The liver injury in patients with B-thalassemia major secondary to iron over load in Thalassemia center of Diwaniyah maternity and children teaching Hospital .
A clinical study in Thalassemia center of Diwaniyah maternity and children teaching Hospital

Suzan Sabber Mutlag*
***Pediatrics Department, College of medicine, University of Al-Qadisiyah**

Abstract

Background:

liver iron concentration assessed by MRI T2* is the better indicator of total-body iron depositions and should be checked in frequent blood transfused patients. MRI T2* can be detect iron overload before iron toxicity becomes clinically apparent.

Aim of study: to prevalence of liver injury among patients with B- thalassemia major secondary to iron over load in Thalassemia center of Diwaniyah maternity and children teaching Hospital**.**

Methods: This a cross – sectional study was carried out on 58 patients (34 males and 24 females) diagnosed β-thalassemia major on the base of the blood investigations (peripheral blood counts and hemoglobin electrophoresis), their age range from 9 years to 36 years. The study was conducted in Thalassemia center of Diwaniyah maternity and children teaching hospital in Al- Diwaniyah Governorate, Republic of Iraq. The Data collection was carried out during the period from the 30th of December 2015 to 11th of August 2016. They were studied for prevalence of liver injury among patients with thalassemia major secondary to iron over load.

Results: Total numbers of B- thalassemia major patients are **58** patient. The numbers of patients with ages less than 10 years are **3 (5.2%)**, patients with ages(10-18)years are **39 (67.2%)**, patients with ages(19-25)years are **12(20.7%).** statistically significant correlation was found between liver function test (LFT) abnormality (ALT, AST) and numbers of blood transfusion per year **(P=0.001)** and also LFT abnormality (ALT, AST) and ferritin levels **(P=0.01).** In our study reported that liver iron concentration was presented normal in 23 patients **(39.7%),** mild iron concentration in 29 patients **(50.0%)** and moderate iron concentration in 6 patients **(10.3%).** There was a significant association between serum ferritin level and the liver iron concentration assess by liver MRI T2* **(P=0.002).**

Conclusion: These results showed that correlation between ferritin, LFT abnormality and liver iron storage detected by MRI T2 in patients with β-thalassemia major. MRI T2* has become the clinical standard to estimate liver iron overload.

Key Words: β-thalassemia major, Serum Ferritin , liver function tests, liver ultrasound examination, MRI T2* for liver Iron overload.

1-1 Introduction

Thalassemia is a genetic hemoglobin disorders characterized by absence of equilibrium between the α-globin and β-globin chain production resulting from either a complete absence of ß- globin chain production ($ß^0$ - thalassemia), or a partial reduction (ß+ thalassemia), while in α – thalassemia , α globin gene production is either absent or partially reduced [(1)].

ß–homozygous thalassemia state presents with variable degrees of anemia from early childhood and are transfusion dependent, clinically known as ß- thalassemia major[(2)]. The optimal treatment for thalassemia major includes regular blood transfusion every 2-5 weeks for long life to keep the pre- transfusion Hb – level above 9-10.5 gm/dl & post transfusion

Hb should not be more than 14-15 gm/dl[3]. The body iron stores appear saturated after giving approximately 20-30 transfusions (500 mg iron/Kg). Increased iron accumulation beyond this level will lead to iron deposition in many organs of the body particularly the liver , heart and endocrine organs leading to present signs of organ injury or damage. Liver abnormalities are hepatomegally , liver dysfunction , and liver cirrhosis . [4]

liver iron concentration assessed by MRI T2* is the better indicator of total-body iron depositions and should be checked in recurrent blood transfused patients [1,3]. Assessed of liver iron concentration(LIC) by , MRI technique which is the reliable and non invasive investigation and good standard to measure iron overload best than serum ferritin[1,5].

(LIC) values are normally up to 1.8 mg/g dry weight .The lower value of the optimal range of LICs for chelating treatment in iron overload due to chronic blood transfusions is 3.2 mg Fe/g dw liver. The upper limit value of the optimal range of LICs for iron overload due to chronic blood transfusions is7.0 mg Fe/g dw liver. IF (7 – 10) mg /gm dry weight lead to the endocrine complications like diabetes mellitus , growth failure , Hypoparathyroidism and hypogonadism. while (10 – 15) mg / gm dry weight associated with liver cirrhosis. lastly if more than 15 mg / gm dry is associated with increased risk for cardiac disease and early death in patients with iron overload due to chronic blood transfusions.

