Original Article

Correlation between Heart, Liver and Pancreas Hemosiderosis Measured by MRI T2* among Thalassemia Major Patients from Iran

Azita Azarkeivan MD[1], Mozhgan Hashemieh MD•[2], Afshan Shirkavand MD[3], Kourosh Sheibani MD[4]

Abstract

Introduction: Major thalassemia patients need lifelong transfusions. The consequence of these repeated transfusions is iron accumulation in different organs. The main aim of the present study was to investigate the correlation between heart, liver and pancreas hemosiderosis in thalassemic patients from Iran.

Methods: This cross-sectional study was conducted on 164 major thalassemia patients at Zafar Adult Thalassemia Center, a referral thalassemia center in Tehran, Iran, from May to November 2014. All patients were on regular blood transfusion at 2–4 week intervals to keep their hemoglobin at a level of 7–9 gr/dL before each transfusion. Demographic data were gathered from patients' history. MRI T2* of liver, heart and pancreas were performed for all patients.

Results: There were a moderate correlation between pancreatic T2* and cardiac T2* relaxation times (r = 0.42, $P < 0.001$), a moderate correlation between T2* of pancreas and liver (r = 0.41, $P < 0.001$), and a weak correlation between T2* relaxation times of heart and liver (r = 0.31, $P < 0.001$).

Conclusion: Poor correlation between liver and heart, as well as a weak to moderate correlation between pancreas and liver T2* relaxation times indicate that relying on liver MRI T2* to predict the exact condition of pancreas or heart iron overload might not be a reliable approach in thalassemia major patients. Our findings suggest the advantage of using pancreas and heart MRI T2* as a non-invasive method for estimation of iron overload instead of relying on liver MRI T2*.

Keywords: Hemosiderosis, Iran, MRI T2*, thalassemia

Cite this article as: A. Azarkeivan, M. Hashemieh, A Shirkavand, K. Sheibani. Correlation between Heart, Liver and Pancreas Hemosiderosis Measured by MRI T2* among Thalassemia Major Patients from Iran. *Arch Iran Med*. 2016; 19(2): 96 – 100.

Introduction

Beta Thalassemia major is a type of hemolytic anemia characterized by defective biosynthesis of beta globin chains.[1] The most important mainstay of treatment in beta thalassemia is packed red blood cell transfusion. Thalassemic patients need lifelong transfusions and the consequence of these repeated transfusions is iron accumulation in different organs, such as heart, liver, endocrine glands, pancreas, lungs, and kidneys.[1]

In recent years, advances in the management of patients with β-thalassemia major has improved the survival of patients,[2] so finding non-invasive methods for estimation of iron overload in different organs of these patients has become an important subject. Serum ferritin acts as a marker for evaluation of iron stores, but some conditions such as inflammation, infection, liver disease or hepatitis can raise the ferritin level, as well.[3] Although biopsy has been suggested as the most reliable method for estimating organ iron overload, its implementation is limited because of its invasive nature.[4]

The T2* magnetic resonance imaging (MRI) technique seems to be an accurate, valid and non-invasive method for assessment of tissue iron stores. This method has revolutionized the management of thalassemia patients, especially in the tailoring of chelation regimens.[5–7] Despite some previous studies on cardiac, hepatic and kidney MRI T2* among Iranian patients, there is no published data on the MRI T2* of pancreas among Iranian patients.[8–13]

Endocrine and exocrine function impairment of the pancreas has been reported to be a common complication among thalassemic patients.[14] One of the most important endocrinopathies among thalassemic patients is diabetes mellitus. The incidence of diabetes mellitus in adult major thalassemia patients varies from 10% to 30% worldwide.[15,16] The exact etiology of diabetes mellitus in thalassemic patients is uncertain, but iron accumulation in pancreas is one of the most probable causes.[17] Iron overload has been defined by T2* values < 6.3 milliseconds, T2* < 20 milliseconds and T2* < 21 milliseconds in the liver, heart and pancreas, respectively.[18,19]

In the present study, we evaluated the correlation between hemosiderosis of myocardium, liver and pancreas among Iranian major thalassemia patients by means of MRI T2*.

