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Iron Load Evaluation of Adrenal Glands and Kidneys by using MRI T2* In Iranian Thalassemia Patients

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ABSTRACT

Introduction: Multi-organ iron load is prevalent crucial side effect in thalassemic patients due to repeated transfusions, and high intestinal iron absorption. MRI T2* has demonstrated its potency as a non-invasive technique for the imaging of hemosiderosis in thalassemia. We aim to investigate the iron load of adrenal glands and kidneys using MRI T2* in adult thalassemia patients and evaluate the serum ferritin correlation of with kidneys, heart, liver, and adrenal glands' iron load.

Methods: Thirty-five thalassemia major (TM) and thalassemia intermediate (TI) patients (age range 18-50 years) from Zafar thalassemia Clinic, were recruited in this survey from September 2019 to October 2020. Magnetic Resonance Imaging (MRI) was used to map iron overload in several organs' regions of interest (ROIs) using fast-gradient-echo multi-echo T2*sequences protocol. T-test and chi-square analysis were done.

Results: Nine (25.7%) patients had left Kidney T2* less than 36ms which could indicate abnormal renal iron load while this was 8 (22.9%) for the right kidney. In the left and right adrenal glands, these numbers were 31 (88.6%) and 29 (82.9%), respectively, below the normal threshold.

Conclusion: Adrenal gland and renal iron overloads were detected in MRI images of thalassemic patients. Correlation for serum ferritin levels and kidney and adrenal glands T2* was found weakly negative. Non-invasive monitoring of the internal organs' hemosiderosis using MRI T2* was found to be beneficial for iron-chelating optimization and preventing irreversible tissue damage.

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Introduction

Thalassemia is an inherited hemoglobinopathy with high global prevalence [1-4]. This disorder has a place to a group of hereditary blood disorders by reduced (β+) or absent (β0) synthesis of the hemoglobin beta globin chains that lead to reduced red blood cells and anemia [4]. The phenotypes of hereditary heterozygous compound beta-thalasseamia incorporate

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severe, transfusion-dependent thalassemia major, or intermediate spectrum.

Patients with TM customarily show noteworthy anemia in early age and require periodical long-life blood transfusion and iron chelation treatment to survive, whereas thalassemia intermedia patients might not [1, 4, 5]. Due to regular blood transfusion, hemosiderosis happens in organs such as the heart, liver, kidneys, and tiny endocrines, causing tissue damage and, in the long run, organ dysfunction. Although iron chelators progress, the survival of TM patients, multi-organ hemosiderosis is still notable [5-7]. While frequent estimation of serum ferritin offers a simple and accessible strategy for quantifying the iron burden, some studies have reported that there is a more prominent correlation between liver hemosiderosis and body iron index and ferritin [8-10]. Liver biopsy as the gold standard assessment method is invasive and not easy to be done for most patients' target organs like the heart, or kidney [4, 8-10].

The MRI protocol (gradient echo T2* and T2 spin echo or R2 relaxometry) was developed in the early 1980s for the non-invasive assessment of iron burden in internal organs. Iron overload in tissues produces local disturbances in the magnetic field so that higher amounts of organ iron content lead to more magnetic field disturbance. This indicates that the deposition of iron in tissues leads to a decrease in field homogeneity and a low T2* signal on MRI [3, 9-12]. Moreover, a superconducting quantum interference device, which is an important, and non-invasive method, has also been introduced for measuring iron overload, which enables researchers to study the effect of iron overload in hemosiderosis patients. However, this method is not accessible to many centers since it illustrates a few typical signatures of such artifacts in the raw data [13-15]. Quantifying liver and cardiac iron using this approach had a significant impact on the early detection and the treatment of hemosiderosis, treatment modifications, and prevention of tissue iron toxicity like cardiomyopathy due to iron overload [8, 16-20]. Global multi-center investigations have demonstrated that myocardial T2* is a significant prognostic indicator for early detection of cardiac dysfunction. Therefore, this technique has great potential for wider application in chelation regimens optimization and prevention of heart failure to increase survival rates [21, 16].

