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Hepatic Iron Deposition Quantification in Patients with β-Thalassemia Using Magnetic Resonance Imaging

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Abstract

Background: Detection and quantification of liver iron overload are significant to initiate treatment and monitoring of iron overload. This study aimed to quantify liver iron deposits in β-thalassemia major patients using MRI T2* and its correlation with age and heart iron deposition.

Methods and Results: This retrospective study included 54 records of patients between 5-16 years of age with hepatic iron deposition due to β-thalassemia major. Data were collected from MRI reports in Picture Archiving and Communication Systems-Radiology Information System (PACS-RIS) and serum ferritin (SF) test results obtained from Hospital Information Systems and written into a dedicated datasheet. The information was recorded on a data collection sheet. The datasheet included all the required data, demographic data, lab results, T2* mapping for iron deposition in the liver and heart, and liver measurements.

All subjects had high SF (from 1120 to 9850 ng/ml) with an average of 4317.93±2779.9 ng/ml. Age and SF correlated positively (r=0.368, *P*=0.0006). A negative correlation was observed between SF and liver T2* (r=-0578, *P*=0.000), whereas between liver T2* and heart T2* correlation had a positive direction (r=0.329, *P*=0.015)

Conclusion: MRI provides accurate, non-invasive, valid, and repeatable techniques, which are more acceptable to patients for assessing iron load. Furthermore, MRI T2* methods measure iron overload within the target organ precisely.(**International Journal of Biomedicine. 2023;13(3):105-109.**)

Keywords: iron deposition • ferritin • β-thalassemia • MRI

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Introduction

Hemochromatosis is a metabolic disorder that causes excess iron deposition, which leads to iron accumulation in the body's organs, especially in the liver, heart, and pancreas, causing dysfunction or severe health complications.[(1)] Hemochromatosis was first described in 1865 by the French physician Armand Trousseau as "bronze diabetes."[(2)] The hereditary nature of hemochromatosis was demonstrated by Marcel Simon and colleagues in the 1970's.[(3)] Secondary hemochromatosis is the result of another disease or condition that creates iron overload.

Hereditary hemochromatosis (HH) is an autosomal recessive disease caused by mutations in the "high iron Fe"(*HFE*) gene. Two of the 37 allelic variants of *HFE* described to date

(C282Y and H63D) are significantly correlated with HH.[4] Homozygosity for the C282Y mutation was found in 52–100% of previous studies on clinically diagnosed probands.[5] Today, approximately 0.4% of Caucasians carry a homozygous[6,7] and approximately 6% a heterozygous *HFE* C282Y mutation.[7] The C282Y mutation causes excessive systemic iron accumulation.[8,9] Normal iron absorption happens in the proximal small intestine, 1–2 mg daily. However, this absorption rate may increase to 4–5 mg daily with progressive accumulation of 15–40 g of iron in patients with hereditary hemochromatosis. Despite this high prevalence, the mutation causes a clinically relevant phenotype only in a minority of cases.[10] HH is observed mostly in people of northern European origin, with a prevalence of approximately 1 per 220–250 persons, while it is less prevalent in patients of African descent.[6,11-12] Some rare forms of HH are increasingly found in patients clinically characterized as HH and negative for C282Y homozygosity in *HFE*.[13] They present with phenotypically proven hepatic iron overload with no other explanation. These forms are distributed in Asian populations, where they may represent the main non-hematological cause of hereditary iron overload.[14-16]

Secondary hemochromatosis is mostly related to multiple red blood cell transfusions in patients with red blood cell disorders involving β-thalassemia major, myelodysplastic syndromes, aplastic anemia, and sickle cell disease.[17] Our study focused attention on thalassemia. β-thalassemia syndromes are the most common inherited hemoglobinopathies caused by a genetic deficiency in beta-globin. Although regular blood transfusion has increased the survival rate among thalassemia patients, treatment of the disease itself could lead to a chain of syndromes, such as iron deposits, that lead to organ dysfunction, which sometimes may cause death.[18]

The liver is one of the main sources of iron storage. Therefore, the detection of liver iron overload initiates treatment and prevents complications. A liver biopsy has been a standard reference for detecting and quantifying liver iron content. Still, its invasive nature limits its implementation, and its accuracy is greatly affected by hepatic inflammation, fibrosis, and uneven iron distribution. Also, serum ferritin (SF) has been used as a surrogate marker, but it is not reliable because its level may be affected by inflammation, vitamin C deficiency, oxidative stress, hepatic dysfunction, or malignancy.[19]

Alternatively, the MRI T2* technique is a valid, non-invasive, and reproducible method for evaluating tissue iron loading and, therefore, more acceptable to patients. It measures iron load within the objective organ by measuring the effect of local distortion of magnetic fields caused by excess iron in tissues. Iron concentrations are based on measurements of proton transverse magnetization decay rates, relaxometry (R2 or R2*), as great signal decay rates indicate great iron absorption.[20,21]

In 2005, Wood et al.[21] measured the R2* from a single, mild hepatic segment by drawing ROI boundaries of the liver, and excluding hilar vessels from obtaining an R2* map by using the gradient-recalled-multi-echo (GRE MR) imaging technique with a single breath-hold for each echo GRE sequence.

