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Correlation of Magnesium Level with Cardiac and Hepatic Hemosiderosis Measured by T2*MRI Technique and Age in Patients with Thalassemia Major

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ABSTRACT

Background: Given the association of hypomagnesemia with cardiac arrhythmia, the aim of this study was to investigate the relationship between serum magnesium levels with age and T2* magnetic resonance imaging (MRI) findings of the heart and liver in patients with thalassemia major (TM).

Materials and Methods: In a descriptive cross-sectional study, a total of 62 patients with β-thalassemia major aged 11-48 years were selected at the Amir-Kabir Hospital, Arak, Iran. Serum magnesium, ferritin, and iron levels of patients were measured, and the rate of cardiac and hepatic hemosiderosis of patients was extracted according to the routine T2*MRI method.

Results: The mean age of the patients at diagnosis was 32.6 years. The comparison of TM patients with and without hepatic/cardiac hemosiderosis demonstrated that mean levels of serum ferritin, serum iron, and age were significantly higher in TM patients with cardiac hemosiderosis than in hepatic/cardiac non-hemosiderosis ($P < 0.05$); however, there was no significant difference in mean levels of serum magnesium in TM patients with and without hepatic/cardiac hemosiderosis ($P = 0.279$). Interestingly, the correlation of age with serum magnesium levels in TM patients revealed a statistically significant and moderate inverse correlation ($r = -0.56$, $P = 0.013$).

Conclusion: Hypomagnesemia may occur in a time-dependent manner. It is recommended that, in addition to cardiac and hepatic T2*MRI, serum magnesium levels be measured by using magnesium replacement if necessary.

Keywords: Magnesium; Hypomagnesemia; Thalassemia major; T2*MRI; Liver; Heart

INTRODUCTION

Thalassemia is a common genetic disorder with autosomal recessive inheritance[1]. Thalassemia is highly prevalent in the Mediterranean area, Africa, Southeast Asia, and the Middle East, including Iran[2].

The prevalence of thalassemia in Europe and North America is lower than in underdeveloped countries[3]. There are two common types of thalassemia: *α*- and *β*-thalassemia. Alpha-thalassemia is uncommon in Iran, but beta-thalassemia is especially prevalent in northern and southern Iran [4].

Thalassemia major, thalassemia minor, and thalassemia intermedia are the three major forms of *β*-thalassemia [5].

Patients with thalassemia major (TM) become dependent on chronic blood transfusions to survive. Each 1 ml of packed red blood cells increases 1 mg of iron in TM patients receiving blood[6]. One of the long-term complications of regular blood transfusion is hemosiderosis, which increases the risk of heart complications such as arrhythmic symptoms and cardiomyopathy, liver disease, hypoparathyroidism, and other endocrine disorders [7-9].

Studies have shown that cardiac arrhythmias in TM patients can be caused by a variety of factors, including iron deposition, calcium flux irregularities, and myocardial fibrosis[10,11]. Hypomagnesemia, which may occur due to hypoparathyroidism in TM patients, may also potentially lead to cardiac arrhythmia [12,13]. In some studies, hypomagnesemia has been reported in TM patients [13].

It is very important to accurately assess organ-specific hemosiderosis and iron deposited in the heart and liver every 6-24 months based on the risk of iron deposition[14]. Measurement of liver iron concentration (LIC) by needle biopsy and serum ferritin are considered the principal methods for predicting total body iron[15, 16]. Today, the safe and non-invasive T2* magnetic resonance imaging (T2* MRI) method is used as a gold standard approach to the evaluation of organ-specific hemosiderosis in TM patients [17]. Evaluation of iron deposited in the heart using MRI T2* is recommended to prevent thalassemic cardiomyopathy and arrhythmias [10, 18].

Given the association of magnesium deficiency and iron deposited in the heart with cardiac arrhythmia and the fact that arrhythmic symptoms and cardiomyopathy are major causes of death in TM patients, the aim of this study was to investigate the relationship between serum magnesium levels with age and T2*MRI findings of the heart and liver in TM patients.

MATERIALS AND METHODS

In a descriptive cross-sectional study from March 2020 to December 2020, a total of 62 patients with β-thalassemia major were selected at the Amir-Kabir Hospital, Arak, Iran.

