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Detection and Quantification of Iron in Liver and Myocardium using MRI

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Detection and Quantification of Iron in Liver and Myocardium using MRI

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Dedication

I am most deeply grateful to My whole loving family for the support and for the patience during the writing process. I sincerely want to thank my dear wife Amal her pragmatic and objective views, helped and supported me I also thank her for the patience, persistence and encouragement. My wife and children, bring the most precious moments in my life.

Bassam Abdul-Aziz Abuarquob

Declaration

I certify that this thesis submitted for the degree of master, is the result of my own research, except where otherwise acknowledged, and that this thesis (or any part of the same) has not been submitted for higher degree to any other university or institution.

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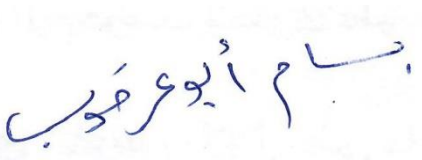
Signed: 

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Abstract

Background: MRI is a medical imaging method that does not use harmful or ionizing radiation so it is safe and can be used to measure the proportions of iron that accumulate in the organs of the human body, especially the heart and liver.

Methods and sample: The study was conducted on 50 patients suffering from major thalassemia and treated through chronic blood transfusion, as well as 20 other patients who do not suffer from Thalassemia or any diseases in the heart or liver through the use of their medical files and their medical history in Alia Governmental Hospital . Magnetic Resonance 1.5 Tesla-type Philips Ingenia .

Retrospective case control study was carried out in the period between December 2018 to March 2019 at the Hebron Governmental Hospital. The Results were compared between liver and heart T2* with SF levels, On one hand and on the other hand results compared between LIC and MIC with T2*, and LIC with MIC.

Results: The average of SF in patients with thalassemia major was 2150 ng/ml (SD 179ng/ml). positive correlation was found between LIC and MIC with SF, also positive correlation was found between SF and T2* of liver and heart .and significant relation between LIC and MIC.

Conclusions: Although the serum ferritin levels normal and abnormal were found among major thalassemia patients, there were results showing elevated iron concentrations in the liver and heart of major thalassemia. There is an urgent need for new and accurate studies to prove the importance of MRI for Determine the location and quantity of iron accumulated in the muscle of the liver ,Heart and other organs especially that this

procedure safe and harmful, In order to give the correct and accurate chelating treatment and follow up and control the improvement in the reduction of iron ratios accumulated.

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List of Abbreviations

ALT: Alanine Aminotransferase

AST: Aspirate Aminotransferase

DR: Digital Radiography

FOV: Field of View

GRE: Gradient Echo

HIC: Hepatic Iron Concentration

IO: Iron Overload

MIC: Myocardium Iron Concentration

MRI: Magnetic Resonance Imaging

MR: Magnetic Resonance

R2: Transverse relaxation rate (1/s) from spin echo

R2*: Transverse relaxation rate (1/s) from gradient echo.

RBC: Red Blood Cell

RE: Reticulo-endothelial

SIR: Signal Intensity Ratio

RIO: Region Of Interest

SNR: Signal-to-Noise Ratio

T: Tesla

TE: Echo Time

TR :Repetition Time

T2: Transverse relaxation time (ms) from spin echo

T2*: Transverse relaxation time (ms) from gradient echo

Chapter One:

Introduction

Thalassemia patients who are treated with blood transfusion to raise the level of red blood cells and raise their hemoglobin levels. Continuous blood transfusion causes iron to be elevated in the body. Each blood unit contains 250 mg of iron[1].

Ferritin serum, which acts as a blood test, does not give full or correct accuracy to the high concentration of iron in the tissues of the body, since the blood test gives the rates of Ferritin and trans ferritin that pass through the blood and may be high because of inflammation in the patient or cancer so this is not accurate reading, They are comprehensive[2].

Scientific studies on the accumulation of iron in the heart and liver proved a direct relationship between high serum ferritin ratios and excess iron in the organs of the human body, but it was difficult to determine the amount of iron in the heart compared to the liver because of the nature of absorption of iron at the heart of the complex [3-6].

Previous studies have shown a weak relationship between high ferritin and excess iron ratios in the heart muscle[7,8]. This study was therefore important in showing the

depth of the relationship between the upper ferritin ratios and the iron accumulated in the liver and heart muscle, using the MRI for thalassemia patients.

1.1 Statement of the problem:

Since the blood serology test through which the serum Ferritin levels indicate the iron levels the body, the fact that the serum Ferritin gives in general and does not determine the organ who had high iron stores in the body, on other hand the Serum Ferritin levels in blood raised when the patient have diseases like infections or cancerous diseases, the urgent need for a safe method is invasive cheap and not painful, such as Magnetic Resonance Imaging for a careful study to determine the amount of iron in the Heart muscle and Liver and modify chelation therapy.

1.2 Study objectives :

The objectives of the present study are :

1-How MRI application improve and determine the concentration of iron in the cardiac and liver.

2- To develop appropriate adjustments daily clinical practice and explore possible complications related to iron.

The specific aims for our study distributed into:

1-Validation of MRI based method (T2*) in determining the amount of iron concentrated in both liver and myocardium detection and quantifications.

2-Imphasize the dual echo of in-phase and out-phase of MRI imaging for Heart and liver iron overload in the body.

3-To produce high image quality for heart and liver using T2* analysis with accurate labeling on the region of interest.

1.3 Research significance:

The main goal of the project is to provide accurate image quality and efficient imaging directed at T2* analysis. And to prove that MRI is a safe, harmless and accurate method to determine the site and amount of iron accumulated in the Myocardium and the liver muscle liver and the correlation of both with each other's and with the serum Ferritin levels.

Chapter Two

Literature Review:

2.1 Definitions

Ferritin: Is an excess iron stores in the human body, which is found in liver cells(hepatic cells) and in the immune system (reticuloendothylial) in the body as the human body does not make iron, but it is acquired from the food we eat[11] .

Iron: One of the most available elements in the human body, which is estimated 3-4 gm, which is necessary in the process of metabolic rate in the body and needed by the cells of the body where the red blood cells[12].

MRI: One of the methods of the medical imaging technology which is non-harmful, which does not contain harmful or ionizing radiation ,and depends on the property of relaxations in the protons after exposed to pulses of radio frequency waves, and is the most accurate medical medical imaging technology, used three-dimensional imaging, it became the useful way which has been used in the detection and quantification of iron overload in different body organs [13].

