MRI Assessment of Liver and Cardiac Iron Concentrations in Some Patients with Beta Thalassemia Major

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ABSCTRACT:

BACKGROUND:

Iron overload is a major concern in blood transfusion dependent beta-thalassemic patient and it is a major cause of cardiac dysfunction. Magnetic resonance imaging T2* has a vital role in liver and cardiac iron deposition and assessment of its severity

OBJECTIVE:

To highlight the role of MRI T2* in assessment of liver and cardiac iron deposition and assessment of other methods of liver and cardiac iron concentration estimation.

PATIENTS AND METHODS:

This cross sectional prospective study had been conducted at the MRI unit of Al-Imamain AL-Khadimain medical city, Baghdad/ Iraq, from December 2015 to December 2016. One hundred, blood transfusion dependent beta-thalassemia major patients had been examined by MRI using T2* images to assess its value which had been changed to liver iron concentration and cardiac iron concentration by using a MEDIS software program.

RESULTS:

One hundred patients (56 male and 44 female) of transfusion dependent beta-thalassemia major had been evaluated for their liver and cardiac T2*, 17 of them shows a mild LIC (liver iron concentration) and normal MIC (myocardial iron concentration), 49 patients show mild increase in both LIC and MIC, 9 show moderate LIC and mild MIC, 16 show moderate both LIC and MIC, 2 show severe LIC with mild MIC, only one shows severe LIC with moderate MIC and 6 of them show severe both LIC and MIC. There is a positive significant correlation between liver T2* and cardiac T2* (P values of 0.017), between liver T2* and LIC (P value of < 0.001), between liver T2* and MIC (P value of 0.031) and that between cardiac T2* and MIC (P value is <0.001). There is non- significant correlation between the age and frequency of blood transfusion with LIC and MIC (P value >0.05). There is also a significant negative correlation between S.ferritin and liver T2*and cardiac T2* (correlation coefficient of -0.251 and -0.397 respectively), with a (P value of 0.014 and 0.00015 respectively). There is non significant correlation between S. ferritin and the severity of LIC and MIC (P value of 0.129 and 0.792).

CONCLUSION:

Magnetic resonance imaging has a vital role as a non-invasive and reliable method in the assessment of liver and cardiac iron deposition in patients with blood transfusion dependent beta-thalassemia major. There is no correlation between S.ferritin level and the severity of LIC and MIC. Patients using Exjade show a lower LIC and MIC than those using Desferal. No correlation between age and frequency of blood transfusion with LIC and MIC in patients on regular chelation.

KEYWORDS: Liver, myocardial iron concentration, S.ferritin, MRI T2*.

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INTRODUCTION:

Iron overload is a common complication of all types of anemias that needs regular blood transfusion. Thalassaemia major is a form of anaemia requiring monthly transfusions from early childhood, with each RBC introducing 200 mg of iron to the patient's system that they lack the natural mechanism to eliminate [1]. In spite of iron chelation therapy, heart failure secondary to post-transfusion iron overload caused by myocardial

siderosis remains the main cause of death in adults [2].

Iron overload occur in those patients as there is no active mechanism to eliminate iron excess (apart from a daily loss of 1-2mg by sloughing of intestinal mucosa and skin), so it will deposit in multiple organs usually after one year from starting regular transfusion [3], mostly the liver causing fibrosis and cirrhosis, heart causing arrhythmia, cardiomyopathy and LV dysfunction, endocrine gland causing diabetes mellitus, hypoganadism, insufficiency of parathyroid & less likely thyroid, pituitary and adrenals [4]. Cardiac iron toxicity is the commonest cause of morbidity and mortality in β-thalassemia major patients and direct rather indirect assessment is important to modify chelation therapy in those with preclinical iron toxicity [5].

Assessment of iron overload has become essential for the therapeutic management of multitransfused patients with beta-thalassemia major because it makes it possible to begin and adapt chelation treatment [6]. Since liver is the first organ for iron storage in patients with transfusion dependent hemoglobinopathy. It is well-known that hepatic iron content is a reliable reflection of overall iron content in the organism. Measurement of liver iron concentration (LIC) is the best parameter to assess iron deposits in the body. Accordingly, it is a key parameter to guide the clinical management of patients with primary or secondary hemochromatosis, characterized by iron overload. Indeed, an accurate quantitative assessment of iron levels should be obtained before initiating therapy [7]. Although chemical analysis of liver biopsies is the method employed for the analysis of LIC (i.e., gold standard), it is an invasive approach and results vary widely [8]. MRI has become the reference technique for assessing LIC, replacing liver biopsy as it is noninvasive and has been shown to provide accurate results compared to the gold standard. It is widely available across the world and several different models for calculating LIC using MRI; both T2 relaxometry [9] and signal intensity ratio (SIR) methods are being used with successful results. MRI had been a safe and accurate method for assessment of LIC in the past decades in patients with transfusion dependent anemias and recently it was widely accepted for monitoring of iron chelation therapy. The paramagnetic properties of the iron in hepatocytes and Kuppfer cells result in local changes in the magnetic field causing a drop of the liver signal.

