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"Hepatic Iron Deposition Among Thalassemia Children "

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ABSTRACT:

Background: Beta thalassemia is linked to repeated blood transfusions and is a leading cause of anaemia. The most frequent side effect of receiving repeated blood transfusions is iron buildup in soft tissues, including the pancreas, liver, and heart. These days, tissue iron content may be determined and iron overload in various organs, such as the liver and heart, can be estimated using magnetic resonance imaging (MRI), a very sensitive and repeatable method that can be used even before symptoms appear.
Purpose: The goal is to evaluate liver iron deposition in thalassemia patients by hepatic MRI.
Methods: Forty-two female and eighteen male thalassemia patients, ages seven to eighteen, who had received numerous blood transfusions were included in the study. Data on diseases and demographics were gathered. Liver enzymes, serum ferritin, and CBC were measured. Hepatic T2* MRI was used to assess all patients for hepatic iron depositions. Based on the presence and severity of iron depositions, patients were categorised into four groups.

Results: In terms of the length of the disease, the number of blood transfusions received throughout time, and the frequency of blood transfusions, there were statistically significant differences between patients with and without hepatic iron depositions. Also, individuals with hepatic iron deposition had considerably higher ferritin levels. Ferritin and myocardial T2* showed a strong correlation with hepatic T2*. Serum ferritin, blood transfusion frequency, blood transfusion length, and illness severity were all statistically significantly different among the groups with mild, moderate, and severe diseases.

Conclusion: Liver T2* decreased significantly in patients with hepatic iron depositions especially in patients with moderate and severe disease. Disease duration, duration, frequency of blood transfusion were significant predictors for hepatic iron depositions and its severity. Liver T2* correlated significantly to ferritin.

Introduction:

Patients with Beta Thalassemia major (TM) may have iron overload due to their frequent requirement for blood transfusions. The liver, heart, and endocrine organs store excess iron. 71% of TM patients die from cardiac failure, arrhythmias, and tissue damage caused by intracellular free iron ***(Pinto & Forni, 2020).***

Iron load and iron chelation treatment are often routinely monitored using serum ferritin, a cheap, accessible blood sample test. However, because inflammation raises ferritin levels and other variables, besides iron load, also alter ferritin levels, the ferritin analyses do not always correspond well with body iron reserves ***(Gluba- Brzozka et al., 2021).***

The most accurate way to quantify the iron load in the body is to do a transcutaneous biopsy and test the liver iron concentration (LIC). However, the process is intrusive and has a number of negative consequences ***(Liden et al., 2021).***

By measuring the T2 and T2∗ relaxation parameters, magnetic resonance may directly and non-invasively detect iron levels by taking use of the paramagnetic characteristics of tissue iron. Water protons are imaged by magnetic resonance as they diffuse close to iron deposits in the tissue of interest, rather than the iron itself. The iron in the tissues works as tiny magnets, disrupting the uniformity of the magnetic field. The protons in the flowing water undergo markedly distinct magnetic profiles and desynchronize from one other. As a result, the picture darkens according to the amount of iron present. This method's simplicity enables quick and accurate measurement of hepatic and myocardial iron ***(Wahidiyat et al., 2018).***

The aim of the present study was to evaluate hepatic iron deposition using T2* MRI technique.

Patients and Methods:

Patient recruitment: At December 2021 to May 2022, fifty thalassemia patients were gathered at El- Tadamon Hospital in Port Said, Egypt. The Faculty of Medicine, Port Said, institutional review board authorised the study (ERN : MED (8/12/2021)s.no (27) PED917 (02)

Population: Children with thalassemia, both sexes, aged 7 to 18, who had undergone several blood transfusions were included in the research. Participants with hepatic, metabolic, or cardiac conditions were not allowed to participate in the study. Patients who declined to take part in the informed consent process were also not included.

