THE UNIVERSITY OF WESTERN AUSTRALIA

Iron overload: an elusive complication in sickle cell disease and thalassaemia

Tim St Pierre

School of Physics, Mathematics, and Computer Science

The University of Western Australia

ARISE

African Research And Innovative Initiative For Sickle Cell Education

Webinar 13th September 2023

Competing interests

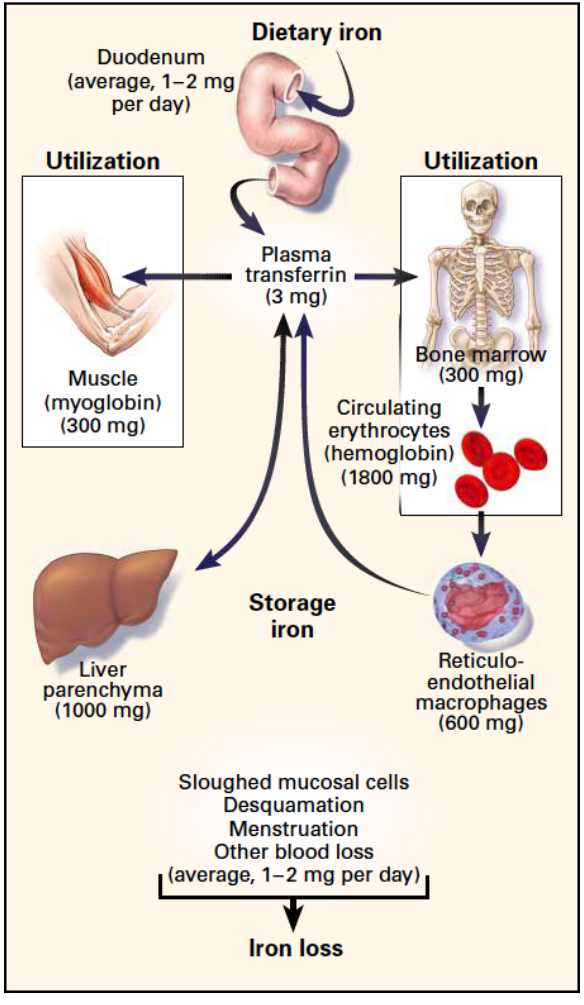
- I have part time employment with Resonance Health Analysis Services Pty Ltd (the providers of FerriScan®, FerriSmart®, and LiverSmart®)

Who am I?

- I am a physicist by training.
- I live and work in Australia.
- My research career has focused on measuring the properties and quantities of iron in biological tissues.
- I have worked with many medical practitioners on applications of magnetic resonance imaging to the measurement of iron concentrations in the human body.
- I have a strong interest in sickle cell disease and thalassaemia.

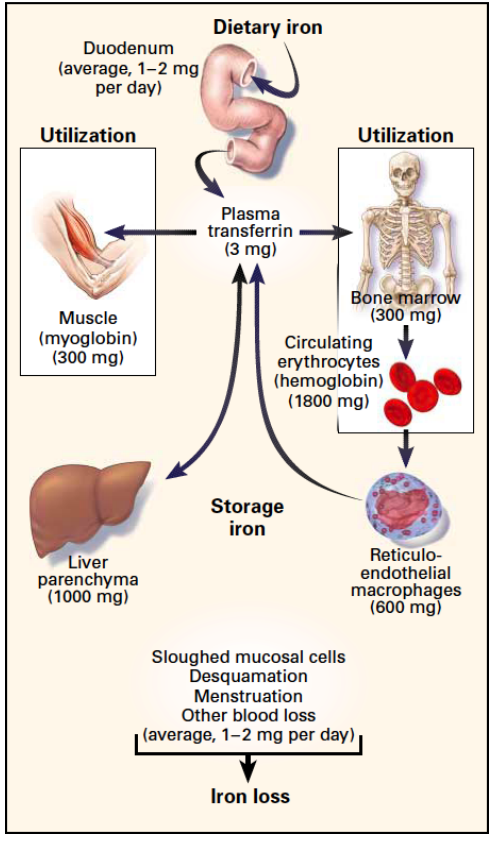
Healthy iron metabolism

- Things to note
  - Healthy human body cannot excrete iron
  - Iron stores controlled by controlling absorption
  - Between 4 and 6 g of iron in the healthy human adult
  - Most of the Fe is in haemoglobin or storage



Things that can go wrong!

