IS HEPATIC IRON OVERLOAD ASSOCIATED WITH LIVER FIBROSIS IN CHRONIC HEMODIALYSIS PATIENTS RECEIVING INTRAVENOUS IRON?

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INTRODUCTION

Magnetic Resonance Imaging (MRI) scans have been shown to provide a reliable estimate of liver iron content (LIC). Measurements in hemodialysis (HD) patients receiving intravenous iron suggest that LIC is increased in the majority of these patients. However, the clinical relevance of increased LIC and the risk of liver fibrosis (LF) are unclear.

Transit elastography (TE) is a useful tool for assessment of LF and has been validated in patients with liver iron overload.

AIMS

The aims of this study was evaluate the presence of LF by TE and other non-invasive methods in HD patients receiving iron therapy.

CHRONIC HEMODIALYSIS PATIENTS – CHARACTERISTICS

INCLUSION CRITERIA	EXCLUSION CRITERIA
•Manteinance hemodialysis of ≥ 12 months. • Parenteral iron therapy over the past 12 months. • Serum ferritin ≥ 500 ng/ml in two consecutive occasions, 3 months apart.	• Age ≤ 18 years • Recent transfusion (< 3 months) • Hepatic cirrhosis, chronic hepatitis C or B infection. • Body mass index ≥ 30kg/m² • Alcohol consumption more than 2 standard drinks per day. • Contraindication to MRI. • Active malignances. • Descompensated heart failure

Assessed for eligibility (n=111)

→ Excluded (n=55)
. Chronic hepatitis C or B (13)
. Cardiac pacemakers (3)
. Malignancy (2)
. Hemodialysis ≤12 months 29)
.Hepatic cirrhosis (3)
.Others (5)

Final assessment by MRI (n=56)

→ Excluded (n=9) Invalid MRI or claustrophobia.

Final assessment by TE (n=47)

→ Excluded (n=9) TE unrealiable results

Final group (n=39)

METHODS

➢ Quantitative MRI of hepatic iron stores, as established by Gandon et al at Rennes University.

➢ TE was performed with Fibroscan (Echosens, Paris). TE values were expressed in Kilopascals (kPa) and they were converted in the corresponding semi-quantitative fibrosis score of METAVIR: F0-F1: 2.5-7.0 KPa (mild or no fibrosis); F2: > 7.0-9.5 KPa (significant fibrosis); F3: >9.5-12.5 KPa (severe fibrosis) and F4: >12.5 KPa (cirrhosis).

➢ **Specific Measuraments:**

-Indirect markers of liver fibrosis: APRI test, FORNS index, and FIB-4 score.
-Biological markers of iron metabolism: ferritin and hepcidin levels, TSAT.
-Oxidative stress markers: F2-isoprostanes methionine sulfoxide.
-C282Y, H63D and S65C mutations of hemochromatosis gene.
-Macrophage activation markers: CD163.
- Inflammatory markers: RCPus, TWEAK.
- Insulin resistance (HOMA).

RESULTS

Clinical Parameters according to MRI-LIC

Characteristics	Overall (n=39)	Mild iron overload (n=25)	Moderate or severe iron overload (n= 14)
Age, years	70 (14)	71(14)	69 (13)
Female sex (n)	13	7	6
Body mass index / kg/m²	24 (3)	25 (3)	24 (3)
Time on dialysis. (months)	77(43)	73 (42)	83(46)
Cumulative iron dose last 6 years (gr)	7.2(2.9)	6.7(2.6)	8.0(3.3)
Diabetes (n)	9	4	5
Hepatic iron content at MRI (µmol/g)	118.9(66.9)	74.4(21)	198.5 (40.1)*
Hemochromatosis gene (n)	1	1	0

