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Original Article

# Assessment of cardiac iron overload in multiply transfused thalassemic children using T2* weighted cardiac magnetic resonance

**Sambhaji Chandrakant Chate[1], Mamta Manglani[1], Mona Pote[1], Bhavin Jankharia[2]**

*From the Department of Pediatrics, [1]LTMMC and GH, [2]Jankharia Imaging Centre, Girgaon, Mumbai, Maharastra, India*

**Correspondence to:** Sambhaji Chandrakant Chate, c/o C B Chate, near saigaon naka, Prashant nagar, Ambajogai - 431517, Beed. Maharashtra. India. E-mail: drsambhaji@gmail.com

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## Abstract

**Background:** Cardiac failure secondary to transfusional iron overload is the most common cause of death in patients with thalassemia. Early detection of myocardial iron deposition is necessary to prevent overt heart failure. **Objective:** Assessment of myocardial and hepatic iron deposition by T2* weighted magnetic resonance (MR). **Materials and Methods:** A total of 32 transfusion dependent thalassemic children were enrolled in a cross-sectional study conducted at thalassemia center in a teaching hospital. Gradient echo T2* MR was done in all patients for the assessment of myocardial and hepatic iron deposition. **Results:** Out of these 32 thalassemic patients studied, 21 (65.6%)were males and 11 (34.4%)were females. The mean age of the enrolled patients was 14.6 years (range 9-24 years). Out of 32 patients studied, cardiac iron deposition (cardiac T2* <20 ms)was present in 14 (43.8%)patients and was absent (cardiac T2* >20 ms)in the remaining 18 (56.3%)patients. The hepatic iron deposition was assessed by T2* MR in 31/32 patients. None of the patients had normal liver iron (hepatic T2* - more than 6.3 ms). Out of those 31 patients, 1 (3.2%)patients had mild (hepatic T2* - 6.3-2.7 ms), 17 (54.83%)patients had moderate (hepatic T2* - 2.7-1.4 ms), and 13 (41.93%)patients had severe (hepatic T2* - <1.4 ms)hepatic iron deposition. No significant correlation could be found between hepatic and cardiac T2* (p=0.415, Cramer's V 0.313). The mean serum ferritin was 5202 ng/ml. No significant association was found between cardiac T2* and serum ferritin levels (p=0.270, Cramer's V 0.350). **Conclusion:** There is no significant correlation between hepatic and cardiac iron deposition. Similarly, no correlation was seen between cardiac iron deposition and serum ferritin levels.

**Key words:** *Cardiac iron overload, Thalassemia, T2* magnetic resonance*

Thalassemias are a group of chronic, inherited anemias characterized by defective hemoglobin synthesis and ineffective erythropoiesis. Patients with these disorders require blood transfusions at regular intervals throughout their lives to eliminate the ensuing anemia and compensatory bone marrow expansion. However, this treatment causes inexorable accumulation of iron in tissues, which, without the treatment, leads to congestive heart failure and is usually fatal in the second decade of life [1].

The heart failure due to myocardial iron overload remains the leading cause of death in patients with transfusion-dependent anemias. Iron overload-induced cardiomyopathy is reversible if intensive chelation therapy is instituted on time. Once heart failure develops and left ventricular function is reduced, the prognosis is poor [2]. Therefore, early detection of myocardial iron deposition is imperative to prevent overt heart failure.

Iron is usually stored in the human body as crystalline iron oxide within ferritin or as hemosiderin. A magnetic resonance imaging (MRI)detects iron indirectly, by the paramagnetic effects of stored iron in the form of ferritin and hemosiderin. Interaction with nearby hydrogen nuclei in tissue water produces changes in the MR signal intensity, susceptibility variability and shortens relaxation times T1, T2, and T2*. Anderson et al. first reported the utility of T2* imaging in detecting myocardial iron content [3]. The T2* relaxation time is measured by summation of tissue relaxation (T2) and magnetic inhomogeneity known as T2 prime (T2')and expressed as (1/T2* = 1/T2 + 1/T2'). Normal cardiac T2* values range from 52±16 ms (applicable only to 1.5 Tesla scanners). Cardiac MRI gradient echo T2* technique is a highly sensitive, non-invasive, diagnostic modality that can detect myocardial iron deposition [3].

