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What is the importance of monitoring iron levels in different organs over time with magnetic resonance imaging in transfusion-dependent thalassemia patients?

Abstract

Introduction: Iron overload is the main pathophysiological driver of organ damage in transfusion-dependent thalassemia (TDT). Magnetic resonance imaging (MRI) provides detailed insights into the distribution and severity of iron accumulation in the different organs.

Areas covered: This special report describes the impact of MRI on clinical and therapeutic management and short- and long-term outcomes in TDT patients. PubMed, Scopus, and Google Scholar databases were searched to identify the relevant studies published before November 2024.

Expert Opinion: Cardiac and hepatic MRI are now well-established modalities, integrated into the clinical practice. They have become essential for tailoring iron chelation therapies to the specific patient's needs and for monitoring treatment efficacy. The improved control of cardiac iron burden has translated into reduced morbidity and mortality. The MRI accessibility remains limited in resource-limited settings and progress in this field relies on educating and training centers to ensure accurate execution and interpretation. The clinicopathological significance, prognostic value and reproducibility of pancreatic iron levels assessment have been established, charting a path toward its clinical use. There are limited data about renal, adrenal, and pituitary iron deposition, and more research is needed to fully establish the functional significance and to standardize and validate the MRI protocols.

Keywords: iron overload, magnetic resonance imaging, transfusion-dependent thalassemia.

Article highlights

- Magnetic resonance imaging enables non-invasive quantification of iron overload in various organs, providing critical insights into tissue-specific iron deposition.
- Hepatic and cardiac magnetic resonance imaging provide an accurate and reproducible non-invasive mean for tailoring individualized iron chelation therapies and evaluating the efficacy of the chosen treatment regimen.
- Magnetic resonance imaging has been a key factor in reducing cardiac mortality in transfusion-dependent thalassemia through early detection and precise management of myocardial iron overload.
- In transfusion-dependent thalassemia, monitoring pancreatic iron levels may improve risk stratification not only for diabetes but also for cardiac siderosis and complications.
- The assessment of renal, adrenal, and pituitary iron deposition may represent an added value in the management of transfusion-dependent thalassemia patients to further reduce organ damage, but more research is needed.

1. Introduction

The conventional management of patients with transfusion-dependent thalassemia (TDT) revolves around the administration of regular red blood cell transfusions and iron chelation therapy (ICT). Although needed for survival[1], transfusions inevitably result in progressive IO in critical organs such as liver, heart, and endocrine system[2,3]. The goal of the ICT is to keep the body's iron levels within safe limits to prevent organ damage and reduce morbidity and mortality[4,5]. Since the rates and mechanisms of iron uptake and elimination differ among the organs[6,7] and the three available iron chelators have a different efficacy on different organs[4,8-10], the design and efficacy monitoring of individually tailored chelation protocols require the precise quantification of organ-specific iron deposition. Magnetic Resonance Imaging (MRI) has established itself as the non-invasive gold standard for this purpose[8,9,11-15]. MRI exploits the paramagnetic properties of iron deposits, which cause microscopic magnetic field inhomogeneities, resulting in a faster decay of the transverse magnetization, with a shortening of the transversal T2 and T2-star (T2*) relaxation times and a darkening of the MRI images proportional to the iron concentration[16] (Figure 1). So, organs with increased IO have shorter relaxation times or higher relaxation rates (R2 and R2*), which are the reciprocal of relaxation times and directly proportional to iron levels. The T2*/R2* relaxometry is most widely used in clinical practice, being faster and easier than the T2/R2 relaxometry, and highly reproducible among observers, sites, and scanners[17-21]. Moreover, T2/R2 relaxometry is not specific for iron being sensitive also to edema, significantly present in TDT patients[22]. The presence of iron also results in a reduction of the longitudinal relaxation time (T1)[16].

This special report aims to describe how MRI, allowing for a robust, reproducible, and non-invasive assessment of iron distribution in all organs (Figure 2), has significantly impacted the management of TDT patients and improved short- and long-term outcomes.

2. Organ-specific MRI

Studies evaluating organ iron deposition by MRI in TDT patients were selected using PubMed, Scopus, and Google Scholar electronic databases. Additional records identified through the list of references or other sources were also included. Only articles written in English were included. The search was performed in November 2024 with no time restrictions for searching articles.

2.1 Liver

The liver is the primary organ for iron storage in thalassemia. Both T2 and T2* techniques, paired with the use of the appropriate calibration curves, have been demonstrated accurate in assessing liver iron concentration (LIC)[23-28]. However, despite the good correlation between the two methods,

individual LIC estimates showed wide limits of agreement, especially for increased LIC, suggesting that substituting one method for another in the follow-up of a single patient is not advisable.

