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Research article

Renal iron deposition by magnetic resonance imaging in pediatric β-thalassemia major patients: Relation to renal biomarkers, total body iron and chelation therapy

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ABSTRACT

Background: The reciprocal of multiecho gradient-echo (ME–GRE) T2* magnetic resonance imaging (MRI) R2*, rises linearly with tissue iron concentration in both heart and liver. Little is known about renal iron deposition in β-thalassemia major (β-TM).

Aim: To assess renal iron overload by MRI and its relation to total body iron and renal function among 50 pediatric patients with β-TM.

Methods: Serum ferritin, serum cystatin C, urinary albumin creatinine ratio (UACR), and urinary β2-microglobulin (β2 M) were measured with calculation of β2 M/albumin ratio. Quantification of liver, heart and kidney iron overload was done by MRI.

Results: Serum cystatin C, UACR and urinary β2 microglobulin as well as urinary β2m/albumin were significantly higher in β-TM patients than the control group. No significant difference was found as regards renal R2* between Patients with mean serum ferritin above 2500 μg/L and those with lower serum cutoff. Renal R2* was higher in patients with poor compliance to chelation therapy and positively correlated to indirect bilirubin, LDH, cystatin C and LIC but inversely correlated to cardiac T2*.

Conclusion: kidney iron deposition impairs renal glomerular and tubular functions in pediatric patients with β-TM and is related to hemolysis, total body iron overload and poor compliance to chelation.

1. Introduction

Iron overload is a common complication of thalassemia syndromes which could lead to organ damage and increased morbidity and mortality [1]. High levels of local iron in the kidney can cause kidney injury that can eventually progress to end stage renal disease. Renal damage may develop through tubule-interstitial and/or glomerular injuries [2]. The success that has been made in the care of patients with thalassemia has led to the emergence of unrecognized complications including several renal abnormalities [3]. Iron chelation therapy can ameliorate these complications but close monitoring of tissue iron is important to track iron accumulation and iron removal therapies [4].

Multiecho gradient-echo (ME–GRE) T2* magnetic resonance imaging (MRI) is an established technique for noninvasive and reproducible assessment of iron overload in the heart and liver [5]. Renal ME-GRE T2* also appears to be a feasible and reproducible method that has been used for evaluating renal iron overload in thalassemia patients [6]. The reciprocal of T2* known as R2* has been shown to rise linearly with chronically determined tissue iron concentration in both heart and liver [7]. The pathophysiologic significance of kidney R2* is unclear. It may have a value as a long-term measure of hemolysis and could be a surrogate for renal iron accumulation in chronically transfused patients [4,6].

Few studies directly investigated kidney iron deposition in β-thalassemia major (β-TM) [4,5]. Therefore, we assessed renal iron overload by MRI and its relation to liver iron concentration (LIC), cardiac

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T2* and biochemical markers of glomerular and tubular function as well as the relation to type of chelating agent and compliance to chelation therapy among pediatric patients with β-TM.

2. Materials and methods

This cross-sectional study included 50 patients with transfusion-dependent β-TM (≤18 years); 25 males and 25 females who were randomly recruited from the regular attendants of the Pediatric Hematology Clinic, Ain Shams University. They were compared to 25 age- and sex-matched healthy individuals enrolled as controls. The control group was proven to be healthy after full clinical examination and laboratory investigations. The mean age of patients was 12.8 ± 3.2 years, while the control group had a mean age of 11.6 ± 3.3 years. An ascent form was signed by patients and controls and informed consent was signed by the guardian of each patient or control before participation. The procedures applied in this study were approved by the Ethical Committee of Human Experimentation of Ain Shams University.

All patients were diagnosed with β-TM based on quantitative analysis of hemoglobin using high performance liquid chromatography (HPLC). Exclusion criteria were any evidence of infection, α-thalassemia, sickle β-thalassemia, symptomatic renal or cardiac disease, hypertension according to age, diabetes mellitus, hypothyroidism, rheumatoid arthritis or other autoimmune diseases.

All included patients were subjected to detailed medical history and thorough clinical examination with special emphasis on disease duration, anthropometric measures, blood pressure, evidence of cardiac disease, viral hepatitis, history of splenectomy, transfusion history (calculated as the transfusion index: volume of transfused packed red cells in ml per kg body weight per year; expressed as the mean value in the last two years) and chelation therapy.

