Y	Y	35 ± 20
	5	M/75	N	N	N	N	50 ± 20
	7	F/66	N	N	Y	N	100 ± 30
	8	M/69	N	N	N	Y	60 ± 30
	9	M/66	N	N	N	N	45 ± 20
	12	M/27	N	N	N	Y	20 ± 20
	13	M/83	N	N	Y	Y	85 ± 30
	14	M/64	N	N	N	N	170 ± 40
	15	M/76	N	N	N	N	180 ± 40
2	3	F/56	Y	N	N	Y	110 ± 30
	10	F/41	Y	N	N	Y	45 ± 20
3	16	F/54	N	Y	N	Y	20 ± 20
	17	M/71	N	Y	N	N	70 ± 30
4	6	M/73	Y	Y	N	Y	55 ± 20
	4	F/54	Y	Y	Y	Y	100 ± 30
	11	F/78	Y	Y	Y	Y	50 ± 20
	1	M/49	Y	Y	Y	Y	110 ± 30

Iv Iron and Blood transfusions prior to hemodialysis start

Six patients (35%), 4 females and 2 males, had received intravenous iron prior to dialysis initiation (median dose 450mg), the 2 men and 2/4 females had also received PBRC transfusion. In addition, 2 other patients had received previously PBRC transfusions (Table 2).

Eleven had already started ESA prior to starting HD.

Nine had not received iron or blood transfusion.

Four groups were therefore constituted for analysis of the results (Table 2, Fig. 1).

1. No iv iron or blood transfusion (n=9)
2. Only iv iron (n=2)
3. Only blood transfusion (n=2)
4. Iv iron and blood transfusion (n=4)

Liver Iron Content (LIC)

Surprisingly, at the start of hemodialysis only 3 out of 17 patients (18%) had normal LIC (<40µmol/g) estimated by MRI (Fig.1).

Of the remaining 14, 4 had LIC values between 101-200 umol/g, considered earlier as moderate overload [3,6] and 10 had LIC values between 40 and 100 considered mild overload. None, however, had severe overload, as found in prevalent hemodialysis patients[3] (Figs.1,2). Analysis of prior iv iron administration revealed that no correlation could be established with LIC values, although median LIC was higher for those patients who had had previous iv iron (Fig.2).

Those with history of previous packed red blood cells transfusion and those who had previous medication with oral iron, didn't show statistically significant higher LIC than those who didn't (p=0,941 and p=0,572 respectively).

Patients under ESA (n=11) had a lower LIC[median 55 (35-100) vs 85 (48,7-172,5) µmol/g], but it was not statistically significant (p=0,223).

No statistically significant correlations were seen between LIC and other markers of iron overload, namely TSAT and ferritin (Table 1), in line with earlier studies that had already found that these biochemical parameters are not always a guide for iron therapy[7,8]. The only statistically significant correlation found in this small group of patients was between LIC and the Charlson comorbidity index (Fig.3).

DISCUSSION:

The majority of CKD patients already show some degree of hepatic iron overload, assessed by MRI, at the time of dialysis start. Unexpectedly, mild to moderate hepatic iron overload were observed even in those patients who had not received significant amounts of iron or any iron at all. Iron has the same effect on the liver signal whatever the overload cause[6], so renal failure and its associated comorbidities are not supposed to interfere with MRI signal per se. However, there is no study validating hepatic MRI with simultaneous liver biopsy to determine LIC in CKD patients.

A third of the patients included were diabetic, 65% overweight or obese, and these have frequently associated hepatic steatosis, which was not actively searched for and ruled out in the study. However, ferritin levels were not unexpectedly high [median 245 (130-426ng/dL) as usual in metabolic dysferritinemia[9] and didn't relate to LIC.

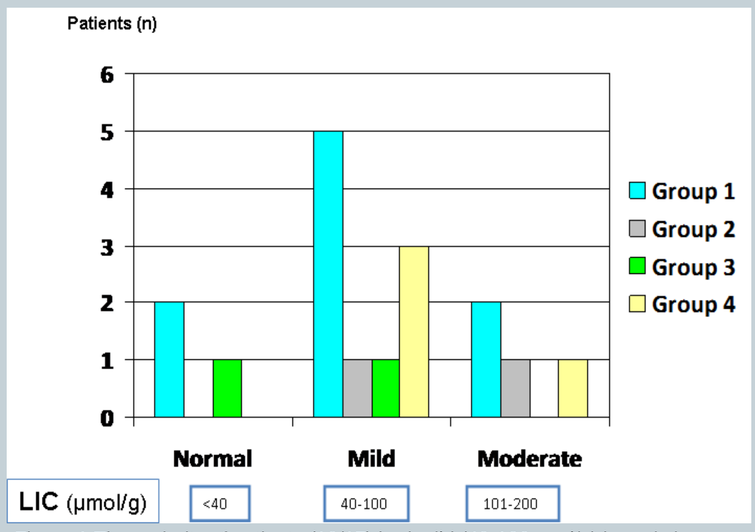

Figure 1.The majority of patients (10/17) had mild (40-100µmol/g) hepatic iron overload at the start of hemodialysis independently of having received iv iron. In addition, 4 patients already had moderate (101-200 umol/g) overload. Only 3/17 had LIC values <40µmol/g, none of these 3 had received iv iron.