Thalassemia: Is one of the most common blood diseases in the Mediterranean, which is caused by a decrease in the number of red blood cells and a decrease in the level of

hemoglobin, which is treated through the transfer of blood to the patient in order to maintain a high quality life. [15]

T2*relaxation: It is a method of magnetic resonance imaging that used the gradients echo pulses in order to make rephrasing of protons in fasten way using small Flip Angles (less than 45°) and short TR ,TE,…..with special analysis program, the T2* hav transverse decaying process. [16]

2.2 Pathophysiology of Iron Overload

The disease of accumulation or increase of iron in the organs of the human body is a very serious disease on the organ that has high rates of the Iron overload disease and may lead to failure of that organ like Heart failure ,Hepatic failure ,Cardiomegaly ,hepatomegaly, and destruction of cells, Iron oxidation lead to produce free radicals which show cancer in the body [18].

The majority of these diseases caused by the increase of iron caused by the process of chronic blood transfusion, which in turn causes the accumulation of the Iron and therefore called the silent disease [19].

Since Magnetic Resonance Imaging is a safe and harmless method, the need to limit the iron that concentrated in organs in very important using the relaxation speed of the cells that contain excess iron and therefore we can determine if the member has the disease or not [20,21].

There is a clinical need to use quantitative and vastly method to avoid excess accumulation of toxic iron in those tissues and monitoring the treatment process [22].

So that the MRI is the accurate and invasive process ,and can be used frequently to monitor the Iron levels in organ during the treatment plane[15]. MRI based on

determining the iron overload in the both liver and heart muscle the process of Transverse Relaxation time of proton (T2*) and Through the formulas of calculating the amounts of IRON [16]. The sensitivity of IRON in liver is highly marked[17]. T2* provide vastly relaxation while SIR provide the amount of signal produced from the tissues .quantitative information on the concentration of iron in the heart muscle and liver have correlation coefficient highly marked also [18]. On other hand Iron concentration is inversely proportional to T2*relaxation, while SIR directly proportional to IRON overload [19].

2.2.1 MRI in Palestine

In Palestine There are many magnetic resonance imaging (MRI) machines in Palestine. There are a large number of tests that done monthly , which are estimated to be more than 5,000 tests . However ,the iron detection and quantification test does not applied in Palestine, we urgently need to apply this method of imaging in order to be routine test daily done . And publicize them in the private and public sectors in order to serve the patients of the major thalassemia and follow up their treatment.

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The imaging of the liver muscle and the myocardium using the technique of Transverse Relaxation Time which called T2* is an easy way have a special program that analyzes the values of the labeled region of interest and then the results through special equations applied and a special computer program had processed . and there are special parameters shown in tables 2.1 and 2.2.

2.2.2 T2* protocols for MRI imaging of Heart and liver .

Table 2.1: T2* heart Parameters.

Pulse sequence	**Multi echo GRE**
Coil	Phased array
Slice Thickness	10mm
Matrix	96-128 x 64-96
FOV	40 x 25-40 (can increase to reduce initial TE)
Bandwidth	Maximum
Flip Angle	20
TR	100ms
TE	Minimum possible (ideal ≤1.0ms)
TE intervals	0.75 to 1.0ms
Number of TEs	10
Fat saturation	On

Table 2.2: T2* liver Parameters

Pulse sequence	**Multi echo GRE**
Coil	Phased array
Slice Thickness	10mm
Matrix	192 – 256 x 108 – 128
FOV	40 x 25-40 (can increase to reduce initial TE)
Bandwidth	Maximum
Flip Angle	20
TR	Minimum – fixed
TE	Minimum possible (ideal 2.0 to 3.0ms)
TE intervals	1.0 to 2.0ms
Number of TEs	10
ECG triggering	On
Sequence type	Black blood or bright blood
Trigger delay	Bright blood: minimum; black blood.
Flow compensation	On for bright blood / off for black blood
Fat saturation	Off

2.2.3 Prognosis of thalassemia

Iron Overload in the liver and heart, resulting from genetic defect in blood disorder , which is treated through the blood transfusion , which caused in the accumulation of iron in the body organs ,which are diagnosed previously through the blood test, looking fore the amount of Ferritin levels in the body and there are other methods such as biopsy which is painful and sometimes the patient is subjected to complications and enter to the hospital, so we need Magnetic Resonance to evaluate the Iron ,which involves the use of T2* relaxation time in determining the ratio of iron through signal intensity ratio (SNR).

2.2.4 Thalassemia Treatment

Patients suffered from Iron overload are treated with special drugs that emulsify heavy metals in the body, which called the chelating drugs, like deferoxemen the doses depend on the amount of Iron concentrated in the organ needed for treatment [19].

Chapter Three:

Methodology

3.1 Introduction:

In this chapter, the researcher will explain the place of study and the study community, determine the description of the study, the sample used, the method of imaging, the materials and the equipment used in this work, in order to work a precise scientific method.

Using fast MRI T2* analysis program, as protocol focusing on assessment of heart and liver iron overload using Relaxation in the transvers plan, with short study time less than 8 minutes[20]. any exam may be done in a any day. the responsible for selecting the patients is hematologist, according to the clinical need for the MRI exam, and provide basic background clinical data (hematocrit ,age, sex, serum ferritin levels, chelation drugs, HB.). The scheduling are arranged with the MRI department in Hebron Governmental Hospital .

The results are analyzed by the radiologist and the Hematologist and stored in the patient files in order to follow the cases. In a following step regulation, images will be uploaded to a hospital server..

3.2 Pilot study:

Radiology Department at Hebron Governmental Hospital by 1.5 Tesla MRI machine Type Philips Ingenia. The Radiology Department. That contain one 16 slice CT machine , tow X-ray machines one Computed Radiography CR. And one full DR. Alia hospital contains 400 bed, hematology , blood bank, surgery, neonate, gynecology, medical departments.

3.3 Research setting:

Hebron Government Hospital south of Palestine. where the study was conducted in the West bank in on patients with major-thalassemia ages between 11-31 years old. Patients sampled with all there complete blood counts tests their ferritin serum. At the same time, a measurement of iron levels in liver and the Heart was done by MRI T2 *protocols and then, the results were compared and stored in medical files in the radiology dept.

3.4 Study population:

The study population consisted 70 cases, 50 patients suffering from thalassemia major and taking blood many ,in Hebron Government Hospitals in West Bank of Palestine. 20 patients as control cases with no Heart or Liver disease ,and never had blood transfusion treatment, from different regions in Hebron. The patient scanned by the T2* protocol, without any fasting or contrast ingestion or injections.

A printed report of the scan patients including both heart and liver iron concentrated assessment is provided to hematologist within one day of the scan. For all patients, a clinical data and testes including age, sex, any diseases, transfusion history, chelation drugs and doses, HB level, ferritin level and of splenectomy is collected from

medical records in Hebron Hospital by the hospital information system after the ethical confederations .

3.5 Sample size:

50 patients suffering from thalassemia major and taken blood transfusion (old, range: 11-31years old; 76% males) were chosen for the study, and 20 controls patients, coming to MRI examinations from December 2018 to March 2019. this research was approved in hospital by the administration, in addition consent form done by the patients themselves and patients privacy .