In 2019 Sobhani et al.[19] assessed the role of multi-echo T2*-weighted image (T2*WI) in MRI quantification of hepatic iron deposition in patients with β-thalassemia major. They explained that patients with high SF are likelier to have higher liver or cardiac iron load.

Thalassemia is an inherited disease that causes many complications, and the treatment of the disease itself could lead to a chain of syndromes, which sometimes may cause death. Despite this, there is a shortage of regional studies to establish regional references.

This study aimed to quantify liver iron deposits in β-thalassemia major patients using MRI T2* and its correlation with age and heart iron deposition.

Materials and Methods

The study included 54 records of patients between 5-16 years of age with hepatic iron deposition due to β-thalassemia major. Patients diagnosed with another hemochromatosis type or MRI contraindicated for him were excluded. The study was carried out at the Medina Maternity and Children Hospital in Al Medina Almonawara from Dec 2021 to May, 2022.

Study design, data collection, and analysis

In this descriptive and retrospective study, patients underwent MRI with a 1.5-T machine (GE, Healthcare) using a body coil or cardiac coil, respiratory triggering or navigators, and peripheral gating. All patients received frequent blood transfusions and chelation therapy (Deferasirox), a dose of approximately 750-1500 mg per day, through 170 days. The demographic data were extracted from patients' documents. Patients underwent liver and cardiac MRIs.

Data were collected from MRI reports in Picture Archiving and Communication Systems-Radiology Information System (PACS-RIS) and SF test results obtained from Hospital Information Systems and written into a dedicated datasheet. The information was recorded on a data collection sheet. The datasheet included all the required data, demographic data, lab results, T2* mapping for iron deposition, and liver measurements.

Statistical analysis was performed using the statistical software package SPSS version 23.0 (SPSS Inc, Armonk, NY: IBM Corp). Baseline characteristics were summarized as frequencies and percentages for categorical variables. Minimum, maximum, and mean±SD were used for summarizing the data. A scatterplot was used to show the relationship between two quantitative variables measured for the same individuals. Pearson's Correlation Coefficient (r) was used to determine the strength of the relationship between the two continuous variables. A probability value of $P<0.05$ was considered statistically significant.

Ethical approvals were obtained from the The institutional review board (IRB) at King Salman bin Abdulaziz Medical City (IRB number: 040-22).

Results

Of the 54 pediatric β-thalassemia major patients between 5 and 16 years of age, the largest group was the 9-12 years, representing 48.1% (Table 1). All subjects had high SF (from 1120 to 9850 ng/ml) with an average of 4317.93± 2779.9 ng/ml (Table 2). Age and SF correlated positively (r=0.368, P=0.0006)

(Table 3). There was a significant positive correlation between age and liver size (r=0.303, *P*=0.026) (Table 3). No correlation was found between liver T2* and age (P=0.662) (Table 3). A negative correlation was observed between SF and liver T2* (r=-0578, *P*=0.000) (Table 3, Figure 1), whereas between liver T2* and heart T2* correlation had a positive direction (r=0.329, *P*=0.015) (Table 3, Figure 2).

Table 1.

The age groups of the patients

Age group	N	Percentage (%)
5 – 8 yrs.	13	24.1
9 – 12 yrs.	26	48.1
13-16 yrs.	15	27.8
Total	54	100

Table 2.

Testing parameters

	Mean	Maximum	Minimum	Variance	SD
Age	2.04	3.00	1.00	0.53	0.73
Weight, kg	30.82	56.00	13.00	94.34	9.71
Ferritin, ng/ml	4317.93	9850.00	1120.00	7728225.88	2779.9
T2* liver	2.49	8.00	0.30	3.83	1.96
T2*heart	24.05	45.70	4.00	131.13	11.45
Liver size, cm	16.74	20.50	12.11	5.86	2.42

Table 3.

Pearson correlations between the variables of the study.

Correlations		SF	Liver size	T2* liver
Age	Pearson Correlation	0.368	0.303	- 0.069
	P-value	0.006	0.026	0.622
SF	Pearson Correlation			-0.578
	P-value			0.000
T2* heart	Pearson Correlation			0.329
	P-value			0.015

