Identifying abnormal iron deposition in chronic liver disease using a quantitative MRI technique (T2* decay): an ROC study.

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Citation

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Abstract

Aim: To identify a cut-off value for the T2* decay of liver parenchyma in cirrhosis to identify patients with iron deposition. Methods: 76 patients (mean age: 58.6 years; 34 females) who underwent MRI of the liver were retrospectively analyzed including 46 patients with cirrhosis and 30 patients without cirrhosis. Mean T2* decay (milliseconds) of liver was determined by average of six regions of interest. Analysis between cirrhotic and non-cirrhotic patients was assessed using student's t-test and receiver operator characteristic (ROC) curve. Results: Mean T2* value for cirrhotic patients (21.9 ms) was significantly lower than that of non-cirrhotics (27.8 ms) (p=.0015). Using ROC curve analysis, a threshold T2* value of 23 ms was optimal for identifying abnormal iron. Conclusions: Liver iron deposition in cirrhosis can be identified by MRI based on T2* decay.

INTRODUCTION

The presence of abnormal iron deposition in the liver has been described in pathology series for patients with cirrhosis (1,2). This abnormal iron deposition appears to be independent of known genetic errors of iron metabolism present in hemochromatosis (3,4). Abnormal liver iron deposition can occur with any etiology of cirrhosis, but studies suggest it may be more severe in the setting of active Hepatitis C viral infection (4,5).

Iron deposition in the setting of cirrhosis appears to be an indicator of ongoing disease activity, particularly in the setting of hepatitis C infection (4,6). Further, studies indicate that the presence of the iron may be independently oncogenic, increasing the risk of development of hepatocellular carcinoma (HCC) (7,8). Given its potential clinical significance, a non-invasive method to identify and measure abnormal iron in the liver would be valuable.

Although hepatic iron deposition can have affects seen on dual echo T1W "in and opposed phase" imaging, the sequence is unable to identify the presence of iron reliably. This is due to the fact that both hepatic fat and iron deposition influence the sequence and in the presence of both, each is underestimated. As explanation, "in and opposed phase" imaging is performed with the first TE timed when the signal vector for water and fat protons, which have slightly different precessional frequencies, are opposite one another or "opposed." At 1.5T, the TE of the "opposed" phase is approximately 2.2 ms and the TE of the "in" phase, when the signal vectors of the two proton types are aligned in the same direction, is approximately 4.4 ms. In a normal liver, the liver has the same signal on either phase, which can be measured by region of interest (ROI) measurement. In hepatic steatosis, the "opposed" phase will have signal loss relative to the "in" phase due to the cancellation of signal from the vector of fat directed opposite to that of water. This signal loss is relatively proportional to the amount of fat present, up to 50%. Conversely, hepatic iron deposition can be identified by lower signal on the longer TE "in" phase sequence due to the physical principle of iron causing more rapid signal loss due to proton dephasing (T2* decay). The signal loss due to more rapid T2* decay is also proportional to the amount of iron. However, using the dual echo T1WI method to identify both steatosis and iron is problematic as their opposite effects on MR signal will tend to lead to an underestimation of both. Therefore, a different MR technique is needed in order to reliably identify the presence of abnormal iron.

MRI has previously been demonstrated to have the ability to identify iron deposition in the liver (9), however to our knowledge no studies have assessed a quantitative MR method for identifying abnormal liver iron in cirrhosis. An

MRI technique for assessing the degree of liver iron deposition has previously been validated in the setting of transfusion dependent anemia by measuring the T2* decay value of liver parenchyma (10). In this study, we apply a similar MR method to identify iron deposition in cirrhosis. We hypothesize that the T2* values of liver parenchyma in patients with cirrhosis will be lower than that of a non-cirrhosis group due to a higher proportion of hepatic iron distribution in the cirrhosis group. Also, using this data, we aim to identify a value for T2* which can be used to define the presence of abnormal liver.

METHODS

POPULATION

81 consecutive patients presenting for MRI evaluation of the liver between August 1, 2008 and November 30, 2008 were retrospectively reviewed in this HIPPA compliant study. The study was approved by our institution's review board with a waiver of informed consent. All patients had a single gradient echo sequence performed as part of a routine liver MRI protocol, and this sequence was used to generate a map of T2* decay using post-processing software.

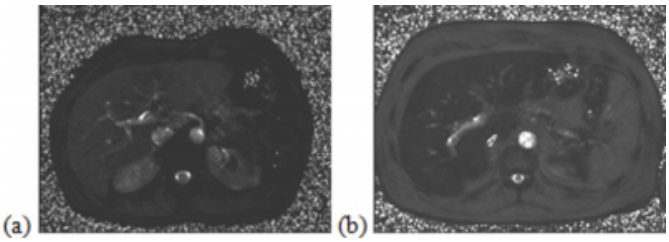
Following identification of the initial study group, patients were classified as having cirrhosis or not following a review of the electronic medical record. Exclusion criteria included documented positive genetic markers for hemochromatosis (3 patients). The remaining patients had no documented liver disease and there were no findings of liver disease suggested on imaging, These patients were assigned to the non-cirrhosis group. Two patients were subsequently excluded including a patient with an advanced malignancy with diffuse hepatic lesions and a patient with a prior left hepatic lobe resection, also for malignancy. The remaining 76 patients (mean age: 58.6 years; 34 females) served as the study group. Included were 46 patients with cirrhosis and 30 patients who served as the non-cirrhosis group.