Patients and Methods

The present study was conducted at Zafar Adult Thalassemia Center, a referral thalassemia center in Tehran, Iran, from May to November 2014. The study was approved by the Ethics committee of Shahid Beheshti University of Medical Science, Tehran, Iran, and written consent was obtained from all participants. All patients were major thalassemia patients and were receiving regular blood transfusions (10 mL packed RBC/kg body weight)

Authors' affiliations: [1]Research Center of Iranian Blood Transfusion Organization, Thalassemia Clinic, Tehran, Iran. [2]Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. [3]Pardis Noor Imaging Center, Tehran, Iran. [4]Clinical Research and Development Center, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
•**Corresponding author and reprints:** Mozhgan Hashemieh MD[2], Imam Hossein Medical Center, Shahid Madani Street, Tehran, Iran.
Tel: +98-912-101-5080, E-mail: mozh_hash@yahoo.com
Accepted for publication: 25 November 2015

at 2–4 week intervals to keep their hemoglobin at a level of 7–9 gr/dL before each transfusion. The majority of the patients were receiving chelation therapy with subcutaneous desferrioxamine mesylate (30–40 mg/kg/d four to five days per week). Patients with a history of hepatitis B and C or acute infections were excluded from the study to avoid these conditions influencing the serum ferritin. The patients were selected from 600 patients who had the inclusion criteria. The sample selection was based on the convenient sampling method. Each patient who fulfilled the inclusion criteria and agreed to be included participated in this study.

Measurement of serum ferritin was carried out by electrochemiluminescence (Elecsys 2010 Chemistry Analyzer, Roche Diagnostics, Basel, Switzerland).

Magnetic resonance imaging protocol

Magnetic resonance imaging was performed for all patients at Pardis Noor Clinic, Tehran, Iran, with a 1.5 Tesla scanner (Achieva 1.5T A-series, Philips Medical Systems)**.**

A standard RF body coil was used in all measurements. We used the Royal Brompton protocol which is based on a single-breath, multi-echo, fast gradient-echo sequence for T2* measurements.[9] For measuring myocardial T2*, scans were synchronized to the cardiac cycle using standard ECG gating.[9] We then took a single 10 mm-thick short axis, mid ventricular slice positioned half way between the base and the apex of the left ventricle.[9] The liver T2* was measured by imaging a single trans-axial slice (10 mm) through the center of the liver. [9] MRI T2* of pancreas was performed in the axial plane, flip angle 200 with 7 mm slice thickness, image matrix 250 × 250 pixel, and field of view of 370 (350–400 mm).

Estimation of sample size and statistical analysis

In order to have 90% power, to detect a correlation as small as 0.25, with a type I error of 0.05, we needed at least 160 samples. We included 164 samples in our study. To assess the normal distribution of data, we used Kolmogorov-Smirnov test and Q-Q plot. To present data, we used mean, standard deviation, median and range, frequency and percent. To evaluate the relation of different factors, we used spearman correlation coefficient. The magnitude of the correlation was defined based on the value of the correlation coefficient. A correlation less than 0.4 was considered as weak, 0.4 to 0.6 was considered as moderate, and more than 0.6 was considered as strong. Also, to fit the proper line to the scatter plot of the variables, we used the Loess method. All statistical analyses were performed using SPSS (IBM SPSS statistics for windows, version 22.0 Armonk, NY: IBM corp.). *P* values less than 0.05 were considered statistically significant.

Results

Between May and November 2014, 164 patients (89 female, 75 male) were included in this study.

The mean age was 30, with a range of 10–60 years. The mean value of serum ferritin was 1544 ± 1470 n/mL. Demographic characteristic of patients are shown in Table 1.

The mean relaxation time of pancreas, heart and liver were 15.41 ± 12.36, 25.23 ± 11.27 and 8.09 ± 9.16 milliseconds, respectively. In the present study, 125 patients (76.2%) had pancreatic iron overload. Fifty six patients (34.1%) had myocardial iron overload including 22 patients (13.4%) with mild, 18 patients (11%) with moderate and 16 patients (9.8%) with severe cardiac hemosiderosis. Also from all participants in our study, 98 patients (59.8%) had liver iron overload and only 9 patients (5.5%) had severe liver hemosiderosis. The mean iron loading in the liver was 4.03 ± 3.24 mg/gr/dry weight. The findings related to liver, heart and pancreas MRI T2* are summarized in Table 2.

In the present study, there was a moderate negative correlation between ferritin and relaxation time of liver T2*(r = -0.57), but a weak negative correlation between ferritin and cardiac relaxation time (r = -0.32, $P < 0.001$) (Table 3). Also, there was a moderate negative correlation between ferritin and pancreas relaxation time (r = -0.46, $P < 0.001$) (Table 3) (Figure 1). When comparing the T2* readings of pancreas, heart and liver, there was a moderate positive correlation between relaxation time of pancreas with liver (0.41, $P <0.001$) (Table 3) (Figure 2) and heart (r = 0.42, $P < 0.001$) relaxation times (Figure 3). Finally, there was a weak correlation between T2* of heart and liver (r = 0.31, $P < 0.001$) (Table 3).

