

## REVIEW

## MRI Measurements of Iron Load in Transfusion-Dependent Patients: Implementation, Challenges, and Pitfalls

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Magnetic resonance imaging (MRI) has played a key role in studies of iron overload in transfusion-dependent patients, providing insights into the relations among liver and cardiac iron loading, iron chelator dose, and morbidity. Currently, there is rapid uptake of these methods into routine clinical practice as part of the management strategy for iron overload in regularly transfused patients. Given the

manifold methods of data acquisition and analysis, there are several potential pitfalls that may result in inappropriate decision making. Herein, we review the challenges of establishing suitable MRI techniques for tissue iron measurement in regularly transfused patients. *Pediatr Blood Cancer* 2016;63:773–780. © 2015 The Authors. *Pediatric Blood & Cancer*, published by Wiley Periodicals, Inc.

**Key words:** anemia; iron overload; magnetic resonance imaging; sickle cell disease; thalassemia; transfusion

## INTRODUCTION

Under normal conditions, dietary iron is absorbed in small quantities (1–2 mg/day) from the gut and circulates in the blood bound to transferrin prior to intracellular use and storage.[1,2] Many patients with hereditary forms of anemia, such as thalassemia and sickle cell disease (SCD), require lifelong blood transfusions, greatly increasing their iron intake. Each unit of packed red blood cells (PRBCs) contains 200–250 mg of iron, yet the body has no mechanism for excreting large excesses of iron.[1] Iron loss is fixed at 1–2 mg/day from the sloughing of gastrointestinal mucosa and blood loss. Therefore, patients receiving chronic transfusions are at risk for iron overload.

Upon saturation of transferrin by excess iron, toxic non-transferrin bound iron (NTBI)—particularly, the redox active fraction called labile plasma iron (LPI)—enters organs, where it converts hydrogen peroxide to free radical ions that damage cell membranes, proteins, and DNA.[1–4] The heart, liver, and endocrine organs are particularly susceptible to the toxic effects of iron overload (Fig. 1).[1,5] The rate of iron loading and unloading differs by organ (generally, liver > pancreas > heart).[6,7] Indeed, the liver loads iron most quickly in poorly chelated patients. However, primary iron loading can occur concurrently in all target organs; that is, hepatic iron overload is not a prerequisite for iron loading in other organs. When transferrin is fully saturated and LPI is increased, there is no particular liver iron concentration (LIC) below which iron loading will not occur in other organs.[6]

Serum ferritin (SF) levels and LIC determined by biopsy have been the traditional methods used to assess total body iron load and risk for organ damage.[8,9] However, SF may not give an accurate representation of a patient's risk and cannot substitute for more direct determinations of iron load in susceptible organs. Liver biopsy is invasive and susceptible to sampling errors. Magnetic techniques to measure iron, such as biomagnetic liver susceptometry and magnetic resonance imaging (MRI), offer advantages over traditional methods. In addition to providing noninvasive determinations of both liver and heart iron load, magnetic techniques aid clinical decision making by identifying patients at risk of iron overload and monitoring effectiveness of chelation therapy.

We provide an overview of imaging techniques used to determine tissue iron concentration, pitfalls of various techniques, and advice for optimizing their clinical utility. This review focuses on the application of these techniques to clinical management of patients with common hereditary anemias, specifically thalassemia and SCD.

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Abbreviations: DBA, Diamond–Blackfan anemia; dw, dry weight; LIC, liver iron concentration; LPI, labile plasma iron; MRI, magnetic resonance imaging; NTBI, nontransferrin bound iron; PRBC, packed red blood cell; SCD, sickle cell disease; SF, serum ferritin; SIR, signal intensity ratio; SQUID, superconducting quantum interference device; TBIS, total body iron stores; TI, thalassemia intermedia; TM, thalassemia major