- Genetic factors
  - Loss of iron absorption control
  - Haemoglobin structure
- Iron bypasses normal absorption mechanism
  - Blood transfusions
  - Iron infusions
- Infection
  - Parasites metabolize iron
- Other

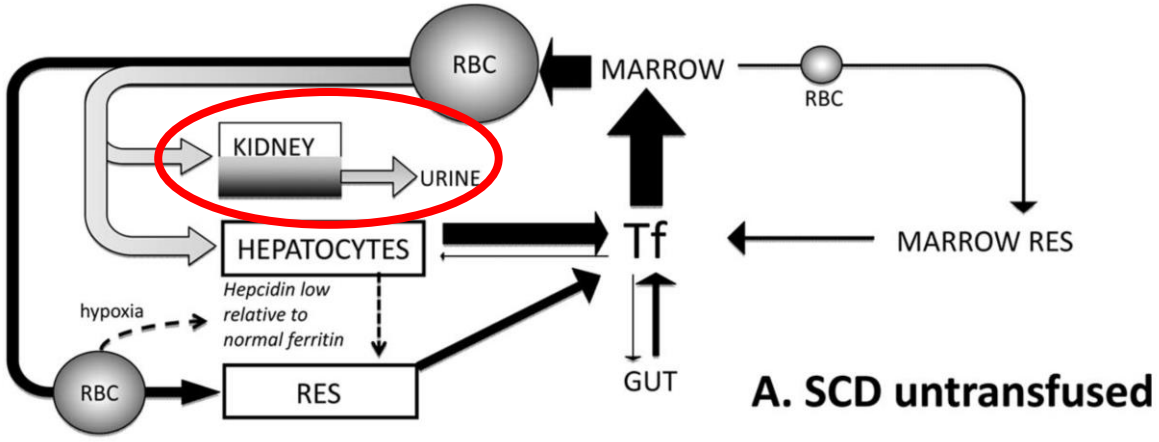


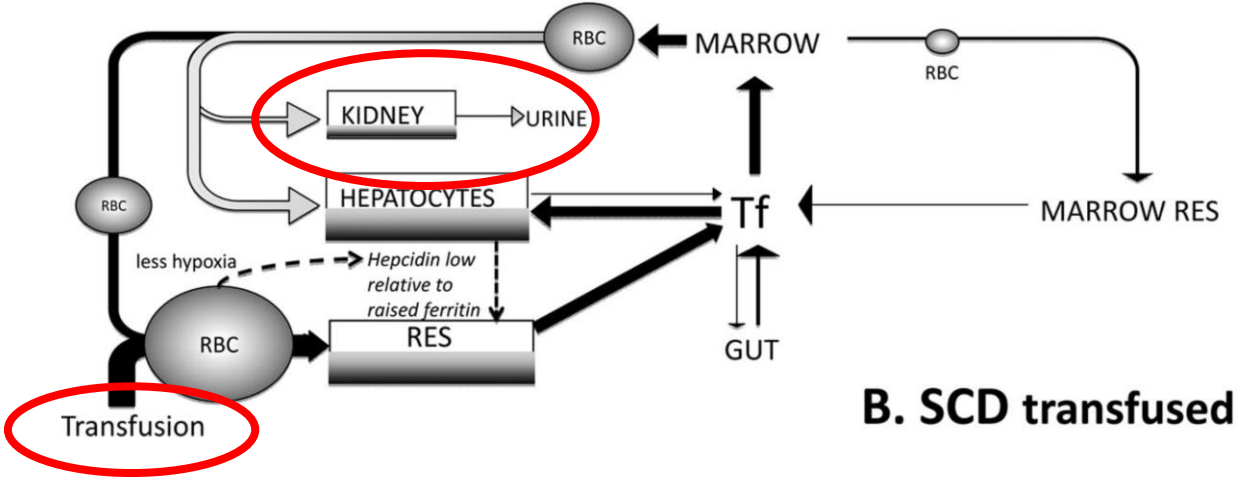
Urinary iron excretion in Sickle Cell Disease

- SCD involves intravascular hemolysis
- Untransfused patients with SCD excrete iron in the urine

Sears, et al. (1966) Blood, 28: 708.

