Liver and Cardiac Iron Deposition in Patients on Maintenance Hemodialysis by Magnetic Resonance Imaging T2*

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Introduction. Magnetic resonance imaging (MRI) sequence acquisition techniques for iron assessment have revolutionized the study of iron overload in different organs. We hypothesized that MRI can accurately and reliably assess possible iron deposition in the myocardium and liver by measurement of T2* value.
Materials and Methods. Seventeen patients with end-stage renal disease on hemodialysis were enrolled. An electrocardiography-gated single breath hold fast multiecho T2* sequence was acquired in the short axis at basal and mid-ventricular levels. The same technique was utilized to estimate liver parenchyma iron content.
Results. Iron deposition in the liver was present in 50% of the hemodialysis patients. No iron deposition was found in the myocardium. A strong univariable inverse linear association was detected between serum albumin and T2* in the liver (r = -0.84, $P < .001$). Patients who had been on dialysis for 10 years and longer had a 91% reduction in their odds of developing iron overload in the liver compared to the referent group (exact odds ratio, 0.09; $P = .048$).
Conclusions. Even though using intravenous iron infusion is a common practice in chronic dialysis patients, it seems the myocardium as opposed to the liver is resistant to or protected against iron deposition. There were no meaningful differences in the relationship between iron overload in the liver and the dialysis time vintage. A more aggressive trend of iron therapy and different formulations of iron infusion could be an explanation of iron deposition in the liver.

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INTRODUCTION

Magnetic resonance imaging (MRI) has evolved in complexity and is now more capable of diagnosing different disorders. In 2001 Anderson and colleagues developed and validated the use of MRI T2* as a noninvasive technique to measure myocardial iron in patients with thalassemia major.[1] Reproducibility of this test was acceptable in several studies.[1-3] The correlation of iron deposition in the myocardium found by MRI versus biopsy in a patient population with thalassemia major was significant, and its values were directly related to tissue iron levels.[4,5] Magnetic resonance imaging is used as a tool to assess organ-specific iron load in patients with transfusion-dependent anemia and in the monitoring of iron chelation treatment.[6-8] Magnetic resonance imaging detects iron indirectly, by the paramagnetic effects of stored iron in the form of ferritin and hemosiderin. The interaction with nearby hydrogen nuclei in tissue water

produces changes in the magnetic resonance signal intensity and susceptibility variability, and shortens relaxation times T1, T2, and T2*. Magnetic resonance imaging sequence acquisition techniques for iron assessment have revolutionized the study of iron overload in different organs. Magnetic resonance imaging is a clinically acceptable noninvasive method of directly assessing iron deposition in myocardium.[9]

Chronic kidney disease (CKD) is a worldwide public health problem.[10] The life expectancy of a patient with CKD is reduced and cardiovascular or heart failure is the main cause of mortality.[11] The causes of heart failure in this population are multifactorial. Iron overload cardiomyopathy due to systemic iron deposition in the myocardium related to multiple blood transfusions, iron infusions, or hemolysis, has an established role in myocardial dysfunction. The prognosis of patients with heart failure secondary to cardiac iron deposition is poor and early recognition of myocardial iron overload is important for early intervention.[12] High iron stores are correlated with higher cardiovascular mortality.[13]

In CKD, erythropoietin deficiency results in the downregulation of surface transferrin receptors. This leads to a shift of iron from erythrocytes into reticuloendothelial system stores, where they are deposited.[14] The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative Practice guideline advises that the hemoglobin (Hb) of patients on hemodialysis be maintained at 10 g/dL to 11 g/dL. To achieve this goal, these patients are administered an average of 4 g of iron annually. This amount of iron administration and occasional blood transfusions are the major causes of iron accumulation in end-stage renal disease (ESRD). In clinical practice, one would use serum markers, ie, serum iron, transferrin saturation, and ferritin, for assessing the total body iron store; however, there is a growing body of literature which suggests that these indirect measures have a poor correlation with body iron load,[15] and therefore, a direct method of evaluation for myocardial iron is needed.

In this study, we hypothesized that MRI would detect iron deposition in the myocardium and liver by measurement of T2* value, which is an independent early predictor of myocardial dysfunction in patients on hemodialysis.

METHODS AND MATERIALS

Participants

A prospective cohort study was conducted to identify factors correlated with T2* in the liver and the cardiac septum. The study protocol was approved by the Institutional Review Board for the Protection of Human Subjects of Texas Tech University Health Sciences Center and University Medical Center, El Paso, TX. Written informed consent was obtained from all of the participants included in the study.