This effect is especially visible on T2-weighted sequences, which are the most sensitive for detecting iron [6]. Liver R2 magnetic resonance imaging (MRI) has almost completely replaced invasive biopsy for the assessment of liver iron in patients with thalassemia in United States, and in parallel, LIC has significantly improved in this patient population over the past decade [10].

Since 1999, a cardiac MRI technique developed by Pennell and Anderson's team at the Royal Brompton Hospital in London has been available that makes use of T2* to achieve a non-invasive method for quantifying myocardial iron overload in patients with thalassemia major [11]. Iron quantification using T2* MRI has significantly modified the management of diseases with chronic iron overload [12]. Reproducibility of this test was acceptable in several studies. The correlation of iron deposition in the myocardium found by MRI versus biopsy in a patient population wit h thalassemia major was significant, and its values were directly related to tissue iron levels. Cardiac T2* MRI enables accurate prediction of the risk of developing iron related cardiac disease is increasingly utilized to tailor iron chelation treatment in patients with thalassemia and is a factor contributing to improved survival in this patient population [13, 14]. Cardiac MRI gradient echo T2* technique is a highly sensitive noninvasive diagnostic modality that can detect myocardial iron deposition and has an advantage of shorter acquisition times and minimization of motion artifacts from myocardial contraction and respiratory movement as compared with spinecho T2 technique [15].

AIM OF THE STUDY:

This study had been done to high light the role of MRI T2* in assessment of iron deposition in liver and heart and assessment of other methods of LIC and MIC estimation.

PATIENTS AND METHODS:

This cross sectional prospective study had been conducted at the MRI unit of Al-Imamain AL-Khadimain medical city, Baghdad/ Iraq, from December 2015 to December 2016, 100 patients with the diagnosis of beta-thalassemia major aged 6-36 years old were included in this study; all of them were on regular blood transfusion and referred by a clinician (to assess liver and cardiac

iron status). Those patients had been evaluated by 1.5 Tesla MRI machine (Magnetom Avanto, Siemens medical system, Germany) using body and cardiac coils. Liver iron concentration was done for all patients by using gradient-recalled echo sequence. The cardiac iron concentration had been evaluated for all patients by applying ECG gated breath hold spoiled gradient-recalled echo sequences.

Exclusion criteria: patients with primary hemochromatosis, patients with thalassemia minor and intermedia, patients with other anemias (sickle cell, hereditary spherocytosis …etc.) and patients with general contra-indications for MRI examination (e.g. Pacemakers, cochlear implants, metallic foreign bodies… etc.).

Ethical concerns: verbal consent had been obtained from all the patients involved in this study.

Collected data had been formulated for this study and had been validated by the supervisor. The data included: name, age, gender, and onset of diagnosis, duration of treatment, type of chelating agent, blood transfusion interval and S.ferritin level.

The parameters used for liver iron assessment:

Breath hold T2 gradient recalled echo sequence was used, TR 200ms, bright blood image, slice thickness 10mm, FOV 40cm, number of TEs (in milliseconds): 12 measures at 1.29, 3.14, 5.04, 6.94, 8.84, 10.74, 12.64, 14.54, 16.44, 18.34, 20.24, 22.14. Single section is taken with 12 different TEs at the mid portion of the liver below the diaphragm, table 1 show normal and abnormal values of liver iron concentration [16].

Table 1: Liver iron assessment values, LIC=Liver iron concentration[16].

	Normal	Mild	Moderate	Severe
T2*	>5.4	4.5-15.4	2.1-4.5	<2.1
R2*	<65	65-224	224-475	>475
LIC (mg/gm)	<2	2-7	7-15	>15

The parameters used for cardiac iron assessment:

ECG gated breath hold spoiled gradient-recalled echo sequences, TR 200 ms, bright blood image, slice thickness of 10mm, FOV 400 cm, number of TEs (in milliseconds): 8 measures at 2.97, 5.54, 8.23, 10.12, 13.61, 16.3, 18.99, 21.68 ms. The section is taken obliquely to show a longitudinal cardiac section which is sectioned at the mid portion of the interventricular septum in the axial plane. table 2 show normal and abnormal values of myocardial iron concentration [17].

