

# Magnetic resonance detection of kidney iron deposition in sickle cell disease: a marker of chronic hemolysis.

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## Introduction

Disorders of hemoglobin synthesis such as sickle cell disease (SCD) and thalassemia major (TM) are among the most common genetic diseases worldwide. Chronic lifelong blood transfusions are required for treatment, but produce iron overload in various tissues, including liver, heart, and endocrine tissues, resulting in life threatening complications [1]. Although iron overload may be managed by chelation therapy, conventional monitoring of tissue iron stores is often difficult. Recently, MRI gradient echo (T2\*) and spin echo (T2) techniques have been developed to noninvasively quantify tissue iron stores in the liver and the heart [2, 3]. The reciprocal of T2\*, known as R2\*, has been shown to rise linearly with chemically determined tissue iron concentration in both liver and heart [4, 5]. Iron also accumulates in the kidneys of SCD and TM patients, but unlike in the other organs, it is unclear whether kidney iron results from chronic transfusion therapy, intravascular hemolysis, or both [6]. Further, the significance of iron in the kidney is poorly understood.

The aim of this study was to use kidney R2\* as a surrogate for kidney iron to examine the pattern, etiology, and significance of renal iron accumulation in chronically transfused patients with SCD and TM. In particular, we sought to answer the following questions. (1) What is the prevalence and distribution of iron in the kidney in these two disorders? (2) Does iron accumulation in the kidney better correlate with transfusion burden or hemolysis? (3) Is renal iron load assessed by the R2\* signal proportional to total body iron burden assessed by MRI-determined hepatic (HIC) or cardiac iron concentration?

## Materials and Methods

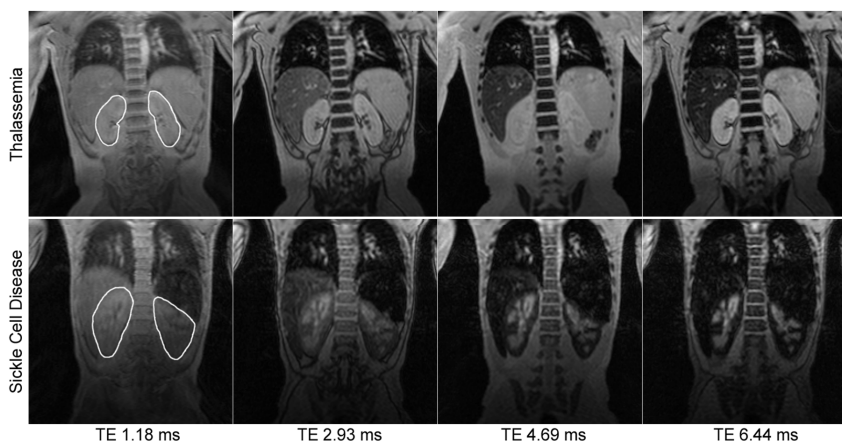
MRI examinations were performed in 75 SCD patients (34 males, 41 females, mean age 14.6 years), 73 TM patients (41 males, 32 females, mean age 19.3 years), and 16 healthy controls (7, males, 9 females, mean age 24.9 years). Multiecho gradient echo protocols were used to measure T2\* reciprocals (R2\*) in the kidney, liver and heart. Kidney R2\* was compared to tissue iron estimates, serum iron markers, and surrogates of intravascular hemolysis by univariate regression. Characteristic MRI images showing TE decay and renal iron signal are demonstrated in figure 1.

## Results

Renal cortical iron was observed in SCD patients, but not in TM patients or normal controls. Mean R2\* was 55.3 ± 45.3 Hz in SCD patients, 22.1 ± 11 Hz in TM patients and 21.3 ± 5.8 Hz in control subjects (p < 0.001). Thirty nine SCD patients (52%) were above the normal range compared with just 5 TM patients. Kidney R2\* decreased with age (R<sup>2</sup> = 0.09, p < 0.02). Renal iron loading was independent of hepatic iron concentration and cardiac R2\*, but correlated strongly with serum lactate dehydrogenase (r<sup>2</sup> = 0.55, p < 0.001) (Figure 2). No correlation was found between kidney R2\* and blood pressure, creatinine, cardiac index, or right and left ejection fraction.

## Conclusion

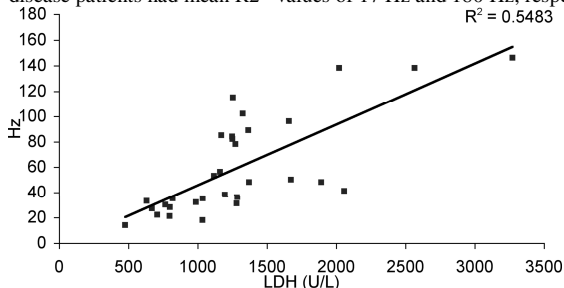
Renal hemosiderosis correlates with intravascular hemolysis but not with total iron load (HIC) in chronically transfused SCD patients. Further studies are necessary to determine whether kidney R2\* can serve as a biomarker for hemolysis-mediated vascular complications in SCD.



## References

1. Gordeuk VR, Bacon BR, Brittenham GM. Iron overload: causes and consequences. *Annu Rev Nutr* 1987; 7:485-508.
2. Brittenham GM, Badman DG. Noninvasive measurement of iron: report of an NIDDK workshop. *Blood* 2003; 101:15-19.
3. Ghugre N, Enriquez C, Wood JC. Myocardial R2 and R2\* vary linearly with cardiac iron in human heart. In: *International Society of Magnetic Resonance in Medicine*. Miami Beach, FL, 2005.
4. Wood JC, Enriquez C, Ghugre N, et al. MRI R2 and R2\* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients. *Blood* 2005; 106:1460-1465.
5. Wood JC, Otto-Duessel M, Aguilar M, et al. Cardiac iron determines cardiac T2\*, T2, and T1 in the gerbil model of iron cardiomyopathy. *Circulation* 2005; 112:535-543.
6. Lande IM, Glazer GM, Sarnaik S, Aisen A, Rucknagel D, Martel W. Sickle-cell nephropathy: MR imaging. *Radiology* 1986; 158:379-383.

**Figure 1.** T2\*-weighted coronal MR images of the kidneys at the first four echo times (TE) from a 10-year-old with thalassemia (top) and a 14-year-old with sickle cell disease (bottom). The region of interest for analysis is shown in the leftmost images. The thalassemia and sickle cell disease patients had mean R2\* values of 17 Hz and 180 Hz, respectively.



**Figure 2.** Kidney R2\* (Hz) was strongly correlated with LDH in SCD patients (n = 31, p < 0.001).