Patients with β-TM received either mono or combined chelation therapy. Mono-chelation was in the form of deferoxamine (DFO) infused subcutaneously in a dose that ranged from 30 to 45 mg/kg/d given subcutaneous using the pump over 8–10 h 5 days/week, oral deferiprone (DFP) in a daily dose that ranged from 75 to 100 mg/kg/d, divided over 3 doses or oral deferasirox (DFX) in a dose 20–40 mg/kg/d once daily. Compliance to chelation therapy was assessed by reviewing patient self-report of dose-taking and the appropriate number of doses taken during each day was checked by prescription refills and pill count; a cutoff point below 80% was considered as poor compliance to the regimen [8]. According to literature, serum ferritin cutoff value 2500 μg/L was used to classify patients into 2 groups as it was defined to be the best for prediction of thalassemia complication [9].

2.1. Laboratory analysis

Laboratory investigations included CBC using Sysmex XT-1800i (Sysmex, Kobe, Japan), examination of Leishman-stained smears for differential white blood cell (WBC) count, hemoglobin analysis by HPLC using D-10 (BioRad, Marnes La Coquette, France), liver function tests (serum albumin, total and direct bilirubin, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), markers of hemolysis (lactate dehydrogenase [LDH] and indirect bilirubin) using Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany). Serum ferritin level was measured on Immulite 1000 analyzer (Siemens Healthcare Diagnostics, Marburg, Germany) at the start of the study with calculation of the mean value of the last year prior to the study in order to know the ferritin trend. Urinary albumin excretion (UAE) was assessed in an early morning fasting urine sample as albumin-to-creatinine ratio by an immuno-turbidimetric method (Cobas C111; Roche Diagnostics, Mannheim, Germany). Patients were classified according to UAE in at least 2 out of 3 consecutive urine samples, 2 months apart into 3 groups; the normoalbuminuria group (UAE < 30 mg/g creatinine), microalbuminuria group (30–299 mg/g creatinine) or the macroalbuminuria group (UAE ≥ 300 mg/g creatinine) [10]. Urinary β2-microglobulin (β2 M) was assessed by enzyme linked immunosorbent assay (ELISA) using DBC Diagnostics Biochem Canada Inc., Ontario, Canada. Urinary β2 M/albumin ratio was calculated. Serum levels of cystatin C were measured by ELISA using kit supplied by SinoGeneclon Co., Ltd (Hangzhou, China).

2.2. Sample collection

Peripheral venous blood samples were collected on potassium-ethylene diamine tetra-acetic acid (K2-EDTA) (1.2 mg/mL) for CBC and hemoglobin analysis. For chemical analysis and enzyme linked immunosorbent assay (ELISA), clotted samples were obtained and serum was separated by centrifugation for 15 min then stored at −80 °C till subsequent use.

2.3. MRI acquisition and image analysis

All patients underwent MRI examination using a 1.5-T scanner (Philips-Intera, Holland) Achieva MR Unit and a 12-element phased array coil. No Gadolinium based contrast agent (GBCA) was used for any of our Patients. Patients were evaluated for liver siderosis using relaxation parameter T2*. LIC measurements were conducted by acquiring eight consequent T2* values and assessing T2* decay. Liver T2* values were converted into LIC values using the calibration curve [11]. LIC of > 7 mg Fe/g dry liver weight was found to be the best threshold for determining the presence of hepatic siderosis [12]

For the measurement of myocardial T2*, a single short 20 s breath-hold axis mid-ventricular slice was acquired at eight simultaneously acquired echo times (TEs 1.4–13.6 ms/echospacing 1.6 ms). The myocardial T2* was calculated using the same method as that in the liver. Cardiac T2* < 10 milliseconds (msec) denotes high risk while 10–20 msec denotes intermediate risk and > 20 msec defines low risk patients [13].