Table 2: cardiac iron assessment values, MIC=myocardial iron concentration[17].

	Normal	Mild	Moderate	Severe
T2*	>20	15-20	10-15	<15
R2*	<50	50-66.5	66.5-100	>100
MIC (mg/gm)	<1.16	1.65	1.65-2.71	>2.71

Data evaluation:

the collected data (images) for each patient had been copied from the MRI monitor into a compact disc which is taken into a computer containing a magnetic resonance analytical software system (MEDIS, MRI) method for calculating liver and cardiac iron concentration by using the following equation: SI =SI0.exp-(TE/T2*).

Liver data evaluation:

by downloading data into that software, a representative image was chosen, a region of interest, usually peripheral and should be away from central blood vessels as much as possible would be taken (the region is created by tagging 5 or 7 points to the selected region which will be connected to form it) (shown in figure 1a), these steps had been done in a single image and would be automatically copied to the other different TEs images involved in the same matrix. The resultant measures were analyzed automatically to give us a curve, which should be further adjusted by exclusion of the points in the plateau phase (shown in figure 1b) to eliminate their negative effect. These fluctuating points in the plateau phase occur due to the magnetic effect of the deposited iron in

the liver that cause very fast T2*decay. The resultant curve will give an estimated value that represents T2* intensity value in ms that should be changed to mg/gm in order to be easily understood by the physician and this had been done by a supplemented Microsoft Excel spreadsheet. Depending on the resulting value we categorized patients into those with, normal, mild, moderate or severe liver iron deposition depending on the table 1.

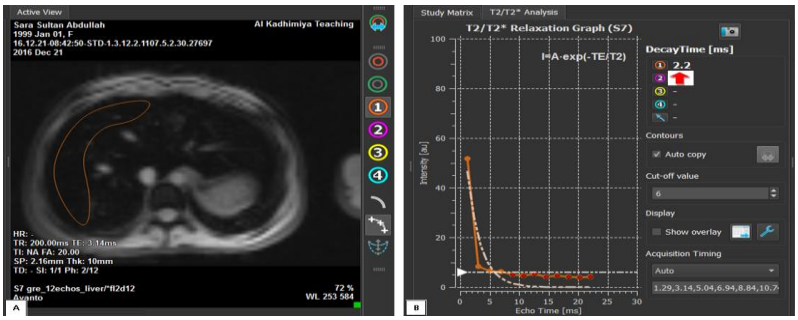

Figure 1: A: Shows the region of interest in liver assessment, B: Resultant curve and numerical value (red arrow) of T2* in ms.

Cardiac data evaluation:

By downloading data into that software, a representative image was chosen, a region of interest, usually the largest portion of the inter-ventricular septum including the endocardium would be taken (the region is created by tagging 5 or 7 points to the selected region which will be connected to form it), (Figure 2 A.), these steps had been done in a single image and would be automatically copied to the other different TEs images involved in the same matrix. The resultant measures were analyzed automatically to give us a curve, which should be further adjusted by exclusion of the points in the plateau phase (figure 2 B.) to eliminate their negative effect. These fluctuating points in the plateau phase occur due to the magnetic effect of the deposited iron in the myocardium and epicardium that cause very fast T2*decay. The resultant curve will give an estimated value that represents T2* intensity value in ms that should be changed to mg/g in order to be easily understood by the physician and this had been done by a supplemented Microsoft Excel spreadsheet. Depending on the resultant value we categorized patients into those with, normal, mild, moderate or severe cardiac iron deposition depending on the table 2.

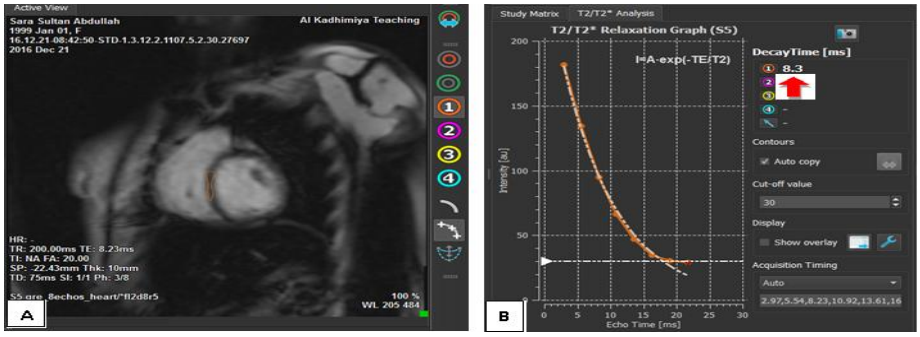

Figure 2: A: Region of interest in heart septum. B: Resultant curve and numerical value (red arrow) of T2* in ms.