Grouping: Four groups were created for the patients based on the severity of their hepatic iron depositions: no deposition (T2*> 15 ms), mild deposition (15- 10.4 ms), moderate deposition (10.4- 6.8 ms), and severe deposition (below 6.8) ***(İdilman et al., 2016).***

Methodology: Patient sheets were used to gather demographic information, and patients or their caregivers were contacted to get any missing information. The collected data included age, sex, age at diagnosis, disease duration, duration and frequency of blood transfusion, splenectomy and iron chelators types. Laboratory results, such as serum ferritin, liver enzymes, and complete blood count, were examined in the patient data records.

Siemens scanner for hepatic MRI (Germany). The method was explained to the youngster and his caretakers. Neither IV contrast nor sedation were applied. The supine posture was used for patient examinations. The patient was able to hear breathe hold instructions by using headphones that were suitable with the MRI equipment to lessen repeated gradient noise.

T2* Weighted imaging: Iron accumulation in the liver may be identified and measured using gradient echo T2*-weighted imaging. By excluding major vessels and bile ducts, the reader was able to acquire a typical T2* value as well as the lowest and highest T2* value quantifiable in areas that were comparatively free from artefacts. ***T1* Weighted imaging:*** To identify and confirm diagnostic picture quality, a sequence of disparate T1-weighted source images were visually analysed. The use of automatically generated quality control maps (such T1*) can help eliminate major artefacts or misregistration.

Statistical analysis: SPSS (version 21, Chicago, IL, USA) was used to do the statistical analysis. Quantitative parametric data, which was regularly distributed, was given as mean and standard deviation; quantitative non-parametric data, which was abnormally distributed, was provided as median (minimum, maximum); and qualitative data was presented as number and percentage. We'll use the following statistical tests: Chi-square test: for comparing data that is categorical. Student t-test: used to compare two groups' quantitative data that is regularly distributed. The Mann-Whitney test is used to compare quantitative data that is abnormally distributed between two groups. One- way analysis of variance (ANOVA) test was used to compare normally distributed data between more than 2 groups. Pearson correlation was used to assess correlation between 2 normally distributed continuous data. A statistically significant p value was defined as one that was less than 0.05.

Results:

The current study comprised fifty thalassemia patients, with a mean age of 11.5 ± 3.5 years, a greater female frequency of 64%, and a mean illness duration of 7.5 ± 3.3 years. Every patient was kept on iron chelators, with Deferasirox being the most popular kind (used 52% of the time), followed by Deferiprone (20%) and Deferoxamine (12%). In 34% of cases, a splenectomy was carried out. The patients who were included had mean haemoglobin levels of 8.7 ± 1.16 g/dL. The average platelet count was 311.18 ± 129.4 while the average white blood cell count was 6.7 ± 3.4. The mean ALT was 46.13 ± 23.5 and the mean AST was 37.5 ± 6.44. Table 1 shows mean ferritin levels of 2549.3 ± 1230 ***(table 1)***.

Table (1): Demographics, baseline, and disease characteristic:

	Total cohort (n= 50)
Age (years) Mean ± SD	11.5 ± 3.5
Sex No. (%) - Male - Female	 18 (36%) 32 (64%)
Age at diagnosis (year) Mean ± SD	3.9 ± 2
Disease duration (years) Mean ± SD	7.5 ± 3.3
Splenectomy No. (%)	17 (34%)
Duration of blood transfusion (years) Mean ± SD	6.6 ± 3.3
Frequency of blood transfusion (time/ year) Mean ± SD	8.5 ± 3.5
Iron chelators No. (%)	42 (84%)
Type of chelators No. (%): - Deferoxamine - Deferiprone - Deferasirox	 6 (12%) 10 (20%) 26 (52%)
Hemoglobin (g/dL)	8.7 ± 1.16
White blood cell (*10^3/mm^3)	6.7 ± 3.4
Platelets (*10^3/mm^3)	311.18 ± 129.4
Aspartate aminotransferase (IU/L)	37.5 ± 6.33
Alanine aminotransferase (IU/L)	46.13 ± 23.5
Ferritin (microgram/ liter)	2549.28 ± 1230.0