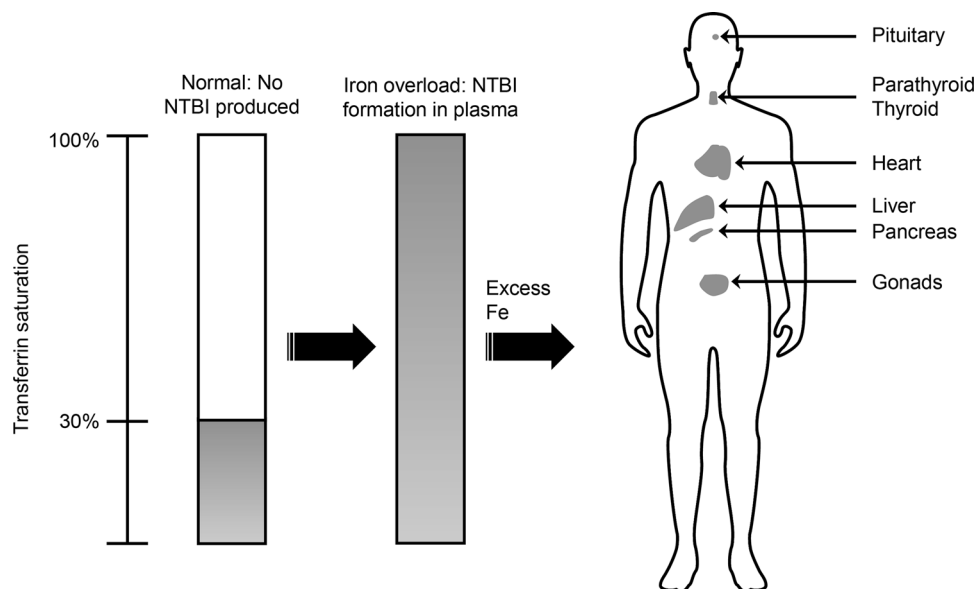
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**Fig. 1.** Schematic of iron overload and damage to organs. During iron overload, NTBI is readily taken up by organs, where it causes damage and subsequent dysfunction.[3] The heart, liver, and endocrine organs are particularly susceptible to damage from iron overload. NTBI, nontransferrin bound iron. Copyright © 2009, Informa Healthcare. Adapted with permission of Informa Healthcare.

## COMMON HEREDITARY ANEMIAS AND PATTERNS OF IRON OVERLOAD

### Thalassemia Major

Patients with thalassemia major (TM) require transfusions beginning early in life to alleviate symptomatic anemia and suppress extramedullary hematopoiesis. Benefits of chelation begin to outweigh risks of iron overload after approximately 10 transfusions.[9] Since the liver is the major site of iron storage, patients requiring chronic transfusions are at risk for liver iron overload.[10] Excess iron is stored initially by Kupffer cells, followed by hepatic parenchymal cells with severe iron overload, resulting in injury that progresses from fibrosis to cirrhosis if untreated.[9,10].

Approximately 36% of patients with TM aged 15–18 years have detectable cardiac iron,[11] but many are asymptomatic.[12] Abnormalities in left ventricular function and left-sided heart failure are the most common cardiac complications in patients who develop cardiac iron overload.[10] Right-sided heart failure occurs less frequently and may present in older patients with severe cardiac iron overload.[10] Heart failure and dysrhythmias from cardiac iron overload are the leading causes of death in patients with  $\beta$ -TM.[13] Cardiac iron loading may be delayed relative to liver iron loading and may not be evident until the second decade of life.[12]

### Thalassemia Intermedia

Due to less severe anemia, patients with thalassemia intermedia (TI) require fewer transfusions than patients with TM.[3] However, ineffective erythropoiesis leads to increased intestinal absorption of iron and increased release of recycled iron from the reticuloendothelial system, which contributes to iron overload.[14] In contrast to TM, TI results in preferential portal and

hepatocyte iron storage, causing patients with TI to have considerable liver iron overload.[14] Cardiac iron loading and symptoms appear later in these patients, and right-sided heart failure is more common.[3]

### Sickle Cell Disease

Patients with SCD, on average, begin transfusions later in life and are transfused less frequently than those with other congenital anemias.[12,15] Young children receiving regular transfusions to prevent stroke are the exception, and develop iron overload in a similar manner to patients with TM.[12] Patients with SCD may also develop fibrosis and eventual cirrhosis due to liver iron loading.[15] Although cardiac dysfunction is common in this population, it is mostly a result of SCD pathophysiology, and cardiac iron deposition is seen only in the most heavily transfused patients.[12] One large study demonstrated that cardiac iron overload occurred in 2–3% of chronically transfused SCD, particularly those patients who are very poorly adherent to chelation therapy.[7]