LIC serves as a useful marker for evaluating total body iron levels, but it has limited predictive power for iron accumulation in extrahepatic tissues, such as the heart and endocrine glands, which rely primarily on the uptake of non-transferrin-bound iron[6,29,30]. Despite successful iron chelation therapy achieving neutral iron balance in the body, extrahepatic iron loading may persist, due to the different kinetics of iron accumulation and removal.

Approximately 30% of thalassemic patients develop liver fibrosis as a result of iron overload, which may progress to cirrhosis, particularly when LIC exceeds 7mg/g/dw[31]. It has been shown that the risk of progression can be mitigated through effective control of LIC using ICT[32]. A randomized controlled trial involving 219 TDT patients treated with ICT demonstrated stability or improvement in liver fibrosis and histological necroinflammation, along with a reduction in alanine transaminase levels[33]. A longitudinal study reported similar improvements in liver function, with significant reductions in transaminase levels before and after treatment with ICT[34].

Unlike biopsy, MRI allows a regular assessment of hepatic iron levels without procedural risks. Both observational studies and clinical trials utilizing MRI for assessing LIC have demonstrated the ICT efficacy in terms of reduction or removal of hepatic siderosis[35,36]. Most importantly, MRI enabled the non-invasive comparison of the efficacy of the different chelators. A comparable efficacy was demonstrated for the three chelators in monotherapy, while the combined use of both deferoxamine and deferiprone was associated with a significantly better improvement of hepatic siderosis[9,14,37,38].

2.2 Heart

Myocardial IO occurs later than hepatic IO. Over time, it can lead to impaired diastolic function, dilated cardiomyopathy, arrhythmias, and heart failure, a major cause of mortality in TDT. Clinical diagnosis is often delayed due to the late onset of symptoms[39,40]. Traditional biomarkers, including serum ferritin and hepatic iron content, correlate poorly with cardiac dysfunction, and brain-natriuretic peptide levels rise only in advanced stages[41]. Standard measures like ejection fraction often detect dysfunction only after significant myocardial damage, and supranormal left ventricular function may mask early signs of cardiac impairment[42]. This diagnostic delay increases the risk of rapid heart failure progression.

Cardiac T2* MRI has emerged as a critical tool for detecting myocardial iron deposition before the onset of overt dysfunction and for identifying high-risk patients[43,44]. Timely identification is paramount for effective management, as iron-induced cardiomyopathy is treatable and reversible if

intensive chelation therapy is initiated promptly[45]. Besides offering a window for timely intervention, cardiac T2* MRI also enabled the comparative evaluation of the efficacy of the different chelation treatments. All three iron chelators have proven effective in reducing myocardial iron with acceptable safety profiles and effects dependent on dosage and treatment duration[8,46-48], but deferiprone has demonstrated superior cardioprotective effects compared to deferoxamine[8,9,18,49-51]. According to a prospective observational study, deferasirox monotherapy is less effective than deferiprone in improving myocardial IO and biventricular function[9], but further confirmatory MRI studies are required. Additionally, combining any two chelators has an additive, if not synergistic chelating effect, resulting in more rapid improvement in cardiac iron load and ejection fraction increase[4].

Several nationwide studies have demonstrated that the introduction of the cardiac T2* MRI has significantly improved the management of cardiac siderosis by enabling more appropriate and personalized chelation strategies, with a consequent significant decrease in heart failure-related morbidity and mortality[52-55]. Anyway, despite significant survival improvements, heart disease remains the leading cause of death of TDT patients[54,56].

Cardiac T2* MRI is nowadays fundamental in the TDT management but it has some limitations, such as the sensibility to susceptibility artifacts and the reduced sensitivity in the detection of mild cardiac iron loading[57,58]. However, the additional measurement of cardiac T1 values emerged as a valid complementary technique to address these issues[59-61] due to its higher sensitivity to the myocardial iron burden. Importantly, in well treated TDT patients with a low cardiac iron burden, T1 values were a risk marker for supraventricular arrhythmias stronger than cardiac T2* values[61].