Descriptive and frequency analysis

The mean value of liver T2* was 5.2 ± 2.6. The T2 value was used to categorise the children based on their hepatic iron deposition: five had no iron deposition, eighteen had mild iron deposition, fourteen had moderate iron deposition, and thirteen had severe iron deposition. R2* values for the liver mean 386.5 ± 143.4 Hz. The average liver iron content (LIC) was found to be 8.69 ± 2.01 mg/g ***(table 2).***

Table (2): Detection of iron deposition in liver by MRI:

	Total cohort (n= 50)
Liver T2* value Mean ± SD	5.2 ± 2.6
Liver R2* value Mean ± SD	386.5 ± 143.4
Live liver iron concentration (LIC) (mg/g)	8.69 ± 2.01
Degree of liver depositions: No. (%) - No - Mild - Moderate - Severe	 5 (10%) 18 (36%) 14 (28%) 13 (26%)

Descriptive and frequency analysis

Patients with and without hepatic iron deposition were studied in order to evaluate risk factors for hepatic iron deposition. The liver T2* mean values were greater in the patients with hepatic iron deposition group, with statistically significant differences (p= 0.011). In terms of age and gender distribution, both groups were similar. There was a statistically significant difference (p=0.03) in the length of illness duration among patients with hepatic iron deposits. Additionally, patients with iron deposition had longer and more frequent blood transfusions, with statistically significant differences (p=0.048; <0.001) between them. Regarding the laboratory results, there were no statistically significant differences between the two groups; however, the hepatic iron deposition group had significantly higher mean levels of serum ferritin (p=0.02) ***(table of 3).***

MRI photos are not available

Table (3): Comparison between patients with and without hepatic iron deposition as regard baseline characteristics:

	No iron deposition (n= 5)	Hepatic deposition (n= 45)	Test of significance	P value
Liver T2*	16.5 ± 1.4	3.9 ± 0.46	9.02	***<0.001***
Age (years) Mean ± SD	13.9 ± 2.3	11.23 ± 3.6	1.6	0.11
Sex No. (%) - Male - Female	 2 (40%) 3 (60%)	 16 (35.6%) 29 (64.4%)	0.004	0.99
Disease duration (years) Mean ± SD	7.2 ± 3.3	10.5 ± 1.8	2.18	***0.03***
Splenectomy No. (%)	0 (0%)	17 (37.8%)	2.86	0.23
Duration of blood transfusion (years) Mean ± SD	6.4 ± 3.4	9.5 ± 1.8	2.03	***0.048***
Frequency of blood transfusion (time/ year) Mean ± SD	7.87 ± 3.14	14.4 ± 0.5	4.5	***<0.001***
Iron chelators No. (%)	5 (100%)	37 (82.2%)	1.06	0.7
Hemoglobin (g/dL)	9.3 ± 0.66	8.68 ± 1.2	1.085	0.28
White blood cell ($*10^3/mm^3$)	6.5 ± 3.1	6.8 ± 3.2	-0.19	0.85
Platelets ($*10^3/mm^3$)	309.6 ± 104.6	311.4 ± 132.9	-0.02	0.98
Aspartate aminotransferase (IU/L)	35.8 ± 1.09	37.6 ± 6.6	-0.6	0.54
Alanine aminotransferase (IU/L)	31.8 ± 9.06	47.7 ± 23	-1.4	0.15
Ferritin (microgram/ liter)	442.2 ± 201.6	2783 ± 332.6	-2.3	***0.02***

X^2: Chi square test; t: student t test; Level of significance < 0.001

Apart from an inverse significant association with serum ferritin (r: -0.58; p<0.001), there were no statistically significant correlations found between T2* liver and age, illness duration, blood transfusion duration, or laboratory examinations. ***Table 4*** shows a statistically significant positive association (r: 0.64; p<0.001) between liver T2* and myocardium T2*.