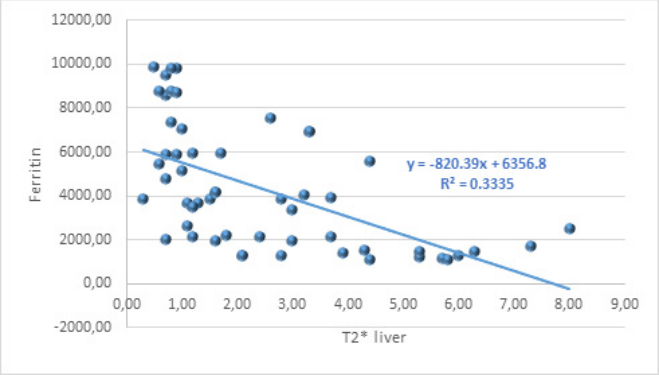

Fig. 1. *Scatter plot with a fit line of SF with T2* liver.*

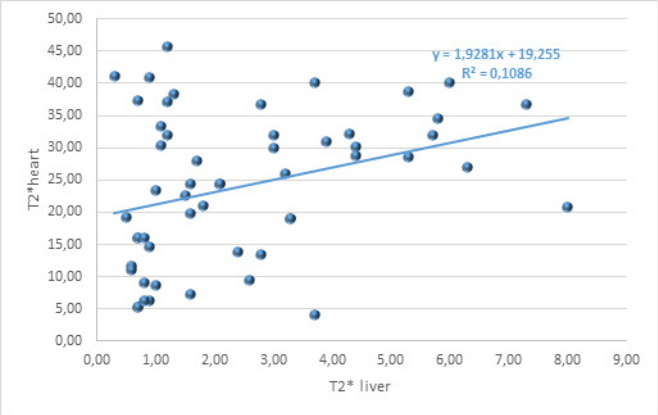

Fig. 2. *Scatter plot with a fit line of T2* heart with T2* liver.*

Discussion

Iron overload in β-thalassemia major patients occurs because the rate of iron entering the body is considerably greater than the rate of clearance, leading to excess iron discharge into the blood. The body has no mechanism for eliminating excess iron, so it is collected and stored in crystalline form within ferritin and hemosiderin. This study's primary objective was quantifying hepatic iron deposition in patients with β-thalassemia by multi-echo T2* weighted sequence through the relaxometry method where short Time to Echo (TE) (0.9 - 11 ms) was used with a breath-hold. Then MRI images were transferred to a post-processing program (GE Cardiac VX) for MRI analytical software. The region of interest (ROI) of about 1-2cm or more was placed in the greater part of the liver parenchyma to measure the signal intensity for each TE.

This study, conducted on β-thalassemia major patients of a range of ages from 5 to16 years, has presented various results for iron overload (mild, moderate, severe). This study followed the method of Wood et al.,[21] which used a multi-echo T2*-weighted sequence with short TEs and a breath-hold for hepatic iron quantification. While short TE is considered key to detecting iron concentration, especially in defining severe iron overload in the liver;[22] also, a long TE makes respiratory motion artifacts appear in images.[23]

Our study showed a moderate positive correlation between age and SF (Table 3). This explains that as age increases, blood transfusions increase and thus lead to increased iron deposits. On the contrary, Bandyopadhyay et al.[23] performed a similar study which demonstrated that patients at a younger age had more elevated ferritin levels, which illustrates that these differences were due to improper chelation regimens or that the patients had not obtained chelation treatment. Furthermore, they observed no significant correlation between the age and liver T2*, similar to our study findings. This explains the heterogeneous distribution of depository iron.

A moderate negative correlation (r=-0.578) was observed between SF level and liver T2*, like Azarkeivan et al.,[24] S Kaban & Ç Damar,[25] and El Sherif et al.[26] This result shows that patients with high SF are more likely to have a

higher liver iron load. A high SF level in the blood may be evidence of iron loading within the body in general; however, the excess iron load distribution among the various organs occurs randomly in the body. Variations in the concentration of iron may usually be related to the chelation protocol.[27] Ferritin level decreases by a factor of 820.39 when liver T2* increases by 1. Heart T2* value increases by a factor of 1.9281 when liver T2* increases by 1.

In our study, there is a positive correlation (r=0.329, *P*=0.015) between liver T2* and heart T2*, while most previous studies, like Kolnagou et al.,[28] showed no correlation between heart T2* and liver T2*. In contrast, El Sherif et al.[26] demonstrated a moderate negative correlation between hepatic and cardiac iron deposition.

The variations in results may be because of distinctions in clinical data, genetic and study population, sample size, SF levels, chelation protocols, and iron deposits in different organs.

Conclusion

Our results indicate negative correlations between iron concentration measurement by liver T2* and SF. There is no significant correlation between age and iron concentration in liver T2*, despite the notable correlation between the age and SF test, illustrating that as age increases, the blood transfusions increase, thus leading to increased iron deposits in the body. The study showed that the iron deposition in the liver is considered an indication of iron deposition in other organs, like the heart, as the study's hypothesis stated. MRI provides accurate, non-invasive, valid, and repeatable techniques, which are more acceptable to patients for assessing iron load. Furthermore, MRI T2* methods measure iron overload within the target organ precisely. Monitoring and follow-up of iron overload using MRI T2* for all hemochromatosis patients is helpful for early detection of any potential complication. Conducting the study on large sample size and other organs is recommended.

Competing Interests

The authors declare that they have no competing interests.

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