### Other Hereditary Anemias

Transfusion-dependent patients with Diamond–Blackfan anemia (DBA), congenital dyserythropoietic anemia, pyruvate kinase deficiency, and other rare conditions may also develop iron overload. Less is known about iron loading in these conditions, and guidelines for management are usually extrapolated from TM and SCD. However, it is apparent that patients with DBA, compared with patients with other transfusion-dependent anemias, have higher levels of NTBI and appear to accumulate iron more quickly in the pancreas and heart.[16,17]

## MONITORING IRON OVERLOAD

### Serum Ferritin

SF measurements are used worldwide due to their ease of implementation, availability, and low cost. Serial measurements are required because SF is an indirect measure of iron load that can be influenced by several factors, such as inflammation, vitamin C deficiency, oxidative stress, hepatic dysfunction, malignancy, and increased cell death.[5,18,19] Serial SF measurements  $>1,000 \mu\text{g/l}$  indicate iron overload in patients with TM,[3] but SF levels may not correlate closely with liver or cardiac iron load, especially when advanced iron loading has begun.[20,21] In some patients, cardiac iron accumulates despite controlled SF levels.[20,21]

Disease characteristics can also affect SF levels.[22] SF underestimates iron load in TI, where hepcidin suppression leads to depletion of macrophage iron and decreased ferritin production.[3] SF may also underestimate iron stores in chronically transfused patients with DBA. In SCD, SF, which is an acute phase reactant, may be increased for several weeks following pain crises and acute chest syndrome.

### LIC Determination by Liver Biopsy

Parenchymal cells of the liver and reticuloendothelial macrophages are the default transferrin-mediated storage sites for dietary and recycled iron.[1] Excess iron accumulates in these liver cells, resulting in injury.[9,10] LIC  $>7 \text{ mg/g}$  dry weight (dw) is an indication for iron chelation therapy in transfusional iron overload.[9,23] More recently, LIC  $>5 \text{ mg/g}$  dw has been proposed as an indication for iron chelation therapy with deferasirox in nontransfusion-dependent thalassemia.[24]

LIC determination by liver biopsy has several limitations. Biopsy is invasive and carries a risk for complications,[25] and liver specimens are subject to sampling variability due to spatial and sample mass heterogeneity.[26–29] However, liver biopsy does allow for histologic assessment of fibrosis, cirrhosis, and necroinflammation. Given the risks associated with this invasive procedure, liver biopsy is not an ideal technique for frequent monitoring of iron loading and chelation therapy effectiveness.

### Magnetic Techniques for Iron Determination

Magnetic techniques offer advantages over traditional methods of determining iron load as they are noninvasive, and therefore more acceptable to patients. Furthermore, these methods measure iron load within the target organ rather than relying on a surrogate indicator.

**Biomagnetic liver susceptometry.** Biomagnetic liver susceptometers were the first instruments to enable noninvasive assessment of LIC.[30] Original instruments incorporated a superconducting quantum interference device (SQUID). A key assumption underlying the SQUID technique is that the paramagnetic response of iron in ferritin and hemosiderin is directly proportional to the number of iron atoms present. However, the paramagnetic proportionality constant varies among different forms of hemosiderin found in different patient groups.[31] Nevertheless, LIC determinations from SQUID have a high degree of correlation with LIC determined from biopsies.[32] The major limitation of this technique for routine use is that few of these

instruments exist, and they are primarily reserved for clinical research due to cost and technical demands of maintaining a superconducting device.

**Magnetic resonance imaging.** MRI techniques for determining iron concentration are based on measuring the effect of local distortion of magnetic fields caused by excess iron in tissues on hydrogen proton behavior.[33,34] Tissue iron concentration is measured indirectly by its influence on the resonance of protons in water and fat.[33,34] The most commonly used MRI approaches for assessing tissue iron concentration are based on measurements of proton transverse magnetization decay rates,  $R_2$  or  $R_2^*$ .[35] Shorter signal intensity half-lives (i.e., greater rates of signal decay) indicate greater iron concentration.[33,34]