Discussion

Assessment of organ specific hemosiderosis is a key point in improving the survival of transfusion-dependent thalassemia patients.[20] The advent of MRI T2* have revolutionized the management of thalassemia patients.[21] The aim of the present study was to investigate the correlation between heart, liver and pancreas hemosiderosis among thalassemia major patients in Iran. Our results showed that 76.2 % of all patients had pancreatic iron overload which is in agreement with similar studies, such as the study by Matter *et al.*[22] Several other studies have reported that pancreatic hemosiderosis occurs in 75%–100% of thalassemia major cases.[16,23–28] In the current study, 34.1% and 59.8% of our patients

Table 1. Demographic data of the patients.

Parameter		Values
Age (yrs)	Mean ± SD	30 ± 10
	Median (range)	29 (10 to 60)
Gender	Female	89 (54.3%)
	Male	75 (45.7%)
Ferritin	Mean ± SD	1544 ± 1470
	Median (range)	1100 (13 to 8000)
	Normal	73 (46.8%)
	Abnormal	83 (53.2%)

Table 2. Findings in liver, heart and pancreas MRI T2*.

Parameter			Value
T2* - Pancreas (ms)	Mean ± SD		15.41 ± 12.36
	Median (range)		11.61 (1.83 to 70)
Pancreas Hemosiderosis	No		39 (23.8%)
	Yes		125 (76.2%)
T2* Heart	Mean ± SD		25.23 ± 11.27
	Median (range)		25.06 (6.02 to 49.98)
Cardiac Hemosiderosis	No		108 (65.9%)
	Yes		56 (34.1%)
		Severe	16 (9.8%)
		Moderate	18 (11.0%)
		Mild	22 (13.4%)
T2* - Liver (ms)	Mean ± SD		8.09 ± 9.16
	Median (range)		4.11 (1.13 to 42.54)
Loading - Liver (mg/g/ dry weight)	Mean ± SD		4.03 ± 3.24
	Median (range)		3.29 (0 to 12.6)
Liver Hemosiderosis	No		66 (40.2%)
	Yes		98 (59.8%)
		Severe	9 (5.5%)
		Moderate	50 (30.5%)
		Mild	39 (23.8%)

Table 3. Spearman correlation of Ferritin, T2* readings of pancreas, heart and liver.

First parameter	Second parameter	r	*P*
Ferritin	T2* - Pancreas (ms)	-.46	<0.001
	T2* - Heart (ms)	-.32	<0.001
	T2* - Liver (ms)	-.57	<0.001
T2* - Pancreas (ms)	T2* - Heart (ms)	.42	<0.001
T2* - Pancreas (ms)	T2* - Liver (ms)	.41	<0.001
T2* - Heart (ms)	T2* - Liver (ms)	.31	<0.001

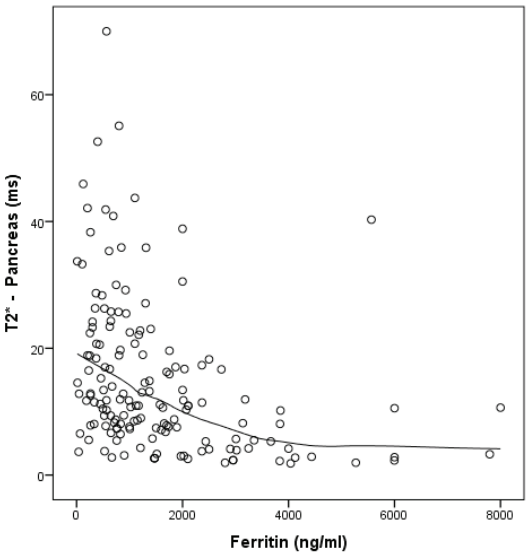

Figure 1. The relation between pancreas MRI T2* relaxation time and ferritin (r = -0.46, *P* < 0.001) and its corresponding fitted line based on Loess method.

