



Role of cardiac MRI in the assessment of heart, liver, and pancreatic iron deposition among Egyptian transfusion dependent sickle cell disease

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وَقُلْ اَعْمَلُوا فَسَيَرَى اللّٰهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ



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List of Abbreviations

/s	Per second
ACS	Acute chest syndrome
AVN	Avascular necrosis
CMR	Cardiovascular magnetic resonance
Ct	Crista terminalis
CT	Computed tomography
CVA	Cerebrovascular accidents
DMT-1	Divalent Metal Transporter
Fe²⁺	Ferrous
fo	Oval fossa
GRE	Gradient echo
Hb	Haemoglobin
Hb S	Sickle haemoglobin
Hb S/β⁰ thalassaemia or Hb S/β⁺ thalassaemia	Hb S-beta thalassemia
Hb SC	Sickle-haemoglobin C disease
HIC	Hepatic iron content
HRCT	High resolution CT scan
LA	Left atrium
LIC	Liver iron concentration
LPI	Labile plasma iron
LV	Left ventricle
MR	Magnetic resonance
MRI	Magnetic resonance imaging
ms	milliseconds
NTBI	Non-transferrin bound iron

PH	Pulmonary hypertension
pRBCs	Packed red blood cells
RA	Right atrium
raap	Right atrial appendage
RBCs	Red blood cells
RES	Reticuloendothelial system
RF	Radiofrequency pulse
ROI	Region of interest
SE	Spin echo
SF	Serum ferritin
SI	Signal intensity
SIR	Signal intensity ratio
SPGR	Spoiled gradient echo
TE	Echo Time
TR	Repetition Time

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Abstract

20% of sickle cell disease (SCD) patients, receive chronic transfusion therapy to prevent further vascular sequelae. This transfusional iron leads to iron deposition in the spleen, liver, and bone marrow. In advanced cases iron also accumulates in parenchymal cells of the liver, heart, pancreas, and endocrine organs. serum ferritin was clinically used to estimate body iron stores; however, its measurement can be confounded by inflammation, abnormal liver function and ascorbate deficiency. Magnetic resonance imaging (MRI) has the ability of being non-invasive, inexpensive, reproducible with no exposure to radiation, is used to assess iron overload in different organs including liver, heart, and pancreas.

In our study, cardiac, hepatic, and pancreatic iron load among Egyptian sickle cell disease patients was assessed using MRI T2* relaxometry method, correlating pancreatic iron load to cardiac, hepatic iron load and to laboratory tests including serum ferritin. It enrolled 65 patients (32 females and 33 males) with median age group 14 years.

In conclusion, we found that MRI is essential for monitoring the overall iron balance in the body as well as for detection of extrahepatic iron deposition. No correlation between liver, heart, and pancreatic MRI T2* indicate that we can't rely only on liver MRI T2* to predict the exact overall condition of sickle cell patients in Egyptian population.

Keywords: MRI T2 *, Sickle cell disease, Ferritin, Iron load.

Introduction

Approximately 20% of sickle cell disease (SCD) patients, such as those with prior neurovascular events or abnormal transcranial doppler examinations, receive chronic transfusion therapy to prevent further vascular sequelae. However, routine transfusion therapy causes these patients to receive roughly 0.4 mg/kg/day of heme iron, which is over 25 times the physiological rate of iron absorption (**Brewer et al., 2009**). This leads to iron accumulation and damage in the liver, heart, and endocrine organs (**Carpenter et al., 2011**).

The human body has no mechanism for excreting excess iron, which is stored as crystalline iron oxide within ferritin and hemosiderin in the body. Transfusional iron leads to iron deposition in the reticulo-endothelial system of the spleen, liver, and bone marrow. In advanced cases iron also accumulates in parenchymal cells of the liver, heart, pancreas, and endocrine organs, which are sensitive to the toxic effects of iron. When the iron-binding capacity of transferrin is exhausted, free iron appears as non-transferrin bound iron (NTBI). The toxicity of NTBI is much higher than bound iron, and promotes hydroxyl radical formation resulting in peroxidative damage to membrane lipids and proteins. In the heart this results in impaired function of the mitochondrial respiratory chain and is manifested clinically as heart failure (**Anderson et al., 2001**).

The clinical manifestations of myocardial siderosis often occur late and once heart failure develops; the outcome is usually poor despite intensive chelation. This iron-induced cardiomyopathy, however can be reversed if intensive chelation is instituted at an early stage. Myocardial iron measurement can therefore play an important role in

assessing the prevalence of myocardial siderosis, predicting the risk of cardiac complications and the tailoring of cardiac optimized iron-chelating treatment (*He, 2014*).

Although serum ferritin is clinically used to estimate body iron stores, it reflects approximately 1% of the total iron storage pool and its measurement can be confounded by many conditions such as inflammation, abnormal liver function and ascorbate deficiency. In contrast to serum ferritin, liver iron can serve as a better indicator of whole body iron; however, liver iron does not reflect heart iron. Significant cardiac iron overload and toxicity can occur despite low liver iron concentration (*He, 2014*).

The disparity between cardiac and liver iron levels can best be explained by differences in mechanisms and kinetics of cardiac and hepatic iron uptake/clearance. Serial assessment of liver and cardiac iron demonstrates that cardiac iron changes lag corresponding changes in liver iron concentration (*Noetzli et al., 2008*).

The liver is the dominant storage organ for excess iron and acquires excess transferrin and non-transferrin bound iron; it also mobilizes iron rapidly and efficiently in times of demand or in response to iron chelation. In contrast, the heart has robust mechanisms to prevent excessive transferrin-mediated uptake. Pathologic myocardial iron overload occurs when iron binding capacity is saturated and labile free iron species begin to circulate. Even then, cardiac iron uptake is delayed compared to many other extrahepatic organs, including the pancreas. Thus, many young patients can exhibit severe hepatic iron loading with no evidence of cardiac iron loading (*Wood and Noetzli, 2010*).

Liver iron was assessed by needle biopsy or, more recently, by non-invasive magnetic resonance imaging

(MRI). As liver iron correlates with total body iron, an alternative to evaluating body iron overload is the measurement of liver iron concentration (LIC). MRI has the advantage of not being invasive and allows an anatomical view of iron overload in the liver. This method enables measurement of iron in milligrams per gram of tissue and estimates of the risk of organic diseases. This technique has also the advantage of being reproducible with no exposure to radiation (*Angulo et al., 2008*).

The measurement of cardiac iron posed a great challenge to the society. Not only endomyocardial biopsy is highly risky, but the measurement taken is also potentially inaccurate due to the small size of the sample obtained and heterogeneous deposition of cardiac iron. The introduction of cardiovascular magnetic resonance (CMR) provided a reliable measure of tissue iron and revolutionized our understanding and management of iron induced cardiomyopathy (*He, 2014*).

Magnetic resonance imaging has the ability of being non-invasive, inexpensive, and widely available in developed countries. It does not image the iron directly but instead images water protons as they diffuse near iron deposits in the tissue of interest. The iron acts as little magnets, destroying the homogeneity of the magnetic field in iron laden tissues. The moving water protons each experience significantly different magnetic profiles and become desynchronized from one another. This causes the image to darken at a rate proportional to the iron concentration (*Wood and Ghugre, 2008*).

Pancreatic iron overload can cause impairment of the exocrine and endocrine function of the pancreas leading to impaired glucose tolerance and diabetes mellitus. Early assessment of pancreas iron and tailored chelation could prevent diabetes and preserve pancreatic reserve. Moreover,