We recruited 17 patients with ESRD on hemodialysis between October 2010 and June 2011. Seven patients were on hemodialysis for 4 months or shorter (group 1) and 10 patients were on hemodialysis longer than 7 years (group 2). Five healthy individuals were also recruited as controls. The included patients were those with CKD stage 5 on hemodialysis who received any amount of intravenous iron and had a serum ferritin above 100 ng/mL and iron saturation above 20%. Healthy controls were age-matched with the patients. Exclusion criteria were having metallic implants (heart pacemakers, inner ear implants, aneurysm clips, or debris), having tattoos, and pregnancy. The study was considered suboptimal either due to technical difficulties or patient-related factors.

A review of medical records including information on age, sex, weight, duration on hemodialysis, laboratory tests, and average amount of iron that each patient had received was undertaken.

Estimation of Myocardial Iron Concentration

Magnetic resonance imaging was performed using a 1.5 Tscanner (Magnetom Espree, Seimens, Erlangen, Germany). An electorcardiography-gated single breath hold fast multiecho T2* sequence was acquired in the short axis at basal and mid-ventricular levels by using the following parameters: field of view, 400 mm; time to repetition by time to echo,160 by 2.6 ms, 4.62 ms, 6.64 ms, 8.66 ms, 10.68 ms, 12.7 ms, 14.72 ms, and 16.47 ms; flip angle, 20°; slice thickness, 10 mm; resolution, 236 by 128; number of excitations, 1; and acquisition time, 18 s. All T2* measurements where made using thalassemia tools (CMR tools Cardiovascuular Imaging Solutions, London, UK) by manual drawing of a transmural region of interest placed in the ventricular septum to avoid potential susceptibility artifacts from the cardiac veins

and air in the lung. The exponential signal decay curve was then constructed and a T2* value was calculated automatically by the preset formula. The same technique was utilized to estimate liver parenchyma iron content. In order to assess the reproducibility of the technique, we used the T2* value of the paravertebral muscles (imaged on the same sequence and field of view) as a standard reference point. T2* relaxation time was measured by summation of tissue relaxation (T2) and magnetic inhomogeneity known as T2 prime (T2′) and expressed as $1/T2^* = 1/T2 + 1/T2'$. Iron overload was defined as a T2* value less than 20 ms in the heart and less than 6 ms in the liver.

Statistical Analyses

Data were analyzed using the SAS (Statistical Analysis System, version 9.3, SAS, Cary, NC, USA). Several types of regression models were utilized depending on the form of the outcome variable. Linear regression was performed with the continuous outcome variable of interest being T2* in the liver measured in milliseconds (ms). The following 8 predictors were included in the model: age, body mass index, serum albumin, parathyroid hormone, hemoglobin, iron saturation, iron per year, and serum ferritin. Since none of the patients had a T2* value indicating iron overload in the cardiac septum (every patient had values > 20 ms) this relaxation parameter was not evaluated in any of the regression models. Variance inflation factors from the multiple linear regression models were examined to determine if collinearity was present. Extreme collinearity was defined as a variance inflation factor greater than 10.[16] The relationship between the time on dialysis and the dichotomous outcome of iron overload was examined using logistic models. Iron overload in the liver was defined as a T2* value of less than 6 ms. Due to the small number of patients who had iron overload, exact logistic regression was performed rather than traditional logistic regression.[17] Dialysis time was modeled first as a continuous variable in years and then as a dichotomous variable (patients who had a value greater than the median, 7.5 years, were compared to those who were on dialysis for 7.5 years or shorter). A final exact conditional logistic regression analysis was performed after restricting the sample to the 10 patients who had been on hemodialysis for greater than 4 months. The dichotomous outcome was iron overload in the liver. The risk factor was the time on dialysis; patients who were on dialysis for 10 or more years were compared to those who were on dialysis less than 10 years but more than 4 months.

Finally, Cox proportional hazards models were created. The dependent variable was the time to iron overload (the time between initiation of dialysis and the MRI studies) in the liver. The censoring variable was iron overload in the liver (a dichotomous variable which was defined above). Two exposure variables, intravenous iron intake and hemoglobin, were entered into the model as continuous variables. Due to the small number of patients with iron overload (n = 5), the Firth penalty was used to reduce the probability of sparse data bias. A second Cox model was created with a dichotomous intravenous iron intake variable and a dichotomous hemoglobin value. Both variables were dichotomized using their respective median values, 312.5 mg for iron intake, and 11.4 g/dL for hemoglobin. Patients who had values above the median were compared to the remaining patients.

A *P* value less than .05 was considered to be significant.

