Kidney Iron Overload in Thalassemic Patients

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Abstract

Background: Improved survival in thalassemic patients has led 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.1 In β-thalassemia major both β-globin genes are mutated, and the production of β-globin chains is severely impaired, resulting in severe anemia.2 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 led 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.15–17 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...
Table 1. Demographic findings of thalassemic patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
<th>Major</th>
<th>Intermediate</th>
<th>Type of thalassemia</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>120</td>
<td>83</td>
<td>37</td>
<td></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></td>
<td>0.166*</td>
</tr>
<tr>
<td>Age</td>
<td>25.9±9.1</td>
<td>24.7±7.3</td>
<td>28.8±11.8</td>
<td></td>
<td>0.052†</td>
</tr>
<tr>
<td>Transfusion duration (yrs)</td>
<td>21.8±6.5</td>
<td>22.5±6.4</td>
<td>19.3±6.6</td>
<td></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></td>
<td>0.333*</td>
</tr>
</tbody>
</table>

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

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</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.018</td>
<td>0.846</td>
</tr>
<tr>
<td>Duration of blood transfusion</td>
<td>-0.135</td>
<td>0.167</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>-0.446</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Liver T2* relaxation time</td>
<td>0.388</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart T2* relaxation time</td>
<td>0.338</td>
<td>0.023</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Partial correlation</th>
<th>Regression†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.087</td>
<td>-0.5</td>
<td>-1.1 to 0.4</td>
</tr>
<tr>
<td>Duration of blood transfusion</td>
<td>0.023</td>
<td>0.1</td>
<td>-0.8 to 0.9</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>-0.292</td>
<td>-0.3†</td>
<td>-0.5 to -0.1</td>
</tr>
<tr>
<td>Liver T2* relaxation time</td>
<td>0.225</td>
<td>0.8</td>
<td>0.2 to 1.4</td>
</tr>
<tr>
<td>Heart T2* relaxation time</td>
<td>0.272</td>
<td>0.4</td>
<td>0.1 to 0.7</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.

Figure 1. The relation between kidney MRI T2* relaxation time and age (r = 0.018, P= 0.846).

Figure 2. The relation between kidney MRI T2* relaxation time and transfusion duration (r = -0.135, P = 0.167).

Figure 3. The relation between kidney MRI T2* relaxation time and serum ferritin (r = -0.446, P < 0.001).
Magnetic resonance imaging
Patients were scanned with a Symphony 1.5T Scanner (Siemens, Germany). A standard RF body coil was used in all measurements. The Royal Brompton protocol based on a single-breath multi-echo fast gradient-echo sequence was used for T2* measurements.
The liver and kidney T2* were determined by imaging a single trans-axial slice (10 mm) through the center of the liver and kidneys. For the measurement of myocardial T2*, scans were synchronized to the cardiac cycle utilizing standard ECG gating. A single 10 mm-thick, short-axis, mid-ventricular slice positioned halfway between the base and the apex of the left ventricle (LV) was acquired.

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. This 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).

Results
Between May 2010 and July 2010, 137 patients were eligible to enter the study. Of these, 17 patients declined to consent for participation. Thus, 120 patients (60 females, 60 males) successfully enrolled.

Patients’ demographic characteristics are shown in Table 1. Patients’ mean age was 25.9 ± 9.1 years. There were 83 patients who suffered from thalassemia major (age: 24.7 ± 7.3 years) and 37 patients who were diagnosed with thalassemia intermediate (age: 28.8 ± 11.8 years). The mean transfusion duration was 21.8 ± 6.5 days, with 22.5 ± 6.4 days for thalassemia major and 19.3 ± 6.6 for thalassemia intermediate patients. Splenectomy was performed in 69 (57.5%) patients. All patients received iron chelation therapy from early childhood (mean therapy duration: 21.8 ± 6.5 years) with a broad range of compliance to treatment, as seen by serum ferritin levels.

There was a statistically significant correlation between age (r = 0.018, P = 0.846) and duration of blood transfusion (r = -0.135, P = 0.167) to kidney T2* relaxation time as shown in Table 2 and Figures 1 and 2.

As the serum ferritin levels increased, the kidney T2* relaxation time decreased. There was a statistically significant, but moderate correlation between serum ferritin and kidney T2* relaxation time in our study (r = -0.446, P < 0.001), as shown in Table 2 and Figure 3.

There was also a weaker, but statistically significant, correlation between kidney T2* relaxation time and liver T2* relaxation time (r = 0.388, P < 0.001), as well as heart T2* relaxation time (r = 0.338, P = 0.023; Table 2).

We calculated the simultaneous relation between kidney T2* relaxation time and other parameters using partial correlation and multiple regression analysis, however, none of the correlations significantly changed (Table 2).

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*). 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. In another study, Koliasos et al. measured liver MRI T2 values and serum ferritin concentrations to estimate kidney iron overload in thalassemic patients and its relation with tubular dysfunction. They found a statistically significant correlation between the urine concentration of albumin and β2-microglobulin, as well as the activity of NAG with serum ferritin concentration and liver iron deposition. These authors suggested that iron overload was the cause of renal dysfunction in homozygous β-thalassemia patients, but the researchers did not directly evaluate the kidneys for the presence of iron deposits. They relied solely on statistical significance, not the strength of correlation. This study found no direct correlation between age and any of the renal measured parameters, which was in line with our
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.\textsuperscript{4,20} 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 condition 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