Liver iron overload assessment by $T_2$ magnetic resonance imaging in pediatric patients: An accuracy and reproducibility study

Hai-Ling Margaret Cheng, Stephanie Holowka, Rahim Moineddin, and Isaac Odame

Version Post-print/accepted manuscript


Publisher's Statement This is the peer reviewed version of the following article: Cheng, H. L.M., Holowka, S., Moineddin, R. and Odame, I. (2012), Liver iron overload assessment by $T_2$ magnetic resonance imaging in pediatric patients: An accuracy and reproducibility study. Am. J. Hematol., 87: 435-437. doi:10.1002/ajh.23114, which has been published in final form at https://doi.org/10.1002/ajh.23114. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

How to cite TSpace items

Always cite the published version, so the author(s) will receive recognition through services that track citation counts, e.g. Scopus. If you need to cite the page number of the author manuscript from TSpace because you cannot access the published version, then cite the TSpace version in addition to the published version using the permanent URI (handle) found on the record page.

This article was made openly accessible by U of T Faculty. Please tell us how this access benefits you. Your story matters.
Liver iron overload assessment by $T_2$ magnetic resonance imaging in pediatric patients: An accuracy and reproducibility study

Hai-Ling Margaret Cheng,1,2,3* Stephanie Holowka,3 Rahim Moineddin,4 and Isaac Odame5,6

$T_2$ magnetic resonance imaging (MRI) provides rapid quantification of liver iron content (LIC). The reciprocal of $T_2$ is directly proportional to iron and has been calibrated against LIC. There has, however, been few independent validation of the $T_2$ method in a clinical setting. In 100 MRI studies on 75 pediatric patients being investigated for liver iron overload, we assess the accuracy and reproducibility of $T_2$-measured LIC, using regulatory approved $T_2$-based FerriScan1 for reference measurements. Results from independent analyses by two observers demonstrated robust inter- and intra-observer agreement (intraclass correlation coefficient (ICC) 5 0.99 and 1.0, respectively). $T_2$-measured and reference LIC were strongly correlated ($r$ 0.94, $P < 0.0001$), with a regression slope of 0.97 over the range 0–25 mg Fe/g. The $T_2$ technique is shown to be accurate and reproducible for rapid, non-invasive LIC quantification.

Iron is used in the production of hemoglobin and is usually stored in the liver and spleen. In several pathologies, iron accumulates as a result of frequent blood transfusions to treat anemia (e.g., thalassemia, sickle cell disease) or as a result of excess iron absorption (e.g., hereditary hemochromatosis). Without treatment, excess iron can result in damage to various body organs, particularly endocrine, liver, and heart. The goal of treatment is to prevent liver damage and heart failure. Monitoring body iron content is, therefore, critical in managing patients with iron overload. Assessment of iron levels is conventionally performed with a liver biopsy, as this is the organ where iron first accumulates. The measured LIC is thus used as a surrogate for total body iron stores. However, biopsy is invasive and limited by sampling variation, thus prompting the need for a non-invasive alternative.

MRI has been studied for over two decades for non-invasive measurement of LIC [1,2]. MRI relaxation times $T_1$ and $T_2$ shorten in the presence of iron, and both have been calibrated against LIC [3–5]. The accuracy of the $T_2$ approach has been validated in numerous clinical studies [6–8], and it is currently offered as a regulatory approved service (FerriScan1), replacing biopsy procedures in many centers worldwide. There are fewer studies of the $T_2$ approach for LIC quantification [9], and validation in a clinical setting has been scarce. $T_2$ imaging offers a significantly shorter scan time compared to the $T_2$ approach, and is ideal for all patients and particularly for children to eliminate the need for sedation. In this study, we evaluate the accuracy and reproducibility of $T_2$-measured LIC against reference $T_2$-based measurements in children with iron overload. To our knowledge, this is the first large-scale clinical validation and comparison of the $T_2$ approach against the current non-invasive gold-standard, Ferriscan1, for liver iron quantification.