MR IMAGING

All examinations were performed on a single MR unit (Siemens 1.5T MAGNETOM Avanto, Siemens Medical Solutions Berlin Germany) with a 6-element torso coil. Images were acquired of the entire liver using a single GRE sequence (TR 169, TE 4.8-28.7 [6 echoes], slice thickness 10mm, FOV 400x 400, 15 slices, acquisition time 44 seconds in 3 concatenations). The echo times (TE) were chosen at intervals to approximate the "in phase" of image acquisition. This was performed in order to eliminate any potential signal loss due to hepatic steatosis." Post-processing was performed on the Siemens Syngo workstation using standard T2 curve fitting software using a monoexponential fit. A T2* map was generated for each image slice using all 6 TE acquisitions, see Figure 1.

Figure 1

Figure 1: T2* maps in patients with (a) average T2* value of 32.3 ms (b) average T2* value of 16.7 ms



MR IMAGE ANALYSIS

Using the T2* maps from the available 15 image slices, representative regions of interest (ROI) were drawn at 6 locations in the liver. All ROI were drawn using the free hand drawing tool on the Siemens Syngo workstation. ROI were drawn of the liver parenchyma to any exclude vessels, obvious artifacts, or liver lesions. Also, all ROI were placed at least 1 cm from the external liver capsule, in order to minimize the effect of signal alteration from adjacent structures or susceptibility artifact from air external to the patient or in the lungs. 4 ROI were drawn at the level of the main portal vein bifurcation, one each to include the left lateral lobe, medial left, right anterior, and right posterior lobes. A fifth ROI was placed in the dome of the liver, with careful attention to maintaining 1 cm from liver capsule. The sixth ROI was positioned over the inferior most aspect of the liver (segments 5/6) but at a level where 1 cm distances from the capsule could be obtained in all directions.

T2* values were recorded based on the average numerical value within each ROI. T2* values for the 6 ROI in each patient were averaged to obtain a "mean ROI" for each patient.

STATISTICAL ANALYSIS

Student's t-test was used to analyze the mean T2* values between patients with cirrhosis and patients without. Analysis was also performed among cirrhosis patients to compare those with documented hepatitis C viral infection and those with other causes of cirrhosis using student's t-test. Significance was assumed at $p<0.05$. A receiver operating characteristic (ROC) curve was generated to

determine an optimal threshold value for classification of abnormal iron deposition based on the T2* value of liver. Also, analysis was performed using the area under the curve (A_z) to determine the overall accuracy of using T2* to identify iron in cirrhosis patients. Statistical analysis was performed using SAS version 9.1 and MedCalc Software (Mariakerke Belgium).

RESULTS

All 76 patients were analyzed, with no studies excluded for technical deficiencies. The mean T2* value of liver parenchyma for patients with cirrhosis was 21.9 ms. This was statistically significantly different than the mean T2* value of patients without cirrhosis, 27.8 ms (p=0.0015). The data is summarized in Table 1. Among those with cirrhosis, the mean T2* value of the 28 patients with Hepatitis C infection was 21.4 ms versus 22.7 ms for the 18 patients with cirrhosis of another etiology. This difference was not significant (p> 0.6).

Figure 2

Table 1: Comparison of mean T2* value between cirrhosis and control patients

	Cirrhosis	Non-cirrhotic
Number of patients	46	30
Mean T2*	21.9243	27.7970
95% CI for the mean	19.2969 to 24.5517	25.8892 to 29.7048
Variance	78.2792	26.1026
Standard deviation	8.8476	5.1091
Standard error of the mean	1.3045	0.9328
Significance		P = 0.0015

Biopsy data from random core liver biopsy for correlation was available for 21 of the 46 cirrhosis patients. Biopsy data were reported as either having evidence of iron staining or not, and in patients with stainable iron present the amount of iron was reported on a 4 point scale from 1 (lowest) to 4 (highest). Of the 21 patients, 16 had evidence of iron and in these patients the mean score was 1.38 (range 1-4). In the 5 patients with no iron present on biopsy, the mean T2* value was 27.9 ms (range 25.3-33.1 ms). The mean T2* value of the 16 patients with stainable iron was 19.8 ms (range 17.3-22.1 ms). No biopsy data were available for any of the patients without cirrhosis but all were assumed to be negative for the purposes of this study.

