T2-star (T2*) Magnetic Resonance Imaging for Assessment of Kidney Iron Overload in Thalassemic Patients

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Abstract

Background: Improved survival in thalassemic patients has lead to the manifestation of morbidities such as renal dysfunction. This involvement suggests the need for a reliable and non-invasive method to assess the degree of kidney iron overload. We conducted the present study to evaluate the relationship between serum ferritin levels, liver, heart, and kidney MRI gradient echo (T2*) relaxation times in thalassemic patients, as a step to evaluate the feasibility of using MRI T2* to assess the degree of kidney iron overload.

Methods: This was a prospective study of 120 (60 males, 60 females) regularly transfused thalassemic patients (mean age: 25.9 ± 9 years) who suffered from major and intermediate thalassemia. Patients attended an adult thalassemia clinic located in Tehran, Iran. Cardiac, hepatic and renal MRI T2* were performed. Serum ferritin levels were measured.

Results: Our results indicated a moderate correlation between kidney MRI T2* relaxation time and serum ferritin ($r = -0.446$, $P < 0.001$). Kidney MRI T2* relaxation time weakly correlated with liver MRI T2* relaxation time ($r = 0.388$, $P < 0.001$) and cardiac MRI T2* relaxation time ($r = 0.338$, $P = 0.023$).

Discussion: The moderate correlation between kidney MRI T2* relaxation time and serum ferritin, and its weak correlation with liver and heart T2* relaxation times indicate that relying on liver and heart MRI T2*, as well as serum ferritin levels to predict the exact condition of kidney iron overload might not be a reliable approach. Our findings suggest the use of kidney MRI T2* as a noninvasive method for evaluating iron overload in thalassemic patients. Further studies to investigate the relation between kidney MRI T2* relaxation times and renal function, as well as the cost benefit of using this method, are suggested.

Keywords: Hemosiderosis, iron overload, kidney, magnetic resonance imaging, thalassemia


Introduction

β-thalassemia syndromes are the most common inherited hemoglobinopathies in the world caused by a genetic deficiency in β-globin chain synthesis. In β-thalassemia major both β-globin genes are mutated, and the production of β-globin chains is severely impaired, resulting in severe anemia. In patients with thalassemia intermedia the clinical severity of thalassemia ranges between the mild symptoms of β-thalassemia trait and the severe symptoms of β-thalassemia major.2

Patients with thalassemia develop severe cardiopulmonary, endocrine and other major organ dysfunctions.3 Several major factors are responsible for physiological and functional abnormalities found in various forms of thalassemia, which include shortened red cell life span, rapid iron turnover, and tissue deposition of excess iron.4,5

Improved survival among thalassemic patients in recent years has lead to the manifestation of morbidities such as renal dysfunction.6 Renal dysfunction among patients might be caused by chronic anemia and iron overload, as well as desferoxamine toxicity7 and seem to be present even in young patients.8 Increased renal plasma flow and a failure of the ability to concentrate urine were first reported among β-thalassemia patients in 1975.9 Since then, there have been several published studies of β-thalassemia patients who have demonstrated high frequencies of proximal tubular dysfunction, proteinuria, aminoaciduria, low urine osmolarity, and excess secretion of proximal tubule damage markers such as N-acetyl-beta-D-glucosaminidase (NAG) and β2-microglobulin, which might be related to increased oxidative stress secondary to tissue deposition of iron.10-14

Early identification of thalassemic patients at high risk of renal failure is important as it allows for measures to delay the progression of renal damage, reducing the incidence of end-stage renal disease.15 Kidney biopsies in thalassemic patients are impractical because of procedural risk and significant patient discomfort. This suggests the need for a reliable and non-invasive method to assess the degree of kidney iron overload.

Recently, MRI gradient echo (T2*) and spin echo (T2) techniques have been developed to quantify tissue iron deposits in the liver and heart with promising results. Hemosiderin molecules produce local disturbances in the magnetic field; greater organ iron content causes increased magnetic field disturbance. This magnetic field disturbance causes more rapid MRI signal decay rates. T2* signal decay rates are measurable and proportional to the tissue iron concentration, which allows for MRI T2* utilization in evaluation of tissue iron load.16-18 In other words, the presence of iron leads to reduced field homogeneity, hence a low T2* signal.

The present study was conducted to evaluate the relation between
serum ferritin levels, liver and heart MRI T2* relaxation times in thalassemic patients, and their kidney MRI T2* relaxation times, as a step to evaluate the feasibility of using MRI T2* to assess the degree of kidney iron overload.

**Patients and Methods**

**Patients**

This study was conducted at the Zafar Adult Thalassemia Center, a referral thalassemia center in Tehran, Iran, from May 2010 to July 2010. Regularly transfused patients with thalassemia major and intermediate thalassemia were enrolled in this prospective study. This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran and written consent was obtained from all participants.