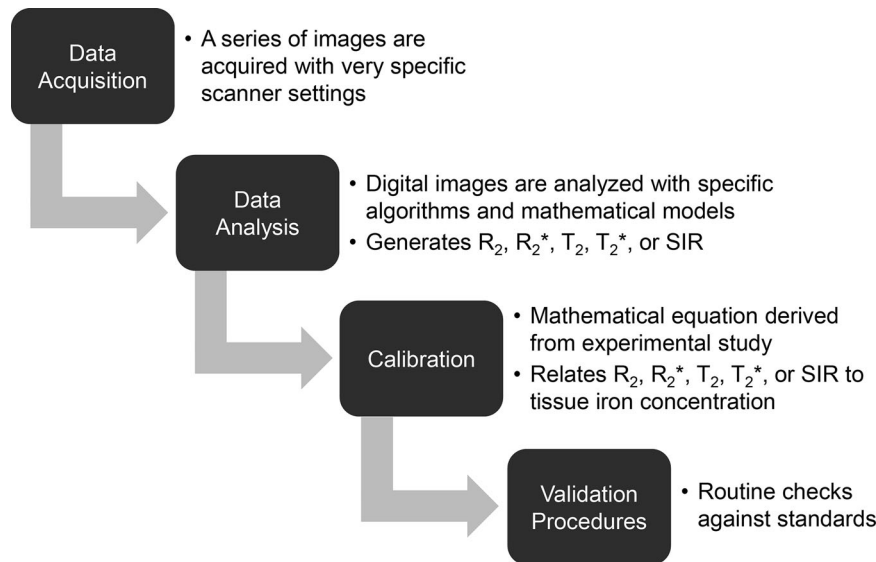
Two general classes of MRI approaches are used for measuring tissue iron concentration: relaxometry and signal intensity ratio (SIR) methods.[34,36] Relaxometry methods measure the rate of signal intensity loss.[33,34] Images of target tissue are obtained at various time points after proton excitation, and an algorithm is applied to the image data to determine the signal decay rate.[33,34] The signal decay rate is known as  $R_2$  or  $R_2^*$ , depending on the method of data acquisition (radiofrequency pulse refocusing method for  $R_2$ ; magnetic field gradient pulse for  $R_2^*$ ). As such, the two are different physical quantities. The characteristic signal decay time  $T_2$  or  $T_2^*$  can be derived from the relaxation rate ( $T_2 = 1,000/R_2$ ;  $T_2^* = 1,000/R_2^*$ ). For LIC, several calibrations have been derived from comparisons between MRI measurements and chemical assays of liver biopsies in different patient cohorts.[20,37–41] Until recently, no calibration was available for heart measurements, so  $T_2^*$  or  $R_2^*$  values were reported without conversion to an iron concentration. Recently, an *ex vivo* study was published regarding the relation between cardiac iron concentration and  $T_2^*$  and  $R_2^*$ .[42] However, the clinical community has already adapted to interpreting cardiac  $T_2^*$  values rather than requiring a calibration to convert to iron concentration.

SIR is a relative measure comparing signal intensity of target tissue to that of tissue that does not accumulate iron (typically paraspinal muscle).[34,43] As such, it is easier to implement than relaxometry methods; however, calibration is still required and subjective decisions are required during data analysis.

It is important to note that the values of MRI parameters calculated from the images depend not only on tissue iron concentration, but also on the details of data acquisition and analysis methods (Fig. 2).[44,45]

### Challenges and Pitfalls in the Widespread Adoption of MRI Techniques

Appropriate calibration and validation is required for universal application of MRI techniques to measure tissue iron concentrations.[38,40,46] We are now seeing a transition from the use of these MRI techniques by specialized research centers to more general use by radiology centers in routine clinical practice. This transition presents challenges—particularly, reliable transfer of methodology from experts to routine users. Major pitfalls include the use of incorrect or drifting calibrations and flawed data analysis methods. Currently, there is a general but unfounded view that different MRI methods are easily interchangeable, transferable, and validated. When assessing accuracy and validity of all MRI tissue iron measurement techniques,



**Fig. 2.** Four key components for an MRI-based liver iron concentration measurement method. It is essential that data acquisition, data analysis, and validation procedures match exactly to those used in the calibration study. Even small deviations from protocols will cause calibration shifts and hence inaccurate measurements. MRI, magnetic resonance imaging; SIR, signal intensity ratio.

the criteria outlined in Table I should be considered.[47,48] It is necessary for hematologists to be familiar with these considerations to know whether the MRI tissue iron measurements that are performed at their institutions are accurate and valid, and, if not, to enable hematologists to enter into meaningful discussions with their radiologist colleagues.