RESULTS

Participants

Characteristics of the participants are shown in Table 1. Group 1 consisted of 7 men with a mean age of 41 ± 3 years. Group 2 included 5 women and 5 men with a mean age of 55 ± 4 years. The control group was composed of 3 women and 2

Table 1. Clinical and Demographic Characteristics of 14 Patients on Short-term and Long-term Hemodialysis

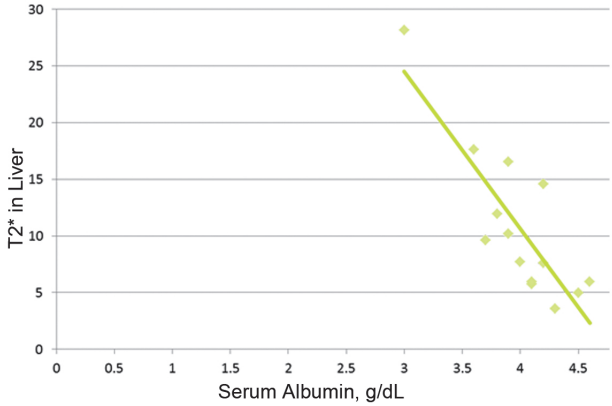
Characteristic	Mean Value (Range)
Age, y	54.9 ± 7.1 (43.0 to 67.0)
Body mass index	27.1 ± 4.9 (20.9 to 34.4)
Intravenous iron intake per year, mg	532.1 ± 588.8 (0.0 to 1800.0)
Years on dialysis	8.9 ± 8.9 (0.25 to 30.0)
Laboratory parameters	
Serum albumin, g/dL	4.0 ± 0.4 (3.0 to 4.6)
Parathyroid hormone, pg/mL	332.7 ± 195.2 (38.0 to 809.0)
Hemoglobin, g/dL	11.5 ± 1.1 (9.2 to 13.1)
Iron saturation, %	37.5 ± 14.2 (20.0 to 62.0)
Serum ferritin, ng/mL	596.5 ± 413.8 (119.0 to 1350.0)
Relaxation parameters	
T2* in liver, ms	10.7 ± 6.7 (3.6 to 28.1)
T2* in cardiac septum, ms	37.4 ± 12.3 (21.4 to 68.6)

men with a mean age of 54 ± 11 years. The average T2* levels in the cardiac septum and liver were 37.4 ms and 10.7 ms, respectively. Three of the patients in group 1 did not have T2* values for the liver.

Linear Regression

A strong univariable inverse linear association was detected between serum albumin and T2* in the liver (r = -0.84, $P < .001$; Figure 1). Multivariable linear regression was performed in order to control for confounding factors. The coefficient of multiple determination was 0.90. The adjusted parameter estimates are found in Table 2. The parameter estimate for serum albumin was -19.55 indicating that on average, for every 1 g/dL increase in serum albumin there was a -19.55 ms decrease in T2* in the liver ($P = .006$) after controlling for age and six other variables.

There was no demonstrable association between higher hemoglobin and iron deposition in the liver in the linear regression model. After adjusting for the remaining parameters, a significant positive association was detected between hemoglobin and T2* in the liver ($P = .047$; Table 2).



Inverse linear association (simple correlation) between serum albumin and T2* in the liver in 14 patients (r = -0.84; $P < .001$).

Logistic Regression

Three exact logistic regression models were created with iron overload as the binary outcome. Dialysis time was modeled first as a continuous variable in years and then as a dichotomous variable (dichotomized by the median, 7.5 years). The exact odds ratio for the association between dialysis time in years and iron overload in the liver was 0.98 (95% confidence interval, 0.85 to 1.11; $P = .79$). The exact odds ratio for the association between the dichotomized dialysis time variable and iron overload in the liver was 0.56, (95% confidence interval, 0.03 to 7.72; $P > .99$).

For the 3rd exact logistic regression analysis, the sample was restricted to the 10 patients who had been on hemodialysis for greater than 4 months. The risk factor of interest was the time on dialysis (10 years or more compared to less than 10 years but more than 4 months). Patients who had been on dialysis for at least 10 years had a 91% reduction in their odds of developing iron overload in the liver compared to the referent group (exact odds ratio, 0.09; $P = .048$).

Survival Analysis

Initially, intravenous iron intake per year and hemoglobin were entered into the Cox model as continuous variables. The adjusted hazard ratios were not significant (data not shown). A second Cox model was created in which intravenous iron intake and hemoglobin were dichotomized at their respective medians. The hazard ratios from this model were not significant either (Table 3).

DISCUSSION

To our knowledge, this is the first study to have investigated the correlation of intravenous iron with possible iron overload in the myocardium in patients on long-term hemodialysis. Cardiac MRI

Table 2. Results of the Multiple Linear Regression Analysis for Association Between T2* in the Liver and Demographic and Clinical Parameters

Variable	Parameter Estimate	Standard Error	*P*
Age, y	-0.40	0.24	.15
Body mass index, kg/m^2	-0.56	0.44	.25
Serum albumin, g/dL	-19.55	4.33	.006
Parathyroid hormone, pg/mL	-0.004	0.007	.57
Hemoglobin, g/dL	5.28	2.01	.047
Iron saturation, %	0.29	0.18	.17
Intravenous iron intake per year, mg	0.007	0.004	.17
Serum ferritin, ng/mL	-0.003	0.003	.44