2.3 Pancreas

Pancreatic iron deposition is a prevalent finding in TDT, detected in over two-third of patients[62,63]. Excess iron in insulin-producing β -cells hampers their functionality, leading to reduced insulin synthesis and secretion[64-66]. This direct toxic effect of iron is one of the main etiologies of diabetes mellitus (DM) in TDT, where a significant link between pancreatic iron levels quantified by T2* MRI and alterations in glucose metabolism has been demonstrated[63,67]. Importantly, the progression toward overt DM is strongly influenced by both the severity and the duration of pancreatic IO. Damage to β -cells is not fully reversible, making early and accurate detection of pancreatic iron and prompt intervention crucial. Given the weak correlations between pancreatic siderosis and serum ferritin or LIC[7,63,68], the most effective method for assessing pancreatic IO is through direct imaging of the pancreas. MRI T2* studies demonstrated that the reduction of pancreatic iron levels is a slow and challenging process which requires aggressive ICT[10,69].

An additional feature of pancreatic MRI is the link between cardiac and pancreatic iron levels,[7,62,63,70-72], with a normal pancreas $T2^*/R2^*$ value showing a negative predictive value of 100% for cardiac iron[7,63,72], likely due to the same L-type calcium iron channels in the two organs. Consequently, the incorporation of $T2^*$ pancreatic measurements into clinical practice is strongly recommended as a prospective marker for assessing cardiac hemosiderosis risk. Performing abdominal MRI may be of high utility in regions where cardiac MRI is not readily available or accessible.

Recent studies demonstrated a strong link between pancreatic siderosis and cardiac complications, including heart failure and arrhythmias[63,73]. In particular, pancreatic $T2^*$ values emerged as a strong independent predictor of supraventricular arrhythmias, which represent the most prevalent type of arrhythmia and cannot be reliably predicted by iron levels in the left ventricle [73]. Therefore, regular monitoring of pancreatic iron levels could enhance risk stratification, not only for diabetes but also for cardiac complications.

2.4 Kidneys

Renal dysfunction in TDT often progresses insidiously, remaining asymptomatic for prolonged periods, and can involve both tubular and glomerular impairment[74]. In particular, high rates of tubular dysfunction have been documented, characterized by conditions such as hypercalciuria, proteinuria, phosphaturia, magnesiumuria, hyperaciduricuria, and elevated urinary excretion of β_2 -microglobulin[75,76]. Although IO has been identified a key factor contributing to renal damage in TDT[76-78], there is limited research on using MRI to directly evaluate kidney iron deposition in TDT. The available studies demonstrated that serum ferritin and hepatic iron levels did not provide an accurate and precise assessment of renal iron burden[79-82]. In a cohort of 50 TDT patients, renal $T2^*$ values were negatively associated with serum cystatin C, recognized as an earlier and more accurate biomarker of glomerular function than creatinine[81]. In another study, renal $T2^*$ values exhibited a significant inverse correlation with uric acid levels, which play a role in both the progression of chronic renal disease and the development of acute renal failure[82]. Although the association of kidney iron with early markers of tubulopathy and glomerulopathy requires further investigation, the preliminary research has important clinical implications. It may be expected that the assessment of renal iron deposition may help in the early detection of subclinical renal dysfunction in TM, furnishing the key to intervening promptly and mitigating the risk of progression to end-stage renal disease.

2.5 Pituitary gland

Iron deposition in the pituitary gland can impair its normal function, leading to critical endocrine complications such as hypogonadotropic hypogonadism, representing the most common endocrinopathy in TDT, and growth hormone deficiency[83]. In the early stages, pituitary siderosis may be asymptomatic. However, as iron deposition progresses, the pulsatile gonadotropin activity becomes markedly reduced, leading to irreversible damage to the hypothalamic-pituitary-gonadal (HPG) axis, ultimately resulting in hypogonadism and its associated complications[84].

Since the pituitary gland is relatively small and located in a magnetically inhomogeneous region, the T2/R2 imaging is generally the preferred method for assessing iron deposition in this area, being less prone to magnetic susceptibility artifacts[85].

Several studies demonstrated that pituitary T2/R2 serves as an effective marker for distinguishing TDT patients with normal pituitary function from those experiencing secondary hypogonadism[71,85-87]. Moreover, pituitary IO was demonstrated to negatively affect reproductive status in both males and females with TDT[88]. Intensive ICT has demonstrated potential in reversing some of the endocrine dysfunctions caused by IO, leading to improvements in pituitary function and partial normalization of gland volume[89]. These findings highlight the importance of early detection of pituitary IO and timely and effective adjustment of ICT in mitigating the harmful effects of IO and preventing an irreversible pituitary damage and associated endocrine complications.