3.6 Inclusion criteria:

a. Patients with chronic regular blood transfusions or with high serum ferritin level, who can enter the MRI without any problems.

b. Patients ≥ 11years old.

3.7 Exclusion criteria:

Patients have defibrillators, cerebral aneurysm or clips contra-indications to MRI exams, permanent pacemakers,…. etc.

3.8 Research design:

Retrospective cross sectional case control study design. Which is a design that is best choose when comparing between patients complaining from a certain disease with others that has not been diagnosed with that disease of interest, the prevalence of risk factors or phenomena in one of the major benefits that may be the easy, short time consuming, costless, and the best design to investigates risk factors or comparing results in between positive and negative cases of interest disease .

Also the researcher used this study design after the existing medical files and hospital information system of the Alia (Hebron Governmental) Hospital comparing patients suffering from thalassemia major with other control cases without blood transfusion history , that coming to routine MRI exams Governmental Hospitals.

3.9 Data collection methods:

Researcher used different Data in his research including

- Data files, that included
    - Personal data
    - Medical files and history
    - Demographics
- HIS of Hebron Governmental Hospital that included
    - MRI images
    - Medical file
    - Lab tests

Medical files at Hebron Hospital are gathered and collected to get information about iron concentration in liver and cardiac muscle, using Magnetic Resonance Imaging in the Hebron Governmental Hospital. The study included 50 patients with thalassemia major who receive chronic treatment through regular blood transfusions and chelation therapy. Iron concentrations in both the heart and liver were detected through MRI. All participating patients were referred from the Hematology Department in hospital.

The information about the patients was recorded, to information related to laboratory tests such as hemoglobin in the blood and the proportion of ferritin serum.

such as the age of diagnosis, the medication received by the patient for treatment, and In addition to the number of blood transfusions.

A group of 20 case who had never received blood transfusions were taken as control group. This group was of patients arriving to MRI exams other than the liver and heart. This group was selected studying their medical records and previous history, making sure that they are not suffering from previous liver and heart diseases. Also, group of this patients were aged 11-31 years.

Regard to pediatric patients, consent form of their parents taken for the examination of this study. In addition, patients older than 11 years old, have been approved for MRI that can enter MRI without problems . The exam done using the body coil (Torso coil) on a 1.5-T (PHILIPS-INGENIA). Multiple Echo Gradients, T2* slices images were taken on the localizer image as shown in (Fig 3.1).

Several images during the single breath-hold with 8-10 echoes, first echo time (TE) of 0.9 ms, and $\Delta TE = 1.1$ ms, and (TR) of 180 ms. Each sequence of protocol take about eight to ten minutes of time.

TE signal intensity measured by, drawing a region of interest (ROI) , area of 1–1.4 cm^2 was taken on the accurate region . ROI in liver muscle was identified by drawing it in the right lobe, that don't contain any blood vessels or bile ducts as shown in (Fig 3.1). The Hankins [20] equation used to emphasize the signal intensity of the different TE values which obtained in the imaging slices using the Excel sheet.

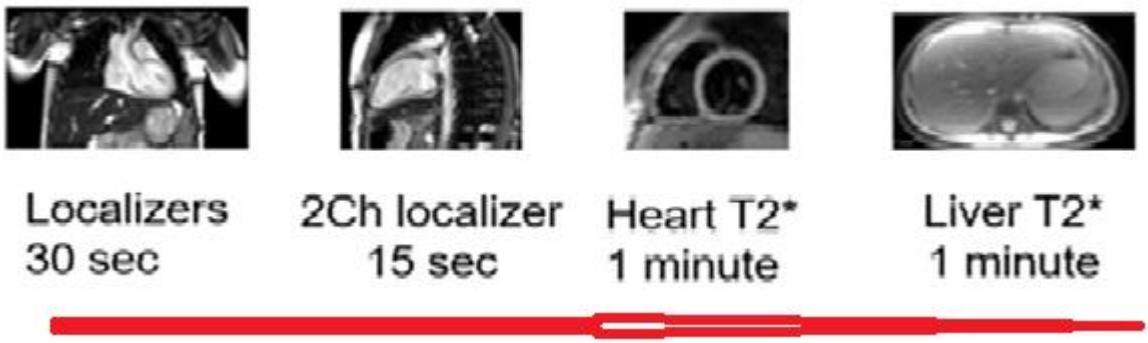

Fig 3. 1 Pilot and axial slices for Liver and heart .

(a) (b)

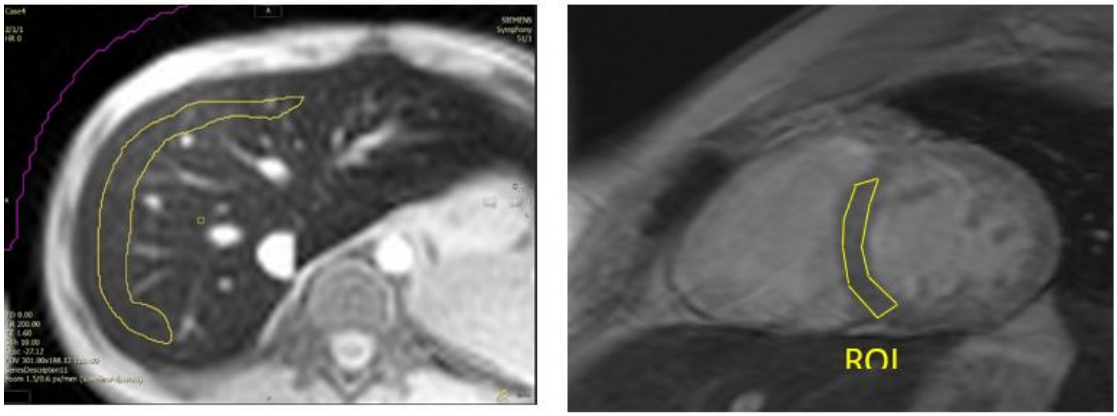

Fig 3. 2 ROI. For liver (a) and heart (b).

The T2* values or the reciprocal R2* (=1/T2*) is calculated by using a gradient echo protocol, which used to measure the concentration of iron accurate than the T2. However, the loss of the signal in cases of high iron is very fast due to the strong local variations in magnetic field and inhomogeneity , this is known as susceptibility effects. For example, the iron molecule contains a high sensitivity to the magnet, which had long magnetization victor in the transverse plan , and this high magnetization detected by T2*gradients echoes sequence [21].

There is a linear relationship between liver T2* with iron cincentration/ and R2* that verify the iron over load in liver, Fig (3.3) shows MR images show the degree of liver IO in the four grades levels of iron, and ROIs of the liver SIR measurements. The amount of iron concentrations in the liver (LIC) was calculated by using the following equation[22] :

$[Fe] = \{-454.85 + (28.02 \times R2*)\}/1000$ where R2* is 1/T2* (Transverse relaxation rate by gradient echo).