**Serum ferritin measurements**

Measurements of serum ferritin were carried out by electrochemiluminescence (ECL) using diagnostic kits from Roche Diag-

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**Table 1. Demographic findings of thalassemic patients.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
<th>Major</th>
<th>Intermediate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>120</td>
<td>83</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Sex, M/F (M%)</td>
<td>60/60 (50)</td>
<td>38/45 (45.8)</td>
<td>22/15 (59.9)</td>
<td>0.166*</td>
</tr>
<tr>
<td>Age</td>
<td>26.9±9.1</td>
<td>24.7±7.3</td>
<td>28.8±11.8</td>
<td>0.052†</td>
</tr>
<tr>
<td>Transfusion duration (yrs)</td>
<td>22.8±6.5</td>
<td>22.5±6.4</td>
<td>19.3±6.6</td>
<td>0.048†</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>69 (57.5)</td>
<td>46 (55.4)</td>
<td>23 (62.2)</td>
<td>0.333*</td>
</tr>
</tbody>
</table>

* Based on chi-square test; † Based on t-test

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**Table 2. Unadjusted and simultaneous relation between kidney T2* relaxation time and age, duration of blood transfusion, serum ferritin, liver and heart T2* relaxation times.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unadjusted Correlation</th>
<th>Unadjusted P-value</th>
<th>Partial Correlation</th>
<th>Adjusted Regression†</th>
<th>Adjusted P-value B 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.018</td>
<td>0.846</td>
<td>-0.087</td>
<td>-0.5</td>
<td>-1.1 to 0.4</td>
<td>0.389</td>
</tr>
<tr>
<td>Duration of blood transfusion</td>
<td>-0.135</td>
<td>0.167</td>
<td>0.023</td>
<td>0.1</td>
<td>-0.8 to 0.9</td>
<td>0.818</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>-0.446</td>
<td>〈 0.001</td>
<td>-0.292</td>
<td>-0.3††</td>
<td>-0.5 to -0.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Liver T2* relaxation time</td>
<td>0.388</td>
<td>〈 0.001</td>
<td>0.225</td>
<td>0.8</td>
<td>0.2 to 1.4</td>
<td>0.010</td>
</tr>
<tr>
<td>Heart T2* relaxation time</td>
<td>0.338</td>
<td>0.023</td>
<td>0.272</td>
<td>0.4</td>
<td>0.1 to 0.7</td>
<td>0.006</td>
</tr>
</tbody>
</table>

B=regression coefficient; CI=confidence interval; †Based on multiple regression analysis (absolute adjusted r = 0.481); ††Regression coefficient reported for 100 ng/mL increase in ferritin.
T2* calculations

T2* values were calculated for patients using in-house software (Noor Medical Imaging Center, Tehran, Iran). A homogeneous region of interest (ROI) derive was outlined in the liver and kidney parenchyma. A homogeneous full-thickness ROI was chosen in the ventricular septum. The mean signal intensity of region was measured for each image, and plotted against the echo time (TE).

Estimation of sample size and statistical analysis

The primary outcome measure was the relation between ferritin and kidney MRI T2* relaxation times. In order to have a power of 90%, to detect a correlation as strong as 0.3 with a type I error of 0.05, we needed a sample size of 112 cases. The study enrolled 120 patients to cover for probable drops.

Summary data were presented as mean ± standard deviation and frequency (percent). Chi-square evaluated the differences in qualitative variables and t-test was used to evaluate the differences in quantitative variables. Pearson’s and Spearman’s tests were utilized to assess the correlation between variables. To demonstrate these correlations, we used a scatter plot with regression and smooth Loess lines. Lastly, to obtain a simultaneous relation between kidney T2* relaxation time and age, duration of blood transfusion, serum ferritin, liver and heart T2* relaxation times, we utilized partial correlation and multiple regression analyses. All statistical analyses were performed by SPSS (version 17.0, SPSS Co., Chicago, IL).

Discussion

Limited effort has been made to directly assess renal iron concentrations and its relation with renal dysfunction among thalassemic patients. We performed kidney MRI T2* in patients diagnosed with either thalassemia major or intermediate in order to study the relation between age, duration of blood transfusion, serum ferritin levels, liver and heart MRI T2* relaxation times and kidney MRI T2* relaxation time. We found no statistically significant correlation between renal MRI T2* relaxation time and patients’ age or transfusion duration. Our results indicated a moderate correlation between kidney MRI T2* relaxation time and serum ferritin. Kidney MRI T2* relaxation time weakly correlated with liver MRI T2* relaxation time and cardiac MRI T2* relaxation time. This is somehow in line with a study by Schein et al. who estimated renal iron overload by utilizing MRI gradient echo (T2*).19 They studied renal iron accumulation in chronically transfused sickle cell disease and thalassemia major patients, using multiecho T2* reciprocals (R2*). Kidney R2* was compared to liver and heart R2* and serum ferritin. They found no correlation between kidney R2* relaxation time and liver or heart relaxation times, and suggested that renal iron toxicity in thalassemia might occur at concentrations below MRI detection limits.

In a study by Rossi et al., whole body MRI T2* was performed for seven healthy volunteers and two patients with diagnoses of myelodysplastic syndrome and thalassemia major (both treated with frequent blood transfusions). They concluded that MRI T2* might find immediate application in the monitoring of patients treated with frequent blood transfusions.20
findings.

Hepatic iron concentrations have traditionally been used as a representation of total body iron load. However, it has been previously demonstrated that liver iron measurements do not directly correlate with other organ iron concentrations, as the liver and tissues such as cardiac tissue have different mechanisms and kinetics of iron uptake, storage, and clearance. Therefore, assessing the risk of heart failure due to iron overload from liver iron concentration may not be accurate. Our study suggests a similar pattern considering the relationship between renal and hepatic iron concentrations, indicating that direct renal imaging is a more accurate method for evaluating renal iron overload.

The moderate correlation between kidney MRI T2* relaxation time and serum ferritin, and its weak correlation with liver and heart T2* relaxation times indicate that relying on liver and heart MRI T2* as well as serum ferritin levels to predict the exact contribution of kidney iron overload might not be a reliable approach. This indicates the importance of kidney MRI T2* as a noninvasive method for evaluating renal iron overload in thalassemic patients. Further studies to investigate the relation between kidney MRI T2* relaxation times and renal function, as well as the cost benefit of using this method, are suggested.

References