A study in 1994 indicated low signal intensity of the renal cortex on T2- weighted images in serious hemolytic anemias, due to iron deposition [22]. Information on the renal or adrenal glands iron monitoring is scarce in studies where kidneys or adrenal glands' iron overload in β-thalassaemia patients have been checked [3, 23-26]. Severe iron burden due to regular transfusions, long-lasting chelating regimen, and anemia are the main factors for renal dysfunction [26-29]. Studies conducted by Hashemieh et al. and Meloni et al. assessed iron overload in kidneys in TM and TI patients, using MRI T2* techniques. They analyzed the correlation of serum ferritin level, and the iron overload of the heart and kidney [3, 30,31].

Following these surveys, we first conducted a retrospective cross-sectional to assess the renal T2* MRI iron load of 821 thalassemic patients for a more detailed analysis of renal iron load monitoring [32]. Iron overload in the adrenal glands has been studied histologically in patients with hemosiderosis [33]. Moreover, functional alterations in the adrenal glands due to iron burden have been indicated in previous studies except in Iran [34, 35]. To our knowledge, only Drakonaki et al. and Guzelbey et al. have quantitatively studied iron deposition in the adrenal glands using MRI [33-34]. Control and case groups have been assessed and compared according to adrenal gland signal intensity values.

This seems to be the first limited study for quantification of both kidneys and adrenal glands of Iranian thalassemia patients. It might be an estimation of these organs' hemosiderosis. We assessed both kidneys and adrenals hemosiderosis by an accurate non-invasive method to check if our thalassemic patients might be at risk. The aim was to determine T2* values of both kidneys and adrenals as an index of iron overload in Iranian TM and TI patients. The study also aimed to investigate the correlation between serum ferritin and hemosiderosis in the kidney, adrenal glands, myocardium, and liver.

Materials and Method

Participants: A cross-sectional study was conducted at the referral Imaging Complex, Tehran, Iran, from September 2019 to October 2020. Iron overload assessment using T2* MRI is performed in this center annually. The study was approved by the Ethics Committee of the Iranian Blood Transfusion Organization (IR.TMI.REC.1396.023), and followed the Helsinki Declaration principles. Informed consent was obtained from all the patients. The inclusion criteria were thalassemia-diagnosed patients aged between 18 and 50 years. Also, patients with renal dysfunction, cardiomyopathy, possible liver and adrenal gland disorders, and diuretic treatment were excluded.

A total of 35 TM and TI patients who met the inclusion criteria were recruited in this study. TM patients were on regular transfusions with the frequency of 2 to 4 weeks. TI patients are considered independent of regular transfusion except in specific conditions. The patients mainly were on iron chelating therapy with Desferioxamine or its combination therapy. Demographic data of gender, age, type of thalassemia, height, weight, age of diagnosis, recent serum ferritin level, and splenectomy status were extracted from the medical records.

For conducting the MRI imaging and taking blood samples, the time elapsed after transfusion was considered at least 10 days for the study.

Magnetic Resonance Imaging: Patients were scanned with a 1.5T MR Scanner (Achieva A-series Philips, Netherlands). A standard radiofrequency body coil was used in all measurements. The Royal Brompton protocol based on a single-breath multi-echo fast gradient-echo sequence was used for T2* measurements. The liver, kidneys, and adrenal glands' T2* values were determined by imaging a single trans-axial slice (10 mm) through the center of the liver and kidneys for the measurement of myocardial T2*. Scans were synchronized to the cardiac cycle using standard ECG gating. A single 10 mm-thick, short-axis, mid-ventricular slice positioned halfway between the base and the apex of the left ventricle (LV) was acquired. Echo images for the liver, kidneys, and adrenal glands were 12, while it was 8 for the heart. T2* values were calculated for patients using CMR-based in-house software (Pardis Noor Medical Imaging Center, Tehran, Iran), validated by a standard iron phantom. The assessment and analysis of liver iron content were based on the method of Prof. Pennell, while the classification of cardiac and hepatic iron overload was applied based on Garbowski updates [36, 37]. A homogeneous full-thickness region of interest in the liver, kidney, and adrenal gland parenchyma was selected in the ventricular septum as shown in Fig 1, in which the ROIs in abdominal cross-section MRI T2* for iron overload processing and calculation have been marked as [1] adrenal gland and [2] kidney. We measured the average intensity of the area in each image and made a plot showing how it changed with the echo time(TE). T2* values were calculated in three different ROIs and were averaged to achieve a representative value for the kidney. The threshold level of kidney T2* relaxation time was determined based on the reported value in the literature, indicating that less than 36 ms is considered as a pathological value [30,31]. Also, the threshold was less than 34.81 ms for adrenal glands [34].