Using appropriate reference standards to generate calibration curves is essential. If a single scanner is used to generate a calibration curve, the bias for that scanner will in principle be zero because that scanner has been used to define the relation between the MRI parameter and tissue iron concentration. However, if the calibration curve is used to interpret results from another scanner or the same scanner but after a significant period of time has elapsed, there may be a measurable bias, and hence loss of accuracy. Due to the ever-present risk of calibration drift, the US Food and Drug Administration requires that measurement devices be calibrated according to defined and controlled general manufacturing practices (Table I).[48] In the context of tissue iron measurement by MRI, the measurement device refers to both data acquisition and analysis methods.

A change in operating technician or data analyst also has the potential to alter output parameters, as do software and hardware upgrades. The most serious errors are caused when using commonly available scanner vendor software packages for calculating  $T_2$  or  $T_2^*$  maps. Most of these mapping algorithms use linear fitting to log-transformed signal intensity data because it is computationally fast; however, these algorithms are not designed to analyze iron-loaded tissue where signal-to-noise ratios are usually low. Even when using nonlinear fitting to raw data, significant deviations in measured relaxation parameters result if the exact data analysis method used in the calibration study is not followed.[44]

Another potential pitfall is properly judging the relative accuracy of MRI compared with other standard measurement techniques. The currently accepted reference standard is the

**TABLE I. Quality Control Issues and GMP Calibration Requirements of Measuring Equipment for MRI Tissue Iron Measurement Techniques**

Critical quality control questions to assess the accuracy and validity of MRI iron measurement techniques

- How many reference standard measurements were made to generate the calibration curve?
- Were reference standard measurements spread evenly across the entire clinical range of relevance?
- How many scanners were tested? (the more the better)
- How many different makes and models of scanner were tested? (the more the better)
- If more than one scanner was tested, was bias between different scanners measured?
- Was repeatability measured? (repeat measurements of the same patient within a short period)
- Was reproducibility measured? Different patient group, different scanners, different makes and models of scanner?
- Does the method give provision for routine calibration and validation against a standard?
- Are the accuracy and precision limits specified?

GMP calibration requirements for measuring equipment[43]

- Routine calibration or validation according to written procedures
- Documentation of the calibration/validation of each device
- Specification of accuracy and precision limits
- Training of calibration personnel
- Use of standards traceable to the NIST, other recognizable standards, or when necessary, in-house standards

GMP, good manufacturing practice; MRI, magnetic resonance imaging; NIST, National Institute of Standards and Technology.

**TABLE II. Thresholds for Parameters Used to Assess Iron Overload in Patients With Thalassemia [3]**

Parameter	Normal	Iron overloaded state		
		Mild	Moderate	Severe
Serum ferritin (ng/ml)	<300	>1,000	<2,500	>2,500
Transferrin saturation (%)	20–50		>50	
LPI ( $\mu$ M)	0–0.4		>0.4	
LIC (mg Fe/g dw)	<1.8	3–7	>7	>15
Cardiac MRI $T_2^*$ (msec)	>20	14–20	8–14	<8
Cardiac $R_2^*$ (Hz)	<50	50–70	70–125	>125

dw, dry weight; LIC, liver iron concentration; LPI, labile plasma iron; MRI, magnetic resonance imaging. Taher et al.[3] Copyright © 2009, Informa Healthcare. Reproduced with permission of Informa Healthcare.

measurement of LIC by chemical assay of biopsy specimens. However, LIC measurements from needle biopsy specimens have large associated sampling errors;[26–29] several measurements are required to enable reliable comparison with the MRI method being evaluated. Thus, accuracy of the technique is essentially a measure of the average bias (or systematic error) of the MRI method of measurement relative to the averaged measurements by biopsy. A recent study judged relative MRI accuracy by performing  $R_2$ ,  $R_2^*$  analysis and biopsy simulations (in which variability and error were factored in), and determined that  $R_2^*$  was most precise in measuring LIC at 12- and 24-week intervals, but there was no advantage to  $R_2^*$  at  $\geq 48$ -week intervals.[49]