Sickle Cell Disease



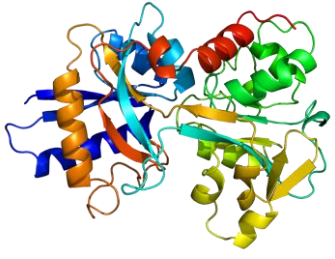


Porter and Garbowski (2013) Hematology, 2013: 447.

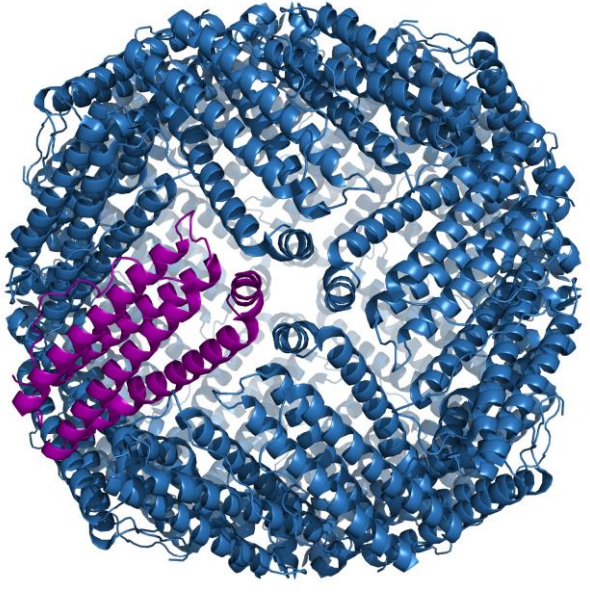
Under normal circumstances…..

Iron atoms in the human body are bound to biomolecules
(e.g the proteins transferrin and ferritin)

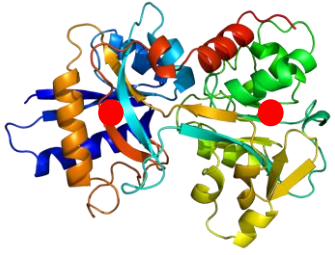
Transferrin



Ferritin

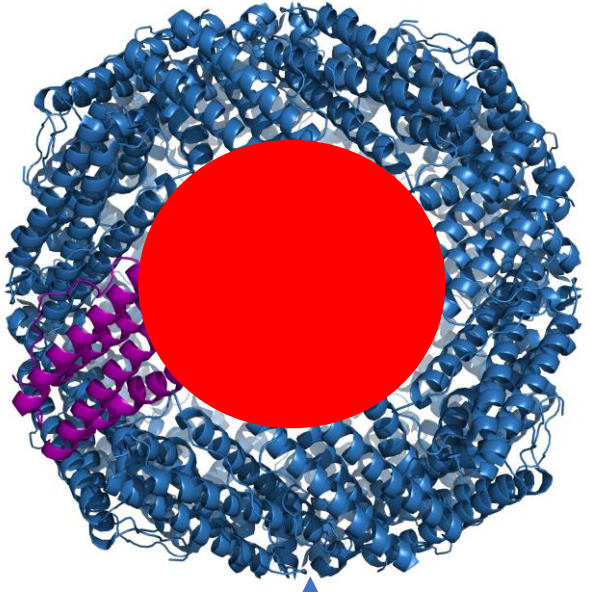


Transferrin



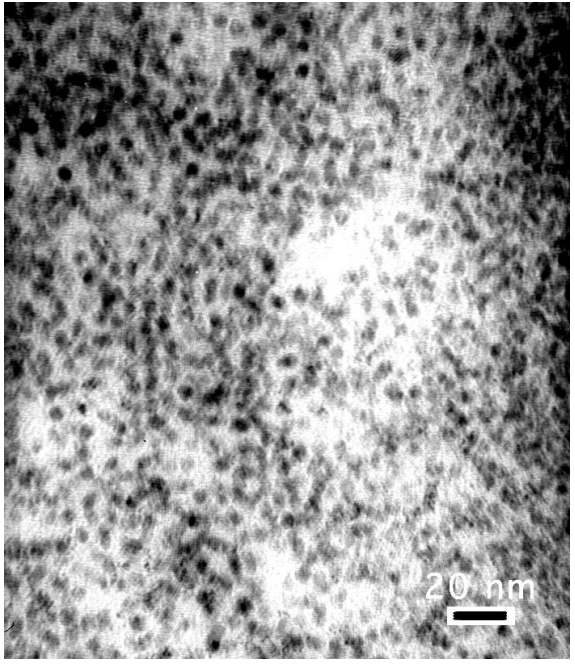
The body's iron "taxi".
Can carry up to two iron atoms.