Thalassemia was diagnosed based on standard methods. All ethical principles were observed according to the ethical protocol approved by the Research Ethics Committee of Arak University of Medical Sciences (IR.ARAKMU.REC.1398.033). All TM patients over 5 years of age were identified and included in the study with informed consent. After obtaining informed consent, TM patients aged 11-48 years were selected and included in the study. A questionnaire was designed to record patient data. All the patients were receiving deferasirox (DFX) before initiating the study. The study was done according to the Declaration of Helsinki [19].

The inclusion criteria included the following: Patients with consumption of DFX and transfusion begin after 2 years of age and start iron chelator treatment before 5 years of age. Study exclusion criteria included patients with renal failure, severe infection, uncontrolled diabetes, conscious dissatisfaction, liver disease, inflammatory diseases, hepatitis B, C, human immunodeficiency virus, thalassemia minor and intermedia, oral intolerance to the drug, unwillingness to continue to participate in the study, and patients who refused to continue the study to the end. Demographic information on the type of iron chelator used, history of magnesium supplementation, and history of splenectomy in patients was recorded in the checklist.

Blood samples from TM patients were collected in serum tubes to measure levels of magnesium, iron, and ferritin. Serum magnesium levels of patients were measured with a Roche/Hitachi Cobas 8000 (Switzerland) system, and the rate of cardiac and hepatic hemosiderosis of patients was extracted according to the routine T2 * MRI method (Siemens Healthineers Germany). The serum ferritin level was assessed by an ELISA kit (Pishtaz Teb Ltd. Tehran, Iran). The serum iron was measured by a colorimetric method (Pars Azmoon kits, Tehran, Iran).

Based on MRI results, patients were divided into 4 groups: cardiac hemosiderosis: normal 20 ≤ milliseconds (ms), mild: 14–19.99 ms, moderate: 10–

13.99 ms, severe: 9.99≥ ms; hepatic hemosiderosis: normal 6.3 ≤ ms, mild: 2.8–6.29 ms, moderate: 1.4–2.79 ms, severe: 1.39≥ ms [20].

Data were analyzed using SPSS version 22 software (SPSS Inc., Chicago, IL). Numerical variables are presented by the mean and standard deviation (SD) or median (minimum-maximum). Pearson's χ^2 test (or Fisher's exact test) and the Student t-test were utilized for qualitative variables and quantitative variables, respectively. Spearman's correlation coefficient was utilized to test the direction and degree of the relationship between variables. If the *P*-value is 0.05 or lower, the result is considered significant.

RESULTS

Of a total of 62 TM patients, 22 (35.5%) were male and 40 (64.5%) were female who had packed red blood cell transfusions every 2 to 4 weeks. The mean ±SD age of the patients at diagnosis was 32.6±7.8 years. The frequency of splenectomy was 42% (26 out of 62 patients).

All patients used DFX as an iron chelator at the time of the study. The mean daily dose of DFX was 20-40 mg/kg/day.

Twenty-eight of TM patients had abnormal cardiac hemosiderosis (≤ 20 ms) and 48 had abnormal hepatic hemosiderosis (≤ 6.3 ms) (Table 1). The T-tests showed no difference in serum levels of magnesium in males and females (data not shown) (*P* = 0.158). Laboratory findings of TM patients are shown in Table 1. The mean ±SD serum magnesium level in all TM patients was 1.95±0.19 mg/dl. The mean ±SD serum ferritin and serum iron level are also measured and summarized in Table 1.

The comparison of TM patients with and without cardiac hemosiderosis demonstrated that mean levels of serum ferritin, serum iron, and age were significantly higher in TM patients with cardiac hemosiderosis than the cardiac non-hemosiderosis (*P* = 0.034, *P*= 0.041, and *P* = 0.031, respectively); however, as presented in Table 2, there was no significant difference in mean levels of serum magnesium in TM patients with and without cardiac hemosiderosis (*P* = 0.279). Similarly, these values were significantly higher in TM patients with hepatic hemosiderosis than the cardiac non-hemosiderosis (*P* = 0.029; *P* = 0.002; *P*=0.045, respectively); however, as presented in Table 2, there was no significant difference in mean levels of serum magnesium in TM patients with and without hepatic hemosiderosis (*P* = 0.735).

As shown in Table 3, there was no significant correlation between serum magnesium level and heart T2*MRI (r: -0.17, *P* = 0.349). Similarly, there was no significant correlation between serum magnesium level and hepatic T2*MRI (r: 0.15, *P* = 0.416). Moreover, no statistically significant correlation was observed between magnesium levels and serum ferritin and serum iron (Table 3).