ROC curve analysis of the T2* values all 76 patients revealed an area under the curve (A_z) of 0.705 (95% confidence interval 0.589 to 0.804; P= 0.001) for identifying iron by a low T2* value. The optimal threshold value for T2* to define the presence of abnormal iron deposition in cirrhosis was determined to be 23 ms (Table 2). At this value, there was a sensitivity of 54.3% and 93.3% for abnormal hepatic iron deposition.

Figure 3

Table 2: Receiver Operator Curve (ROC) Criterion Values

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
<=17.2	36.96	23.2 - 52.5	96.67	82.7 - 99.4	11.09	0.65
<=17.47	39.13	25.1 - 54.6	96.67	82.7 - 99.4	11.74	0.63
<=18.62	41.30	27.0 - 56.8	96.67	82.7 - 99.4	12.39	0.61
<=19.28	43.48	28.9 - 58.9	96.67	82.7 - 99.4	13.04	0.58
<=20.17	45.65	30.9 - 61.0	96.67	82.7 - 99.4	13.70	0.56
<=20.47	45.65	30.9 - 61.0	93.33	77.9 - 99.0	6.85	0.58
<=20.8	47.83	32.9 - 63.1	93.33	77.9 - 99.0	7.17	0.56
<=21.15	50.00	34.9 - 65.1	93.33	77.9 - 99.0	7.50	0.54
<=22.08	52.17	36.9 - 67.1	93.33	77.9 - 99.0	7.83	0.51
<=22.95 *	54.35	39.0 - 69.1	93.33	77.9 - 99.0	8.15	0.49
<=23.27	54.35	39.0 - 69.1	90.00	73.4 - 97.8	5.43	0.51
<=23.35	54.35	39.0 - 69.1	86.67	69.3 - 96.2	4.08	0.53
<=23.72	58.70	43.2 - 73.0	83.33	65.3 - 94.3	3.52	0.50
<=23.82	58.70	43.2 - 73.0	80.00	61.4 - 92.2	2.93	0.52
<=23.95	60.87	45.4 - 74.9	80.00	61.4 - 92.2	3.04	0.49
<=24.03	60.87	45.4 - 74.9	76.67	57.7 - 90.0	2.61	0.51
<=24.12	60.87	45.4 - 74.9	73.33	54.1 - 87.7	2.28	0.53

DISCUSSION

The results of this study indicate that abnormal iron deposition, which is often present in cirrhosis, can be identified by MRI using T2* decay. Using ROC analysis, a threshold value of 23 ms in CIRRHOSIS patients had a sensitivity of 54.3% and specificity of 93.3% for abnormal iron deposition in the liver as compared with a population without cirrhosis. This value may be a useful cut-off for identifying abnormal iron deposition in cirrhosis, as routine dual echo T1W sequences have significant limitations.

Only 2 patients in the non-cirrhosis population had a mean T2* value below 23 ms. Subsequent review of the medical record in these patients revealed that both patients had had a history of a malignancy (lymphoma, breast cancer). Although complete documentation regarding treatment history was not available for review, both patients had documented prior systemic chemotherapy for their primary disease. Factors related to these treatments may have been responsible for the unusually low T2* values of the liver parenchyma in these patents.

Potential limitations of this study include the sample size. A larger study group may be needed to further validate the results, particularly the value of 23 ms as a threshold for abnormal iron deposition in cirrhosis patients. Having a larger population would tend to reduce the effect of unseen selection biases based on disease etiology or stage of disease which could have been present in this study. In particular, a larger sample size could serve to confirm the trend observed of greater iron deposition in patients with hepatitis C infection. Importantly, the non-invasive nature of MRI offers

the opportunity to readily acquire such data on a large scale.

Another potential limitation of the study is that liver biopsy confirmation of the presence of abnormal iron was not available for all patients. Correlation of T2* values with direct measures of liver iron are inherently difficult unless dry weight iron is obtained. As this measure is not typically performed in cirrhosis patients, it was not available to study. Only the qualitative histological assessment of visible iron from the biopsy specimen was available. However, there appears to have been a good relative correlation between the results of the qualitative assessment from liver biopsy and T2* values in the 21 cases available. Moreover, as measurement of T2* value has been previously validated as a technique for measuring liver iron, the lack of direct correlation was not felt to represent a significant limitation.

MRI methods to identify and quantify abnormal liver iron deposition have potential clinical benefit as they are non-invasive. With increased understanding of the pathologic role iron deposition plays in cirrhosis, the ability to quantify iron by MRI may take on increased clinical significance. MRI iron quantification can be readily included in a routine liver MR protocol, which many patients already incur in the routine course of care. Further, post processing of images to obtain the T2* value are simple and are increasingly available on modern MR platforms.

In conclusion, hepatic iron deposition is an important clinical indicator which can be identified and quantified non-invasively by MRI using T2* decay evaluation. This MRI technique could be readily incorporated into routine MRI evaluation and used to assess large populations of cirrhosis patients in order to more definitively determine the clinical significance of iron deposition in cirrhosis.

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