HeartT2* we used the basic method in determining the amount of iron concentrations. T2* is accurate than T2 imaging in the calculation of the iron concentration of myocardium because it depends on gradient echo sequences instead of spin-echoes which is faster in slicing images [23]. In tissues having a few iron concentrations both of R2* and T2* used as in the Heart muscle. The different TEs echoes value were used to determine the signal intensity, was done using the formula: SI = e–TE/T2*[17].

For myocardial iron concentration (MIC), the gradient echoes was taken in single breath hold using the vital gated like the ECG. The triggering heart rate was used in conjunction with the heart cycle.

Images were taken during the ventricles contraction ,using the same parameter for every echoe . The protocol parameters taken with single breath hold were as follows: TR = 180 ms, 8-10 echoes, TE_1 = 1.2 ms, and longest TE_2 of 21 ms. To measure the signal intensity from heart muscle in the period of ventricles contractions , the ROI was drawn with a 1.0–1.2cm^2 as shown in (Fig 3.4). The MIC was determined using this equation:

$[Fe] = 45(T2^*)^{-1.22}$ where T2* (Transverse relaxation rate by gradient echo) [24].

While the excel sheet for MIC value was calculated using the following equation [25]:

$$SI(TE) = A * e^{-TE/T2*}$$

Where SI (TE) is the signal intensity at particular TE and A is the computational SI at TE=0[12]. Values of cardiac T2* (CT2*) <20 ms were considered to indicate cardiac diseases which was classified as milled to moderate (10 ms< CT2* <20 ms) and severe when (CT2* <10 ms)[22]. LIC >3 mg/g dry weight (dw) was considered to be liver disease which was classified on severe (LIC >15 mg/g dw) , moderate (7< LIC <15 mg/g dw), mild (3< LIC <7 mg/g dw) [12].

According to the statistical analysis in this study which based on SPSS software version 18. The Average values of LIC, MIC, and SF were calculated. In addition, the correlation coefficient was calculated for MIC, LIC, T2*, and SF levels. for comparison of mean values T-test was used. $p< 0.05$ was considered to be a significant change. The other different values were analyzed by the correlation coefficient.

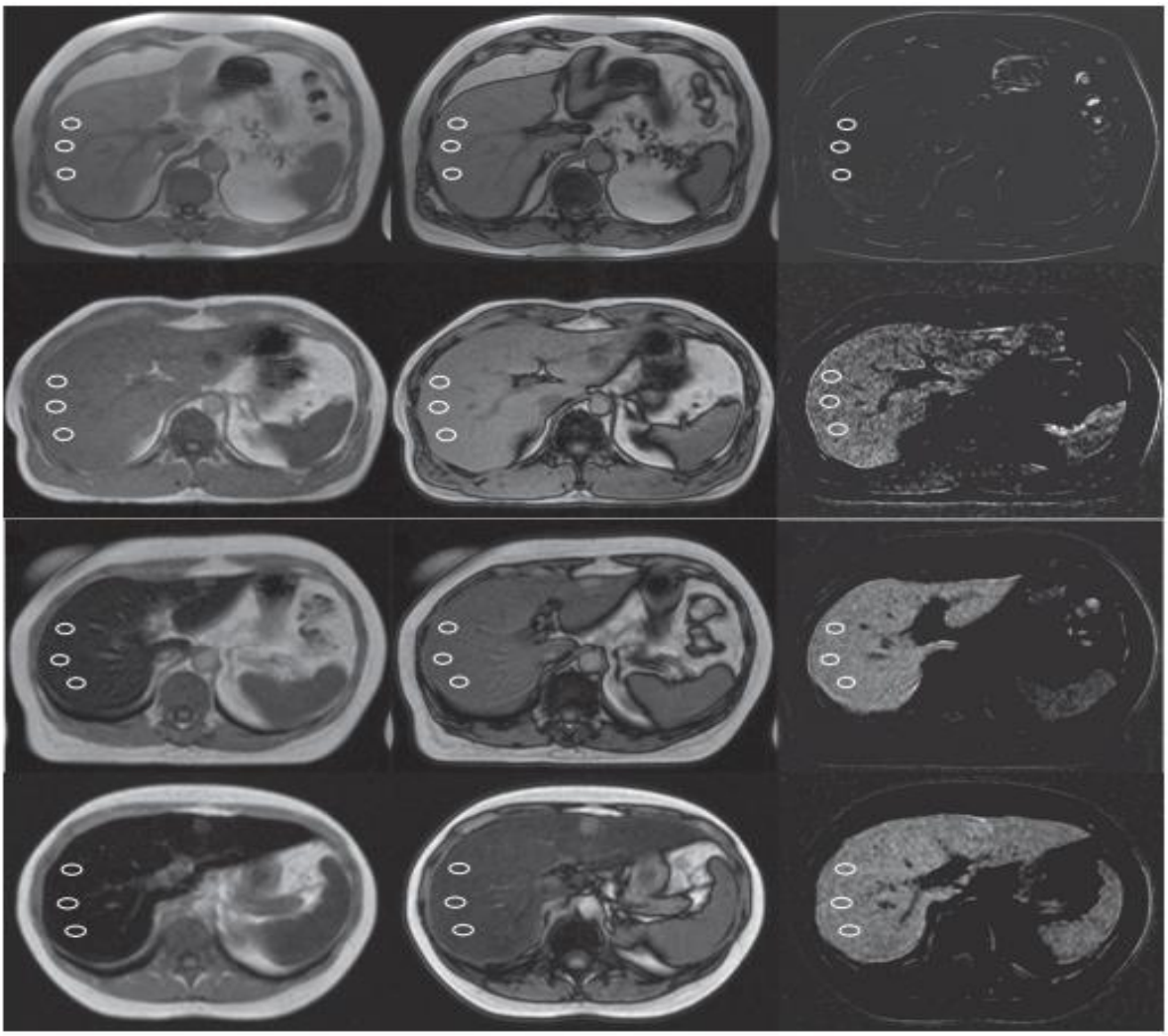

Fig 3. 3 MR axial images of the four grading of liver IO, and ROIs of the liver demonstrating SI measurements.