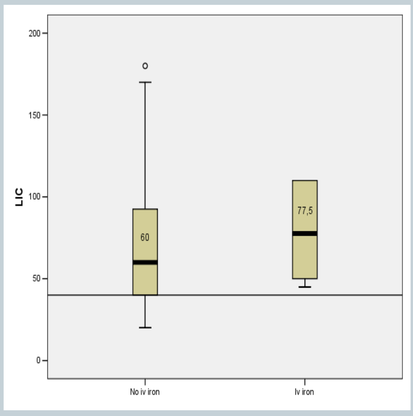

Figure 2: Median LIC (µmol/g) of patients who received previous iv iron (n=6) was 77,5 (IQR 48,8-110), while those who didn' t (n=11) had median LIC of 60 (IQR 35-100); p=0,541 (n.s.)..

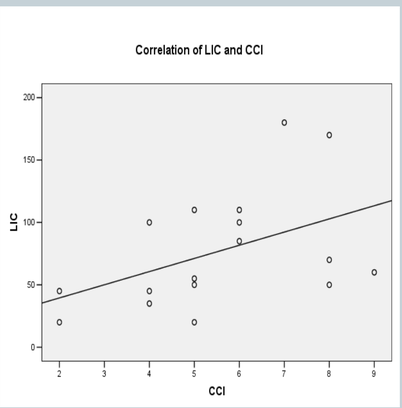

Figure 3: Correlation of LIC and Charlson Comorbidity Index (CCI); Spearman's Rho 0,549; p=0,022

Weakness and strength of the present study

The main limitation of the present work is the small number of patients studied. In spite of that, 3 clear conclusions can be reached:

- LIC is perhaps the best marker of iron overload in CKD, confirming results of other recent studies [3,7,8].
- The 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].
- The study provides for the first time evidence of the value of verifying LIC before HD is started, which may reveal an already mild or moderate overload.

References:
1. Bailie GR, et al. Variation in intravenous iron use internationally and over time: the Dialysis Outcomes and Practice Patterns Study (DOPPS) Nephrol. Dial. Transplant. (2013) 28 (10): 2570-2579
2. Miskulin DC, Zhou J, Tangri N et al. Trends in anemia management in US hemodialysis patients 2004–2010. BMC Nephrol 2013; 14: 264
3. Rostoker G., et al. Hemodialysis-associated Hemosiderosis in the Era of erythropoiesis-stimulating Agents: A MRI Study. Am J Med 2012;125(10): 991-999
4. Rostoker G.; Cohen, Y. Magnetic Resonance Imaging Repercussions of Intravenous Iron Products Used for Iron-Deficiency Anemia and Dialysis-Associated Anemia. Journal of Computer Assisted Tomography. 38(6):843-844, November/December 2014
5. Charlson E, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373-83
6. Gandon Y., Olivie D., Guyader D., Aubé C., Oberti F., Sebille V., et al. Non-invasive assessment of hepatic iron stores by MRI. Lancet, 363 (2004), pp. 357–362
7. Ferrari P., et al. Serum Iron Markers Are Inadequate for Guiding Iron Repletion in Chronic Kidney Disease. Clin J Am Soc Nephrol. 2011 Jan; 6(1): 77–83
8. Holman R, Olynyk JK, Kulkarni H, Ferrari P. Characterisation of hepatic and cardiac iron deposition during standard treatmente of anemia in haemodialysis. Nephrology (Carlton). 2016 Jan 29.
9. Chen Y, et al. Dysmetabolic hyperferritinemia is associated with normal transferrin saturation, mild hepatic iron overload, and elevated hepcidin. Ann Hematol. 2011 Feb;90(2):139-43.
10. Vaziri N. Epidemic of Iron Overload in Dialysis Population Caused by Intravenous Iron Products: A Plea for Moderation. Am J Med 2012, 125 (10): 951-952

Acknowlegments: The present work was done with data acquired as part of the routine analysis of patients who enter dialysis, funded therefore by the regular services of the Portuguese National Health Service. We gratefully acknowledge Maria de Sousa for her interest, encouragement and help in preparation of the manuscript.