Interestingly, the correlation of age with serum magnesium levels in TM patients revealed a statistically significant and moderate inverse correlation (r = -0.56, *P* = 0.013).

Serum ferritin levels revealed an inverse correlation with cardiac T2*MRI (r = -0.36, *P* = 0.002) and hepatic T2*MRI (r = -0.31, *P*=0.039) and a direct correlation with age (r = 0.62, *P* = 0.022).

In addition, the inverse correlation between hepatic and cardiac T2*MRI values with age was weak and statistically insignificant (r = -0.40, *P* = 0.041 and r = -0.19, *p* = 0.047, respectively).

No statistically significant correlation was observed between hepatic T2*MRI and cardiac T2*MRI values (r = 0.11, *P* = 0.863).

Table 1: Cardiac and hepatic T2*MRI and laboratory findings of TM patients

Patient parameters	Unit	Value
Cardiac		
T2*MRI (ms)	Mean±SD	25.8±7.01
Hemosiderosis (n, %)	Normal (20≤)	34 (55)
	Abnormal:	28 (45)
	Severe (9.99≥)	2 (3.23)
	Moderate (10-13.99)	14 (22.5)
	Mild (14-19.99)	12 (19.35)
	Min	9.03
	Max	41.65
Hepatic		
T2*MRI (ms)	Mean±SD	8.65±8.41
Hemosiderosis (n, %)	Normal (6.3≤)	14 (22.6)
	Abnormal:	48 (77.4)
	Severe (1.39≥)	4 (6.45)
	Moderate (1.4-2.79)	20 (32.26)
	Mild (2.8-6.29)	24 (38.71)
	Min	1.77
	Max	34.18
Serum magnesium (mg/dl)	Mean±SD	1.95±0.19
	Min	1.7
	Max	2.6
Serum ferritin (ng/ml)	Mean±SD	1650.5±961.3
	Min	676.8
	Max	2620.9
Serum iron (µg/dl)	Mean±SD	189.3±48.6
	Min	146.3
	Max	259.7

MRI: magnetic resonance imaging; ms: milliseconds; SD: standard of deviation; TM: thalassemia major

Table 2: Evaluation of the relationship between hepatic and cardiac hemosiderosis with mean age, the levels of serum magnesium, serum ferritin, and serum iron in TM patients

Variables	Age (years)	Serum magnesium (mg/dl)	Serum ferritin (ng/ml)	Serum iron (µg/dl)
Cardiac				
T2*MRI hemosiderosis:				
Severe	32.7±5.6	1.92±0.16	2156.3±159.8	231.3±27.1
Moderate	25.1±4.3	1.91±0.30	1556.5±286.4	211.8±30.3
Mild	23.2±6.6	2.01±0.28	1313.2±369.2	191.1±28.7
Normal (Non- hemosiderosis)	18.3±5.5	2.06±0.16	1101.4±269.7	165.2±31.5
P value	0.031	0.279	0.034	0.041
Hepatic				
T2*MRI hemosiderosis:				
Severe	33.5±6.8	1.85±0.07	2307±236.6	236.0±23.1
Moderate	31.3±7.6	1.90±0.22	1499.4±258.1	212.3±21.8
Mild	25.6±6.4	1.93±0.17	1384.3±146.4	201.9±25.6
Normal (Non- hemosiderosis)	20.1±5.1	1.99±0.13	1138.5±290.7	177.1±22.9
P value	0.045	0.735	0.029	0.002

Data are presented as mean ± standard deviation; TM: thalassemia major

Table 3: Spearman's correlation test result

Variables	Correlation coefficient	Sig. (2-tailed)	95% CI
Serum magnesium-Cardiac T2*MRI, ms	-0.17	0.349	-0.065-0.630
Serum magnesium-Hepatic T2*MRI, ms	0.15	0.416	0.058-0.499
Serum magnesium- Serum ferritin	-0.11	0.468	-0.097-0.674
Serum magnesium- Serum iron	0.23	0.590	0.103-0.708
Cardiac T2*MRI- Hepatic T2*MRI	0.11	0.863	0.103-0.387
Serum ferritin-Cardiac T2*MRI, ms	-0.36	0.002	-0.211-0.655
Serum ferritin-Hepatic T2*MRI, ms	-0.31	0.039	-0.297-0.847
Age-Cardiac T2*MRI, ms	-0.40	0.041	-0.234-0.650
Age-Hepatic T2*MRI, ms	-0.19	0.047	-0.088-0.456
Age- Serum magnesium	-0.56	0.013	0.221-0.606
2- Serum ferritin	0.62	0.022	0.313-0.714
Age- Serum iron	0.41	0.163	0.223-0.931