Ferritin



Safe iron storage chambers.
Can store up to 3 or 4 thousand iron atoms.

Excess iron is primarily stored in the liver as a type of rust!



Transmission electron microscope image of iron loaded liver

Each blob in the image is a particle of rust containing about 3000 iron atoms

Unbound iron is toxic!

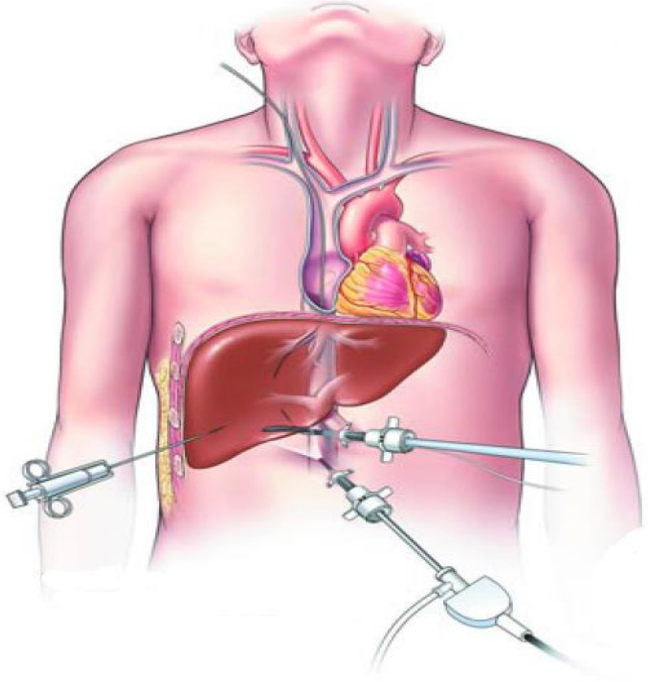
- At high concentrations of excess iron, not enough biomolecules to safely bind iron.
- A form of iron known as “non-transferrin-bound iron” or NTBI is released into the body
- NTBI can spread to other organs such as the heart and pancreas
- NTBI can cause cell damaging chemical reactions
  - => liver damage
  - => pancreas damage
  - => heart damage

How can we measure the concentration of iron in the liver?

- Liver biopsy
  - Cut out a piece of the liver and send to chemistry laboratory for analysis (Ouch!!)

- Exploit the magnetic properties of iron and measure non-invasively
  - Superconducting quantum interference device based magnetic susceptometry (SQUID)
  - Magnetic resonance imaging