1.2 Aim of the study:-

This study was clarified the prevalence of liver injury among patients with thalassemia major secondary to iron over load in Thalassemia center of Diwaniyah maternity and children teaching Hospital**.**

The correlation of liver injury with certain variable factors including gender of the patients ,age , number of blood transfusion , serum ferritin ,liver function tests, magnetic resonance imaging (MRI T2*) of the liver.

2- Patients and Methods

A cross – sectional study design was adopted on 58 patients (34 males and 24 females) diagnosed β-thalassemia major (homozygous thalassemia) on the base of the diagnosed β-thalassemia major on the base of the blood investigations (peripheral blood counts and hemoglobin electrophoresis), their age range from 9 years to 36 years. All these patients were negative tested for A,B,C hepatitis. All these patients were treated with various transfusion regimens depending on hemoglobin's level and chelating agent in daily does adjusted according to ferritin level.

The study was conducted in Thalassemia center of Diwaniyah maternity and children teaching hospital in Al- Diwaniyah Governorate, Republic of Iraq. The Data collection was carried out during the period from the 30th of December 2015 to 11th of August 2016. They were studied for prevalence of liver injury among patients with thalassemia major secondary to iron over load.

The questionnaire and data collection:

1- The informations were taken from the patients or their families (mother ,father) and the card visit. Data include :age ,sex , address, age at diagnosis of thalassemia, age of starting blood transfusion, Frequency of blood transfusion per year, chelating agent.

2- measurements such as height was measured using an age appropriate stadiometer and weight was measured by weight scale.

3-Laboratory Investigation: Blood samples were obtained from all patients and sent for serum ferritin, liver function tests inside Thalassemia center of Diwaniyah maternity and children teaching hospital in Al- Diwaniyah Governorate, liver ultrasound examination, magnetic resonance imaging (MRI T2*) of the liver done in Kadhemiya teaching hospital in Baghdad Governorate.

Procedure:-

The patients' serum ferritin, AST, , ALT levels, liver ultrasound examination, magnetic resonance imaging (MRI T2*) of the liver were detected. Ferritin was measured by ELISA device (ACC U-BIND ELIZA MICROWELLS) depended on ng/mL. ALT and AST was measured by the analyzer device automatically (made in Japan) depended on mg/dL. A, B, and C hepatitis tests were done by ELISA device. MRI T2 was used to measure the patients' liver iron load using the MRI device (R2*-MRI or its reciprocal T2*-MRI), with signal intensity ratios (SIRs) to adjacent tissues has been used to measure liver iron. [6,7,8]

In MRI T2*, relaxation time measured in millisecond(ms) display the severity of iron overload in the liver, with different values. [9,10]

Table 1: Relaxation times displaying the severity of hepatic iron overload

severity of hepatic iron overload	Relaxation times(ms)
Normal	**≥6.3**
Mild	**2.8-6.29**
Moderate	**1.4-2.79**
Sever	**≤1.39**

Statistical analyses

Statistical analysis was analyzed by using SPSS (statistical package for social sciences) version (16) computer soft ware of Excel 2007 . A level less than 0.05 was considered as statistically significant.

3-Results

General characteristics of the study sample

Total numbers of B- thalassemia major patients are **58** patient. The numbers of patients with ages less than 10 years are **3 (5.2%)**. The numbers of patients with ages(10-18)years are **39 (67.2%)**. The numbers of patients with ages(19-25)years are **12(20.7%).** The numbers of patients with ages more than25years are **4(6.9%)**. These results are outlined in table (**2**).

Table 2: Age groups of B- thalassemia major patients

Age	Frequency	Percent
<10	3	5.2
10-18	39	67.2
19-25	12	20.7
>25	4	6.9
Total	58	100.0

Numbers of male distribution of B- thalassemia major patients are **34(58.6%)**. Numbers of female distribution of B- thalassemia major patients are **24(41.4%)**. These results are outlined in table (**3**).

Table 3: Gender distribution of B- thalassemia major patients

	Frequency	**Percent**
Male	34	58.6
Female	24	41.4
Total	58	100.0

Classification of B- thalassemia major patients according to chelating agents

The percentage of patients taken Dexferaxamine (Desferal) was **(63.8%),** while percentage of patients taken Desferasiroxe (Exjade) was (**36.2%**). Table (**4**) shows these results.