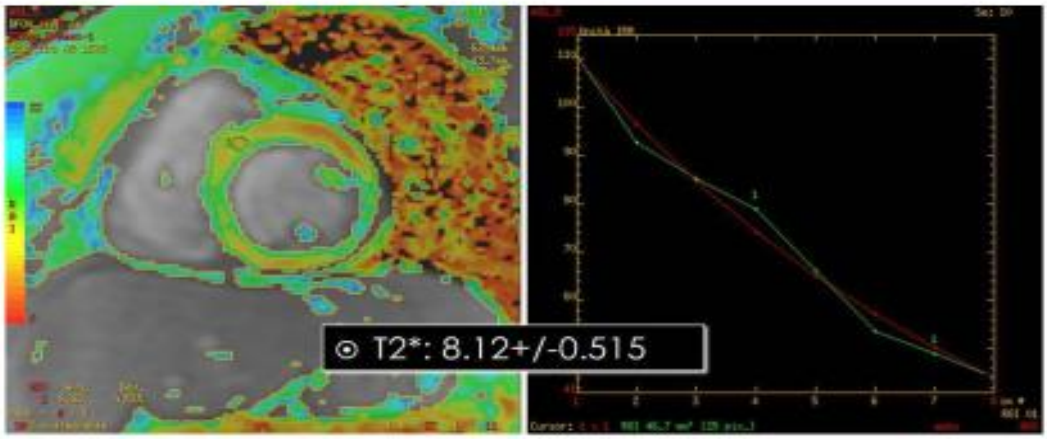

Fig 3. 4 severe heart iron concentration evaluated with ROI (rejion of interest) in the ventricular septum.

3.10 Signal Intensity Ratio (SIR):

Signal Intensity Ratio depends on the signals that collected from the tissue and noise. The signal intensity of the tissues that do not contain iron like musculoskeletal muscles and fat, is accurate method to compare the tissues that containing high iron where the signal drops off. The torso body coil used to acquire the liver slicing images [27]. The liver ROI is placed in a non-blood vessel or biliary ducts to avoid any possible of artifact. When we want to make a comparison, fat and skeletal muscles are the best reference to MRIT2* analysis. Comparing to skeletal muscle, the high iron overload liver has higher signal intensity. Therefore, the signal intensity from liver containing iron overload can be easily distinguished. The sequences parameters of the T2* protocol including the Bandwidth and voxel size which should be accurate because it affected the liver to muscle signal intensity ratio. other tissue can be used as reference for signal, but the fatty signal intensity really is significant compared with the tissue of the liver , also it has significantly different between children and adults[20] .

Myocardium measured in two ROI one in the right and the second in the left paraspinous muscles, while the liver signal intensity measured at region of interest located in the right lobe avoiding vessels. Therefore, mean signal intensity of the liver that calculated by taking ratio between liver and muscle or fat with same size of ROI. And band width. Increasing LIC will decrease the intensity of liver/muscle ratio [21]. Thus, the LIC values greater than 400 μmol/kg (22.5 mg/kg) cannot be accurate quantified [12]. Proton density or the exponential ratio may cause SI alternative so that TE/T2 to the following equation may be used as a solution of this alternating [25].

$$SI = NH * \left(1 - e^{-\frac{\mathrm{TR}}{\mathrm{T1}}}\right) * e^{-\mathrm{TE/T2*.}}$$

Si: signal intensity ,NH: intensity at 0 time ,e :exponential rate, TR :repetition time , T1:longitudinal recovery time ,TE: echo time ,T2* decaying in transverse plane.

3.11 Statistical analysis:

(SPSS) version 18 ,used for the collected and analyzed data. T test and P value, was used to analyze the variances in concentration of iron in both liver and heart muscles between thalassemia major patients and normal participants using a two-tailed student's T test as appropriate statistical way . Results are expressed in both mean and ±SD.

Chapter Four:

Results and Discussion:

4.1 Results:

Liver and Cardiac iron detection was done for 50 patients with thalassemia major, were enrolled in this study. With age between 11–31 y (mean 20.6 ± 6.18 SD, median of 21), of which 38 (76%) were males and 12 (24%) were females. 20 patient as controls with age range was 11- 31 y (mean 21.6± 5.64 SD, median of 21Y), of which 12 males were (60%) and 8 females were(40%).

The distribution of the six in the controls and cases was not statistically significant ($p<0.15$). The height range of the controls was 123–166 cm (mean 158.5 ± 10.2 SD) and of cases was 136–165 cm (mean 161.7 ± 11.45 SD), there are not statistically significant difference found ($p <0.51$). The weight range of the controls was 53–85 kg (mean 67 ± 13.4 SD) and of cases was 52–85 kg (mean 67 ± 12.1 SD), we don't found difference statistically significant ($p>0.422$).

ALT range values of the controls was 14–148 U/L (mean 48.3 ± 25.4 SD) and of controls was 17-29 U/L (mean 17.50 ± 4.7 SD), there is statistically significant difference ($p < 0.001$). AST range among the cases was 13–123 U/L (mean 13.4 ± 17.6 SD) and

among the of controls was 12–26 U/L (mean 17.50 ± 2.7 SD), there is statistically significant found ($p < 0.001$). Hemoglobin levels of the controls was 11.4–14.8g% (mean 12.8.4 ± 1.12 SD) and of cases was 6.7.2–10.1 g% (mean 7.49 ± 0.741 SD), there is statistically significant difference ($p < 0.001$).

SF of the patients with thalassemia major was averaged 2150 ng/ml (SD 179 range: 96–12,8 median: 1621.5). While the mean SF among the controls was 88.7 ng/ml (SD 15.03, range: 42–121, median: 74.5).

There is 8 previous splenectomy between the cases. But don't show any statistically significant differences in patients with and without splenectomy in the values of , heart T2* and MIC, liver T2*, LIC and SF levels values.

Among the 50 case, mean LIC was 5.696 mg/g (SD 8.879, range: 0.43– 31.6, median: 2.29) and mean LIC in controls was 0.65 mg/g (SD 0.34, range: 0.1–1.1, median: 0.82).

41 patient with abnormal LIC and 9 patient with normal LIC values among the patients with thalassemia major and taking blood transfusion regularly .

Among the 50 patients with thalassemia major, 9 (18%) patients were having normal liver T2*>6.2ms., while 14(28%) patients were mild T2* 2.2-6.1 ms. 15 (30%) patients having moderate T2* 1.4-2.1ms, 12(24%) patients having sever T2* < 1.4ms .

liver T2*, R2*, LIC ,Heart T2*,R2*for heart and MIC in the 50 patients with thalassemia major, and SF levels that have abnormal and normal values are shown in Table 4.1 . there is significant variation ($p < 0.001$) was seen in mean LIC between group of cases having normal and abnormal SF levels . on other hand There was a significant

difference found in MIC ($p < 0.001$) between the cases with normal and abnormal SF levels.