Measuring liver iron concentration by biopsy



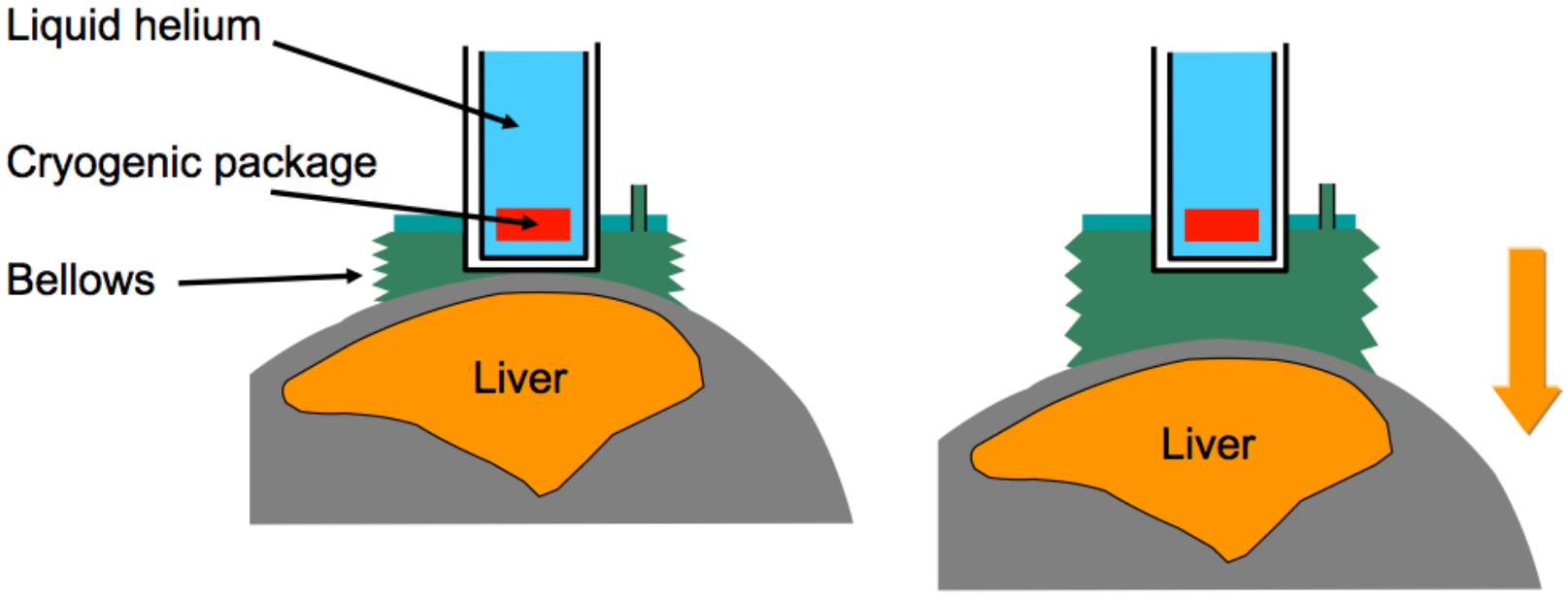
- Percutaneous
- Laparoscopic
- Transjugular

Major Complications

Death	1:10,000 – 1:12,000