## CLINICAL APPLICATION OF MRI ASSESSMENTS

Hematologists have long made largely subjective decisions about chelation therapy based on the general degree of iron loading from intermittent measures of LIC and change in SF levels over time. The clinical utility of regular MRI measurements is not simply to determine the degree of iron loading, but to use this information to make informed, data-driven decisions about initiation and adjustment of chelation therapy. Indeed, increasing use of MRI to guide chelation therapy in patients with thalassemia has contributed to reduced iron burden.[50,51]

### Monitoring Body Iron Levels and Organ-Specific Iron Overload

**MRI measurement of LIC.** Patients who have received >10 units of PRBCs (or 100 ml/kg PRBCs) may have accumulated sufficient liver iron to warrant an initial MRI scan to help determine the need for chelation therapy.[52] For patients with elevated or increasing SF levels and those beginning or changing iron chelation regimens, MRI LIC should be determined to establish a baseline.[53] Patients with LIC up to 1.8 mg/g dw are in the normal range (Table II).[3] Higher LICs, especially >15 mg/g dw, are associated with severe adverse effects, including liver fibrosis and dysfunction.[3,54] Recently, it has been shown that LIC  $\geq 7$  and  $\geq 6$  mg Fe/g dw are the best thresholds for discriminating the presence of vascular and endocrine/bone morbidities, respectively, in  $\beta$ -TI.[14]

**MRI measurement of cardiac iron.** Cardiac iron accumulation is rare in patients who have received <70 units PRBCs.[55]

However, cardiac iron load by MRI can be measured during the same examination as LIC using a different data acquisition method, and may identify those patients at high risk of cardiac dysfunction before they experience a reduction in left ventricular ejection fraction or dysrhythmias.[3] Patients with cardiac  $T_2^*$  values >20 msec have normal cardiac iron levels (Table II). Decreasing cardiac  $T_2^*$  values correspond with increasing levels of cardiac iron and increasing risk of cardiac dysfunction.[56] Patients with absent or ineffective erythropoiesis, such as DBA and TM, and those with suboptimal chelation therapy may have clinically significant cardiac (and other organ) iron accumulation at a very young age. Therefore, it is reasonable to measure cardiac  $T_2^*$  as early as feasible and not necessarily delay cardiac imaging until the second decade of life.[16]

**Discordance between liver and cardiac iron.** Several studies have shown that the liver and heart have different iron accumulation and removal rates; LIC does not correlate strongly with cardiac iron stores in cross-sectional studies.[20,57–59] In particular, delayed loading and slower unloading have been observed in the heart compared with the liver.[6] Moreover, the heart can load iron primarily, even in the absence of significant hepatic iron overload and despite maintenance of stable total body iron stores (TBIS) balance by chelation.[6] Consequently, it is necessary to measure both liver and cardiac iron levels in appropriate patient populations.

**MRI measurement of iron in other organs and tissues.** Clinical utility of MRI measurements in other organs and tissues, such as the pancreas and pituitary gland, is under study. Pancreatic  $R_2^*$  measurements have not been standardized and can be confounded by fat. However, in patients with TM, SCD, or DBA, the pancreas accumulates iron more quickly than the heart.[6,7] As such, assessments of pancreatic iron deposition via  $R_2^*$  can potentially serve as an early predictor of cardiac iron overload.

### Monitoring Effectiveness of Chelation Therapy

Currently, there are three iron chelators approved for use in the United States, Canada, and Europe. Deferoxamine is approved for frontline use and is administered by slow subcutaneous (or intravenous) infusion because of its short half-life.[60] Deferasirox is also approved for frontline use and is administered once daily as an oral suspension or as a new oral tablet formulation available in some countries.[61] Deferiprone is approved for second-line chelation therapy and is an oral agent administered three times daily.[62] The use of magnetic techniques to monitor liver and cardiac iron has been reported for all three chelators in several large clinical trials.[63–68] In general, all available chelators reduce liver and cardiac iron load, with combination therapy producing greater short-term gains. However, many of these studies included small numbers of patients, so care should be taken when extrapolating results to a larger patient population. The longer term data available for deferasirox appear to show that cardiac iron removal is slower relative to liver iron removal.[63–65]