Statistical analysis:

data were analyzed by IBM SPSS statistics version 24. Spearman correlation test had been used to find the correlation between liver T2* with LIC and MIC, cardiac T2* with LIC and MIC, also spearman test had been used to correlate S.ferritin level, liver T2* in ms, LIC in mg/gm, cardiac T2*value in ms and MIC in mg/gm, paired sample T-Test with Boostrap to assess P value and confidence interval had been done between LIC in mg/gm and MIC in mg/gm, and between them and age, type of treatment and blood transfusion frequency. All tests considered independent and P value of < 0.05 is considered significant.

RESULTS:

The study included 100 patients, 56 were male (56%) and 44 were female (44%) with male to female ratio of 7:5.5. Their age ranges between 6-36 years old, with mean age of (16.82years+SD 5.797).

Regarding LIC 66 patients had mild iron overload, 25 patients had moderate iron overload and only 9 had sever iron overload as shown in table 3. Regarding MIC 17 patients had normal MIC, 60 patients has mild iron overload, 17 patients had moderate iron overload and only 6 patients has sever iron overload as shown in table 3. Of the 100 patients included in this study there were 66 patients with mild increase in LIC (17 patients had MIC and 49 show a mild increase in LIC). 25 patients show a moderate increase in LIC (9 of them shows mild increase in MIC and 16 shows a moderate increase in MIC). The remaining 9 patients with severe LIC are distributed as follow (2 of them show mild increase in MIC, 1 shows moderate increase in MIC and 6 show severe increased MIC), these fining were shown in table 3.

Table 3: The relationship between LIC and MIC in beta-thalassemia major patients, according to severity of iron overload.

		MIC				Total
		Normal	Mild	Moderate	Severe	
LIC	Mild	17	49	0	0	66
	Moderate	0	9	16	0	25
	Severe	0	2	1	6	9
Total		17	60	17	6	100

Liver and cardiac T2* correlations: there is a statistically significant negative correlation (P value <0.05) between the liver T2* (ms) value, LIC and MIC, and a significant negative correlation between cardiac T2* value (ms), LIC and MIC (as shown in table 4) that we depend on T2* value to asses LIC and MIC in mg/gm as a more decrease in liver and cardiac T2* value will be associated with significant increase in iron concentration in both liver and heart respectively, and an increase in liver T2* value is associated with increase in cardiac T2* value, so we can correlate these values (T2* in ms or iron concentration in mg) with the other parameters such as S.ferritin and treatment type,…etc.

Table 4: Correlation between T2* values in ms with LIC and MIC in mg/gm.

		Liver T2* in ms	Cardiac T2* in ms
LIC in mg/gm	Correlation coefficient	-0.989	-0.248
	P value	<0.001	0.017
MIC in mg/gm	Correlation coefficient	-0.224	-0.996
	P value	0.031	<0.001

Age and frequency of blood transfusion correlation: there is no statistically significant correlation between patients with beta-thalassemia major regarding the frequency of blood transfusion and patient's age in correlation with LIC and MIC (P value > 0.05).

Serum ferririn correlation: there is a significant positive correlation between S. ferritin and LIC, S. ferritin and MIC, (correlation coefficient of 0.255 and 0.369 respectively) with a (P value of 0.12 and 0.0015 respectively). There is also a significant negative correlation between S. ferritin and liver

T2*, cardiac T2* (correlation coefficient of -0.251 and -0.397 respectively), with a (P value of 0.014 and 0.00015 respectively), these findings were Shown in table 5. On the other hand there is no significant correlation between S. ferritin level and the severity of LIC and MIC, as shown in table 6.

Table 5: Correlation between S .iron ferritin in ng/ml with liver and cardiac T2*values in ms and with LIC and MIC in mg/gm.