Bleeding	1:100
Bile leak	1:1,000
Any pain	1:4
Significant pain	1:10 – 1:20

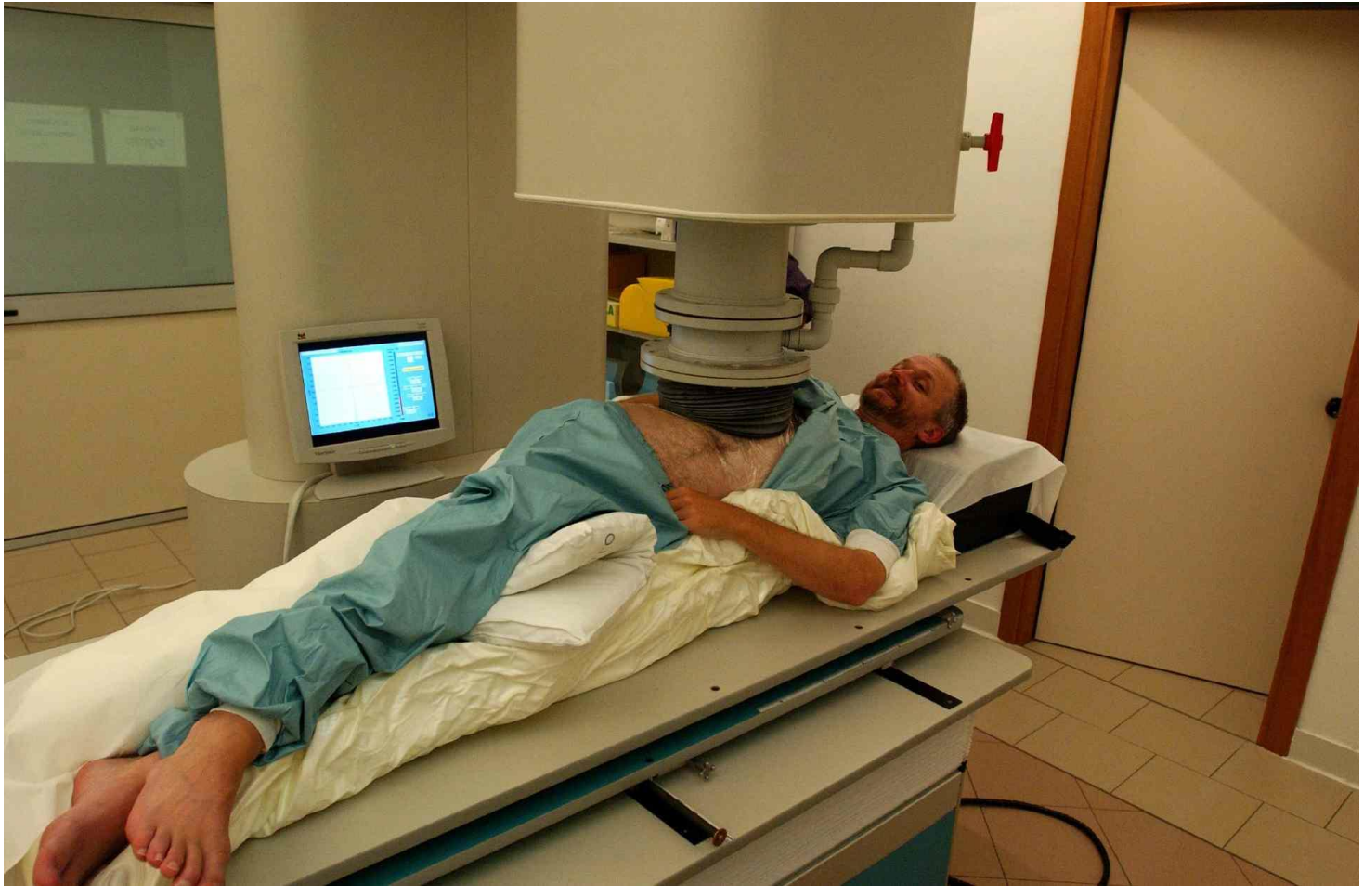
Siegel et al (2005) Cleveland Clinic J Med 72, 199-224