*** P: < 0.0001**

Biochemical Parameters according to MRI - LIC

Parameter	Overall (n=39)	Mild iron overload (n=25)	Moderate or severe iron overload (n= 14)
Hemoglobin (g/dL)	11.6 (1.6)	12 (1.8)	10.8 (0.7)
TSAT (%)	34 (14)	33 (14)	35 (12)
Serum ferritin (ng/mL)	576 (243)	571 (254)	586(232)
Serum Hepcidin (nM)	7.1 (2.5)	7 (2.8)	7.4 (2.0)
HOMA	5.5 (6)	6 (7)	4 (3)
Platelet count (x 10 ⁹/L)	183(63)	182(69)	186(52)
Albumin (g/dL)	3.9(4)	3.9(4)	3.9(4)
Total Bilirrubin (mg/dL)	0.14(0.1)	0.13(0.0)	0.17(0.1)
AST (UI/mL)	16(11)	17(14)	14(5)
ALT (UI/mL)	14(7)	15(8)	11(6)
GGT (U/L)	25(24)	27(25)	22(23)
Alkaline phosphatase (U/L)	129(69)	123(70)	141(68)
PCRus (mg/dL)	11.3 (18)	14.5 (21)	5.8 (6.3)
TWEAK (pg/mL)	1179 (432)	1205.6 (500.6)	1137.4 (303)
CD163 (ng/mL)	205.7 (56.6)	209 (60.2)	199.6 (51)
8-iso-PGF2α (nM)	1.47(0.5)	1.56 (0.6)	1.31 (0.4)
Methionine sulfoxide (nM)	1.68 (0.4)	1.6 (0.4)	1.7 (0.4)
Methionine sulfoxide (oxidized %)	18.1 (4.7)	18.2 (5)	18.2 (4.5)

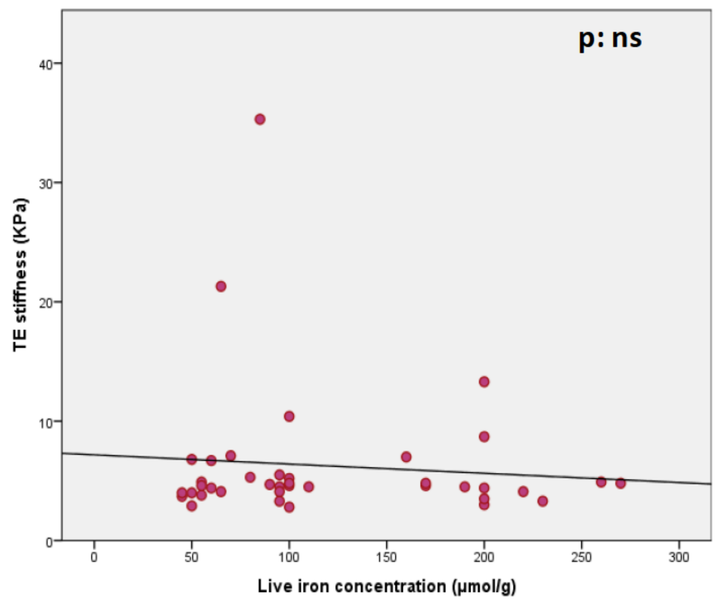
METAVIR Fibrosis stage

F 0/1 → n=34
F 2 → n= 1
F 3 → n= 2
F 4 → n= 2

	METAVIR stage F0/1 – 2 n(35)	METAVIR stage F3-F4 n(4)	P
TE stiffness (Kpa)	4.6(1.2)	20(11.1)	<0.0001
Hepatic iron content at MRI (µmol/g)	119.7(68.4)	112.5(60)	ns
APRI Test	0.20(0.10)	0.92(0.60)	<0.0001
FORNS Index	6.27(1.47)	9.43(1.05)	<0.0001
FIB-4 Score	1.46(0.8)	8.2(7.8)	<0.0001

Relationship between TE stiffness and laboratory and clinical data

	r	P
Waist	0.40	0.01
Serum glucose	0.33	0.04
GTP	0.46	0.003
CD163	0.49	0.003
FORNS index	0.35	0.02



In a multivariate logistic regression analysis, FORNS index was the only independent variable associated with TE stiffness: OR 2.79 (95% CI: 1.33-5.86) P: 0.007

CONCLUSIONS

✓ The majority of HD patients receiving intravenous iron supplementation have hepatic iron overload on MRI, although only a small proportion have liver fibrosis assessed by TE.

✓Longer follow-up and larger cohort of HD patients are needed to confirm the absence of LF in this population

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