Myocardial iron overload cannot be predicted from serial measurements of serum ferritin or liver iron content. Conventional assessment of cardiac function by electrocardiography, echocardiography only detects advanced cardiac disease [4,5]. T2* weighted cardiac MR (CMR)is the gold standard investigation for early detection of cardiac iron overload [3].

The present study is undertaken to assess the cardiac iron deposition by T2* weighted MR and its correlation with

hepatic iron deposition and serum ferritin levels in patients with transfusion-dependent thalassemia.

## MATERIALS AND METHODS

The present prospective study was conducted at thalassemia center in Lokmanya Tilak Municipal Medical College, Sion, Mumbai, India. A total of 32 transfusion dependent thalassemic patients were enrolled in the present study. Approval from Institutional Ethical Committee was taken and informed consent from patients or parents (for patients <18 years old) was obtained. Thalassemic children >7 years of age who were on regular blood transfusions administered at 2-4 weeks intervals to maintain pre-transfusion hemoglobin above 9 g/dl and received blood transfusions for minimum 5 years, irrespective of presence or absence of a congestive cardiac failure (CCF)were included in the study. Thalassemic children with congenital cardiac defects and those with claustrophobia were excluded.

All the enrolled patients were subjected to detailed history, clinical examination, estimation of serum ferritin levels and gradient echo T2* MR for the assessment of myocardial and hepatic iron deposition. The area measured for myocardial iron assessment was interventricular septum. Gradient echo T2* MR was performed using 1.5T Sonata scanner from Siemens by a single breath hold technique and cardiac T2* and liver T2* measurements were noted [3,6].

The data obtained were analyzed using the SPSS 15.0 software by applying Chi-square test. A $p<0.05$ was considered statistically significant. The strength of association between the two variables was measured by Cramer's V. Cramer's V ranges from 0 to 1. The strength of association increases from 0 toward 1 [7].

## RESULTS

Out of 32 thalassemic patients studied, 21 (65.6%) were males and 11 (34.4%) were females. The mean and median age of the enrolled patients was 14.6 years and 14 years, respectively (range 9-24 years). Out of 32 patients studied, cardiac iron deposition (cardiac T2* <20 ms) was present in 14 (43.8%) patients and was absent (cardiac T2* >20 ms)in the remaining 18 (56.3%) patients. The mean cardiac T2* was 24.05 ms (range 3.6-57 ms). Among the 14 patients having cardiac iron deposition, 8 patients had mild (cardiac T2* between 12 and 20 ms), 1 had moderate (cardiac T2* between 8 and 12 ms) and 5 had severe (cardiac T2* <8 ms) cardiac iron deposition.

Fig. 1 shows a correlation of age with cardiac iron deposition detected by T2* MR. The number of patients showing cardiac iron deposition and the severity of the same was found to increase with the age as shown in Fig. 1. All the 5 patients having signs of CCF on clinical examination had

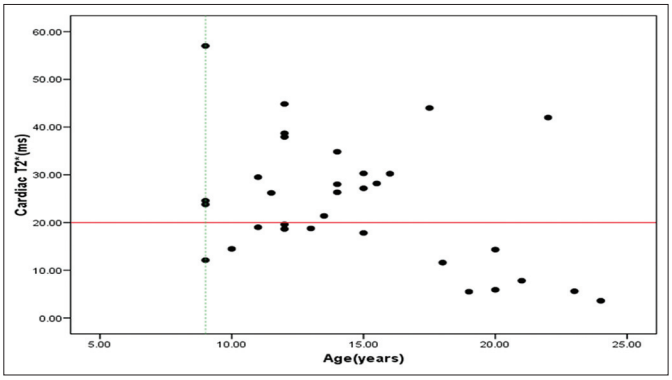


**Figure 1: Correlation of age with cardiac iron deposition**

severe cardiac iron deposition (cardiac T2* <8 ms). There was a strong association between severe cardiac iron deposition and signs of CCF (p=0.0001, Cramer's V 1.000).