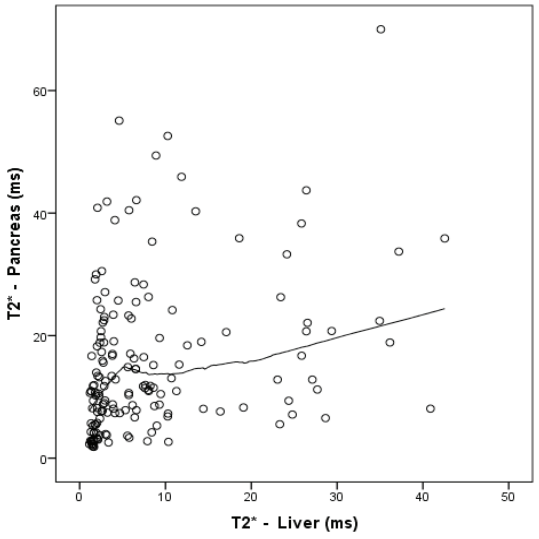

Figure 2. The relation between pancreas and liver MRI T2* relaxation time (r = 0.41, *P* < 0.001) and its corresponding fitted line based on Loess method.

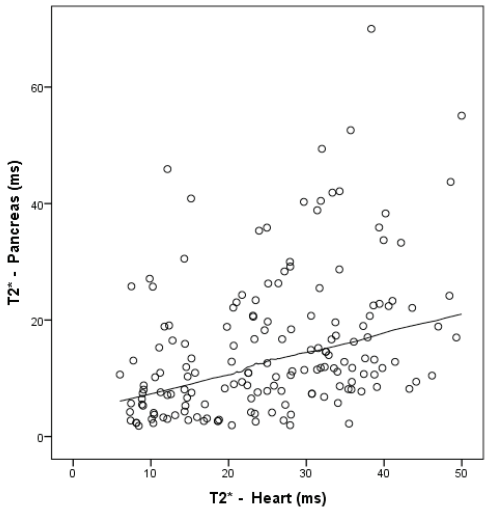

Figure 3. The relation between pancreas and cardiac MRI T2* relaxation time (r = 0.42, $P < 0.001$) and its corresponding fitted line based on Loess method.

had cardiac and liver iron overload, respectively. Also, serum ferritin level was higher than 1000 ng/mL in 83 cases (53.2 %).

There was a negative weak correlation between serum ferritin and cardiac MRI T2* relaxation time (r = -0.32, $P < 0.001$). Thus, ferritin level could not accurately predict cardiac iron overload, as measured by T2* magnetic resonance imaging. This finding is in concordance with previous published data,[9,29–32] and further emphasizes the importance of MRI T2* as a more accurate method for investigating cardiac iron overload. Also, we found a negative moderate correlation between ferritin and the relaxation time of liver T2* (r = -0.57, $P < 0.001$). This finding is also in line with results from other studies.[26,33,34] Therefore, serum ferritin cannot satisfactorily estimate the iron burden of liver.

Also, another important aspect of our study was a moderate negative correlation between ferritin level and pancreatic T2* relaxation time (r = - 0.46, $P < 0.001$). Similar to our findings, Au *et al.* showed that hemosiderosis of the pancreas could not be accurately predicted by ferritin levels.[25] Argyropoulou *et al*. also found no correlation between pancreas hemosiderosis and serum ferritin levels.[4]

Our results showed a moderate correlation between pancreas and liver T2* relaxation time (r = 0.41, $P < 0.001$). This finding is in concordance with Au *et al.,*[25] and Matter *et al.*,[22] whereas de Assis *et al.,*[29] and Papakonstantinou *et al.,*[24] found no correlation between liver T2* relaxation time and pancreatic relaxation time. In other words, liver siderosis is a poor predictor of pancreatic hemosiderosis.[29]

In the present study, we found a moderate correlation between pancreatic and cardiac T2* relaxation time (r = 0.42, $P < 0.001$). This finding is similar to other studies findings.[25,28,29] Noetzli *et al*., have reported that pancreatic hemosiderosis would precede cardiac iron overload. These authors have suggested the possibility of predicting cardiac siderosis almost 10 years in advance by studying the pancreas iron deposition in thalassemic patients.[28] There was also a week correlation between T2* of heart and liver (r = 0.31, $P < 0.001$)

According to our results, liver MRI T2* or serum ferritin levels cannot predict pancreatic and cardiac siderosis, indicating that body tissues have different iron deposition patterns. This can be attributed to organ specific mechanisms of iron uptake and release, the heterogeneous distribution of transferrin receptors and differential iron transport kinetics.