Table.4.1: Mean Liver T2*, R2*, LIC and Heart T2*, R2* MIC among cases with normal and abnormal SF

Parameters	Liver T2* Mean (SD)	Liver R2* Mean (SD)	LIC Mean (SD)	Heart T2* Mean (SD)	Heart R2* Mean (SD)	MIC Mean (SD)
Normal SF	19.14 (13)	93.4 (76.7)	1.6 (2.3)	46.19(7.17)	19 (6.6)	0.61 (0.19)
Abnormal SF	3.2 (3.2)	562.4 (121)	5.696 (8.69)	22.7 (10.1)	53.4 (34.2)	1.5 (1.3)

LIC Liver iron concentration*; MIC* Myocardial iron concentration; *SF* serum ferritin

Regarding to the 50 patients with the thalassemia major , 9 (18%) patients had normal (degree one) LIC, 10 (20%) patients had degree 2 (light) LIC, 13 (26%) patients had degree 3 (moderate) LIC, and 18 (36%) patients had degree four (severe) LIC. The 9 patients with normal LIC in the cases also had normal MIC, while 27 patients had normal MIC and 23 had abnormal MIC among the 41patient with abnormal LIC.

Table 4.2.demonstrate the distribution of the normal and abnormal MIC and LIC of the 50 patients having thalassemia major and taking blood transfusion regularly , 9 patients normal LIC , 41 patients with abnormal LIC, 27 patients with normal MIC , 23 patients abnormal MIC , 23 patients with abnormal LIC and MIC .

Table .4.2: Distribution of cases with normal and abnormal LIC and MIC

	Normal MIC (%)	Abnormal MIC (%)	Total (%)
Normal LIC	9 (18%)	27 (54%)	9 (18%)
Abnormal LIC	41 (82%)	23 (46%)	41 (82%)
Total	50 (100%)	50 (100%)	50 (100)

LIC liver iron concentration; *MIC* Myocardial iron concentration

In the 50 patients with the thalassemia major , 5 (10%) patients had grade 4 (severe) MIC, 4 (8%) patients had grade 3 (moderate) MIC, 14 (28%) patients had grade 2 (light) MIC, and 27(54%) patients had normal (grade 1) MIC.

The 27 cases with normal MIC, 9 had normal LIC and 18 had abnormal LIC. Cases with normal MIC the average SF levels was 543.5 mg/g, and in cases with abnormal MIC SF levels was 5378.8 mg/g.

There was a significant differences was seen between the mean SF levels in the cases with normal and abnormal MIC ($p < 0.01$).

In the figure 4.1 there is positive correlation between Liver and heart T2* with SF levels ($r = 0.314$, $p< 0.013$) .

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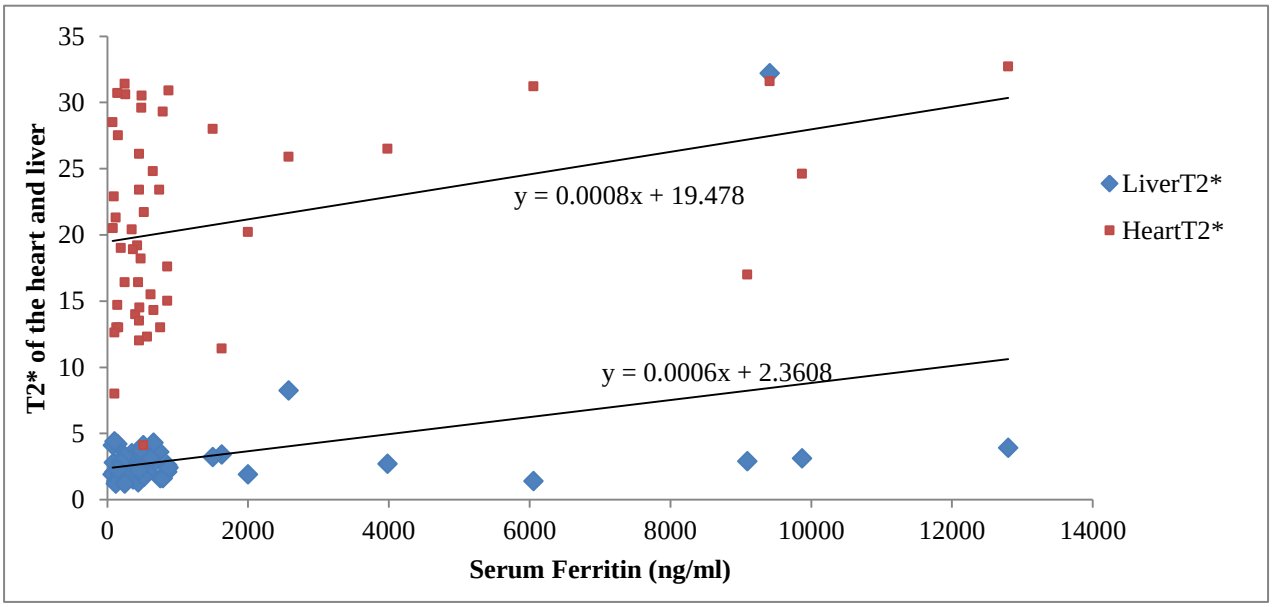

Figure 4.1. correlation between heart and liver T2* with Serum Ferritin.

LIC had positive correlation with SF ($r = 0.531$, $p < 0.001$). MIC had positive correlation with SF ($r = 0.427$, $p < 0.001$).

Also there is positive correlation coefficient between Liver and heart T2* ($r = 0.344$,).

($p<0.01$).

There was also positive correlation found between LIC and MIC ($r = 0.437$, $p< 0.001$) as shown in figure 4.2 .

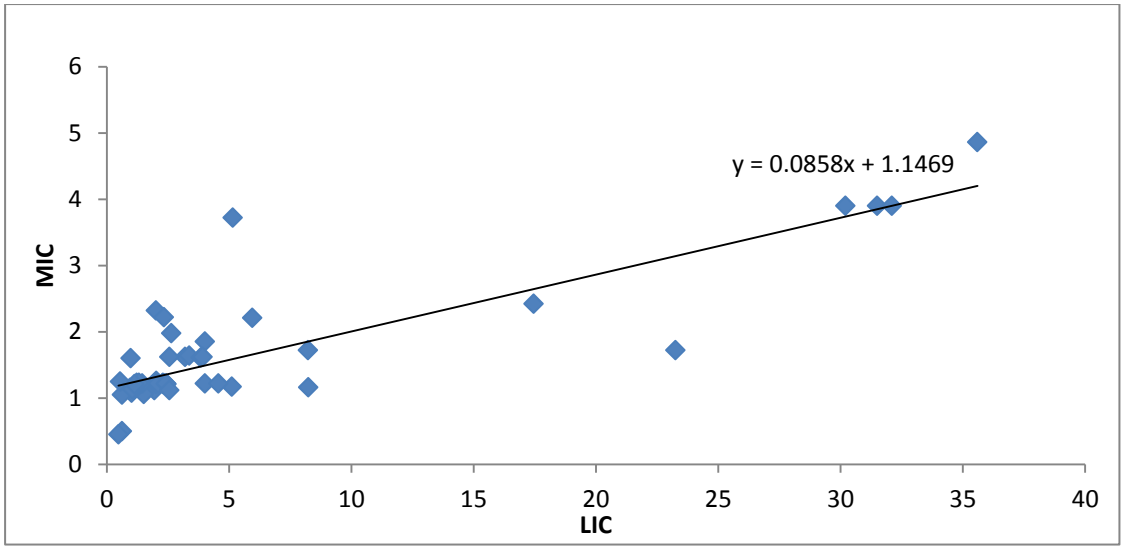

Figure 4.2. Correlation between MIC and LIC.