Kidney R2* was measured in five axial slices, covering the pancreatic and renal area; each slice was acquired in a single end-expiratory breath-hold by an ME–GRE T2* sequence. Sequence parameters were: ten echo times (TEs), spaced from 1.2 msec to 13.9 msec. The mean renal T2* value was calculated as the average of T2* values in the two kidneys. To evaluate intra-observer variability, the images were analysed twice by the same radiologist. To evaluate the inter-observer variability, the same images were analysed by two different radiologists blinded to each other's results. Patients were compared to control values corresponded to the standards for age and gender reported elsewhere [4,5,14]. The lower limit of normal for the mean kidney T2* value was 31 msec [5]. The total liver, cardiac and renal MRI scan duration was 15 min. During MRI assessments, all patients were cooperative and tolerated the techniques.

2.4. Statistical analysis

Analysis of data was done using Statistical Program for Social Science version 21 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation or median and interquartile range (IQR; 75th and 25th percentiles). Qualitative variables were described as number and percent. Kolmogrov Smirnov test was used for testing the distribution of normality. In order to compare parametric quantitative variables between two groups, Student *t*-test was applied. For comparison of non-parametric quantitative variables between two groups, Mann-Whitney test was used. Qualitative variables were compared using Chi-square (X^2) test or Fischer's exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, a Spearman correlation test was performed. Multivariable linear regression analysis was employed to determine the relation

Table 1
Clinical and laboratory data and MRI parameters of the studied patients with β-thalassemia major.

Variable	β-TM (n = 50)
Age (years), mean ± SD	12.8 ± 3.2
Males, n (%)	25 (50)
BMI SDS, median (IQR)	−0.89 (−1.6 to −0.28)
Systolic BP (mmHg), mean ± SD	95.9 ± 11.2
Diastolic BP (mmHg), mean ± SD	70.7 ± 9.5
Transfusion index (mL/kg/year), mean ± SD	244.4 ± 33.7
Splenectomized, n (%)	19 (38)
Viral Hepatitis C, n (%)	18 (36)
Duration of chelation (year), mean ± SD	9.7 ± 3.0
Type of chelation, n (%)#	
Monotherapy	14 (28)
Deferoxamine	2 (14.3)
Deferasirox	9 (64.3)
Deferiprone	3 (21.4)
Combined therapy	36 (72)
Poor compliance to chelation, n (%)	21 (42)
Renal T2* (msec), median (IQR).	39 (30.7–48.4)
Renal R2* (Hz), median (IQR)	25.9 (20.7–32.5)
LIC (mg/g liver dry weight), median (IQR)	12.2 (7.07–22.52)
Cardiac T2*(msec), median (IQR)	27.35 (22.2–33)
WBC count ($x10^9$/L), media (IQR)	8.1 (6.4–12.3)
Range	3.3–61.9
Pretransfusion hemoglobin (g/dL), mean ± SD	7.2 ± 1.12
HbF (%), median (IQR)	75.6 (64–81.9)
Indirect bilirubin (mg/dL), median (IQR)	0.9 (0.6–1.87)
ALT (IU/L), median (IQR)	31.5 (22–56)
AST (IU/L), median (IQR)	28 (19–46)
Serum albumin (mg/dL), mean ± SD	3.9 ± 0.77
Lactate dehydrogenase (IU/L), median (IQR)	391.5 (300–619)
Serum ferritin (μg/L), median (IQR) #	2284 (1800–4771)

BP: blood pressure; LIC: liver iron content; WBC: White blood cells; Hb: hemoglobin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; #: in the last year prior to the study.

between renal R2* and other variables. A p value < 0.05 was considered significant in all analyses.

3. Results

The clinical and laboratory data as well as MRI parameters of the studied β-TM patients are shown in Table 1. Forty-three (86%) patients had LIC > 7 mg Fe/g dry liver weight and 12 (24%) patients had renal T2* < 31 while 40 (80%) patients had cardiac T2* > 20 msec. Renal R2* was significantly higher and renal T2* was lower among the studied patients compared with standard control values. Fig. 1 illustrates the axial cuts of the renal MRI of one of the patients with a renal T2* value of 15 ms (< 31 ms).

Serum cystatin C, UACR and urinary β2 M as well as urinary β2 M/albumin were significantly higher in β-TM patients than the control group in the presence of normal serum creatinine, uric acid and urea levels (Table 2). Twenty-two (44%) patients had renal dysfunction (30% of patients had microalbuminuria while 14% had macroalbuminuria).