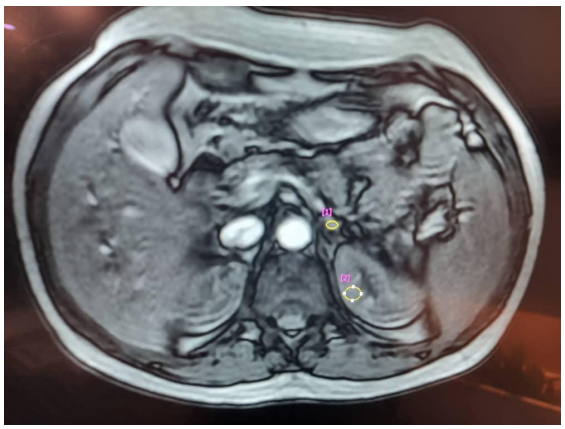

Figure 1. ROIs in abdominal cross-section MRI T2* for iron overload processing and calculation: [1] Adrenal gland and [2] Kidney

Statistical analysis: Quantitative and qualitative data analyzed and were described as mean±standard deviation and frequency and percentage respectively. The normality was checked via the Shapiro Wilks test. The independent samples t-test, paired samples t-test, and Chi-square were used to for comparisons. The correlation between the variables was evaluated by Pearson's correlation coefficient. The level of significance was equal to 0.05 and the confidence interval was 95%. For all statistics analyses, SPSS (version 26) software were applied.

Results

The demographic information of the 35 thalassemic patients is summarized in Tables 1(a, b). As it can be seen, of the details regarding age, type of thalassemia, Hb, Ferritin, diagnosis age blood transfusion interval, etc., are presented quantitatively.

The mean T2*values of the heart and liver were 26.76±8.33 and 6.94±6.02, respectively. Also, 74.28% of the studied patients had normal myocardial iron T2*, while only 58.7% of them had a hepatic iron load in the mild to severe class. The LIC of the patients was also 9.14±9.90 mg/g/dry weight. Table 2 shows the left and right kidneys and adrenal glands of thalassemia patients.

Nine patients (25.7%) had left kidney T2*<36ms which might indicate abnormal renal iron load. This was 8 (22.9%) for the right kidney T2*. The T2* values of adrenal glands were 31(88.6%) and 29 (82.9%) below the normal threshold (34.81 ± 8.74 ms), respectively, for the left and right adrenal glands. Mean T2* values of right and left kidneys and the adrenal glands in both intermedia thalassemia vs. thalassemia major have been assessed and presented in Fig. 2.

A negative weak correlation was found

Table 1 (a). Descriptive clinical demographic data information of the patients

	N	Minimum	Maximum	Mean	Std. Deviation
Age	35	18	50	34.54	9.690
Diagnosis/months	35	3	240	64.29	71.943
Start of Treatment/ month	35	6	240	66.80	71.974
transfusion days	32	20	90	28	16
Start of Iron Chelation/months	35	0	504	99.57	108.867
Desferal dose/ week	35	0	30	16.57	7.429
oral dose/day	35	0	1500	171.77	484.081
Hb g/dL	35	7.1	10.7	8.9	1.8
Ferritin	35	234	6000	1455.91	1209.496