Response to chelation therapy depends on the rate of transfusional iron loading.[68] Thus, several measurements and calculations, at least done annually, are necessary to allow the clinician to monitor the effectiveness of chelation therapy quantitatively and make data-driven adjustments to the chelation

**TABLE III. Necessary Yearly Measurements and Calculations to Inform Chelation Therapy**

Data and measurements
Record the volume of all transfused PRBCs (or net volume of PRBCs if phlebotomy or erythrocytapheresis is used)
Measure LIC yearly using MRI in all patients
Measure cardiac T <sub>2</sub> * yearly in specific populations (disorders with absent or ineffective erythropoiesis, such as TM or DBA, and patients with poor control of TBIS regardless of underlying disease)
Main calculations
Total body iron stores (TBIS)
Yearly change in TBIS
Transfusional iron intake rate
Iron excretion rate
Fraction of transfused iron that is excreted

DBA, Diamond–Blackfan anemia; LIC, liver iron concentration; MRI, magnetic resonance imaging; PRBCs, packed red blood cells; TM, thalassemia major.

regimen to achieve an appropriate net iron balance (Table III). All of this information needs to be considered in the context of trends in SF, liver function tests, growth and development (for pediatric patients), and endocrine studies.[69] Prior to the availability of MRI techniques, determining the degree of transfusional iron overload was invasive and performed infrequently. The following case study is an example of how the clinical management of a patient with transfusional iron overload has been facilitated by the use of MRI assessments.[68]

*Case Study:* A patient with a consistent transfusional iron intake rate (mean 0.36 mg Fe/kg/day) (Table IV) over 6 years had stably elevated SF during the first 3 years (2,500–3,500 ng/ml). The first two LIC determinations showed an increase in TBIS despite excellent adherence to chelation at typical doses (Table IV). The imbalance between iron intake (transfusions) and iron excretion rate (chelation) was quantified by calculation of iron excretion/iron intake. Only 90% of the transfused iron was being removed by chelation. A modest increase in the chelator dose increased chelation effectiveness in the subsequent ~3 years (140–170% of transfused iron was removed). The last SF was 869 ng/ml and the last LIC by MRI was 2.9 mg/g dw. In summary, with the availability of MRI measurements of LIC in 2007, the patient's iron loading and chelation effectiveness could be monitored more frequently (yearly, compared with every 2–3 years by liver biopsy), producing timely changes in chelation therapy and rapid resolution of severe iron overload.

### Promoting Adherence to Chelation Therapy

Treatment adherence can be difficult for all patients, but especially for asymptomatic patients who have no tangible way to feel the benefits of chelation. For these patients, reviewing the increasing LIC over time can quantitatively demonstrate the need for better adherence. Likewise, serial LIC measurements that show decreasing LIC can also demonstrate the benefits of chelation to asymptomatic patients and reinforce adherence. Routine education about disease states and chelation therapy has been shown to correlate with improvements in compliance and decreases in LIC.[70] Therefore, patient education and engagement needs to be incorporated into every visit.

**TABLE IV. Case Study: Quantitation and Successful Resolution of Severe Iron Overload**

Transfusional iron intake—Measurements and calculations											
Dates of serial LIC measurements		Interval between LICs (days)	Transfused PRBCs (ml)	Hematocrit of PRBCs	Transfused pure RBCs (ml)	Transfusional Fe intake (mg)	Weight (kg)	Transfusional Fe intake rate (mg/kg/day)			
June 4, 2002	May 25, 2004	721	11,789	0.55	6,484	7,003	26.5	0.37			
May 25, 2004	January 25, 2007	975	17,668	0.55	9,717	10,495	30	0.36			
January 25, 2007	February 13, 2008	384	7,315	0.55	4,023	4,345	33.2	0.34			
Change in hepatic and total body iron stores—Measurements and calculations											
Date	Interval (days)	Liver Fe		Weight (kg)	TBIS (g)	ΔTBIS (g)	ΔTBIS rate (mg/kg/day)	Fe excretion rate (mg/kg/day)	Fe intake (mg)	Fe intake rate (mg/kg/day)	Fe excretion/Fe intake (%)
		(μg/g dry)	Method								
June 4, 2002	–	35,204	Biopsy	21.2	7.91	–	–	–	–	–	–
May 25, 2004	721	30,433	Biopsy	26.5	8.54	0.63	0.03	0.33	7,003	0.37	89
January 25, 2007	975	12,704	MRI-R2	30.0	4.04	–4.50	–0.15	0.51	10,495	0.36	142
February 13, 2008	384	2,900	MRI-R2	33.2	1.02	–3.02	–0.24	0.58	4,345	0.34	171