4.2 DISCUSSION:

The results of this study show that MRI T2* imaging and analysis can be used as invasive tool for detection and quantification of iron overload in both liver an heart. Biopsy of these at thalassemia major patients who receive blood transfusion as chronic that used to detect and quantify the iron concentrations is invasive and inaccurate. In addition, sometimes requires patients to enter the hospital due to the complications in about 0.5% of cases with thalassemia major [28].

. Also this study showed that a high MIC and LIC, in spite of the rate levels, of SF is low in these patients. This gives impression that the chelation therapy should be increased.

T2* MRI is non-invasive (not needing hospitalization) . This technique showed that , the ability to determined iron concentrations in the liver muscle and myocardium has become measurable. The basis of this technique is to accelerate relaxation T2* signal decay, this because T2*W gradient echo (GRE) images with iron overload is vastly decaying and better than the signal in T2W spin-echo [19]. When iron is overloaded in

tissues the SIR is high and higher the darkening images . The darker areas mean that high iron concentrated and this leads to shortening relaxation time and vastly drop in signals [29].

The variances in the inhomogeneity of the magnetic field, results from increased the degree of iron overload allow GRE sequences to be the better sensitivity than spin echo sequences. This is due to inhomogeneity and spin spin relaxation process [23]. Also MRI considered to be safe technique that it does not produce ionizing radiation, it is very safety in children medical imaging especially when need for follow-up treatment and monitoring [22].

The result showed positive correlation between SF and LIC and between SF and MIC. However, the correlation of SF level with LIC was positively more than MIC. with increase SF level, the iron burden would increase [27].

In patients with thalassemia major , the relation between heart T2* and SF values was positive correlation ($r = 0.40$, $p< 0.0004$). but it was seen negative correlation by Voskaridou et al[4].

In this study the correlation between liver and heart T2* with SF ($r = 0.314$, $p< 0.01$) is positive. Also The relationship between SF and LIC ($r = 0.531$, $p < 0.001$) is positive correlation , correspond to the previous article [21]. On other hand there is relationship between liver and heart T2* ($r = 0.344$, $p< 0.011$)which is also positive . At the same time, the relationship between LIC and MIC was positive ($r = 0.437$, p 0.002).

While Christoforidis et al[8] found that there is better relationship between Liver T2* and SF levels, identical to the results of this study, ($r = 0.342$, $p < 0.001$). But Heart T2* MRI ($r = -0.186$, $p <0.011$) [30] opposite this study . Also he founds a moderate relationship .

This study proved positive relationship between the amount of iron in Heart and liver, this relationship with positive correlation , also the relationship between the relaxation of the liver and heart with iron overload is positive and significant relationship in spite of low levels of SF. with SF levels.

Chapter Five:

Conclusion, summary , recommendation:

5.1 Conclusion:

MRI considered to be the safe and accurate way to determine, and measure the amount of iron that deposit and accumulated in the muscle of the liver and heart, through the use of the property of relaxation techniques, that decaying in the transverse plan , the rat of the speed of the relaxation increases with the increase in the amount of iron stored in the tissue of the organ that need to be examined, and can calculate the amount of iron accurately through the use of special equations, The liver and the heart depend on the percentages of arising signals from the tissue of the cell, which increases with increasing the proportion of iron, which makes it accelerate in decreasing, MRI is a non-invasive and non-painful technique used for assessing the amount of iron in the liver and the heart muscles, and in the near future it is expected to be used frequently for this purpose to make monitoring treatment and chelating drugs plane and doses.

5.2 Summary :

1. Iron overload lead to liver cirrhosis, congestive heart failure, hepatocellular carcinomas and endocrine damage .
2. Iron can be calculated and measured by using T2* method in any organ of the human body .
3. Iron concentrated in liver or heart treated by chelating drugs so it is necessary to monitoring an follow up patient treated by using MRI T2* analysis.
4. The percentage of IRON deposit in organ leads to increase the signal intensity an vastly decaying .
5. Accurate chelating dose can be determined by the amount of Iron concentrated in liver and heart which is determined by T2* analysis .

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كشف وقياس الحديد في الكبد وعضلة القلب باستخدام التصوير بالرنين المغناطيسي

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المشرف: د. محمد حجوج

الملخص بالعربية :

خلفية البحث: التصوير بالرنين المغناطيسي هو وسيلة امنة وغير مؤذية تستخدم للكشف عن كمية الحديد المتراكمة في عضلة القلب, والكبد لمرضى التلاسيميا الكبرى . تهدف هذه الدراسة الى تقييم كل من تركيز الحديد في الكبد وفي عضلة القلب لمرضى التلاسيميا الكبرى باستخدام التصوير بالرنين المغناطيسي .

الطرق والعينة: تناولت الدراسة الحالية عينه من 70 حالة تتراوح اعمارهم بين 11- 31سنة, منهم 50مريض يعانون من مرض التلاسيميا, و20مريض يعانون من امراض اخرى, ولا يعانون من امراض في القلب اوالكبد وليس لديهم اي تاريخ مرضي يتعلق بنقل الدم اليهم , حيث تم اجراء التصوير بالرنين المغناطيسي باستخدام خاصية الاسترخاء العرضي والتي تدعى (T2*) لجميع الحالات: حيث تم الحصول على قياسات بواسطة نفس جهاز التصوير بالرنين المغناطيسي وهو من نوع فيلبس انجينيا 1.5 تسلا, وذلك في قسم الاشعة في مستشفى الخليل الحكومي .

الدراسة تمت باثر رجعي وبشكل مقارنه بين حالات طبيعية لا تشكو من التلاسيميا واخرى مصابة بمرض التلاسيميا وتمت خلال الفترة ما بين كانون الثاني 2018 واذار 2019.

وتم مقارنه النتائج مع مستويات مصل الفريتين ,حيث تم استخدام صور الرنين المغناطيسي والسجلات الطبية للمرضى باثر رجعي كما تمت مناقشة الفرق بين الحديد الزائد في عضلت القلب والكبد.

النتائج: كان معدل مصل الفريتين بين الحالات 2150 نانو جرام لكل ميل جرام. والانحراف المعياري 179 نانو جرام لكل ميل جرام. تم العثور على ارتباط كبير في المرض بين تركيز الحديد في الكبد وهي 5.69 ميلجرام لكل جرام (الوزن الجاف من نسيج العضو) وتشبع الكبد بالحديد, وكذلك تم العثور على ارتباط كبير ولكن اضعف في المرضى بين تركيز الحديد في عضلة القلب ومستويات مصل الفريتين وكانت (8 ميلجرام) . حيث كانت معدلات الحديد عند 11 مريض غير طبيعية في الكبد و عند 3 مرضى غير طبيعية في القلب.