Table 1 (b). Descriptive clinical demographic data information of the patients

		N	%
Sex	Male	8	%22.9
	Female	27	77.1
Thalassemia	Major	24	68.6
	Intermedia	11	31.4
History of Splenectomy	No	9	25.7
	Yes	26	74.3
	Yes	26	74.3
Cardiac iron overload	Normal (>20ms)	28	80.0
	Mild(15-20 ms)	4	11.4
	Moderate(10-15ms)	2	5.7
	Severe(<10ms)	1	2.9
Hepatic iron overload	Normal (>17ms)	4	11.4
	Mild (>6.2ms)	12	34.3
	Moderate(3.1-6.2ms)	11	31.4
	Severe (2.1-3.1)	3	8.6
	very severe (<2.1)	5	14.3

between serum ferritin levels and kidney T2* relaxation time values (r1=-0.343, and r2=-0.348, P-value<0.001, respectively, for the left and right kidneys) while a weak negative correlation was found between serum ferritin levels and adrenal gland T2* ms (r3= -0.214, and r4= -0.43 P-value<0.001, respectively, for the left and right ones).

The analyzed data for Pearson correlations (Significant at the 0.05 level, 2-tailed) for cardiac and hepatic T2* milliseconds with both adrenal glands and kidneys indicated a significant correlation between hepatic with Left/right adrenal glands iron overload (0.369*), while there was no significant correlation with adrenal

Table 2. Comparison of left and right adrenals T2*

	Mean±SD		p-value
	left	right	
T2* adrenal (ms)	25.31±6.84	26.92±8.27	0.230
T2* kidney (ms)	51.65±20.92	52.73±20.47	0.670

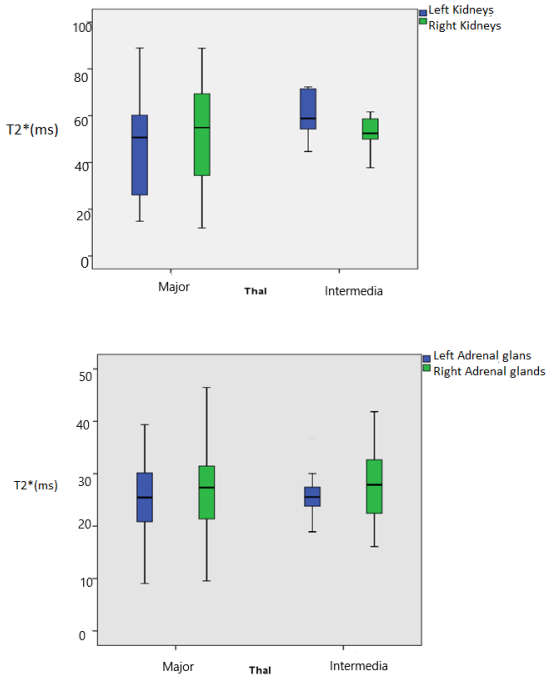

Figure 2. Box plot of kidneys and adrenal glands T2* relaxation time compared in thalasseamia groups