One-hundred $T_2$ and $T_2$-MRI examinations were performed on 75 patients. One examination had an extremely high LIC that exceeded the detection range of Ferriscan1; this examination was excluded from the analysis. Children generally displayed a uniform distribution of iron throughout the liver, as demonstrated on the $T_2$ maps of a patient with thalassemia major (Fig. 1). There is a marked reduction in LIC as a result of iron-chelation therapy.

Reference $T_2$-measured LIC averaged in all examinations was 9.1 ± 7.3 mg Fe/g (range, 0.8–40.9 mg Fe/g). The $T_2$ method yielded a mean LIC of 8.6–8.6 mg Fe/g amongst the two observers (range, 1.3–30.9 mg Fe/g).

Figure 2 illustrates the accuracy and reproducibility of $T_2$-measured LIC. There was a strong correlation with reference measurements ($r$ 0.94, $P < 0.0001$) and a linear regression slope of 0.97 over the range 0–25 mg Fe/g. Above this threshold, where iron loading is considered extremely high, a consistent underestimation exists. Both inter-observer (ICC 5 0.99) and intra-observer (ICC 5 1.0) agreements were robust.

The therapeutic target for iron-chelation therapy in iron-overloaded patients is a LIC below 7 mg Fe/g. The intensity of iron-chelator therapy is guided by how the measured LIC compares with this threshold. Generally, the higher the LIC, the more intense the therapy, but above a certain limit of around 20 mg Fe/g, the therapy regimen remains the same at maximal tolerable doses. Therefore, it is most important that LIC measurement is accurate in the low- to mid-range (<25 mg Fe/g) and able to indicate high LIC in the high-range (>25 mg Fe/g) even if not on a one-to-one scale. The accuracy of our results agree with other recent studies that have reported on the $T_2$ method [9,10]. These studies considered only LIC levels below 25 mg Fe/g, which are lower than ours but nonetheless demonstrate the value of the technique for iron quantification. In our study, where patients with extremely high iron overload were included, our $T_2$ method correctly classified them in the heavy iron overload category despite consistent underestimation compared to reference measurements. The underestimation can be alleviated with the use of shorter echo times around the 1.0 msec range. Future work will address improved accuracy in the high LIC regime using very short echo time acquisitions.

Figure 1. Representative axial $T_2$ maps of a liver iron-overloaded patient. A: A patient with thalassemia major presented with a heavily iron-overloaded liver, with $T_2$ and reference LIC measurements of 26 and 30 mg Fe/g, respectively. B: After iron-chelation therapy for 15 months, the LIC returned to normal range, with $T_2$ and reference LIC measurements of 4.1 and 2.7 mg Fe/g, respectively. Regions-of-interest drawn to outline the liver is shown in red. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Our study provides the largest reported pediatric patient population to date with paired $T_2^*$ and $T_2$-based measurements of LIC. The short scan time requirement of a $T_2^*$-MRI examination offers a distinct advantage to young children, who would otherwise require sedation in order to remain still for the duration of a long $T_2$-MRI examination. Our results demonstrate that $T_2^*$-measured LIC is as reliable as $T_2$-derived measurements that are the current non-invasive gold-standard. Furthermore, our $T_2^*$ method is highly robust, showing excellent reproducibility between operators and between repeated assessment by the same operator. Our results corroborate previous findings [4,9,10] and provide further evidence for the use of $T_2^*$-MRI for rapid, accurate, and reproducible non-invasive LIC quantification in iron-overloaded patients.