When the studied parameters of renal function were compared among patients with mean serum ferritin above or lower than 2500 μg/L, significantly higher serum cystatin C, UACR and urinary β2 M as well as urinary β2 M/albumin were found to be associated with high ferritin cutoff. However, no significant difference was found as regards LIC, cardiac T2* or renal R2* in relation to serum ferritin cutoff levels (Table 3).

As shown in Table 3, DFX therapy alone or combined was associated with significantly higher levels of glomerular and tubular markers as well as renal R2* while cardiac T2* was lower compared with other chelating agents (DFO or DFP). However, serum ferritin was comparable between patients receiving DFX therapy and other chelating agents (median [IQR], 2045 [1929–3104] μg/L versus 2450.5 [1456–5064.9] μg/L; p = 0.779). No significant difference was found as regards compliance to chelation therapy between groups.

Moreover, low renal T2* cutoff < 31 msec was associated with higher cystatin C levels (median [IQR], 1812.5 [1550–2892.5] versus 1400 [1000–1750] μg/L; p = 0.009) and poor compliance to chelation (75% versus 31.6%; p < 0.001). Both LIC and renal R2* were significantly higher in patients with poor compliance to chelation therapy (median [IQR], 17.18 [8.9–23.9] versus 10.2 [4.2–15.1] mg/g liver dry weight; p = 0.026 and 50 [44.3–56.1] versus 24 [18.4–27.1]; p < 0.001, respectively) while cardiac T2* was decreased compared with the good compliance group (median [IQR], 24.6 [18.8–26.9] versus 31.7 [27.5–36] msec; p = 0.001).

Significant positive correlations were observed between serum cystatin C and indirect bilirubin (r = 0.319, p = 0.024), LDH (r = 0.850, p < 0.001) and serum ferritin (r = 0.408, p = 0.003) (Fig. 2). Urinary β2 M was inversely correlated to pre-transfusion hemoglobin levels (r = −0.302, p = 0.033). There were no significant correlations between LIC and serum cystatin C, urinary β2 M as well as urinary β2 M/albumin (p > 0.05). Renal R2* was positively correlated to LDH (r = 0.618, p < 0.001), cystatin C (r = 0.574, p < 0.001) and LIC (r = 0.442, p = .001) but inversely correlated to cardiac T2* (r = −0.512, p < 0.001) (Fig. 2). However, we could not demonstrate a significant correlation between Renal T2* or R2* and each of age, disease duration, mean pre-transfusion hemoglobin or serum ferritin (p > 0.05). Multivariable linear regression analysis showed that LDH, cystatin C and cardiac T2* were the significant independent variables related to increased R2* among patients with β-TM.

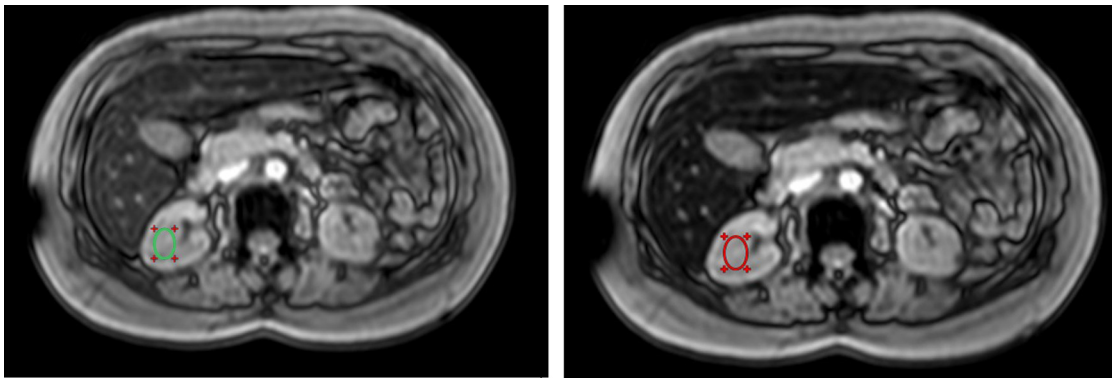

Fig. 1. Axial cuts acquired over kidney (TE = 4), with region of interest placed at mid pole of kidney revealing a low T2* value of 15 msec (< 30 msec) calculated by simple mathematical models using Microsoft Excel Spread Sheet V 3.0 (Juliano Lara Fernandes and Ulrik Gramet) where values of both signal intensity and TEs were manually inputted into an Excel Spread Sheet.