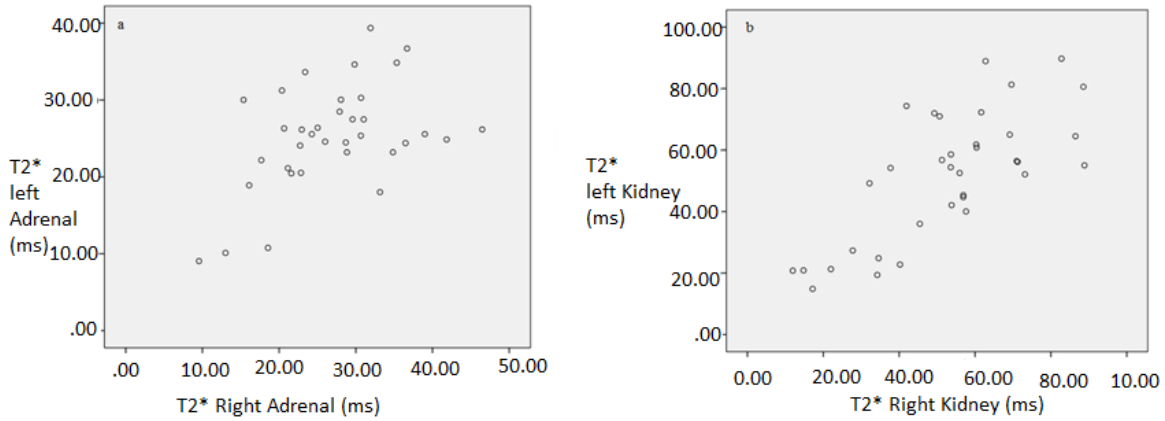

Figure 3. Scatter plot of kidney T2* relaxation time of a) both adrenal glands, b) both kidneys

glands or kidneys and heart iron load.

Scatter plots of T2* relaxation time of both kidneys and adrenal glands T2* relaxation time are presented in Fig. 3. Based on this scatter plot, 85.75% of the involved patients had abnormal iron load or hemosiderosis of both adrenal glands. This was found to be 24.3% for hemosiderosis of both kidneys while 20% and 88.6% of the patients had abnormal cardiac and hepatic iron overload.

Discussion

Beta thalassemia is a global prevalent hereditary hemoglobinopathy [2]. In spite of long-life treatment care of blood transfusion and iron chelation, and longer life expectancy in beta-thalassemia patients compared to the past, therapeutic-related complications like cell damage of organs and endocrines remain [2, 6]. Cell damage from heavy iron burden and hemosiderosis in thalassemic patients seems to lead to injuries in vital organs or endocrine glands like kidneys and adrenal glands [25, 36]. Chronic anemia and hypoxia in thalassemic patients in addition to iron overload might cause oxidative stress, lipid peroxidation, and irreversible cell damage [36-38]. After the introduction of the MRI T2* method to assess hemosiderosis in the tissues, several extensive studies have been published on the heart and liver while fewer details are available concerning other organs and endocrine glands [9, 16-21, 39]. Hence, MRI has been introduced as an essential tool in the management of patients with thalassemia, given the limitations of current metrics to assess iron storage in different organs. Due to its non-ionizing property, evaluations using MRI T2* are simple, fast, and with no radiation. The milligram of dry iron in liver (liver iron concentration, LIC) can be accurately evaluated by T2* and T2 techniques, with high reproducibility and correlation [36-40]. Now, we are accustomed to MRI T2* measurements of the heart and liver as we know the cutoffs for heart failure. Adrenal gland is one of the most important endocrine glands that might suffer from inefficiencies in thalassemia. Some of the symptoms of adrenal gland insufficiency are arthralgia, muscle pain, chronic fatigue and gastrointestinal complaints [33]. Iron overload in adrenal glands might be detectable using MRI T2* as hypo-intensity images. A few surveys have showed a correlation between the liver and adrenal gland hemosiderosis. Moreover, no significant correlation has been reported between adrenal gland signal intensity and patient age or serum ferritin level [33, 34]. Regarding the kidneys, although there are some studies, apparently none of them have studied the renal cutoff correlated with renal function [39, 40]. While there are numerous studies on hepatic and cardiac iron overload assessment in Iran and worldwide, there are limited hemosiderosis quantifying data for kidneys and adrenal glands in Iranian thalassemia patients. This study was conducted to assess both kidneys and adrenals hemosiderosis by an accurate non-invasive MRIT2* for potential risk. The aim was to investigate the pattern of iron load in both kidneys and adrenal glands in Iranian TM, TI patients. We studied the correlation between renal, adrenal glands hemosiderosis with serum ferritin, and T2* values of the liver and heart iron overload. The results of this study showed a weak negative correlation between kidney T2* relaxation time and serum ferritin, with a weak correlation observed between kidney T2* relaxation time and liver and heart T2* relaxation time. The results indicated that the hepatic hemosiderosis seems to be more prevalent in thalassemic patients. It appears that the mechanisms and dynamics of the absorption, storage and elimination of iron in these tissues are different,

