Evaluation of cardiac and hepatic iron overload in thalassemia major patients with T2* magnetic resonance imaging

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ABSTRACT

Objectives: Recent advancements have promoted the use of T2* magnetic resonance imaging (MRI) in the non-invasive detection of iron overload in various organs for thalassemia major patients. This study aims to determine the iron load in the heart and liver of patients with thalassemia major using T2* MRI and to evaluate its correlation with serum ferritin level and iron chelation therapy.

Methods: This cross-sectional study included 162 subjects diagnosed with thalassemia major, who were classified into acceptable, mild, moderate, or severe cardiac and hepatic iron overload following their T2* MRI results, respectively, and these were correlated to their serum ferritin levels and iron chelation therapy.

Results: The study found that 85.2% of the subjects had normal cardiac iron stores. In contrast, 70.4% of the subjects had severe liver iron overload. A significant but weak correlation (r = −0.28) was found between cardiac T2* MRI and serum ferritin, and a slightly more significant correlation (r = 0.37) was found between liver iron concentration (LIC) and serum ferritin.

Discussion: The findings of this study are consistent with several other studies, which show that patients generally manifest with liver iron overload prior to cardiac iron overload. Moreover, iron accumulation demonstrated by T2* MRI results also show a significant correlation to serum ferritin levels.

Conclusion: This is the first study of its kind conducted in Indonesia, which supports the fact that T2* MRI is undoubtedly valuable in the early detection of cardiac and hepatic iron overload in thalassemia major patients.

Keywords: T2* MRI; thalassemia major; cardiac iron; hepatic iron

Background

Thalassemia major (TM) is a genetic disorder of hemoglobin synthesis that results in significant anemia. Without red blood cell transfusions, most patients with thalassemia would die by the age of 10 [1]. The excess iron acquired from the transfusions can progressively accumulate in various organs, especially the liver, heart, and endocrine organs [2]. Initially, the liver loads with iron. However, once the capacity of transferrin to take up excess iron is surpassed, free iron appears (non-transferrin bound iron NTBI) and begins to enter other organs through alternate pathways aside from the transferrin receptors. Initially, the cells may utilize the excess iron by using it for enzymes and mitochondria, as well as to store ferritin, but if this continues, ultimately the cellular capacity to utilize the free iron will be overwhelmed. Moreover, as intracellular free iron (labile cellular iron – LCI) is toxic, tissue damage may also occur, leading to morbidity and mortality [3]. Humans have no active mechanism to excrete the excess iron from the body. Iron chelation therapy (ICT) is therefore essential for the excretion of excess tissue iron and reducing morbidity and mortality.

Cardiac problems, such as heart failure and arrhythmia, account for up to 71% of all death in thalassemia major patients, and is therefore the leading cause of mortality [4]. In addition, liver fibrosis due to iron overload can be found in 30% of patients [5]. Mortality due to cardiac complications was 46% in our center until 2013.

Measuring tissue iron, total body iron, and adjusting iron chelation therapy appropriately is crucial to patient management. The different methods of evaluating iron profile all have some advantages and disadvantages. Serum ferritin is widely used as a surrogate marker for iron overload. However, it is also an acute phase protein, and hence its levels can be influenced by inflammation, the use of chelation therapy, infection, vitamin C levels, and liver damage [6,7]. Until recently, liver biopsy was considered the gold standard to detect iron overload. However, it is invasive and is...
associated with several complications. It can also be erroneous due to the heterogeneous distribution of iron throughout the liver, and is not suitable for related long-term follow-up.

Recently, biopsy is being replaced by magnetic resonance imaging techniques. $T_2^*$ MRI can measure the concentrations of iron in the liver and the heart, and is non-invasive. The result of $T_2^*$ MRI is particularly beneficial in tailoring the appropriate chelation treatment for each individual patient. In 2012, the Thalassemia Clinical Research Network issued a recommendation stating that $T_2^*$ imaging of liver and heart should be performed at least annually, beginning at the age of 10 years old. The imaging may be performed more frequently in patients with dangerous levels of cardiac iron as demonstrated by $T_2^*$ values <10 or excess levels between 10 and 20 ms [8]. Another study in China suggested that MRI evaluation of iron be performed from about 6 years of age [9], and a USA study recommends that it should be conducted even earlier [10].

The objective of this study is to evaluate cardiac and liver iron overload in TM patients in Thalassemia Center at Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia based on $T_2^*$ MRI results, and to determine the relationship of these values with their serum ferritin level and the chelation therapy provided.