None of the patients had serum ferritin value <1000 ng/ml. 10 out of 32 (31.25%)patients had serum ferritin values between 1000 and 2500 ng/ml and remaining 22/32 (68.75%) patients were having serum ferritin values more than 2500 ng/ml. Out of 10 patients having serum ferritin values between 1000 and 2500 ng/ml, cardiac iron deposition was present in 3 (30%) patients and out of 22 patients having serum ferritin values more than 2500 ng/ml, cardiac iron deposition was present in 11 (50%) patients. The mean serum ferritin was 5202±3546 ng/ml. No significant association was found between cardiac T2* and serum ferritin levels (p=0.270. Cramer's V 0.350)as shown in Fig. 2.

Hepatic T2* was noted in 31/32 patients due to technical difficulty in 1 patient. Out of these, 1 (3.2%) patient had mild (hepatic T2* - 6.3-2.7 ms), 17 (54.83%)had moderate (hepatic T2* - 2.7-1.4 ms)and 13 (41.93%) had severe (hepatic T2* - <1.4 ms) hepatic iron deposition. None of the patients had normal liver iron (hepatic T2* >6.3 ms).

One patient having mild hepatic iron deposition had no cardiac iron deposition. Out of 17 patients with moderate hepatic iron deposition, 6 (35.3%) had a cardiac iron deposition. Of these 6 patients, 5 had mild, and 1 had a severe cardiac iron deposition. Out of 13 patients having severe hepatic iron deposition, 8 (61.5%) had cardiac iron deposition. Of these 8 patients, 3 had mild, 1 had moderate, and 4 patients had severe cardiac iron deposition. In our study, no significant correlation could be found between hepatic T2* and cardiac T2* (p=0.415, Cramer's V 0.313) as shown in Fig. 3. Fig. 4 depicts the discordance between cardiac and hepatic iron deposition [3].

## DISCUSSION

The mainstay of therapy in β-thalassemia major is transfusion therapy. However, due to multiple red cell transfusions, excess iron is deposited in various organs including the heart. Cardiac complications represent significant morbidity and remain the