Pituitary iron levels were found significantly correlated with hepatic, pancreatic, and cardiac iron levels[71,87,90] and it has been hypothesized that the kinetics of pituitary iron deposition is intermediate, falling between the rapid accumulation observed in hepatic tissue and the slower iron uptake characteristic of pancreatic tissue. Importantly, long-term hypogonadism has been demonstrated to predict severe myocardial siderosis[91]and to play a significant role in the development of cardiovascular complications[92]. Although these findings need to be confirmed by larger prospective studies, they emphasize that monitoring and early treatment of pituitary iron levels may also play a role in the prevention of pathologic cardiovascular outcomes.

2.6 Adrenal gland

According to a recent metanalysis, adrenal insufficiency (AI) is a common endocrine complication in TDT, with an overall prevalence of about 25.6% [93]. AI develops insidiously, with symptoms such as fatigue, arthralgia, and muscle pain being nonspecific and overlapping with those of chronic anemia, making early detection challenging. The primary concern with undiagnosed AI is the risk of a life-threatening acute adrenal crisis, particularly during periods of significant physiological stress[83,94]. This underscores the importance of regular monitoring and vigilance to prevent potentially severe outcomes. IO plays a critical role in the pathogenesis of AI, affecting either the

adrenal cortex (primary AI) or the pituitary gland (secondary or central AI)[93]. In cases of primary AI, iron impairs the adrenal cortex's ability to produce cortisol, which is essential for managing stress, infections, and physical exertion.

There is a scarcity of imaging studies focusing on iron deposition in the adrenal glands. Two studies using the T2* MRI technique were concordant in detecting a high prevalence (68% and 83%) of IO in adrenal glands, while contradictory results were reported about the association of adrenal T2* values with serum ferritin and hepatic iron levels[95,96].

The absence of studies linking the adrenal IO with biochemical parameters of adrenal function limits the understanding of its extent and impact on adrenal dysfunction. It is plausible that addressing iron toxicity at an early stage may help prevent tissue damage and functional failure in the adrenal glands.

2.7. Spleen

Spleen iron levels can be evaluated by repurposing liver MRI T2* scans, allowing for the efficient use of existing data without additional scanning time or cost. All available studies demonstrated a significant correlation between hepatic and splenic iron levels[97-102], while controversial data exist about the correlation between splenic and cardiac iron levels[98-102]. The spleen plays a key role in iron homeostasis and represents the body's second-largest organ involved in iron storage. So, incorporating splenic iron assessment into routine MRI scans for patients could enhance the understanding of the kinetics of iron distribution and clearance. However, no study has specifically addressed the functional implications and contribution to disease pathology of splenic IO.

2.8. Bone marrow

Iron deposition in the bone marrow not only disrupts the hematopoietic microenvironment but also contributes to chronic inflammation, reduced osteoblast activity, and enhanced osteoclast function[103]. Additionally, elevated bone marrow iron levels are associated with an increased risk of invasive aspergillosis, a severe and often fatal complication following hematopoietic stem cell transplantation (HSCT)[104], which is a curative treatment for thalassemia[105]. Therefore, the quantification of bone marrow iron may be particularly useful when planning for bone marrow transplantation, to optimize patient outcomes and reduce associated risks. A significant association between hepatic iron levels and iron in bone marrow measured both by the T2*[106] and the T2 relaxometry[107] has been demonstrated. However, the correlation was only moderate, suggesting that the best approach is the iron assessment directly in the bone marrow. This can be done without extending acquisition time, since bone marrow T2* measurements can be derived from the same MRI sequences used for liver iron quantification.

3. Conclusion

MRI has become an indispensable tool in TDT, enabling detailed, non-invasive assessment of iron accumulation in vital organs. This capability is critical for tailoring the ICT to individual patient needs, minimizing iron-related organ damage, and improving long-term outcomes[52,54]. Standardized and validated MRI techniques are now available for cardiac, hepatic, and pancreatic iron quantification, providing reliable data to guide treatment adjustments[108,109]. In particular, MRI techniques are routinely used for the cardiac and liver iron assessment, although limitations remain, particularly in resource-constrained settings where access to advanced MRI technology and expertise is limited. Additionally, organ-specific challenges persist, as protocols for iron quantification in the other endocrine glands, kidneys, and other underrepresented tissues require further research and validation before routine clinical implementation.

4. Expert Opinion

In TDT, regular monitoring and management of iron burden are the key to prevent long-term organ damage. Unlike traditional and no longer sustainable approaches that relied on invasive biopsy methods or indirect serum ferritin measurements, MRI provides reproducible, accurate, and non-invasive organ-specific assessments of iron deposition[110]. This capability is particularly critical due to the differences in iron uptake, transport, storage, and kinetics among the organs, which limit the possibility of using hepatic siderosis as an accurate marker of iron deposition in the other organs[6,7].