Table 4: Classification of of B- thalassemia major patients according to chelating agents

chelating agent	Frequency	Percent
Dexferaxamine (Desferal)	37	63.8
Desferasiroxe (Exjade)	21	36.2
Total	58	100.0

Correlation between liver function test (ALT,AST) level and other indices

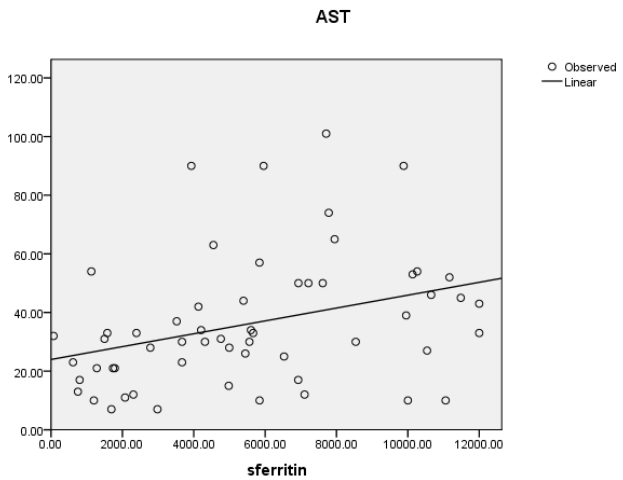
This study was showed statistically significant association between LFT abnormality (ALT, AST) and numbers of blood transfusion per year (P=0.001) and also LFT abnormality (ALT, AST) and ferritin levels (P=0.01), (Table.5, Figure.1, Figure.2). while no significant association was found between LFT abnormality and ages (P=0.74)or chelating agents(P=0.52) or TSB level (P=0.14). Table **(5),** Figure **(1),** Figure**(2)** show these results.

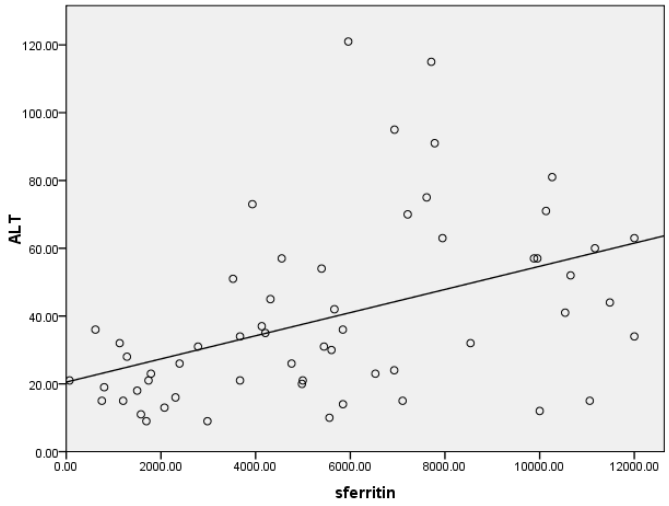
Table 5:-Correlation between liver function test (ALT,AST) and other indices

LFT(ALT,AST) abnormality	**Age groups**	**No. of blood transfusion Per year**	**Chelatng agents**	**S. ferritin level**	**TSB**
Normal (44)	16.93±5.84	18.75±5.26	36.82±10.67	4751.3±3343.30	2.28±1.40
Abnormal (14)	16.14±3.54	24.04±11.17	37.71±5.78	8077.3±2383.103	1.67±1.01
P-value	0.74	0.001	0.52	0.01	0.14

R= 0.339

Figure1:- Correlation between AST level and s. ferritin level





R=0.442

Figure2:- Correlation between ALT level and s. ferritin level

Correlation between liver enlargement by ultrasonography and serum ferritin

There was no statistically significant assocaition was showed between liver enlargement and s.ferritin (P=0.91). Table **(6)** shows these results.

Table 6: Correlation between liver enlargement and s.ferritin

	S ferritin		
Liver enlarge by ultra-sonography	Mean	Std. Deviation	p-value
Normal (32)	5562.8	3319.483	0.91
Enlargement (26)	5543.6	3635.168	
Total	5554.2	3433.462	

Severity of iron liver concentration asses by Liver MRI

The study was reported liver iron level respectively normal in 23 patients (39.7%), mild iron overload in 29 patients (50.0%) and moderate iron load in 6 patients (10.3%). These findings are shown in Table 7.