Table 2
Renal markers among patients with β-thalassemia major and healthy controls.

Variable	Controls (n = 25)	β-TM (n = 50)	p value
Urea (mg/dL), mean ± SD	20.4 ± 9.2	25.5 ± 10.5	0.102
Uric acid (mg/dL), mean ± SD	4.4 ± 1.2	5.8 ± 1.98	0.067
Serum creatinine (mg/dL), mean ± SD	0.26 ± 0.11	0.38 ± 0.18	0.131
Cystatin C (μg/L), median (IQR)	720 (625–810)	1450 (750–1625)	< 0.001
Urinary β2 microglobulin (mg/L), median (IQR)	2 (1.5–2.1)	5.5 (4–7)	< 0.001
UACR (mg/g creatinine), median (IQR)	9.4 (7.8–12.2)	24.7 (10.7– 43.6)	< 0.001
Urinary β2 M / albumin, median (IQR)	0.18 (0.14–0.22)	0.29 (0.14–0.76)	0.034

UACR: urinary albumin creatinine ratio; β2 M: β2 microglobulin. Data were expressed as mean and standard deviation where Student t test was used for comparisons or as median (interquartile range) where Mann-Whitney test was applied.

Table 3
Renal biomarkers, MRI parameters and compliance to chelation among patients with β-thalassemia major in relation to serum ferritin and DFX therapy.

Variable	Ferritin < 2500 μg/L (n = 26)	Ferritin ≥ 2500 μg/L (n = 24)	p value	DFX alone or combined (n = 27)	Other chelating agents# (n = 23)	p value
Urea (mg/dL), mean ± SD	25.7 ± 7.7	25.4 ± 9.41	0.909	26.54 ± 8.26	24.37 ± 8.74	0.371
Uric acid (mg/dL), mean ± SD	5.6 ± 1.1	6.1 ± 0.84	0.100	5.91 ± 0.95	5.70 ± 1.03	0.464
Serum creatinine (mg/dL), mean ± SD	0.38 ± 0.20	0.39 ± 0.17	0.934	0.35 ± 0.18	0.41 ± 0.18	0.261
Cystatin C (μg/L), median (IQR)	1400 (1000–1625)	1812.5 (1400–2625)	0.011	1750 (1400–2625)	1400 (1000–1550)	0.001
Urinary β2 microglobulin (mg/L), median (IQR)	5 (4–6)	6.5 (5–250)	0.007	6 (5–290)	5 (4–6)	0.011
UACR (mg/g creatinine), median (IQR)	15.7 (10–30)	35 (18.1–77.8)	0.022	25.2 (8.4–101.7)	24.2 (11.3–34.4)	0.869
Urinary β2 M/albumin, median (IQR)	0.24 (0.12–0.4)	0.46 (0.17–2.05)	0.042	0.45 (0.16–1.9)	0.23 (0.08–0.30)	0.011
Renal T2*(msec), median (IQR)	39 (29.6–47.3)	39.2 (31.8–49.8)	0.071	34.1 (22.4–42.1)	40.8 (36.9–53.8)	0.041
Renal R2* (Hz), median (IQR)	25.7 (23–33.8)	26.25 (20.15–30)	0.064	28.6 (24–42.6)	24.3 (17.9–28.1)	0.015
LIC (mg/g liver dry weight), median (IQR)	9.55 (4.2–19.1)	18.05 (11.2–23.5)	0.008	13.74 (7.07–22.92)	11.25 (6.92–22.52)	0.800
Cardiac T2*(msec), median (IQR)	26.5 (23.2–31.1)	29.3 (21.9–36.6)	0.415	25.8 (19.6–30.5)	32.5 (25.2–37.5)	0.009
Poor compliance to chelation, n (%)	10 (38.5)	11 (45.8)	0.598	13 (48.1)	8 (34.8)	0.341