**Methods**

Until October 2016, there were 1570 thalassemia patients registered in the Thalassemia Center at Dr. Cipto Mangunkusumo Hospital, Jakarta. Most of the patients (75%) were prescribed with 75 mg/kg/d of deferasirox (DFX) or 40 mg/kg/d of desferrioxamine (DFO) , four to five times per week, or a combination of 75 mg/kg/d of DFP 75 mg/kg/d, seven times per week + 30 mg/kg/d of DFO, twice a week.

This cross-sectional study was performed on 162 TM subjects. Any patient requiring regular blood transfusions in our unit is regarded as a TM patient. All patients were treated with regular blood transfusion and iron chelation therapy. The cardiac function was evaluated using echocardiography by a cardiologist blinded to clinical information, in particular the chelation therapy. The cardiac iron load was determined by $T_2^*$ MRI, and the liver iron concentration was calculated from $R_2^*$ (the inverse of $T_2^*$) according to the Wood formula (see below) [11]. The ethical approval was this study was granted by the Faculty of Medicine, Universitas Indonesia prior to conducting the study.

**Serum ferritin level**

Because of its ease of access, serum ferritin level was performed to evaluate iron overload, potential complications from the iron, and monitor patients’ compliance. The serum ferritin level principally demonstrated purported trends in iron loading. An amount of 3 mL of blood was obtained from each patient for serum ferritin evaluation. Its concentration was analyzed using electrochemiluminescence immunoassay (ECLIA) method with a Cobas 601 machine (Roche Diagnostic).

**Echocardiography**

Conventional echocardiography was performed at rest by senior fellows in the Pediatric Cardiology Clinic, Department of Child Health, Universitas Indonesia. The parameters tested were systolic function (fractional shortening and ejection fraction derived from fractional shortening through m-Mode echo view automatic calculation) and diastolic function (ratio of the early (E) to late (A) ventricular filling velocity). Normal systolic function was defined as ejection fraction >55% and fraction shortening >27%; while normal dyastolic function was defined as E/A ratio <1.

**Cardiac and liver MRI**

$T_2^*$ MRI was performed in Department of Radiology, Universitas Indonesia, using 1.5 Tesla MRI scanner (Siemens Avanto Germany). Myocardial $T_2^*$ was analyzed using dedicated software (Thalassemia-Tools; Cardiovascular Imaging Solutions, London, United Kingdom) with regions of interest in the ventricular septum which avoid susceptibility artifact. The MRI $T_2^*$ of the liver was determined using a single 10 mm slice through the center of the liver, which was scanned at 12 different echo times (TE). The TE used was 1.3–23 ms. Each image was acquired during an 11–13 s breath-hold, using a gradient-echo sequence. The repetition time (TR) was 200 ms, the flip angle used was 20°, the base resolution matrix was 128 pixels, the field of view was 39.7 cm × 19.7 cm, and the sampling bandwidth was 125 kHz. The gradient-echo ($R_2^*$) and the spin-echo ($R_2$) images were fit to monoexponential equations with a variable offset: $S(TE) = Ae^{−TE} × R_2^* + C$. The constant, C, was necessary to compensate for contributions from instrumentation noise and effects from iron-poor species such as blood and bile duct.

Results of cardiac $T_2^*$ were categorized as severe ($T_2^* < 10$ ms), moderate ($10 < T_2^* < 14$ ms), mild ($14 < T_2^* < 20$ ms), and acceptable ($T_2^* > 20$ ms) myocardial involvement [12,13]. The results of liver $T_2^*$ were converted to liver iron concentration (LIC) in mg/g using the equation $(0.0254 × R_2^*) + 0.202$, where $R_2^*$ is 1000/$T_2^*$. Acceptable liver iron was defined as LIC <3.5 mg/g, while mild, moderate, and severe were 3.5–7.0, 7.0–12.0, and >12.0, respectively [11].
Statistical analysis

The data analysis was conducted using SPSS 20 (Chicago SPSS, SPSS Inc., Chicago, IL) and GraphPad Prism 6. Comparison of cardiac T2* and LIC value among iron chelator groups was performed with Kruskal–Wallis test. Spearman test was used to correlate between serum ferritin level and cardiac T2* and LIC. A p-value of <0.05 was considered statistically significant.

Results

The subjects consisted of 78 (48.1%) males and 84 (51.9%) females. The median age was 14 (3–43) years old. Homozygous β-thalassemia was most common type, which was found in 119 of our subjects (73.5%), followed by 43 with double heterozygous β-thalassemia/HbE (26.5%). Most of the patients received ICT and DFP (71.6%), and a lesser percentage were treated with DFX (14.8%), DFO (6.2%), or alternating combination of DFO and DFP (7.4%). The median serum ferritin level was 3793 (245.6–12 456) ng/mL. Most of the subjects (69.1%) had serum ferritin levels greater than 2500 ng/mL.