Table 3. Adjusted Hazard Ratios from a Cox Regression Model of Time to Iron Overload in the Liver

Variable*	Adjusted Hazard Ratio†	95% Confidence Interval	*P*
Hemoglobin			
>11.4 g/dL	0.18	0.02 to 1.51	.11
≤11.4 g/dL	1	(Referent)	-
Intravenous iron intake per year			
>312.5 units	1.20	0.19 to 7.46	.85
≤312.5 units	1	(Referent)	-

*Hemoglobin and iron intake per year were dichotomized at their respective median values.
†Each hazard ratio is adjusted for the remaining variables shown in the table.

gradient echo T2* technique is a highly sensitive noninvasive diagnostic modality that can detect myocardial iron deposition and has an advantage of shorter acquisition times and minimization of motion artifacts from myocardial contraction and respiratory movement as compared with the spin-echo T2 technique.[18]

Our major conclusion is that the myocardium, as opposed to the liver, is somehow protected and resistant to iron accumulation. Even though using intravenous iron infusion is a common practice in chronic dialysis patients, it appears the amount of iron in the infusions is not high enough to cause depositions in the myocardium. Therefore, intravenous iron in average doses is not likely a contributing factor in uremic cardiomyopathy. The constant movement of the heart and poor reticuloendothelial cell function in the myocardium may explain the resistant pattern of the myocardium pertaining to iron deposition.[19]

Second, we found iron overload in the liver of 50% of the patients who were on long-term hemodialysis. The exact mechanism of iron deposition in the liver of the ESRD population is not clear. There should be several contributing factors involved. The main explanation is the shift of the iron from the red blood cells to the reticuloendothelial system (Kupffer cells) in the liver. One still may argue that the other half of the ESRD population did not show evidence of this hepatic deposition. Ferrari and coworkers observed that cumulative iron infusions with more than 6 g have substantially increased the risk for hepatic iron deposition.[15] There are exceptions to this observation as many patients who received higher doses of iron had no evidence of iron deposition in the liver. The integrity of liver health and function, inflammation status, nutrition and evidence of cirrhosis should have important roles in this process.

Furthermore, when we dichotomized our dataset, the subset of patients on hemodialysis longer than 10 years had a 91% reduction in their odds of developing iron overload in the liver. A post hoc analysis of our data revealed that among the six patients who were on dialysis for 10 years or more, the median annual iron dosage was 250 mg while among the 11 patients who were on dialysis for less than 10 years the median annual iron dosage was 400 mg (exact Wilcoxon $P = .39$). While our dataset is limited, it appears that nephrologists are adhering to the Kidney Disease Outcomes Quality Initiative Practice guideline and have been treating iron deficiency aggressively over the past 10 years.

Iron deposition in the liver of 50% of our chronic hemodialysis patients is a significant finding. Canavese and colleagues reported iron deposition in the liver of 70% of their dialysis patients.[20] The short- or long-term clinical implication of iron deposition in the liver in the ESRD population is not fully studied.[21] The growing body of literature about the role of iron and oxidant injury might serve as an alarm to use iron products more cautiously.[22] A more aggressive trend of iron therapy and different formulations of iron infusions over the past 10 years, compared to the prior use, could be an explanation of our findings.[23-25] Further studies are needed to support our speculation.

Third, we report a correlation between serum albumin and iron deposition in the liver. This finding is opposite of classic hemochromatosis in which low albumin combined with high iron deposition is a typical presentation. This observation indirectly confirmed that the iron deposition in this population is in the reticuloendothelial cells as the albumin synthesis is intact. This correlation was still strong after correcting for transferrin and ferritin. Unfortunately, we did not have the patients' hepcidin level, but further studies are warranted in this area given the key role that this protein plays in the iron homeostasis mechanism.[26]

Finally, we found an association between higher hemoglobin levels and a lower risk of iron overload in the liver. The body uses the iron to produce hemoglobin. It does make sense that for maintenance of higher hemoglobin, the body uses more iron, and therefore, has less chance for iron deposition.

There were multiple confounding factors that may limit the power of our data. A small sample size due to the cost of MRI T2* and a lack of diversity in our patient population (the majority were of Hispanic descent) are the main factors.

CONCLUSIONS

The present study suggests that even with average dosages of iron infusions during hemodialysis, the heart is resistant and the liver is susceptible to iron depositions. At this time, we are not aware of any short- or long-term liver damage due to iron deposits. We cannot deny or ignore the fact that 50% of the ESRD populations on long-term hemodialysis have iron depositions in their livers. A more aggressive trend of iron therapy and different formulations of iron infusions could be the main culprits. More studies are needed to understand and confirm the clinical implications of iron deposition in the liver and potential oxidant injury.

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CONFLICT OF INTERESTS

None declared

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