	LIC (mg/gm)	MIC (mg/gm)	Liver T2* (ms)	Cardiac T2* (ms)
Correlation coefficient	0.255	0.369	-0.251	-0.379
P value	0.012	0.0015	0.014	0.00015

Table 6: Correlation of median S. ferritin level in ng/ml with the severity of LIC and MIC.

		Median of S.ferritin	Monte Carlo Significance (CI of 99%)
LIC in mg/gm	Mild	4655	0.129
	Moderate	4995	
	Sever	10263	
MIC in mg/gm	Normal	4995	0.792
	Mild	4313	
	Moderate	5000	
	Sever	10263	

Correlation with treatment type: by correlating different types of treatment (desferal vs exjade) with LIC and MIC values in the study, a significant difference had been found (P value <0.05) that patients with Exjade intake show lower LIC and MIC values than those patients on desferal, as shown in table 7.

Table 7: Comparison of Treatment with Desferal and Exjade with LIC and MIC in mg/gm.

Parameters	No. of patients	LIC (mg/gm) Mean ± SD	MIC (mg/gm) Mean ± SD
Desferal	59	7.826±4.478	4.1515±9.09
Exjade	41	5.623±2.670	1.761±0.946
P value		0.01	0.02

The following figures (3-) show images of some cases included in the study.

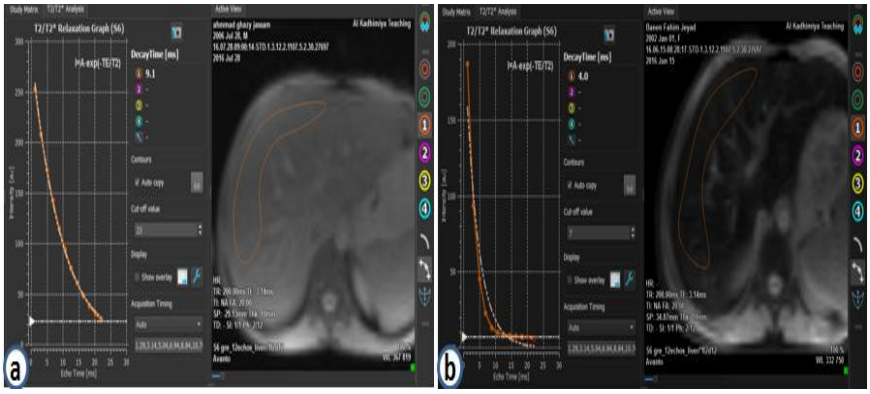

Figure 3: a: 10 years old male patient with beta-thalassemia major, MRI shows mild liver iron deposition, LIC =3.4 mg/gm. b: another 14 years old female patient with beta-thalassemia major, MRI shows a moderate liver iron deposition, LIC=7.83mg/gm.

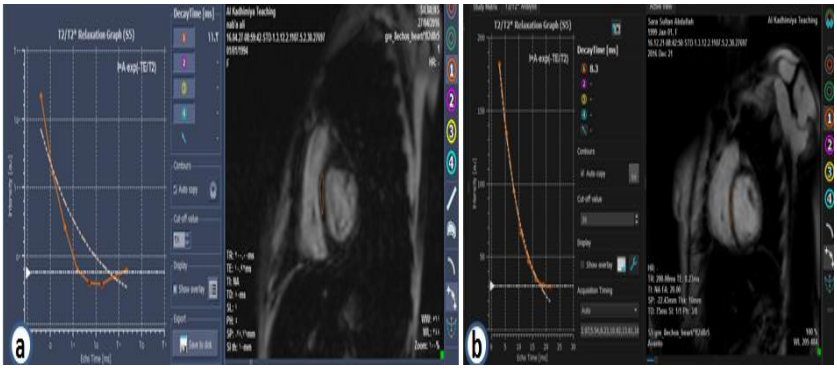

Figure 4: a: 20 years old female patient presented with fatigability with beta-thalassemia major, MRI shows a moderate cardiac iron deposition, MIC=2.36mg/gm. b: another 27 years old female patient with thalassemia major presented with shortness of breath, MRI shows a sever cardiac iron deposition, MIC=3.4mg/gm.

