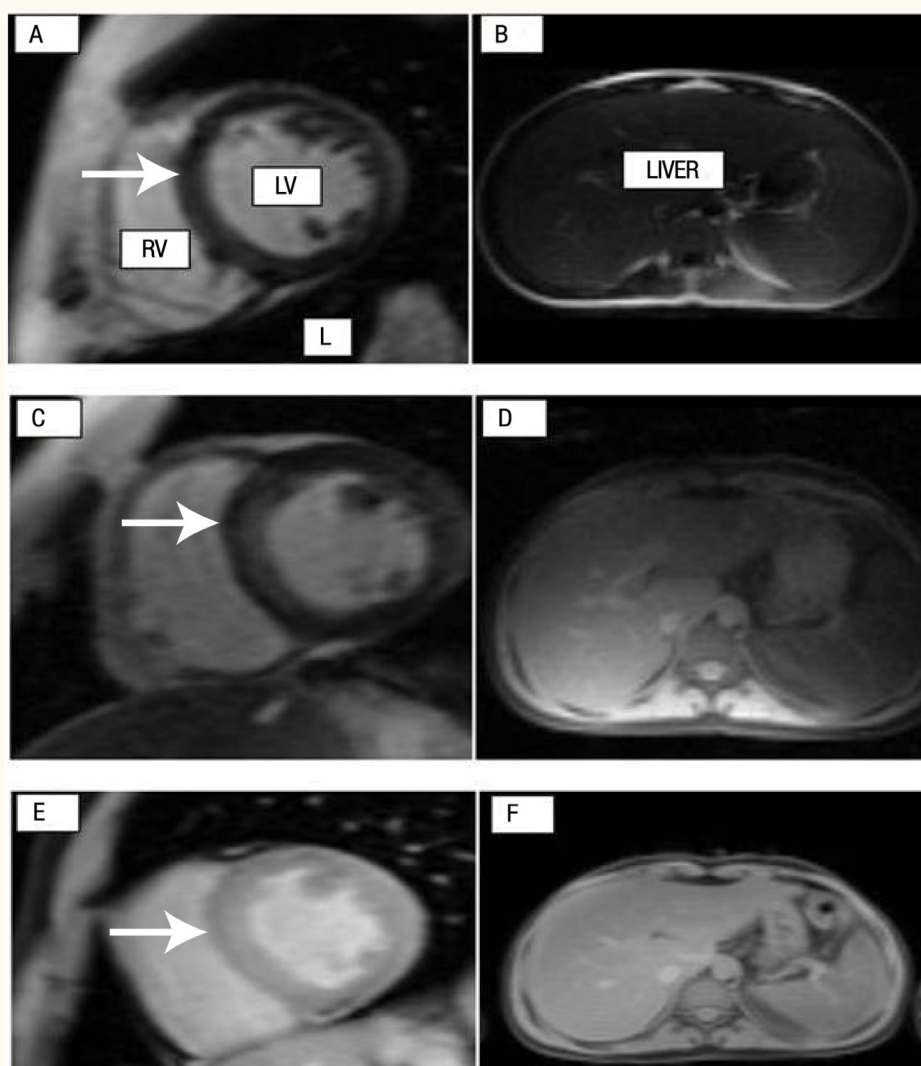


## Utility of Magnetic Resonance Imaging T2\* in Diagnosing and Monitoring Severe Cardiac and Hepatic Siderosis

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الفائدة من التصوير بالرنين المغناطيسي T2\* في تشخيص ومراقبة ترسب الحديد القلب والكبد الحاد

شاهينة داعر، معز حسن، فينوده بنجواني، أنيل بثير، حمود الذهلي، أروى الريامية



**Figure 1** A–F: Magnetic resonance T2\* images showing the degree of iron overload in the patient over a six-year period (2008–2014). The interventricular septum (arrow) is the region of interest when assessing cardiac siderosis. A & B: Images taken in 2008 showing the severe cardiac siderosis (T2\*: 4.5 ms) and marked hepatic iron overload (T2\*: 1.3 ms; liver iron concentration [LIC]: 25.6 mg per g of dry weight [mg/gdw]). C & D: Images taken in 2010 showing minimal improvement in the cardiac iron content (T2\*: 5.6 ms) despite the early effect of iron chelation on the liver (T2\*: 5 ms; LIC: 5.3 mg/gdw). E & F: Images taken in 2014 showing appreciable lightening of both organs with improvement in cardiac iron content (T2\*: 11.4 ms) and normalisation of hepatic iron (T2\*: 14.1ms; LIC: 2 mg/gdw).