In conclusion, poor correlation between liver and heart, as well as a weak to moderate correlation between pancreas and liver T2* relaxation times indicate that relying on liver MRI T2* to predict the exact condition of pancreas or heart iron overload might not be a reliable approach, so using one organ MRI readings to predict iron overload in other organs has serious limitations. Our findings also suggest the advantage of using the pancreas and heart MRI T2* as a non-invasive method for estimation of iron overload instead of relying on liver MRI T2*.

Conflict of interest

None of the authors has a conflict of interest with the subject matter of the present study.

References

1. Lukens JN. The thalassemias and related disorders, quantitative disorders of hemoglobin synthesis. In: Lee GR, Bithell TC, Foerster J, et al, eds. *Wintrobe's Clinical Hematology*. 9th ed. Philadelphia: Lea & Febiger; 1993: 1102 – 1145.
2. Hershko C, Link G, Konijn AM, Cabantchik ZI. Objectives and mechanism of iron chelation therapy. *Ann N Y Acad Sci*. 2005; 1054: 124 – 135.
3. Wood JC, Ghugre N. Magnetic resonance imaging assessment of excess iron in thalassemia, sickle cell disease and other iron overload diseases. *Hemoglobin*. 2008; 32(1-2): 85–96.
4. Argyropoulou MI, Kiortsis DN, Astrakas L, Metafratzi Z, Chalissos N, Efremidis SC. Liver, bone marrow, pancreas and pituitary gland iron overload in young and adult thalassemic patients: a T2 relaxometry study. *Eur Radiol*. 2007; 17(12): 3025–3030.
5. St. Pierre TG, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK, et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. Blood. 2005; 105(2): 855 – 861.
6. Kirk P, He T, Anderson LJ, Roughton M, Tanner MA, Lam WWM, et al. International reproducibility of single breath-hold T2* magnetic resonance for cardiac and liver iron assessment among five thalassemia centers. *J Magn Reson Imaging*. 2010; 32(2): 315 – 319.