**Methods**

**Patient population.** Seventy-five patients, aged 12.4 ± 5.0 (range, ages 5–23), with iron overload were enrolled in this Institutional Review Board-approved prospective study. The diverse population included patients with thalassemia major (38), thalassemia intermedia (3), sickle cell disease (23), Diamond–Blackfan anemia (3), Fanconi anemia (2), hereditary spherocytosis (1), autoimmune hemolytic anemia (1), congenital sideroblastic anemia (1), pyruvate kinase deficiency (1), Hodgkin lymphoma (1), and hereditary hemochromatosis (1). Of these patients, 70 received frequent red cell transfusions.

**MRI technique.** $T_2^*$ and $T_2$ data were acquired on all patients on a clinical 1.5 Tesla Siemens scanner (Avanto). The $T_2$ protocol employed a multi-slice spin-echo sequence (scan time 5 30 min 20 sec): 11 axial slices, slice thickness (TH) 5 5 mm, matrix 5 192 3 256, repetition time (TR) 5 2500 msec, number of excitations (NEX) 5 1; repeated for five echo times (TE) 5 6, 9, 12, 15, 18 ms. The $T_2^*$ protocol employed a non-breath-held multi-slice multi-echo gradient-echo sequence (scan time 5 3 min 22 sec): 11 axial slices, TH 5 6 mm, matrix 5 101 3 192, variable field-of-view (FOV) (default 5 350 mm), flip angle 5 608, TR 5 500 msec, NEX 5 4; 11 equally spaced TE 5 (2.3–30) msec.

Reference LIC calculations based on $T_2^*$ data were provided by FerriScan. $T_2$ data were analyzed using in-house software (Matlab v.7.0) on a single axial slice chosen by the observer. Analysis was based on the optimal method described in Ref. 11 for achieving accuracy. $R^2$ ($1/T_2^*$) was computed at every pixel location using a constant offset model ($S_0 = e^{-TR/T_2^*}$ (Ref. 1 C) (eq. 1). A region-of-interest (ROI) was manually drawn on the ROI map to encompass the entire liver, excluding obvious blood vessels and ducts. The LIC (mg/g) was computed from the ROI-median $R^2$ value using the calibration curve $[Fe]=0.0254 $R^2$ +0.202$ (eq. 2) (Ref. 4).

Two independent observers performed analysis and prescribed ROIs with no knowledge of FerriScan’s results. One observer repeated the analysis in each patient on a different axial slice to determine slice-dependent and intra-observer variation.

**Statistical analyses.** Descriptive statistics were used to describe the sample. Inter-observer and intra-observer agreement of measurements was assessed in terms of the intraclass correlation coefficient (ICC). Pearson correlation was used to measure the agreement between $T_2^*$-measured and reference LIC. Linear regression was used to estimate the slope of the regression line fitted to the absolute LIC measured by the $T_2^*$ method versus reference $T_2$-based measurements.

**Author Contributions**

H.L.M.C. developed the $T_2^*$-MRI analysis for liver iron quantification, designed and conducted the study, analyzed and interpreted the data, and wrote the manuscript; S.H. analyzed the data; R.M. performed statistical analysis and wrote the manuscript; I.O. designed and conducted the study and wrote the manuscript.

1*Department of Medical Biophysics, Faculty of Medicine, University of Toronto, Toronto, Canada; 2Physiology & Experimental Medicine, The Research Institute, The Hospital for Sick Children, Toronto, Canada; 3Department of Diagnostic Imaging, The Hospital for Sick Children, Toronto, Canada; 4Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, Toronto, Canada; 5Division of Haematology/Oncology, The Hospital for Sick Children; Toronto, Canada; 6Department of Pediatrics, Faculty of Medicine, University of Toronto, Toronto, Canada

*Correspondence to: Hai-Ling Margaret Cheng, PhD, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8. Tel.: 1-416-813-5415. Fax: 1-416-813-7352. E-mail: hai-ling.cheng@sickkids.ca

Conflict of interest: Nothing to report.

Published online 06 Month 2012 in Wiley Online Library (wileyonlinelibrary.com).

DOI: 10.1002/ajh.23114

**References**


American Journal of Hematology

AQ3

AQ4