DFO: Deferoxamine, DFP: Deferiprone; DFX: Deferasirox; UACR: urinary albumin creatinine ratio; β2M: β2 microglobulin; LIC: liver iron content. #: DFO or DFP alone or both combined. Data were expressed as mean and standard deviation where Student t test was used for comparisons or as median (interquartile range) where Mann-Whitney test was applied

4. Discussion

Renal dysfunction might occur in asymptomatic patients with β-TM even before having the manifestations of any other complications [15]. Several major factors may be responsible for the renal dysfunction associated with β-TM including shortened red cell life span, chronic hypoxia, rapid iron turnover, and tissue deposition of excess iron. Moreover, the use of specific iron chelators may harm the kidney [16].

Concerning urinary findings, the current study showed significantly higher levels of UACR in β-TM patients than the control group where 22 (44%) patients had renal dysfunction (30% patients had micro-albuminuria while 14% had macro-albuminuria) but with normal serum creatinine, uric acid and urea levels. Nevertheless, there was a significantly elevated urinary excretion of β2 M and β2 M/albumin ratio in β-TM patients and urinary β2-M was inversely correlated to hemoglobin levels. Higher frequencies of renal affection have been reported by other studies [15,17].

Asymptomatic renal dysfunctions are prevalent in young TM and thalassemia intermedia (TI) patients. Increased urinary β2 M of 33.5-55% was reported in Egyptians or other population. It was positively correlated to transfusion index, serum ferritin and proteinuria (24–71%) [18,19].

Cystatin C is believed to be a more robust endogenous marker of early affection of glomerular filtration rate (GFR) than creatinine as it is produced at a constant rate [20]. It is a sensitive early biomarker for monitoring glomerular and tubular dysfunction in children with β-TM [21]. In this study, significantly higher levels of serum cystatin C were observed in thalassemia patients compared with healthy controls. Positive correlations were found between serum cystatin C and indirect bilirubin, LDH and serum ferritin. This could imply the role of hemolysis on tissue iron overload and organ dysfunction, particularly poorly chelated and inadequately transfused patients [16,22].

There was no significant correlation between serum cystatin C and β2 M or between any of these markers and kidney function tests (serum creatinine, urea and UACR) or LIC in this study. On the other hand, Behairy et al. [21] found that serum cystatin C and β2 M were positively correlated with urea, creatinine, serum ferritin, UACR, duration of chelation therapy and frequency of blood transfusion/year while both markers were negatively correlated with creatinine clearance, hemoglobin, and estimated GFR in children with β-TM. Kacar and colleagues [23] also reported a significant positive relation between cystatin C and β2 M as well as serum ferritin and liver iron deposition.

Limited effort has been made to directly assess the relation of renal iron concentrations with renal dysfunction among β-TM patients. To explore the relation between iron overload and renal dysfunction, we assessed tissue iron overload by kidney MRI T2* and R2* as surrogate markers for kidney iron deposition. A previous study reported that R2* measurements are more robust to variations in the length scale of iron deposition and more accurately reflect bulk magnetic susceptibility of tissues [7]. Some investigators prefer to report rates of signal decay, R2 or R2*, instead of the half-lives T2 or T2*, stating that these parameters are directly proportional to iron, rather than inversely proportional to iron, thus rise linearly with chemically determined tissue iron concentration in both liver and heart [24–26].

We found that 12/50 (24%) of our studied patients had low renal T2* cutoff < 31 msec while renal R2* was significantly higher than standard control values. In contrast, Schein and associates [4] showed that mean kidney R2* of patients with β-TM was 22.1 ± 11 Hz in TM patients with only 5/73 (6.8%) patients being outside the normal range. They suggested that renal iron toxicity in thalassemia would have to occur at concentrations below the MRI detection limit. However, a number of investigators have claimed iron damages of thalassemic kidneys [27].

