Use of Magnetic Resonance Imaging to Monitor Iron Overload

John C. Wood, MD, PhD[a,b,*]

KEYWORDS

• Iron overload • Thalassemia • Sickle cell disease • Chelation
• Magnetic resonance imaging • Iron • Liver • Heart

KEY POINTS

- Serum ferritin and transferrin saturation remain valuable in tracking the therapeutic response to iron-removal therapies.
- These inexpensive techniques have many shortcomings that preclude using them safely as sole monitors for chelator efficacy.
- Magnetic resonance imaging has become the de facto gold standard for tracking iron levels in the body because it is accurate, reproducible, and well tolerated by patients, and can track iron levels in different organs of the body.
- The latter characteristic is important because the mechanisms and kinetics of iron uptake and clearance vary across somatic organs.
- The author's clinical practice is presented as a reference, but individual experiences will still be colored by local expertise as the technologies continue to mature and be more widely distributed.

MONITORING TRANSFUSION BURDEN

Each unit of packed red blood cells (PRBCs) contains between 200 and 250 mg of iron. In fact, the iron can be calculated from the hematocrit (Hct) using the following relationship:

$$\text{Transfusional iron intake (mg/kg)} = \text{blood volume (mL/kg)} \times \text{Hct} \times 1.08\ \text{mg/mL} \quad (1)$$

[a] Department of Pediatrics, Children's Hospital, Los Angeles, Keck School of Medicine, University of Southern California, 4650 Sunset Boulevard, Los Angeles, CA 90027, USA; [b] Department of Radiology, Children's Hospital, Los Angeles, Keck School of Medicine, University of Southern California, 4650 Sunset Boulevard, Los Angeles, CA 90027, USA
* Cardiovascular MRI Laboratory, Children's Hospital Los Angeles, 4650 Sunset Boulevard, MS #34, Los Angeles, CA 90027.
E-mail address: jwood@chla.usc.edu

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where Hct is calculated from the PRBCs provided by the blood bank.[1] The volume of transfused blood in 1 year can be converted to a predicted change in liver iron concentration (LIC) if no chelation is taken, using the following equation[2]:

$$\Delta LIC = \text{Transfusion iron intake}/10.6 \quad (2)$$

Thus a patient receiving 150 mL/kg/y of PRBCs having an Hct of 70% would increase the liver iron by 10 mg/g in the absence of iron chelation. As a rule of thumb, each 15 mL/kg transfusion will raise liver iron by approximately 1 mg/g dry weight.

Therefore, tracking transfusional iron exposure is a logical and conceptually simple way of predicting iron chelation needs, a priori. It is clearly useful in deciding when to initiate iron chelation therapy. Systematic intensification of transfusion requirements, such as may occur during hepatitis C treatment, should prompt preemptive changes in iron chelation. However, there are 2 major limitations to using transfusional burden to adjust chelation. In practice, values may be difficult to track because amounts released from the blood bank are systematically larger than are given to the patients. More importantly, there are complicated interactions between transfusion iron rate and chelator efficacy that may be patient and disease specific, creating differences between predicted and observed response to therapy.

SERUM MARKERS OF IRON OVERLOAD

Ferritin is an intracellular iron-storage protein that is essential for all living cells because it maintains labile cellular iron levels within a safe range while protecting cells against iron deficiency in the future. The circulating serum ferritin pool mostly arises from the liver and reticuloendothelial systems, and its biological role is unclear. The relationship between serum ferritin and total body iron stores is complicated. Correlation coefficients between ferritin and liver iron concentration are typically around 0.7, leaving 50% of the variability unexplained.[3,4] More importantly, the confidence intervals for predicting LIC values from serum ferritin measurements are enormous. A patient having a serum ferritin level of 1500 ng/mL could have a LIC as low as 3 or as high as 30 mg/g dry weight. As a result, toxicity thresholds based on serum ferritin levels can be dangerously misleading.

Serum ferritin may be so unreliable because it is an acute-phase reactant[5] that rises sharply with inflammation. The liver is the major source of circulating ferritin, and even minor liver insults will sharply increase serum ferritin.[6] By contrast, ascorbate deficiency leads to inappropriately low serum ferritin values relative to iron stores.[7] Lastly, serum ferritin levels depend on the transfusion rate in addition to the body's iron stores. Nontransfused iron-overloaded patients, such as those with β-thalassemia intermedia, have much lower ferritin values for a given total-body iron concentration.[8]

Intrapatient trends in serum ferritin improve its predictive value.[8] The author typically measures serum ferritin values with every transfusion, and trend median values over a period of 3 to 6 months. Nonetheless, ferritin and LIC trends remain discordant more than 30% of the time.[9] Periods of discordance can span months to years.[9]

Despite its limitations, serum ferritin is undoubtedly the world's most widely used method for tracking iron stores because of its low cost and universal availability. **Box 1** summarizes guidelines for improved use of serum ferritin to trend iron overload.

Transferrin saturation is also an important and widely available serologic marker of iron balance. It represents the earliest and most specific marker of primary hemochromatosis, and is a key screening marker in all diagnostic algorithms for this disease.[10] Increased transferrin saturation can also be used as an indicator to initiate iron