Correlation is significant at the 0.05 level (2-tailed); CI: confidence interval

DISCUSSION

It has been reported that if hypomagnesemia is not diagnosed quickly and treated properly, it can be potentially fatal[21]. In some studies, hypomagnesemia has been reported in TM patients[13, 22, 23]. In this study, the serum magnesium level of patients in different stages of hepatic or cardiac hemosiderosis was measured, and no significant difference was observed in the serum magnesium level of patients in different stages of cardiac or hepatic T2*MRI.

In this study, the serum magnesium level in TM patients with normal hepatic/cardiac T2*MRI (non-hemosiderosis) was higher than the abnormal hepatic/cardiac T2*MRI, although insignificant. Also, the magnesium level for both the hepatic and cardiac T2*MRI in different stages was in the range of a normal serum level (1.7–2.5 mg/dl). Correspondingly, no correlation was observed between serum magnesium level and cardiac or hepatic T2*MRI values. In a study about the serum magnesium level in TM patients, the authors found the serum magnesium levels of the TM patients were statistically higher than the control group; however, magnesium levels were normal in both groups [24]. The results of our study showed that there was no correlation between serum magnesium levels and serum iron. In accordance with our results, Şahin *et al*. showed that there was no correlation between serum magnesium levels and other elements, including serum iron and selenium[24]. In a previous study, the authors showed that serum magnesium levels are affected by the type of iron chelators, and therefore, monitoring serum magnesium levels is beneficial in patients receiving DFX (25). On the other hand, in that study, magnesium levels in TM patients showed a negative correlation with serum ferritin levels[25], which was consistent with the results of our study, although this correlation was not statistically significant.

In our study, magnesium levels showed a positive correlation with serum iron levels, although it was insignificant. In parallel with our study, Genc *et al*. showed that serum iron and serum magnesium had a positive correlation [25].

Fung *et al*. demonstrated that TM patients have a reduced intake of many key trace elements, including magnesium. Interestingly, the authors reported that intake of some key trace elements appears to worsen with age[23]. In addition, in our current study, magnesium levels in TM patients showed a moderate negative correlation with age. Therefore, it seems that magnesium replacement is needed with the increasing age of TM patients.

The results of this study revealed cardiac and hepatic hemosiderosis in 45% and 77.4% of the TM patients, respectively. In the study of Azarkeivan *et al*. [26] the prevalence of cardiac and hepatic hemosiderosis was found to be 34.1% and 59.8%, respectively, and in the study of Soltanpour *et al*. [27] the prevalence of cardiac and hepatic hemosiderosis was found to be 38.3% and 41.6%, respectively, which were lower than the prevalence found in our study. The higher values of cardiac and hepatic T2*MRI in our study are probably attributed to the age of TM patients.

In our study, there was a poor negative correlation between serum ferritin and hepatic/cardiac MRI T2*. These results indicate that serum ferritin levels cannot accurately predict cardiac and hepatic hemosiderosis, which is in accordance with previous studies[26-29]. Also, the statistically significant correlation of age between cardiac T2*MRI values and hepatic T2*MRI values was poor in this study. Similar reports have been shown in previous studies[27, 30, 31].

The results of this study, in accordance with some previously published studies [32, 33], showed that the correlation between cardiac and hepatic hemosiderosis is very weak, and thus hepatic hemosiderosis cannot predict cardiac hemosiderosis. The cause of this event may be a different pattern of iron deposition in different organs.

CONCLUSION

In conclusion, hypomagnesemia may occur in a time-dependent manner. Due to the prevalence of hypomagnesemia and its association with cardiac arrhythmias and age in TM patients, it is recommended that, in addition to cardiac and hepatic T2*MRI, serum magnesium levels be measured by using magnesium replacement if necessary. It is also recommended that more studies be performed on older patients to evaluate the levels of trace elements, including magnesium

CONFLICTS OF INTEREST

None declared.

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