Biomagnetic liver susceptometry

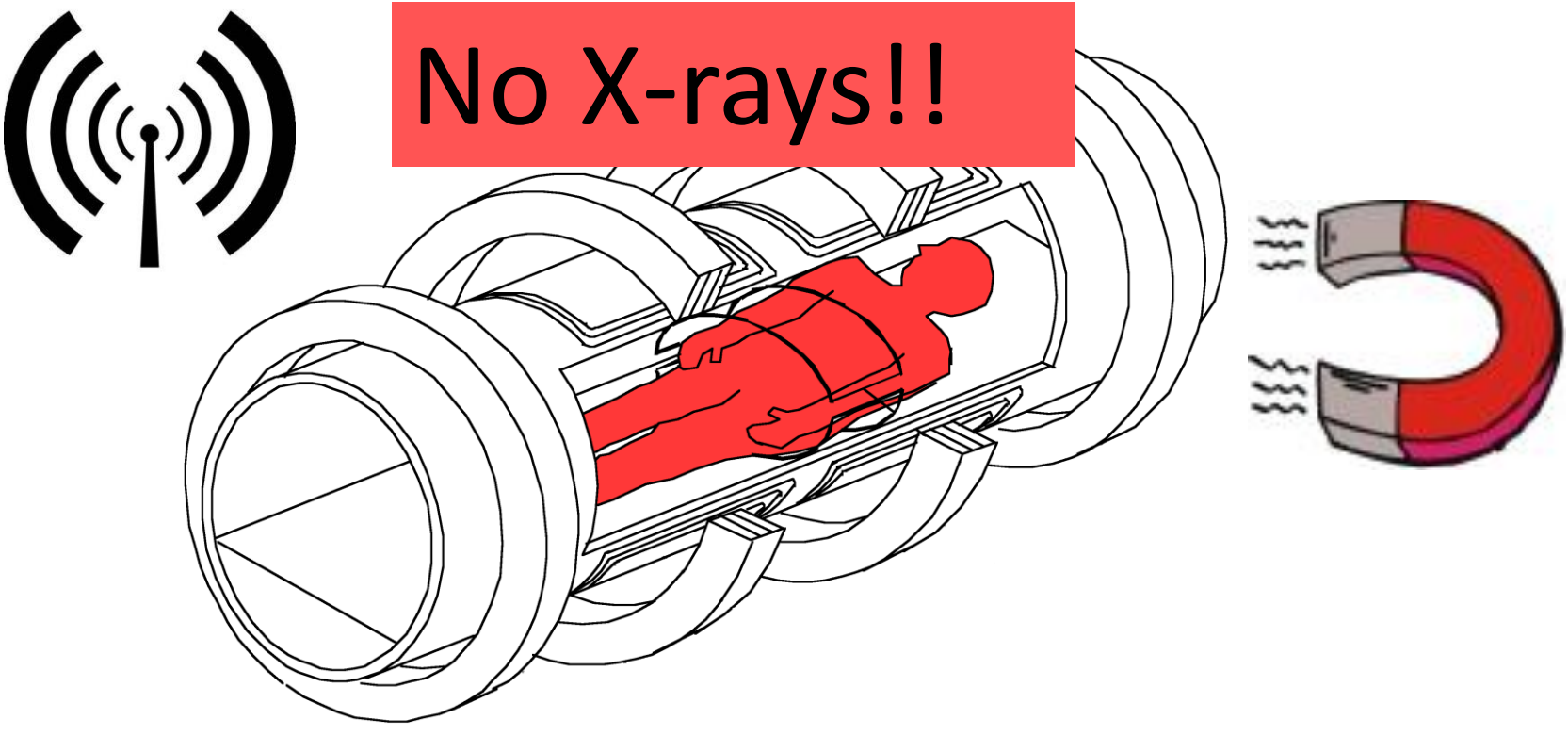


Fischer R. In: Andra W, Nowak H, editors. Magnetism in medicine: a handbook. Berlin: Wiley-VCH; 1998. p. 286-301.