DISCUSSION:

Blood transfusion has increased the overall survival and quality of life in transfusion dependent hemoglobinopathies; but can lead to iron deposition and tissue damage especially in heart, liver, and endocrine glands [18]. Iron overload is a risk factor of mortality in highly transfused patients. It is the main prognostic factor in beta-thalassemia major. Iron overload induced heart failure; arrhythmia and cardiomyopathy are preventable conditions, although these conditions are mainly multi-factorial in β-thalassemic patients [19]. Moreover, thallasemia major patients develop a cardiomyopathy characterized by a multifactorial etiopatogenesis. Other than iron, chronic anemia, myocarditis, and endocrine abnormalities seem to be determining factors as well [20]. Magnetic resonance imaging (MRI) has been successfully used for the evaluation of myocardial and liver iron overload. MRI is the only technique able to provide non-invasive information about iron overload, as well as microcirculation defects and the detection of myocardial scars [21]. The highly sensitive and reproducible magnetic resonance imaging (MRI) T2* technique has revolutionized thalassemia management [22] providing a direct assessment of cardiac and hepatic iron content and evaluating the effectiveness of iron chelation therapy [23]. Current life expectancy in TM patients is definitely improved in the last 15 years, mainly thanks to widespread use of MRI for detecting iron overload in target organs (liver and heart) [14].

The distribution of our 100 patient were as follow: 66 patients with mild increase in LIC (17 patients had MIC and 49 show a mild increase in LIC). 25 patients show a moderate increase in LIC (9 of them shows mild increase in MIC and 16 shows a moderate increase in MIC). The remaining 9 patients with severe LIC are distributed as follow (2 of them show mild increase in MIC, 1 shows moderate increase in MIC and 6 show severe increased MIC). Other studies like Eghbali F et al [24] and Majid Z et al [19] show a different patient distribution according to severity of LIC and MIC with higher percentage in normal LIC (23.3%, 41.2%) and mild MIC (76.7%, 41.17%) respectively , mild LIC (46.7%, 17.6%) and mild MIC (15%, 16.47%), moderate LIC (25%, 35.3%) and MIC (5%, 21.17%) and severe LIC (5%, 5.88%) and MIC (3%,21.17%) respectively which may be due to different patient sampling as the second study including β-thalassemia intermedia in addition to thalassemia major, and difference in general patients health care as most of our patient sample had a low socio-economic levels and poor treatment compliance, so higher levels of LIC and MIC are expected.

The resultant analysis of our results show a correlation between the liver iron overload and cardiac iron deposition, these findings are in agreement with the results of previous reported studies by Leila J. Noetzli et al [25] and Chen X et al [26], so in patients who could not tolerate cardiac MRI or in centers who haven't a cardiac coil, liver MRI could be used to assess cardiac iron deposition status.

The resulting negative correlation with age and frequency of blood transfusion goes in agreement with other studies by Eghbali F et al [24] and Majid Z et al [19].

Although there is a significant positive correlation between S.ferritin and LIC, and MIC and these results were similar to results previously reported by Wood et al JC [27] and Majid Z et al [19], but our results show that the S.Ferritin is not a reliable method to assess the severity of iron deposition in these organs, this findings is in agreement with Kirik et al [20] which is an important part in chelation manipulation, and these findings were in agreement with other reported studies which consider S.ferritin as an unreliable method to estimate liver and cardiac iron overload especially in monitoring response to therapy e.g. Kolangu A. et al [28]. Serum markers of iron metabolism such as ferritin and the transferrin saturation index are imprecise for the assessment of iron overload [7, 29]. The substitution of ferritin levels for assessment of iron burden in this patient population may lead to suboptimal iron management. MRI is a noninvasive, low risk alternative for iron assessment, and therefore more acceptable to patients and providers [30]. This difference may be due to patient sampling difference as there is a high possibility of liver and cardiac iron deposition in patients with high ranges of S.ferritin in comparison with a non-significant association in low ferritin levels as liver and cardiac deposition which could be seen in low or normal ranges of S. ferritin, on the other hand seen, increased S.ferritin in cases of inflammation give a falsely high result with normal liver and cardiac iron levels, or because of the type and method of chelation used as desferal give a rapid reduction of S.ferritin which may give a wrong low figure.

Regarding the type of treatment used, we noticed that patients on exjade therapy shows lower levels of liver and cardiac deposition when compared with Desferal and this could be explained by the long duration of action and a high patient compliance with Exjade, these findings were similar to that seen by Maria Domenica Cappellini et al [4].

CONCLUSION:

MRI has a significant role as a non-invasive and reliable method in the assessment of liver and cardiac iron deposition in patients with blood transfusion dependant beta-thalassemi major. There is no correlation between S.ferritin level and the severity of LIC and MIC. The patients using Exjade show a lower LIC and MIC than those using desferal. There is no correlation between age and frequency of blood transfusion with LIC and MIC in patients on regular chelation treatment.

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