Table (4): Correlation of liver T2* to demographics and laboratory findings:

	Correlation coefficient (r)	P value
Age	0.17	0.25
Disease duration	0.19	0.17
Blood transfusion duration	0.2	0.14
Hemoglobin	0.1	0.49
White blood cells	0.02	0.89
Platelets	0.26	0.07
Aspartate aminotransferase	-0.16	0.27
Alanine aminotransferase	-0.24	0.098
Ferritin	-0.58	***<0.001***

r: Pearson correlation; Level of significance < 0.05.

Regarding age, sex distribution, and length of illness, there were no statistically significant differences found between the groups with mild, moderate, severe, and no deposition. Compared to other groups, the group with severe hepatic iron accumulation experienced blood transfusions more often and for longer periods of time, with statistically significant differences (p=0.035; <0.001). Regarding the usage of iron chelators, there were no statistically significant differences between the groups ***(table 5).***

Table (5): Comparison between different grades of hepatic iron depositions according to T2 regarding baseline demographics, disease, and treatment data:

	No deposition (n= 5) (10%)	Mild (n= 18) (36%)	Moderate (n= 14) (28%)	Severe (n=13) (26%)	p value
Liver T2*	16.5 ± 1.36	7.09 ± 2.4 a	2.24 ± 0.47 a, b	1.34 ± 0.45 a, b	***<0.001***
Age (years) Mean ± SD	13.9 ± 2.3	12.2 ± 3.4	10.6 ± 4.4	10.4 ± 2.5	0.16
Sex No. (%) - Male - Female	2 (40%) 3 (60%)	8 (44.4%) 10 (55.6%)	4 (28.6%) 10 (71.4%)	4 (30.8%) 9 (69.2%)	0.78
Disease duration (years) Mean ± SD	6.7 ± 1.8	7.3 ± 3.4	6.3 ± 2.9	6.4 ± 3.3	0.3
Splenectomy No. (%)	0 (0%)	10 (55.6%)	4 (28.6%)	3 (23.1%)	0.066
Duration of blood transfusion (years) Mean ± SD	5.2 ± 2.5	5.9 ± 2.9	7.6 ± 3.3	9.5 ± 1.8 a, b	***0.035***
Frequency of blood transfusion (time/ year) Mean ± SD	8.4 ± 2.4	8.1 ± 1.3	8.4 ± 4.5	14.4 ± 0.5 a, b, c	***<0.001***
Iron chelators No. (%)	5 (100%)	16 (88.9%)	10 (71.4%)	11 (84.6%)	0.4

X^2: Chi square test; F= ANOVA test; level of significance< 0.05.
a: Significant difference against no deposition group
b: Significant difference against mild deposition group
c: Significant difference against moderate deposition group

The tested groups did not differ statistically significantly in terms of haemoglobin, platelets, white blood cell count, AST, or ALT. Serum ferritin showed a statistically significant difference ($p<0.001$) between the tested groups, with the highest mean values in the groups with severe iron deposition and the lowest mean values in the group without deposition ***(table 6).***

Table (6): Comparison between different grades of hepatic iron depositions regarding laboratory findings:

	No deposition (n= 5)	Mild (n= 18)	Moderate (n= 14)	Severe (n=13)	F	p value
Hemoglobin (g/dL)	9.2 ± 0.65	8.6 ± 1.2	8.6 ± 0.6	8.8 ± 1.6	0.5	0.66
White blood cell ($*10^3/mm^3$)	6.4 ± 3.5	8.2 ± 4.3	5.8 ± 0.6	5.8 ± 2.1	1.5	0.23
Platelets ($*10^3/mm^3$)	309 ± 104.6	365.4 ± 156.3	243.4 ± 94.6	309.6 ± 103.4	2.55	0.067
Aspartate aminotransferase (IU/L)	35.8 ± 1.09	36.3 ± 7.01	37.1 ± 2.5	39.6 ± 8.9	0.7	0.54
Alanine aminotransferase (IU/L)	31.8 ± 15.7	45.9 ± 20.8	49.14 ± 15.7	48.16 ± 19.1	0.7	0.54
Ferritin (microgram/ liter)	442.2 ± 201	1464.1 ± 717 a	2607 ± 1333 a, b	4799.23 a, b, c	12.44	***<0.001***

