Iron Overload. Iron overload (IO) or excessive body iron burden is a serious condition resulting from increased dietary gastrointestinal absorption, multiple erythrocyte transfusions, or both. Increased intestinal iron uptake leading to significant iron deposits is seen in hereditary hemochromatosis and also in hematologic conditions with ineffective erythropoiesis. Repeated erythrocyte transfusions are used in many hematologic diseases to either supply red blood cells when there is ineffective bone marrow erythropoiesis [e.g., thalassemia major (TM), myelodysplastic syndromes, Diamond-Blackfan anemia (DBA), congenital dyserythropoietic anemia] or to prevent complications of the disease [e.g., sickle cell disease (SCD)], by suppressing the bone marrow’s production of red blood cells or supplying functionally normal ones. Survivors of cancer, especially those undergoing bone marrow transplantation, may also receive numerous transfusions as part of their treatment. IO in pediatric patients mainly results from repeated blood transfusions. Each milliliter of transfused blood has approximately 1 mg of iron. With repeated transfusions, iron accumulates at a very fast rate as there is no physiologic mechanism for its elimination. Patients undergoing chronic transfusions have an iron excess of 0.3–0.4 mg/kg/day, and laboratory signs of iron overload can be detected after 15–20 transfusions.

Organ Involvement. Excess iron accumulates in nearly all tissues, but most notably in the liver, heart, thyroid, spleen, pituitary gland, and pancreas, causing organ dysfunction, substantial morbidity, and increased mortality. The normal hepatic iron content (HIC) is less than 2.4 mg Fe/g dry weight. Liver is one of the main target organs in IO. During the process of iron loading, iron deposition in the liver is substantial; therefore, hepatic disease is a very common finding of systemic IO. The degree of liver dysfunction is directly dependent on the amount of hepatic iron deposition. Progressive iron accumulation eventually leads to hepatomegaly, liver synthetic abnormalities, fibrosis, and finally, cirrhosis and liver failure. Also, the risk of developing hepatocellular carcinoma increases significantly in patients with cirrhosis secondary to IO. Hepatic iron can accumulate to extreme amounts, with HIC values more than 67 mg Fe/g being reported, placing these massively iron-overloaded patients in great danger of the toxicities of iron. Cardiac failure is a complication of major concern in patients with increased body iron burden. Myocardial iron deposition leads to arrhythmias and progressive heart dysfunction, and remains the most common cause of death in patients with TM. Myocardial siderosis can also occur in other hematologic diseases treated with repeated blood transfusions, such as DBA, and less frequently in SCD. Cardiac dysfunction is associated with the degree of iron deposition in the myocardium, and HIC values persistently ≥ 15 mg Fe/g of liver dry weight are associated with increased cardiac morbidity and early death in patients with TM.

Monitoring IO. Accurate assessment of body iron burden is essential to manage IO patients properly by instituting measures to unload iron, such as initiating iron chelation therapy or
therapeutic phlebotomy, or adjusting the dose and intensity of chelation.\textsuperscript{21-23} In addition, close monitoring of body iron burden can help avoid adverse effects of excessive iron chelation. Annual or more frequent assessments of iron burden are necessary. Because HIC consistently mirrors total body iron, the chemical analysis of hepatic specimens obtained through needle biopsy is considered the reference method to evaluate iron excess in systemic IO.\textsuperscript{24} Liver biopsy, however, is an invasive procedure that carries risks such as pain, bleeding, and infection, in turn leading to suboptimal patient adherence.

**Role of MRI.** Non-invasive methods to estimate IO with magnetic resonance imaging (MRI) are an alternative to biopsies especially in pediatric patients. MRI is sensitive to tissue iron concentration because the magnetic properties of iron change tissue specific relaxation parameters, especially the transverse relaxation times T2 and T2*. An effective MRI-based method to estimate HIC has been reported by \textit{Gandon et al.}\textsuperscript{25} Relatively good correlation has been shown between HIC by biopsy and liver tissue relaxation rates R2 (\( = 1/T2 \))\textsuperscript{26} and R2* (\( = 1/T2^* \)).\textsuperscript{27-29} The FDA-approved, calibrated R2-based method takes ~15-20 min and requires advanced, centralized post-processing (Ferriscan, Resonance Health) for HIC estimation.\textsuperscript{30} In contrast, R2*-based methods typically require acquisition times of about 20 s and are performed within a single breath hold. The shorter acquisition times render R2* methods favorable for pediatric patients. When sedation is required (typically in children < 7 years) signal averaging is an effective means to compensate for respiratory motion artifacts. Iron deposition in the pancreas, spleen, and kidneys is typically assessed by the same sequence within the same imaging session. R2*-post processing is relatively simple, however, recently advanced R2* acquisition and processing approaches have been proposed to account for confounding factors such as lipids, or background distortions due to susceptibility differences at air tissue boundaries.\textsuperscript{31,32}

For patients who regularly receive blood transfusions (i.e., TM patients),\textsuperscript{18,33} cardiac failure is the major cause of death. Progressive heart damage from iron overload can cause left ventricular systolic and diastolic dysfunction; left ventricular systolic dysfunction (decreased ejection fraction) is usually a late finding of heart disease from iron accumulation.\textsuperscript{34} This is most alarming because it progresses rapidly and is difficult to manage. It is therefore imperative to quantitatively monitor cardiac iron deposition in these patients to be able to apply intensified iron-chelation in time and to guide the therapy. Because of the reduced imaging time compared to T2-based techniques, T2*-based approaches are preferred for myocardial iron assessment,\textsuperscript{27,35} and multi-gradient echo sequences are typically combined with cardiac gating techniques to obtain myocardial T2* values within a single breath hold. If breath hold acquisitions are not realizable, e.g. in very young children, multiple acquisitions are averaged to reduce motion artifacts. As there is no biopsy calibration available for cardiac iron, risk stratification is based on T2* values measured in the interventricular septum.\textsuperscript{36} A myocardial T2* value of < 20 ms which implies increased myocardial iron has been shown to be associated with an increased risk of decreased left ventricular function.\textsuperscript{27} The risk of a decreased left ventricular ejection fraction amounts about 10%, 18%, 38%, and 70% in the T2* ranges of 10-20ms, 8-10ms, < 6ms, and T2*<4ms, respectively.\textsuperscript{36,37}

Hypogonadism resulting from pituitary dysfunction due to iron siderosis is a frequent complication in TM patients.\textsuperscript{38,39} The role of MRI is to identify the patients who are at great risk
of developing this complication. Especially in adolescence an intact function of the pituitary gland is necessary to regulate growth and sexual maturation; pituitary dysfunction, therefore, directly impacts the quality of life of the patient.\textsuperscript{38} MR protocols for measurement of pituitary iron are based on T2-relaxometry\textsuperscript{40} and T2*-weighted neuro sequences.\textsuperscript{38}

In this presentation the following topics related to \textit{The Role of Pediatric MRI in Iron Quantification} will be overviewed: (a) iron metabolism and storage, (b) etiology of IO in children, (c) organ-specific MR pediatric protocols to measure IO, and (d) the impact of IO assessment by MRI on the clinical management and quality of life of the children.

**Selected Bibliography**