Cardiac and hepatic MRI are well-established and routine techniques and have been included in clinical guidelines on the basis of evidence that they have significantly contributed to reduce the organ damage and to improve the overall prognosis and quality of life of TDT patients[1,109]. Indeed, they quickly have become a cornerstone in establishing effective iron chelation regimens, enabling to tailor the therapy (type of chelator and dosage) to individuals' specific needs and to monitor the treatment efficacy. By tracking changes in iron levels, serial MRI assessments provide insights into the effectiveness of chelation regimens and enable timely adjustments[8,9,11,14]. In terms of follow-up, it is recommended to repeat the MRI annually after the first evaluation, with intervals ranging from six months to two years depending on clinical circumstances and resource availability[108]. For instance, MRI scanning should be performed every 6 months for high-risk patients (cardiac T2* <10 ms, reduced ejection fraction, poor compliance, or treatment interruptions), while a 2-year interval may be adequate for patients without hepatic and cardiac IO and with stable chelation. As regards as the assessment of pancreatic siderosis, its clinicopathological significance, prognostic value,

reproducibility, and transferability among different MRI platforms have been established[7,20,62,63,70,71,73], paving the way for its broader clinical adoption.

Advances in MRI technology have made protocols faster, simpler, and more cost-effective, leading to an increase in the number of centers worldwide that offer these examinations. Nevertheless, significant gaps remain, particularly in resource-limited settings where access to MRI remains constrained due to high costs, lack of trained personnel, and limited infrastructure. Addressing these barriers is essential to achieving equitable access to this key technology for all patients globally. Another key improvement to be achieved is the routine clinical implementation of iron quantification in the non-pancreatic endocrine glands, kidneys, and other underrepresented tissues. However, knowledge about iron deposition in the kidneys, adrenal glands, and pituitary gland remains limited. The functional implications of iron overload in these organs are poorly understood, and additional research is required to elucidate their roles in disease progression and patient outcomes. For these organs, there is also a complete lack of studies aimed at demonstrating the effect of specific chelators or their combinations in removing iron accumulation. Additionally, MRI protocols require ongoing standardization and validation to enhance their clinical utility and cross-platform consistency.

Artificial Intelligence (AI) is going to radically change the MRI field, improving image analysis and reducing diagnostic errors. AI algorithms could process and interpret image data, emulating human cognitive capabilities. Through training of deep learning models by labeled examples, AI is capable to directly extract complex information from raw image data. AI techniques are going to be applied in body iron quantification by several techniques[111]. In the MRI field, deep learning has already been applied to directly classify liver and cardiac IO[112,113]. Direct classification of IO from MRI images could provide a "second opinion" useful to identify human errors in the image analysis procedure and could also serve as an "external service" useful in centers with a small volume of patients to be referred for IO assessment. In the future, developing standardized protocols for AI models and addressing critical ethical concerns, such as data privacy and the implications of AI-driven decision-making, will be essential for ensuring its safe and effective integration into healthcare.

In summary, MRI has become a cornerstone in the management of TDT by enabling precise, non-invasive iron quantification. Continued advancements in technology, research, and clinical implementation—particularly for underexplored tissues—will further strengthen its role in improving outcomes for patients with iron overload. Overcoming accessibility challenges and standardizing protocols remain critical priorities to ensure that this transformative tool benefits patients worldwide.

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Declaration of interest

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FIGURE LEGENDS

Figure 1. Exemplification of the MRI T2* relaxometry technique for iron overload assessment in the liver. MRI images are acquired at increasing echo times (TEs) following the decay of the MRI signal, due to the progressive vanishing of tissue magnetization. In a patient without iron overload (A), the signal darkening is slower than in a patient with moderate iron overload (B). In general, the speed of the signal decay is proportional to the tissue iron content. The signal decay can be quantified by plotting the MR signal vs. TEs and fitting the decay curves with an appropriate exponential model, obtaining the T2* value (C).

Figure 2. Anatomical targets and sequences for MRI assessment of iron overload. Both T2 and T2* techniques are used in the liver and the bone marrow. The T2* technique is usually used for the pancreas, spleen, kidneys, and adrenal gland, while the T2 technique is employed for the pituitary gland. The T2* technique is the gold standard for myocardial iron overload assessment, but the complementary use of the T1 technique has been advocated to increase the sensitivity for mild iron levels.