F= ANOVA test; level of significance< 0.05.
a: Significant difference against no deposition group
b: Significant difference against mild deposition group
c: Significant difference against moderate deposition group

Discussion:

The children that were included had mean values of 11.5 ± 3.5 years, with 64% of them being female. The mean illness duration was 7.5 ± 3.3 years, and the mean age at diagnosis was 3.9 ± 2. Thirty children with thalassemia who had comparable illness duration (7_15 years) and mean age (11.2 ± 1.93) were included in a recent study by Kalekar et al. He did discover a greater male preponderance, nevertheless ***(Kalekar et al., 2022).*** Additionally, Rao et al. recruited 25 children with thalassemia whose median age was 16 (range 14–19) years; nevertheless, 60% of the participants in his research were male ***(Rao et al., 2022).*** On the other hand, Abtahi et al.'s study had 52 patients who were older and mostly male (56%) ***(Abtahi et al., 2019).*** In addition, Leung et al. included 44 patients with a mean age of 19.5 years and a predominance of males ***(Leung et al., 2009).***

Blood transfusions were given an average of 6.6 ± 3.3 years and 8.5 ± 3.5 times annually. Prior research involved maintaining patients on varying frequency of routine blood transfusions ***(Abtahi et al., 2019; Rao et al., 2022).*** Iron chelators were used to sustain about 84% of the patients. Deferasirox was the most often utilised iron chelator (52%). Deferoxamine (12%) and deferiprone (20%) were two other forms that were employed.

Contrary to the current investigation, Habib et al. demonstrated that patients were more commonly getting oral deferasiro × 20–40 mg/kg/day or subcutaneous deferoxamine mesylate 30–40 mg/kg/day as part of chelation treatment ***(Habib & Ayad, 2021).*** Additionally, desferoxamine was shown to be the most commonly given chelation agent as a monotherapy by Rao et al. (64%). Desferoxamine, desferiprone, desferasirox, or a combination of these compounds were administered to patients as chelation agents ***(Rao et al., 2022).***

The results of the laboratory showed low haemoglobin and increased ALT as the most obvious abnormalities. Ferritin in serum has a mean of 2549.8 ± 1230. Serum ferritin level in Abtahi et al. was 2584 ± 19.3 ng/ml (Abtahi et al., 2019). In a similar vein, patients of Rao et al. and Habib et al. had low mean haemoglobin levels and increased liver enzymes. Additionally, they published ferritin mean levels similar to the current findings (2354 ± 234; 2567 ± 156.3, respectively) ***(Rao et al., 2022; Habib & Ayad, 2021).***

The mean T2 of the liver in the current research was 5.2 ± 2.6, with a variable % of patients having varying degrees of hepatic deposition and a low number of patients having no iron depositions. According to Shehata et al. ***(Shehata et al., 2019)***, the cases' mean hepatic T2* value was 5.2 ± 4.3 (0.82–18.4) ms, with a median of 2.9 ms. Leung et al. (2009) revealed that the hepatic T2* was comparable to 4.5 ± 2.8. The median hepatic T2* was found by Fattahi et al. to be 7.5 (0.5-22) ***(Fattahi et al., 2021).*** The liver's lower T2* was demonstrated by Habib et al. As he demonstrated that the MRI-T2* of the liver ranged from 1.1 to 41 ms (median = 3.5), Habib et al. revealed reduced T2 values in hepatic iron deposition ***(Habib & Ayad, 2021).***

Age, sex, or length of illness did not significantly differ among the various hepatic iron deposition groups in the current investigation. ***Heris et al., (2021)*** found no significant age or sex differences between the hepatic iron deposition group, which is consistent with the current investigation. In contrast to the present investigation, Habib et al. demonstrated a strong link between age or the length of the condition and the liver's T2 ***(Habib & Ayad, 2021).*** This study involved over 25 children. Additionally, Shehata et al. found no connection between patient age or sex and hepatic T2* ***(Shehata et al., 2019).*** Leung et al. had previously achieved similar results ***(Leung et al., 2009).*** Furthermore, Shamsian et al. did not find any appreciable variations in terms of sex or age ***(Shamsian et al., 2012).*** As hepatic T2* liver and illness severity rose with increased length and frequency of blood transfusion, there were statistically significant differences between different degrees of hepatic iron deposition and duration or frequency of blood transfusion. On the other hand, Leung et al.