7. Tanner MA, He T, Westwood MA, Firmin DN, Pennell DJ; Thalassemia International Federation Heart T2* Investigators. Multi-center validation of the transferability of the magnetic resonance T2* technique for the quantification of tissue iron. *Haematologica*. 2006; 91(10): 1388 – 1391.
8. Zamani F, Razmjou S, Akhlaghpoor S, Eslami SM, Azarkeivan A, Amiri A. T2* magnetic resonance imaging of the liver in thalassemic patients in Iran. *World J Gastroenterol*. 2011; 17(4): 522 – 525.
9. Azarkeivan A, Hashemieh M, Akhlaghpoor S, Shirkavand A, Yaseri M, Sheibani K. Relation between serum ferritin and liver and heart MRI T2* in beta thalassaemia major patients. *East Mediterr Health J*. 2013; 19(8): 727 – 732.
10. Barzin M, Kowsarian M, Akhlaghpoor S, Jalalian R, Taremi M. Correlation of cardiac MRI T2* with echocardiography in thalassemia major. *Eur Rev Med Pharmacol Sci*. 2012; 16(2): 254 – 260.
11. Gholizadeh N, Akhlaghpoor S, Soltanian-Zadeh H, Fatemizadeh MR, Alinaghizadeh AS, Akhtari AS, et al. Optimization of liver iron load assessment by Pixel-Based T2* MRI in thalassemic Patients. *Open J Radiology*. 2012; 2(2): 46 – 51.
12. Eghbali A, Taherahmadi H, Shahbazi M, Bagheri B, Ebrahimi L. Association between serum ferritin level, cardiac and hepatic T2-star MRI in patients with major β-thalassemia. *Iran J Ped Hematol Oncol*. 2014; 4(1): 17 – 21.
13. Hashemieh M, Azarkeivan A, Akhlaghpoor S, Shirkavand A, Sheibani K. T2-star (T2*) magnetic resonance imaging for assessment of kidney iron overload in thalassemic patients. *Arch Iran Med*. 2012; 15(2): 91 – 94.
14. Kattamis C, Ladis V, Tsoussis D, Kaloumenou I, Theodoridis C. Evolution of glucose intolerance and diabetes in transfused patients with thalassemia. *Pediatr Endocrinol Rev*. 2004; 2 (suppl 2): 267 – 271.
15. Chatterjee R, Bajoria R. New concept in natural history and management of diabetes mellitus in thalassemia major. *Hemoglobin*. 2009; 33 (suppl 1): S127 – S130.
16. Toumba M, Sergis A, Kanaris C, Skordis N. Endocrine complications in patients with thalassaemia major. *Pediatr Endocrinol Rev*. 2007; 5(2): 642 – 648.
17. Li MJ, Peng SS, Lu MY, Chang HH, Yang YL, Jou ST, et al. Diabetes mellitus in patients with thalassemia major. *Pediatr Blood Cancer*. 2014; 61(1): 20 – 24.
18. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2008; 10(1): 42.
19. Wood JC. Magnetic resonance imaging measurement of iron overload. *Curr Opin Hematol*. 2007; 14(3): 183 – 190.
20. Gujja P, Rosing DR, Tripodi DJ, Shizukuda Y. Iron overload cardiomyopathy: better understanding of an increasing disorder. *J Am Coll Cardiol*. 2010; 56(13): 1001 – 1012.
21. Kremastinos DT, Farmakis D. Iron overload cardiomyopathy in clinical practice. *Circulation*. 2011; 124(20): 2253 – 2263.
22. Matter RM, Allam KE, Sadony AM. Gradient-echo magnetic resonance imaging study of pancreatic iron overload in young Egyptian beta-thalassemia major patients and effect of splenectomy. *Diabetol Metab Syndr*. 2010; 2: 23.
23. Midiri M, Lo Casto A, Sparacia G, D'Angelo P, Malizia R, Finazzo M. MR imaging of pancreatic changes in patients with transfusion-dependent beta-thalassemia major. *AJR Am J Roentgenol*. 1999; 173(1): 187 – 192.
24. Papakonstantinou O, Ladis V, Kostaridou S, Maris T, Berdousi H, Kattamis C, et al. The pancreas in beta-thalassemia major: MR imaging features and correlation with iron stores and glucosedisturbances. *Eur Radiol*. 2007; 17(6): 1535 – 1543.
25. Au WY, Lam WW, Chu W, Tam S, Wong WK, Liang R. A T2* magnetic resonance imaging study of pancreatic iron overload in thalassemia major. *Haematologica*. 2008; 93(1): 116 – 119.
26. Ooi GC, Khong PL, Chan GC, Chan KN, Chan KL, Lam W, et al. Magnetic resonance screening of iron status in transfusion-dependent beta-thalassaemia patients. *Br J Haematol*. 2004; 124(3): 385 – 390.
27. Au WY, Lam WW, Chu WW, Yuen HL, Ling AS, Li RC, et al. A cross-sectional magnetic resonance imaging assessment of organ specific hemosiderosis in 180 thalassemia major patients in Hong Kong. *Haematologica*. 2008; 93(5): 784 – 786.
28. Noetzli LJ, Papudesi J, Coates TD, Wood JC. Pancreatic iron loading predicts cardiac iron loading in thalassemia major. *Blood*. 2009; 114(19): 4021 – 4026.
29. de Assis RA, Kay FU, Rosemberg LA. Iron overload in Brazilian thalassemic patients. *Einstein*. 2011; 9(2): 165 – 172.
30. Leung AW, Chu WC, Lam WW, Lee V, Li CK. Magnetic resonance imaging assessment of cardiac and liver iron load in transfusion dependent patients. *Pediatr Blood Cancer*. 2009; 53(6): 1054 – 1059.
31. Di Tucci AA, Matta G, Deplano S, Gabbas A, Depau C, Derudas D, et al. Myocardial iron overload assessment by T2* magnetic resonance imaging in adult transfusion dependent patients with acquired anemias. *Haematologica*. 2008; 93(9): 1385 – 1388.
32. Fragasso A, Ciancio A, Mannarella C, Gaudiano C, Scarciolla O, Ottonello C, et al. Myocardial iron overload assessed by magnetic resonance imaging (MRI)T2* in multi- transfused patients with thalassemia and acquired anemias. *Eur J Intern Med*. 2011; 22(1): 62 – 65.
33. Perifanis V, Christoforidis A, Vlachaki E, Tsatra I, Spanos G, Athanassiou-Metaxa M. Comparison of effects of different long-term iron-chelation regimens on myocardial and hepatic iron concentrations assessed with T2* magnetic resonance imaging in patients with beta-thalassemia major. *Int J Hematol*. 2007; 86(5): 385 – 389.
34. Mazza P, Giua R, De Marco S, Bonetti MG, Amurri B, Masi C, et al. Iron overload in thalassemia: comparative analysis of magnetic resonance imaging, serum ferritin and iron content of the liver. *Haematologica*. 1995; 80(5): 398 – 404.