Only 50 of the 162 subjects had echocardiography results. The mean of EF, FS, and E/A ratio were 65.3 ± 5.56, 36.6 ± 4.6, and 1.57 ± 0.29, respectively. All subjects had normal systolic and diastolic function. Statistical analysis showed no significant correlation of systolic and diastolic function between the two groups, normal and abnormal cardiac T2* (Table 1).

The median cardiac T2* was 34.4 (3.3–76.0) ms. The prevalence of normal myocardial iron based on the results of cardiac T2* was 85.2%. Among 24 (14.8%) subjects with excess myocardial iron, 12 (50%) had mild, 4 (16.7%) moderate, and 8 (33.3%) severe myocardial iron loading. The mean LIC was 15.5 ± 6.5 mg/g dry weight. In contrast, there were no subjects with normal LIC. Most subjects had severe liver iron involvement (70.4%), while a smaller proportion had mild (15.4%) and moderate (14.2%) liver iron involvement. There was no significant correlation between LIC and cardiac T2* (p = 0.038, r = −0.163). Cardiac T2* values showed no relationship with age. The youngest subject with an abnormal cardiac T2* result was 8 years old.

There was a significant but weak correlation (r = −0.28) between cardiac T2* and serum ferritin, with a slightly higher clinical significance (Figure 1, r = 0.37).

On comparing the cardiac T2* values in a cross-sectional analysis of the four iron chelator groups (Figure 3), there were significant differences between groups with DFP and the combination of DFP + DFO having the highest cardiac T2* (lowest cardiac iron). In addition, the DFP group had the lowest LIC levels compared to other groups (Figure 4). There were also no significant differences in cardiac T2* and LIC between beta and beta/HbE thalassemia (Figures 5 and 6).

Discussion

This cross-sectional analysis of cardiac and liver iron loading showed that the majority of our patients had acceptable cardiac iron and all of them had liver iron overload. Cardiac and liver iron load showed no relationship with age. However, there was a significant but weak correlation with serum ferritin level, confirming other studies which reported that there was little

Table 1. Echocardiography profiles among myocardial iron overload groups.

| Echocardiography | Cardiac T2*               | p value |
|------------------|--------------------------|---------|
|                  | Normal (n = 43)          | Abnormal (n = 7) |
| Ejection fraction| 67.80 ± 5.48             | 63.80 ± 4.10   | >0.05  |
| Fraction shortening| 37.00 ± 4.73            | 34.40 ± 3.20   | >0.05  |
| E/A ratio        | 1.58 ± 0.31              | 1.54 ± 0.19    | >0.05  |

Figure 2. Correlation between serum ferritin and LIC T2* (p < 0.001, r = −0.28).
Clinical relevance between cardiac and hepatic iron load and ferritin. One of the notable yet disturbing features found was that four of the children less than 10 years of age had excess cardiac iron.

Regardless of the fact that ferritin is not so well correlated to the total body iron load [14], as well as the iron load of the various organs of the body, it is still believed that following trends is useful to provide some evaluation with regards to the efficacy of treatment as well as patients’ adherence.

The range of serum ferritin levels in this study varied widely from 100 to more than 10,000 ng/mL. Since most of the patients had a high serum ferritin level, it indicated that poor acceptance of ICT and lack of availability of iron chelators remain the greatest obstacle to iron control. Serum ferritin levels >2500 ng/mL has been suggested as a risk factor associated with an increased risk of heart disease, liver cirrhosis, impaired growth, and delayed puberty [15–17]. Other than the lack of availability and poor compliance in some patients, the incidence of infection among TM patients in our center remain quite high, which may also contribute to a higher ferritin level. Nonetheless, the data from this study confirms those of other studies indicating that ferritin does not necessarily reflect iron overload in body organs, particularly the heart.

Echocardiography is another method to identify the effects of cardiac iron overload. However, this eventually depends on operator expertise. All patients with abnormal cardiac T2* value had a high ejection fraction and good diastolic function. Those normal values could be interpreted as normal cardiac function. This supports the concept that conventional echocardiography is not sufficiently sensitive to pick up cardiac dysfunction and therefore does not permit early intervention [18]. Several studies concluded that tissue Doppler echocardiography was better than conventional echocardiography to distinguish cardiac dysfunction [19,20], and also correlates significantly with
cardiac T2* [21]. Diastolic dysfunction generally occurs before systolic dysfunction. A previous study in Jakarta found 84.2% diastolic dysfunction in subclinical patients with tissue Doppler echocardiography parameters. Diastolic parameters can also be a sensitive method to identify early cardiac involvement when patients do not present with the clinical features of cardiac failure [22]. A problem found in our center is that physicians generally do not conduct echocardiography if there are no symptomatic complaints.