were unable to show a meaningful correlation between the severity of the condition and the quantity or frequency of blood transfusions ***(Leung et al., 2009).***

According to ***Shamsian et al. (2012),*** there was no discernible relationship between the start and duration of blood transfusions and hepatic T2*. Regarding the usage of iron chelators, no variations were seen between the groups under investigation. It is likely that Leung et al. did not find a relationship between the length of chelation therapy and hepatic T2* ***(Leung et al., 2009).*** Furthermore, Shamsian et al. discovered no meaningful association between chelator treatment and hepatic T2 ***(Shamsian et al., 2012).***

The current study demonstrated no link between hepatic T2* and various laboratory studies, with the exception of serum ferritin, and no statistically significant variations between different degrees of hepatic iron deposition related distinct laboratory results. Serum ferritin showed the lowest mean levels in the no deposition group and the highest mean values in the severe group, indicating statistically significant differences between the various degrees of hepatic iron deposition. As shown in tables 11 and 12, serum ferritin therefore had an inverse correlation with liver T2 (r: -0.58; p <0.001). Most likely, T2 liver, the amount of iron deposition, and serum ferritin were found to be significantly correlated by Habib et al. ***(Habib & Ayad, 2021).***

Additionally, Shehata et al. found a substantial inverse relationship between serum ferritin and hepatic T2* ***(Shehata et al., 2019).*** Similarly, in children with thalassemia, Eghbali et al. demonstrated a strong association between serum ferritin and hepatic T2* ***(Eghbali et al., 2014).*** Similar strong link was also found by Majd et al. ***(Majd et al., 2015).*** According to Zamani et al. ***(Zamani et al., 2011),*** serum ferritin is a useful indicator of hepatic iron loading. Furthermore, Shamsian et al. found that a greater ferritin level was seen in the livers of those with higher iron loads ***(Shamsian et al., 2012).*** Significant differences were seen between the examined groups in terms of AST and serum ferritin, with larger amounts identified in the group with severe hepatic deposition ***(Heris et al., 2021).*** On the other hand, ferritin and hepatic T2* were not shown to be correlated by ***Puliyel et al. (2014)***, who reported that serum ferritin was not able to predict hepatic iron excess.

T2* myocardial and hepatic T2* showed a positive, statistically significant connection in the current investigation (r: 0.639; p< 0.001). Similarly, Shehata et al.'s study ***(Shehata et al., 2019)*** discovered a small but significant association (r = 0.3) between liver and heart T2* (p = 0.02). Leung et al., on the other hand, did not find a significant association between hepatic and cardiac T2* ***(Leung et al., 2009).*** Additionally, Abdallah et al. failed to find a significant relationship between hepatic and cardiac T2* ***(Abdallah et al., 2021).*** Research by Wahidiyat

et al. and Merchant et al. revealed that there is no correlation between myocardial iron and the severity of hepatic iron overload ***(Wahidiyat et al., 2017), (Merchant et al., 2011).*** Furthermore, ***Shamsian et al. (2012)*** found no evidence of a significant association between hepatic and cardiac T2*.

Finally, MRI liver T2* was able to discriminate between patients with and without hepatic iron deposition as it decreased significantly in patients with hepatic iron. Also, liver T2* was associated with disease severity as it decreased significantly in patients with moderate and severe disease in comparison to patients with mild disease. Disease duration, frequency of blood transfusion and serum ferritin were considered significant determinants for hepatic iron deposition and its severity.

List of abbreviations:

Abbreviation	
MRI	Magnetic resonance imaging
TM	Thalassemia major
LIC	Liver iron concentration
IV	Intravenous
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
R	Pearson correlation

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