LV = left ventricle; RV = right ventricle; L = liver.

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**P**ATIENTS WITH BETA THALASSAEMIA MAJOR (TM) require regular blood transfusions in order to survive; however, these transfusions are associated with a risk of iron overload. Toxic levels of iron accumulate mainly in the liver, heart and endocrine organs, causing multiple complications, and can only be removed by the regular use of iron chelating agents. Different modalities exist for monitoring body iron levels. Serum ferritin (SF) has been commonly used as it is widely available and has a low cost. However, SF is an acute-phase reactant and can be spuriously elevated in the presence of inflammation or infection. In addition, although serial measurements of SF are useful in monitoring patients with iron overload, they do not reflect organ-specific iron levels.

Historically, a liver biopsy for the assessment of hepatic iron (in mg per g of dry weight [mg/gdw]) has been the gold standard.<sup>1</sup> A liver iron concentration (LIC) of >15 mg/gdw indicates severe iron overload and is associated with increased morbidity and mortality.<sup>2</sup> However, it is invasive and does not accurately reflect hepatic iron content in the presence of heterogeneous iron distribution. The current state-of-the-art methods for measuring organ iron overload are magnetic resonance imaging (MRI) techniques. Although R2 MRI is a robust technique for measuring hepatic iron content, MRI T2\* is more widely available and can assess both hepatic and cardiac iron.<sup>3,4</sup> The latter is particularly important as in many cases neither SF nor LIC correlates well with cardiac iron content.<sup>4</sup> For instance, a patient can have a relatively low SF level and LIC but still have dangerously high levels of myocardial iron. Anderson *et al.* showed that a cardiac MRI T2\* of <20 ms is indicative of cardiac iron overload, while measurements of <10 ms are associated with severe cardiac siderosis.<sup>4</sup> Recent data confirm that patients with cardiac MRI T2\* of <10 ms are at a much higher risk of heart failure and other cardiac events than those with measurements of >10 ms.<sup>5</sup> Using MRI techniques, it is possible to evaluate iron overload in different organs in a non-invasive manner as well as safely monitor the effects of chelation therapy.

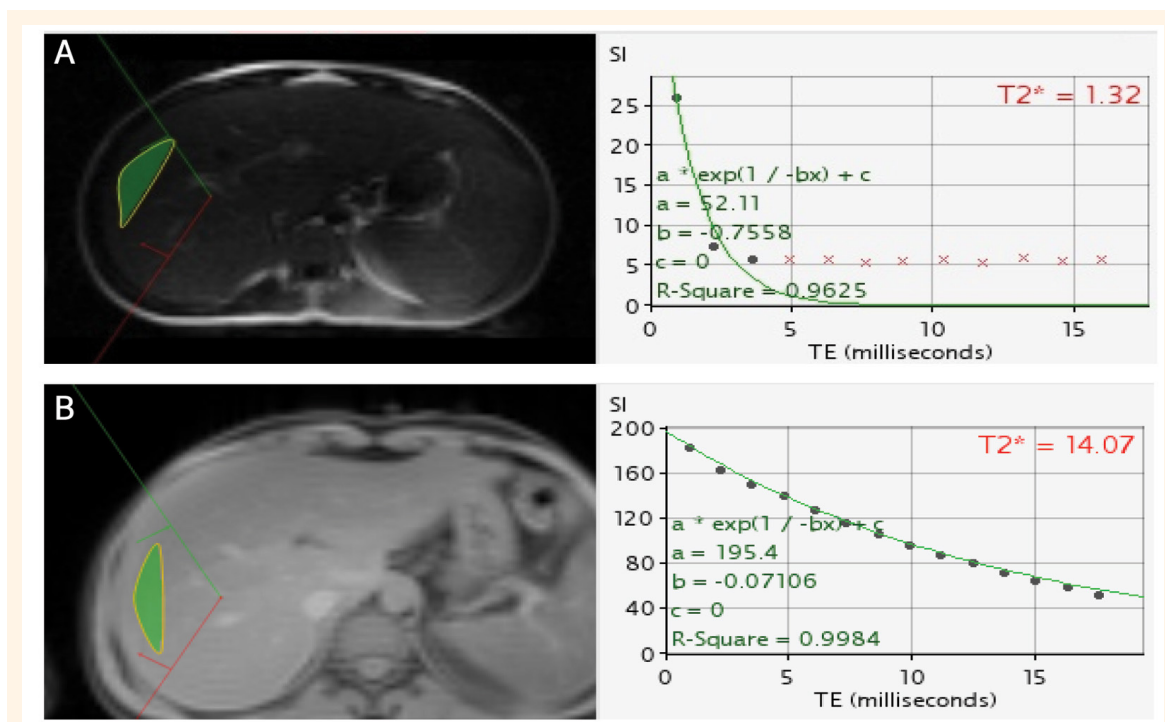
MRI T2\* imaging has been used at the Sultan Qaboos University Hospital (SQUH) in Muscat, Oman, as part of the regular management of TM patients since 2006. MRIs are performed using the 1.5T Siemens Sonata scanner (Siemens Healthcare Corp., Malvern, Pennsylvania, USA) according to protocols described by Anderson *et al.* and Westwood *et al.*<sup>4,6</sup> T2\* values were calculated using software from CMRtools (Cardiovascular Imaging Solutions Ltd., London, UK). Hepatic iron (LIC) was calculated from liver MRI T2\* scans as described by Wood *et al.*<sup>7</sup>