especially in the transfusion-dependent patients [3, 9]. Therefore, applying the MRI imaging T2* technique highlights the need for the clinicians to quantitatively estimate organs at risk by iron hemosiderosis monitoring. In addition, 24.3% of the patients in our study had iron hemosiderosis in both kidneys with T2* values less than renal threshold (22.85%, 25.71% for the right and left kidneys, respectively). This seems to be in accordance with the results reported by Meloni et al. who found that 33.6% of their thalassemia population had a pathological value (T2*<36 ms) of kidney iron deposition [30,31, 39]. In addition, the percentage of the abnormal iron load in both right and left adrenal glands was calculated at 82.85% which might show that a considerable number of the patients suffered from iron overload in adrenal glands. The data reported by Meloni et al. study have also shown a significant correlation between iron load in the adrenal gland and the liver, which is consistent with our findings [33, 34].

Although various studies have been conducted on monitoring cardiac and hepatic iron load of the thalassemia patients by non-invasive MRI methods to become the standard of care [41], fewer studies are available for renal, especially adrenal glands' hemosiderosis in thalassemia using T2* technique of MRI. In Iran, we have just found a study for determining the prevalence of adrenal insufficiency in children with β-thalassemia major. The results of this study showed that in patients with a normal baseline cortisol level, the low-dose test could efficiently detect hidden secondary adrenal insufficiency [42].

In this imaging study, we observed that the prevalence of iron deposition was approximately 24.3% in both kidneys and 82.85% in adrenal glands in thalassemia patients. Non-invasive MRI T2* method provides promising results for the evaluation of iron burdens in internal tissues and organs. It is promising for non-invasive detection of the adrenal insufficiency in thalassemia patients, based on monitoring the iron overload in them at various times.

Our study suffers from a number of limitations. We conducted this limited population study due to the expenses involved in T2* imaging which are not covered by insurance and limited research grants. Hence, more extensive and multi-center studies are recommended for more accurate understanding. Finally, only the MRI T2* iron load calculations and analysis were used for this study. For deeper findings, the application of R2 relaxation protocol using MRI is recommended for investigating renal or adrenal glands' hemosiderosis in thalassemic patients compared to the T2* measurements. In addition, it might be a beneficial suggestion to have MRI iron overload assessment and correlations with more reliable clinical tests in normal thalassemia patients and those who suffer from dysfunctions of kidneys or adrenal glands.

Conclusion

This MRI technique can assist the clinicians in early detection of renal or some endocrine complications in beta-thalassemia patients based on iron overload assessment of adrenal glands and kidney. The early diagnosis of renal and adrenal iron overload complications might shed a light for specialists on iron chelating optimization influence treatment strategies and patient outcomes while preventing tissue damage in organs and glands due to toxic iron. Similar to the toxicity and function failure of the vital tissues, it might be also developed in renal and adrenal glands and in this way some earlier care might help prevent kidney failure in thalassemic patients.

Ethics approval and consent to participate

The study was approved by the Iranian Blood Transfusion Organization Ethics Committee (IR.TMI.REC.1396.023).

Consent for publication

"Not applicable."

Availability of data and materials

All data from this study are included in the published article.

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Conflict of interest

"The authors declare no competing interests".

Abbreviations

Confidence Interval: CI
Liver Iron Content: LIC
Magnetic Resonance Imaging: MRI
Millisecond: ms
Red Blood Cells: RBC
Region of Interest: ROI
Superconducting quantum interference device: SQUID
Thalassemia Intermediate: TI
Thalassemia Major: TM

Authors' contribution

Shirkavand A, Ph.D.: Medical Physics researcher, data collection, drafting and revising the

manuscript.

Razaghi Z, Ph.D.: Statistics methodologist, analyzing and interpreting the data, supervising the analysis in drafting and revision.

Akhlaghpoor S MD: Radiology concepts and design, essential reagents or tools, draft plan and revising the manuscript.

Azarkeivan A MD: Hematology clinical specialist of thalassemia patients, assisted in essential interpretation of the data and drafting and revision of the manuscript.

Karimi M MD: Consultant in the field of hematology and thalassemia, English edition and revision of the manuscript.

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