In this study, a significant positive correlation between serum cystatin C and renal R2* while cystatin C levels were negatively correlated to renal T2*; however, no correlation was found between Renal T2* or

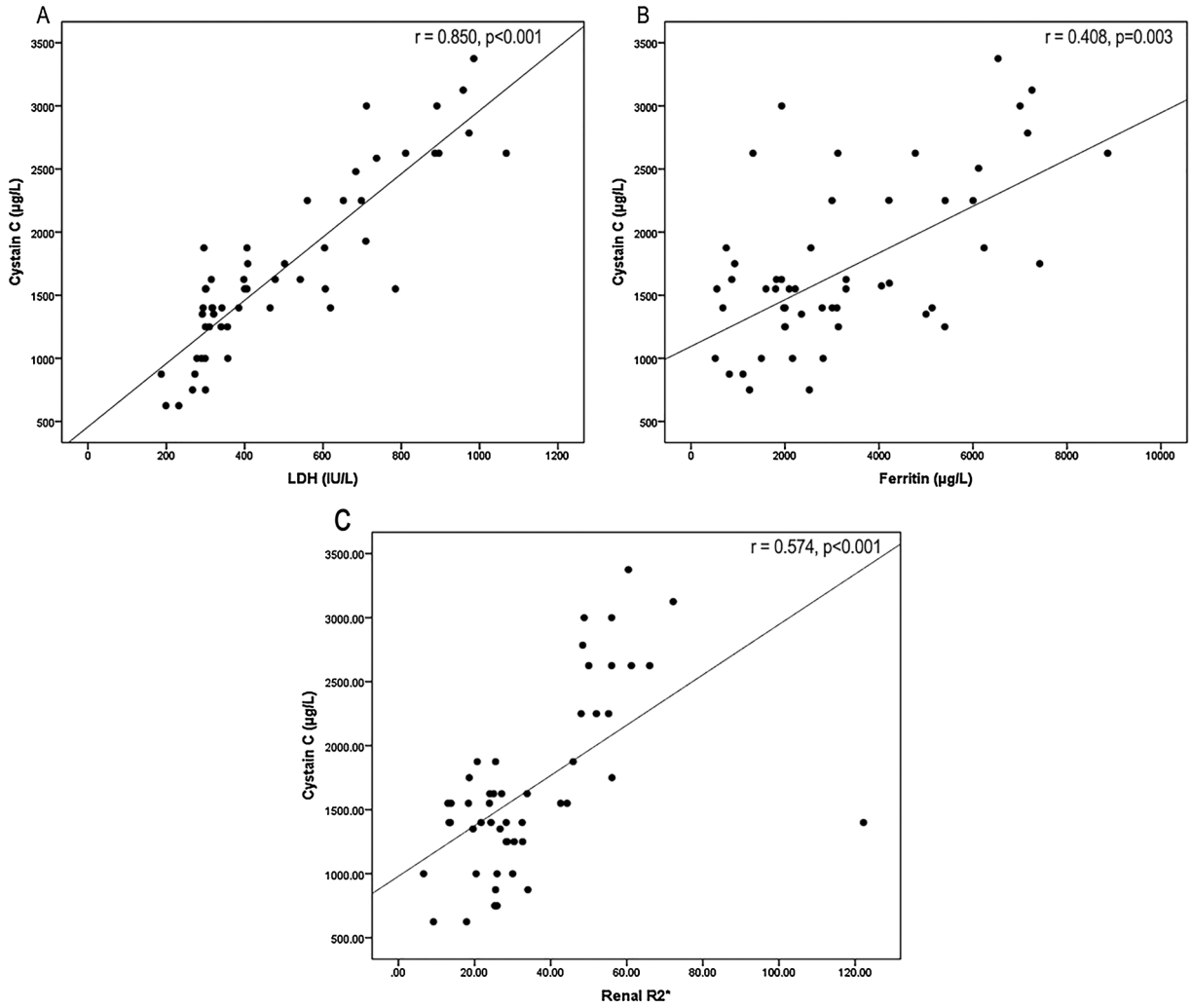

Fig. 2. Positive correlations between serum cystatin C levels and lactate dehydrogenase (A), serum ferritin (B), and renal R2* (C) among patients with β-thalassemia major.