## Comment

Figures 1 and 2 show MRI T2\* images of a patient with TM over a six-year period. The patient was referred to SQUH in 1991 at the age of seven years and had never previously been chelated. He subsequently underwent different chelation protocols including monotherapy with deferoxamine (DFO) from 1991–2001 and combined DFO and deferasiprone (DFP) from 2001–2005. Poor family compliance with the chelation therapy resulted in the patient having persistently high SF levels, ranging between 6,000 and 7,500 ng/mL (normal range: 20–300 ng/mL). In 2005, he was enrolled in a multicentre trial on the efficacy of deferasirox. Although his SF levels had fallen from 7,400 ng/mL to 6,042 ng/mL by the end of the trial in 2008, MRI T2\* images revealed significant cardiac and hepatic siderosis (4.5 ms and 25.6 mg/gdw, respectively) [Figures 1A & B]. Intensive chelation with continuous intravenous DFO and oral DFP was recommended; however, the patient was reluctant to commit to the prolonged hospitalisation necessary for this protocol. After further counselling, the patient opted to use continuous subcutaneous DFO (4 gm/day) and DFP (100 mg/kg/day) and subsequently demonstrated excellent compliance to this treatment. Reviewing the MRI T2\* images during follow-up helped to support this compliance, as the patient was able to see for himself that the images progressively became lighter in colour with the decrease in iron overload over time [Figures 1A–F].

Figure 1 highlights the advantage of MRI T2\* in assessing and monitoring organ-specific iron levels. A review of the patient's serial MRI T2\* results revealed that his hepatic iron content decreased well before any change in the cardiac iron levels. This is consistent with the findings demonstrated by Noetzli *et al.* in a longitudinal study; there appears to be a 'lag' period for iron overload and the effect of chelation therapy on the liver and heart, whereby the former is the first organ to 'load' with iron if chelation is inadequate.<sup>8</sup> The liver is also the organ that shows an earlier effect of chelation compared to the heart [Figures 1C & D].<sup>8</sup> Recent imaging studies [Figures 1E & F] of this patient showed that the cardiac MRI T2\* had improved to 11.4 ms and his hepatic iron content had fallen to normal levels (2 mg/gdw). His latest SF level was 403 ng/mL. It is probable that removal of cardiac iron could have been achieved much faster if intravenous DFO had been used.

This case highlights a number of points. Firstly, it underlines that the use of MRI T2\* can be an invaluable tool in the assessment and follow-up of organ iron load. Secondly, severe iron overload may take a long time to respond to chelation therapy. It is



**Figure 2A & B:** Analysis of the liver T2\* magnetic resonance image (MRI) using CMRtools (Cardiovascular Imaging Solutions Ltd., London, UK). The greater the tissue iron load, the lower the T2\* value. **A:** Liver MRI analysis in 2008, with a T2\* of 1.3 ms (25.6 mg per g of dry weight [mg/gdw]). **B:** By 2014, a marked improvement can be observed (T2\*: 14.1 ms; iron content: 2 mg/gdw).

important that neither the physician nor the patient expect rapid results, particularly regarding cardiac iron. Persistent counselling and support are essential. Thirdly, as illustrated in this case and as confirmed in other studies, SF is a poor indicator of cardiac siderosis. Finally, this case demonstrates that it is rarely too late to reverse severe iron overload. Continuous efforts should therefore be made in counselling non-compliant patients.

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