Calculations (based upon sequential pairs of LIC determinations): Transfused pure RBCs = Sum of transfused PRBCs in interval between LICs (ml) × hematocrit. Transfusional Fe intake = pure RBCs × 1.08. Transfusional Fe intake rate = Transfusional Fe intake/weight (kg)/interval between LIC measurements (days). TBIS = [10.6 × LIC (μg/g) × weight (kg)]/10<sup>6</sup>. ΔTBIS = TBIS (current) – TBIS (last). ΔTBIS rate = (ΔTBIS × 1,000) / weight (kg)/interval between LIC measurements (days). Fe excretion rate = [Fe intake (mg) – (ΔTBIS × 1,000)]/weight (kg)/interval between LIC measurements (days). Fe intake = Total PRBC volume during interval (ml) × average hematocrit of units × 1.08. Fe intake rate = Fe intake/weight (kg)/interval between LIC measurements (days). Fe excretion/Fe intake (%) = (Fe excretion rate/Fe intake rate) × 100. Fe, iron; LIC, liver iron concentration; PRBC, packed red blood cells; RBC, red blood cells; TBIS, total body iron stores; Δ, change.

## Costs of monitoring

The costs of monitoring LIC vary widely. Some determinants of MRI costs include scanner time, number of sequences obtained, sedation or anesthesia, professional fees (e.g., radiology, anesthesiology), and the charge for Ferriscan® (\$300). Determinants of biopsy costs include sedation or anesthesia, where the biopsy is performed (e.g., operating room, interventional radiology suite), where recovery occurs (e.g., intensive or acute care unit), equipment charges, professional fees (e.g., gastroenterologist, surgeon, interventional radiologist, pathologist, anesthesiologist), tissue processing and pathology fees, and measurement of tissue iron. Indeed, quantitation of hepatic iron by MRI may cost more or less than a liver biopsy at a particular center. At the author's (CTQ) institution, the estimated charge for a liver biopsy is \$6,580, compared to \$4,380 for hepatic MRI with T2\* and R2 sequences. Practically, MRI can be performed more frequently than biopsy, so life-long charges may be greater for MRI when performed annually or more frequently than liver biopsies. Nevertheless, costs of MRI should be considered in the context of (i) costs of obviated liver biopsies and (ii) the late costs of poorly controlled iron overload.

## CONCLUSIONS

MRI offers several advantages over traditional approaches to iron measurement. It is noninvasive and more acceptable to patients for frequent assessments and provides direct assessments of target organs, with results equivalent to or better than LIC from biopsy.[37,71] Additionally, MRI may also provide information on the fibrotic stage of the liver, potentially identifying patients who still require biopsy for histologic analysis; however, further research is required to enable such measurements to be clinically useful.[71,72] Myocardial iron measurement by MRI has a strong correlation with iron concentration from *ex vivo* hearts, making MRI an obvious choice because biopsy of this organ is impractical.[42]

Heterogeneity in timing and degree of organ-specific iron loading underscores the need to monitor both liver and heart iron load directly to identify all at-risk patients. Heart iron measurements are indicated in patients with absent or ineffective erythropoiesis, such as DBA, TI and  $\beta$ -TM, and those with suboptimal chelation. Only a small proportion of patients with SCD develop cardiac hemosiderosis, so the utility of cardiac T2\* measurement remains to be established for this population.[59,73]

Although significant obstacles to universal application of MRI techniques remain, hematologists no longer need to make subjective decisions about chelation therapy based on the general degree of iron loading inferred from infrequent measures of LIC from liver biopsy and changes in SF levels over time. Periodic MRI assessments provide quantitative data for the calculation of chelation effectiveness, which allow hematologists to make informed, data-driven, timely decisions about initiation and adjustment of chelation therapy. However, hematologists need to engage in meaningful discussions with their radiologist colleagues to ensure that MRI assessments of tissue iron at their institutions are accurate and valid.

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