R2* and age or disease duration; as reported recently [5]. We used the lower limit of normal for the mean kidney T2* value (31 ms) reported by Grassedonio et al. [5] as a cutoff and found higher cystatin C levels in patients with renal T2* < 31 msec but no significant difference between thalassemia patients with renal T2* above or lower than 31 msec as regards β2 M, serum creatinine and urea. Among our β-TM patients, renal R2* was positively correlated to LIC and inversely correlated to cardiac T2*. Yet, neither Renal T2* nor R2* were correlated to serum ferritin level. The significant independent variables related to increased R2* among patients with β-TM were LDH, cystatin C and cardiac T2*.

In this context, Hashemieh et al. [6] evaluated the relationship between serum ferritin levels and liver, heart, and kidney MRI in thalassemia patients. They found a moderate correlation between kidney MRI T2* relaxation time and serum ferritin. Kidney MRI T2* relaxation time was weakly correlated with liver MRI T2* relaxation time and cardiac MRI T2* relaxation time. Bhandari and Galanello [28] reported that renal disease is an independent risk factor for increased cardiac risk. On the other hand, Schein and associates [4] did not find a significant correlation between kidney R2* and hepatic iron concentration, nor with heart R2*. In our series, the absent correlation between renal T2* or R2* and serum ferritin indicate that relying on serum ferritin levels to predict the exact condition of kidney iron overload might not be an appropriate approach.

While some investigators observed an elevated urinary excretion of β2 M, which was related to the duration of treatment and dosage and mode of administration of the drug [29], others argued that in patients on DFX chelation, serum cystatin C was significantly higher than those without chelation. They also demonstrated that patients receiving DFX had significant lower eGFR and creatinine clearance than those without iron chelation therapy [16,30]. Grangé et al. [30] suggested that DFX could also increase iron absorption and cause de-compartmentalization of chelated iron in various organs, especially the kidneys, resulting in renal damage. In contrast, Papassotiriou et al. [31] found that cystatin C concentration remained stable during DFX treatment and argued that any changes observed do not reflect renal injury but appear to be a consequence of the effects of DFX on hemodynamic parameters.

It is worth to note that in our study, DFX therapy alone or combined was associated with significantly higher levels of glomerular and tubular markers as well as renal R2* and LIC, while cardiac T2* was significantly lower. We attributed our results to the poor compliance of this group of patients where 48.1% of patients were non-compliant.

In a multicenter randomized phase 3 registration trial comparing DFX and DFO therapy in patients with β-TM, mild dose-dependent increases in serum creatinine were noted in 38% of patients receiving DFX, most frequently at doses of 20 or 30 mg/kg, compared with 14% in the DFO arm [32]. Recently, Piga and colleagues [33] revealed some modest variations in renal tubular markers with DFX treatment with an observed lack of correlation between serum ferritin and GFR as well as renal blood flow; although they attributed part of their results to the

small sample size, yet the possibility that this inconsistent relationship could reflect the mild and transient effect of DFX on renal haemodynamics was suggested.

A key challenge of chelation therapy is to achieve regular adherence to treatment regimens throughout a lifetime, as even short periods of interruption to treatment can have damaging effects. In fact, inadequate compliance with iron chelation therapy in TM is common and results in substantial morbidity and mortality, as well as increased costs [34]. Therefore, it could be expected to find that low renal T2* cutoff < 31 msec was associated with poor compliance to chelation among our patients and renal R2* was significantly higher in those with poor compliance to chelation therapy.

In the current study, the mean age of patients was 12.8 ± 3.2 years. It is worth mentioning that the technique of renal MRI requires short breath holding, which makes its routine use for young children less than 10 years difficult, yet; data showed that the first assessment of iron overload might be necessary and applicable for children as early as 5 years old, if they can tolerate the scans without sedation, particularly in countries with a large number of patients and problems related to the availability of iron chelation and compliance to therapy [35,36].

One limitation of this study includes the presence of a relatively small sample size; since the study addressed many variables of renal impairment in β-TM, a larger sample would have been more appropriate. Also, further investigating the difference between different iron chelators as monotherapy may have provided additional information.

In conclusion; we suggest that kidney iron deposition impairs renal glomerular and tubular functions in pediatric patients with β-TM and is related to hemolysis, total body iron overload, and poor compliance to chelation. Both kidney MRI T2* and R2* are important for assessment of early renal iron overload in thalassemia patients.

Conflict of interests

The authors declare that they have no conflict of interests.

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