الخلاصة : ان معدلات الاسترخاء العرضية التي تقاس بالرنين المغناطيسي ,R2 (1/T2), R2* (1/T2*) هي اداه قيمه وامنة , لتقدير ترسب الحديد في الكبد والقلب للمرضى الذين يعانون من التلاسيميا الكبرى, كما انها اظهرت ارتفاع في تركيز الحديد في الكبد والقلب على الرغم من ان مستويات مصل الفريتين منخفضه في مرضى التلاسيميا, مما يشير الى الحاجه الماسة الى تركيز العلاج باستخدام الاستحلاب واستخراج الحديد المتراكم وهذا بحاجه الى تأكيد من دراسات مستقبليه اوسع واشمل.

Ethical considerations:

This study has Permissions obtained from both ethical approval comity of AL-QUDS University and Palestinian Ministry of Health, the permission was given to each member of the study and participating. All the information was given to patients and the participating, Without coercion or coercion and the members were given the freedom to agree to join the research or not to participate freely and the patient was given the option to accept or refuse to participate in the study**.** Each participant in this study was informed in detail about the method of work of the study and how the work of the examination in full and he signed and approved the work of that study.

Appendices

Appendix 1: Patient check list for MRI

□ date for scheduling clinical diagnose

□ Recruits of patient inform (Clinicians)

□ The request form for MRI exam (support in personnel patient).

□ Clinical patient Form (Clinicians)

□ MRI protocol list form for safety and protect (, targeted exams) and software for

□ Saving procedures for MRI study

□ Transfer DICOM images to Packs System (Radiologists)

□ Transfer Clinical data to HIS (Clinicians)

Appendix 2 Patient Check List
Patient check list that should be written on the day of exam.

Patient Name : .....Patient ID……. Date of Birth: / /. …..length in cm: ……...Weight in Kg……

. It is necessary for the benefit of the patient and the interest of the technical staff to be filled out this questionnaire, in order to: ensure the safety of the patient, the accuracy of the examination, and in order not to risk the risk on you and the technical staff, please be correct, accurate and complete where it will be signed, and approved as an official document by the technical staff.

Do you have (or have you ever had) the following?	
Pacemaker	Yes No
Pacing wires / defibrillator / PICC line	Yes No
Brain aneurysm clip	Yes No
Cochlear Implant	Yes No
Artificial heart valve	Yes No
Neurostimulator / Bio stimulator	Yes No
IVC filter	Yes No
Any type of intravascular coils, filters or stents	Yes No
Swans-Ganz catheter	Yes No
Brain shunt tube	Yes No
Metal pin, plates, rods, screws, prostheses	Yes No
Ocular (eye) prosthesis	Yes No
Stapes (ear) implant	Yes No

Any other form of implant	Yes No
Hearing Aid	Yes No
Dentures, braces (including magnetically activated dentures)	Yes No
Transdermal (skin) patches e.g. Nicotine patches	Yes No
Shrapnel or bullet wounds	Yes No
Wig, toupee, hairpiece	Yes No
A tattoo (including tattooed eyeliner)	Yes No
Any type of body piercing	Yes No
Implanted pain relief pump	Yes No
Implanted Insulin Pump	Yes No
Asthma	Yes No
Anemia	Yes No
Kidney disease	Yes No
An angiogram performed	Yes No
An operation in the last six weeks	Yes No
Do you understand all these questions?	Yes No

I sign on that I understood and understood all of the questionnaire contained in the questionnaire without coercion or ignorance of the former and I signed

Patient or parents signature : ..... Date of signature: ...../.../.....

نموذج استبيان سلامة المرضى واستمارة الموافقة على التصوير بالرنين المغناطيسي

هذا الاستبيان من اجل موافقتكم على السماح بعمل تصوير بالرنين المغناطيسي للكبد والقلب من اجل قياس ومعرفة كمية الحديد المخزنة في القلب والكبد حيث ان مدة التصوير لا تتعدى عشرة دقائق علما ان التصوير بالرنين المغناطيسي هو طريقة لتصوير الجسم باستخدام موجات الراديو الغير ضارة. ولا توجد أشعة سينية ضارة. وهذا بحث علمي يشرف عليه اساتذة مختصون من جامعة القدس كلية الدراسات العليا د. محمد حجوج ودائرة التصوير الطبي في جامعة القدس ابو ديس .ويشكل هذا البحث جزءا اساسيا من مشروع رسالة ماجستير الذي اقوم به في قسم التصوير الطبي –مسار التصوير الوظيفي.

نامل ان تتكرموا علينا بالمشاركة في هذه الدراسة العلمية لخدمة المرضى ذوي العلاقة وخدمة القطاع الصحي الفلسطيني

وتطوير البحث العلمي . اوافق ◯ لا اوافق ◯

ارجو ان تسمحوا لي بعمل هذا التصوير لمرة واحدة علما ان جميع البيانات والمعلومات سرية وتخص هذا البحث العلمي فقط .ولكم الحق في الانسحاب من المشاركة متى شئتم .

مع الاحترام : بسام عبدالعزيز موسى أبوعرقوب .

الاسم:.....رقم الهوية.....

تاريخ الميلاد:..... الوزن (كلغ).....

طبيعة عملك.....البريد الالكتروني.....

الجنس.....الهاتف.....

هل لديك أي جسم غريب معدني او رقعة طبية معدنية، إذا كانت الإجابة بنعم ، متى كان تاريخ هذه الزرعة المعدنية الطبية؟ .. ..

هل لديك وثائق حول الزرع ورقمه المتسلسل؟.....

هل تعاني من نوبات منتظمة؟.....

هل لديك اختبار حديث لوظائف الكلى.....

هل لديك اضطراب كلوية .....

هل عندك خوف من الأماكن المغلقة؟ .....

هل لديك رد فعل تحسسي لأي نوع من الأدوية؟ .....

هل لديك أي عملية جراحية ، إذا كانت الإجابة بنعم ، متى كان تاريخ العملية.....

هل أنتي ، أو هل يمكن أن تكوني حامل؟ .....

هل أنتي مرضعة؟.....

لقد قرأت وفهمت وأكملت على حد علمي ، الأسئلة الواردة في النموذج وقمت بالموافقة على هذا وأوافق على التصوير بالرنين المغناطيسي لعمل الفحص المطلوب.

توقيع المريض.....تاريخ التوقيع.....

توقيع تقني اختصاصي التصوير بالرنين المغناطيسي.....تاريخ التوقيع.....