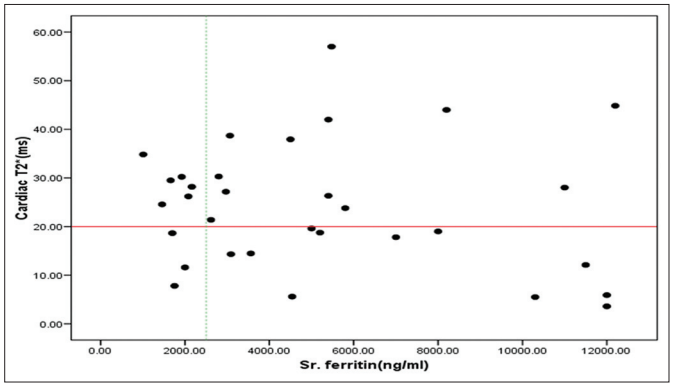


**Figure 2: Correlation between cardiac T2* and serum ferritin levels**

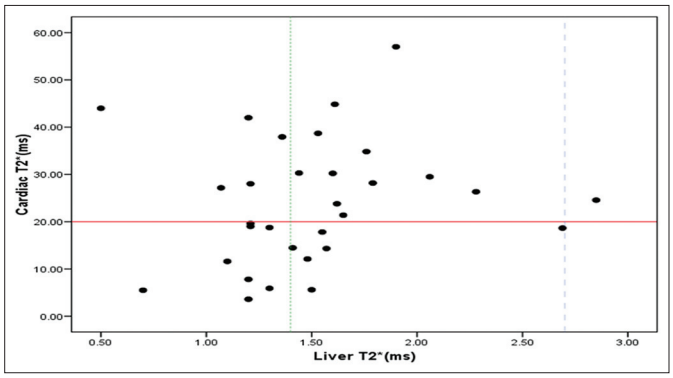


**Figure 3: Correlation between liver T2* and cardiac T2***

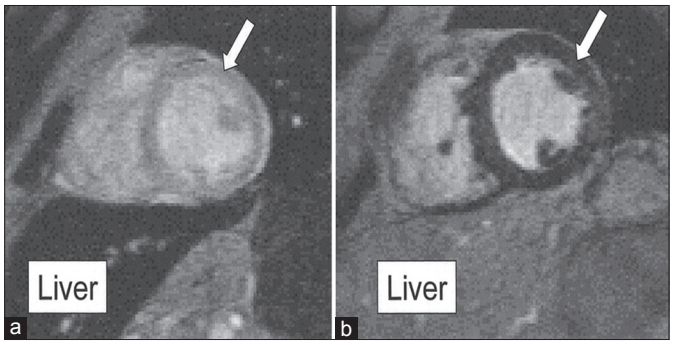


**Figure 4: (a and b) Discordance between liver and myocardial iron deposition**

leading cause of mortality in transfusion-dependent thalassemia patients[8]. Conventional cardiac monitoring, including physical examination, electrocardiography, echocardiography, or serum ferritin levels fail to predict manifest or subclinical myocardial involvement resulting from iron overload [4,5]. The cardiovascular MRI T2* correlates well with myocardial iron levels[9]. This study also showed the association of myocardial iron overload and CCF in multiply transfused thalassemic patients.

Mavrogeni et al. compared myocardial iron deposition assessed by CMR with cardiac biopsy data in 25 patients and concluded that heart T2 relaxation time appears in agreement with cardiac biopsy, both in high and low iron deposition and is a useful non-invasive index in beta thalassemia[10]. Ghugre et al. also supported the clinical use of cardiac MRI in iron overload syndromes[11]. Casale et al. measured myocardial and liver iron overload by T2* multiecho technique in 107 thalassemia major children and advised the first T2* CMR for assessment of cardiac damage as early as feasible to tailor chelation treatment[12]. Multislice multiecho T2* MRI provides a noninvasive, fast, reproducible means of assessing myocardial iron distribution[13]. Quatre et al. also validated the application of cardiac MRI to monitor cardiac iron overload in patients who have undergone multiple transfusions [14].

In our study, cardiac iron deposition was present in 14/32 (43.8%)patients. None of the patients under 9 years of age demonstrated cardiac iron deposition and all 5 patients with severe cardiac iron deposition were more than 19 years of age. The number of patients showing cardiac iron deposition and its severity was found to increase with the age of the patients. Similar results were observed in a study of 77 thalassemic children done by Wood et al. [15]. In their study, no patient under 9.5 years of age demonstrated an abnormal cardiac T2* (<20 ms)while 24% of patients aged 9.5-15 years and 36% of patients aged of 15-18 years had detectable cardiac iron. Recently, to determine the optimal initial age of cardiac iron screening with MRI T2*, Chen et al. retrospectively reviewed cardiac T2* assessments from 102 thalassemia major patients (aged 3-32 years)and concluded that cardiac iron overload can occur in young thalassemia major patients, even as young as 5.5 years old [16].

No significant association could be found between cardiac T2* and serum ferritin levels. Similar results were found in a large cohort of 106 thalassemia patients studied by Anderson et al. [3]. Wood et al. [17], Hankins et al. [18], Chacko et al. [19], Mavrogeni et al. [10], Eghbali et al. [20] and Konen et al. [21] also found similar results that there was no correlation between serum ferritin and cardiac T2*. In contrast to our study, Shamsian et al found a significant correlation between serum ferritin levels and cardiac T2* ($p<0.001$) in the study of evaluation of iron levels in cardiac and hepatic tissues using MRI T2* in 93 patients with β-thalassemia major [22]. In our study, no significant correlation could be found between hepatic and cardiac T2*. Similar observations were noted in studies done by Anderson et al. [3], Di Tucci et al. [23] and Mavrogeni et al. [24].

## CONCLUSION

The number of patients showing cardiac iron deposition and its severity was found to increase with the age of the patients. However, no significant association was found between cardiac T2* and serum ferritin level. Similarly, no significant correlation was found between hepatic and cardiac iron deposition.

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