Table 7: Severity of iron liver concentration asses by Liver MRI

	Iron Liver concentration	Frequency	Percent
Liver MRI	normal	23	39.7
	mild	29	50.0
	moderate	6	10.3
	Total	58	100.0

Association between serum ferritin level and hepatic iron concentration assess by liver MRI

This study was showed a significant association between serum ferritin level and the iron liver concentration assess by liver MRI T2* (P=0.002). These findings are shown in Table 8 and figure 3.

Table 8 Association between serum ferritin level and hepatic iron concentration assess by liver MRI T2*

	liver MRI T2*	N	Mean	Std. Deviation	
S ferritin	normal	23	4576.83	3617.34936	0.002
	mild	29	5421.33	2702.84180	
	moderate	6	9942.83	2880.39181	
	Total	58	5554.23	3433.46182	

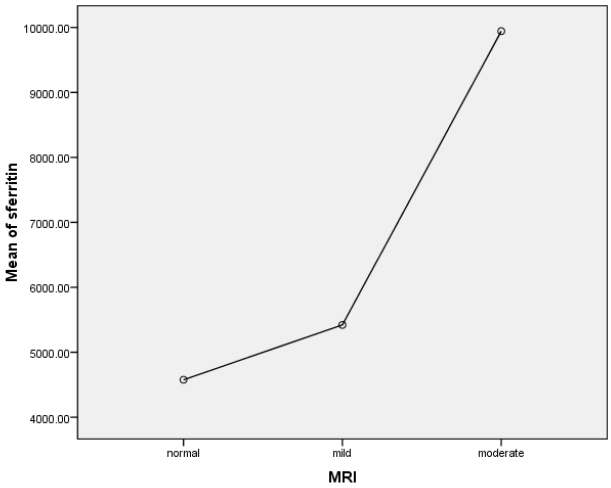


Figure (**3**) Association between serum ferritin level and hepatic iron concentration assess by liver MRI T2*

4-1 Discussion

The present study investigated the level of serum ferritin in B- thalassemia major patients and assess the correlation of serum ferritin with different variable.

In table 4 shows the significant correlation between LFT and numbers of blood transfusion per year(p=0.001). This result is consistent with Bandyopadhyay U study in India [(11)]. Chronic blood transfusions considers the commen cause of iron overload in B- thalassemia major. One unit of blood transfused includes about 250 mg of iron[(12)] . 25 units of blood transfused to the patient per year leads to accumulate 5 grams of iron per year without of chelating therapy[(13)].

In table 4,figure1,figure2 show the significant correlation between serum ALT (R=0.442)and AST (R= 0.339) concentrations and serum ferritin levels in beta-thalassemia patients, (p=o.o1) due to release of the liver enzymes of damaged hepatocytes (especially from cytoplasmic and mitochondrial parts) to the plasma[(14)]. These results are consistent with studies of Maher Y. Abdalla et al [(15)]in jordan (There is a significant association between serum ALT (R=0.315) and AST (R=0.291) levels and serum ferritin levels in beta-thalassemia patients).

In table 8 and figure3 show significant correlation between serum ferritin level and the iron liver concentration assess by liver MRI T2* (P=0.002). This result is consistent with other studies such as Voskaridou E study in Athens, Greece[(16)] , Cunningham MJ study in North America[(17)] and Zamani F study in Iran[(18)]. Because of the liver is the first organ to store iron in the body, so that increased level of serum ferritin is related to increased liveriron level and vice versa. This means ,it is important to clearance liver iron excess as early as possible to decrease the risk of liver damage(especially cirrhosis) and

other organs such as the heart, endocrine organs and bone.

4-2 Conclusions

In summary, in our study we tried to clarify the correlation between serum ferritin , LFT abnormality and hepatic iron storage measured by MRI T2* in patients with β-thalassemia major. MRI T2* has become the clinical standard to estimate liver iron overload.

Recommendation

This study clarified the importance to keep normalized hemoglobin level , good fallow up of iron over load by monitoring of serum ferritin and MRI T2* with regular chelation therapy .

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