Currently, the best method to detect iron overload is T2* MRI. The incidence of abnormal cardiac T2* (<20 ms) among the subjects was lower than that mentioned in other published studies from other countries. A study in Hong Kong found 50% abnormal cardiac T2* [23], and another study in Iran obtained a value of 58% [24]. Our study showed that serum ferritin level had statistically significant correlation with liver and cardiac T2*, and as previously stated, this had little clinical value to determine cardiac and hepatic risk. In addition, serum ferritin may be useful for evaluating adherence and trends over time, as well as to offer encouragement to patients. Eghbali et al. [25] found a correlation between serum ferritin level and liver T2*, but not cardiac T2*.

Although T2* MRI could substitute serum ferritin and biopsy, this test is expensive and there is currently only very limited equipments set up to perform it in Indonesia. Therefore, serum ferritin remains the primary screening tool in developing countries, and it should be tested every 3 months following ferritin trends, based on the International Thalassaemia Federation guidelines.

The correlation between LIC and cardiac T2* was weak in this study \( r = -0.163 \). This is similar to other studies which found no correlation between the two variables [13,26–28]. The magnitude of liver iron overload does not correlate with myocardial iron. This means that although the level of iron overload in the liver was severe, the myocardial iron overload could still be normal or mildly increased. As previously discussed, this can be explained by the fact that the iron obtained from blood transfusion is not reused for erythropoiesis, and will primarily saturate initially in the reticulo-endothelial system of the liver, spleen and bone marrow, after which free iron will appear in the circulation. Iron will begin to accumulate in the heart and other organs once this occurs [29].

The median levels of T2* cardiac and LIC varied between chelator regimes. This study showed differences in cardiac and liver iron overload according to the chelation regimes. Several studies indicated that DFP is superior for myocardial iron removal compared to DFO [30], and is also linked with improved survival [31–33]. Another prospective study in Taiwan found that DFP was more beneficial in improving cardiac function compared to DFO, but there were no statistically significant differences between the two groups in terms of reducing serum ferritin levels and hepatic iron overload [33].

An important aspect that can be considered from these results is the changes in the iron chelation regimen received by the subjects, which can be modified either by the type of iron chelation treatment, the dose, or the combination, in accordance to that which would best suit the subjects. However, changing treatment regimens, particularly in developing countries, can be difficult due to financial issues and the limited coverage of the national insurance. A reasonable alternative that has been attempted is to maximize the use of monotherapy or provide alternating combination therapy, which have shown promising results. The provision of psychological support and education to patients and family members are extremely important and have shown benefits in terms of compliance to treatment.

Our patients generally preferred DFP compared to DFO due to its oral administration. Both its acceptability and better efficacy in removing cardiac iron can explain the reason for the low incidence of excess cardiac iron among our patients. Meanwhile, the availability of DFX is very limited and the optimal doses cannot be provided due to the high cost. Subjects showed less iron overload, especially in the liver, if the dose of DFP and DFX are increased to 100 and 40 mg/kg, respectively.

The youngest patient who had an abnormal cardiac T2* result was 8 years old. A study in China reported three patients aged 6 years old who developed severe cardiac iron overload, and another study from USA also showed cardiac iron load in TM patients before the age of 10 years. This further confirms that cardiac T2* should be performed early, even though it will require adequate cooperation from the child, since T2* MRI in our center is performed without sedation. In the USA, patients may be sedated for MRI, but this is regarded as being relatively invasive and has not been accepted universally [10].

In conclusion, a large majority of the subjects were found to have high iron overload, indicating a need to re-evaluate the iron chelation therapy being received and ensuring the optimal tailored dosage for each individual patient. This study found that hepatic and cardiac MRI were extremely valuable in determining total body iron and specific organ iron overload early, even within the context of significantly limited resources. Since serum ferritin did not prove to be an adequate measure of iron overload in these patients, it is important to ensure that iron load assessments by T2* MRI are made more accessible to the patients, and these results should be used to encourage patients to take their chelation therapy and tailor it to reduce their iron load and thereby the risks of morbidity and mortality.
Disclosure statement

No potential conflict of interest was reported by the authors.

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