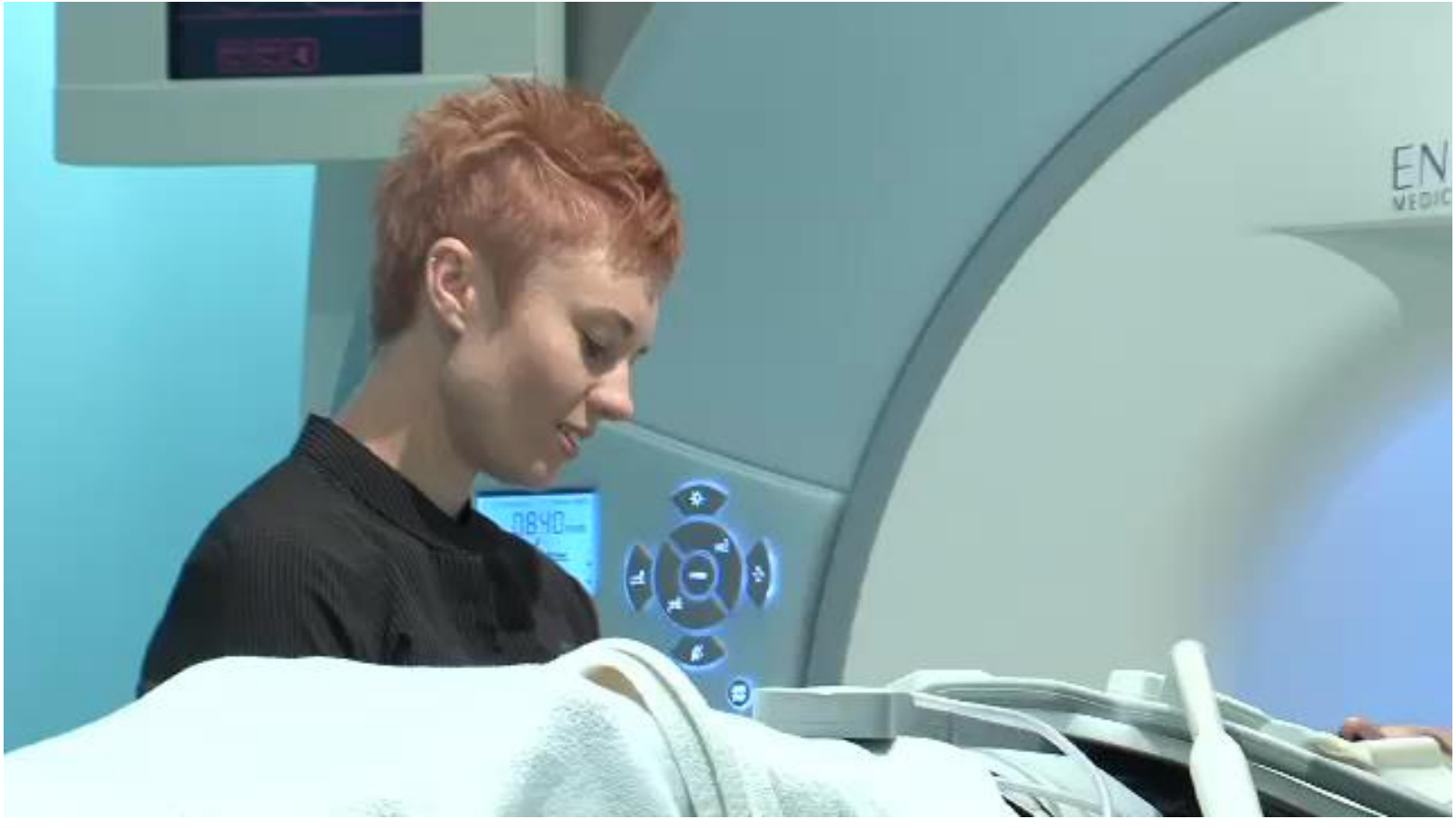
Biomagnetic liver susceptometry



Magnetic Resonance Imaging (MRI)

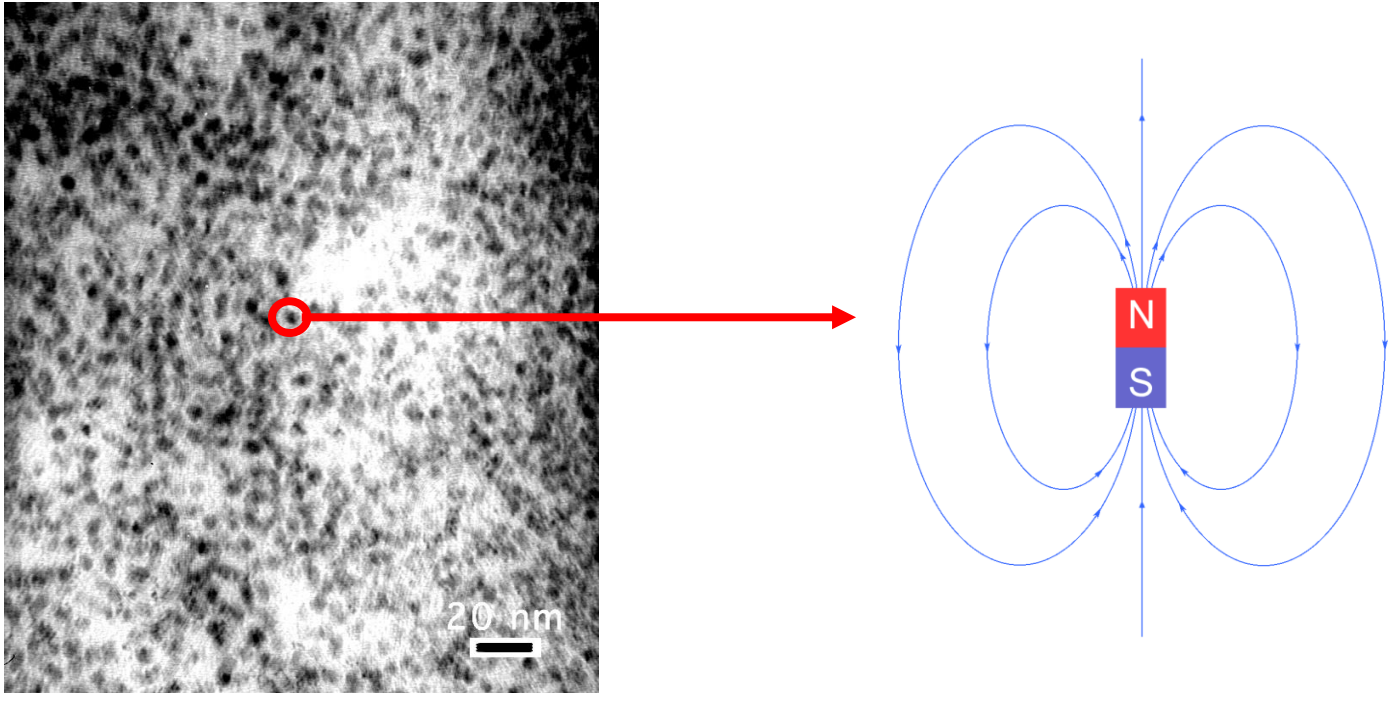


Magnetic Resonance Imaging (MRI)



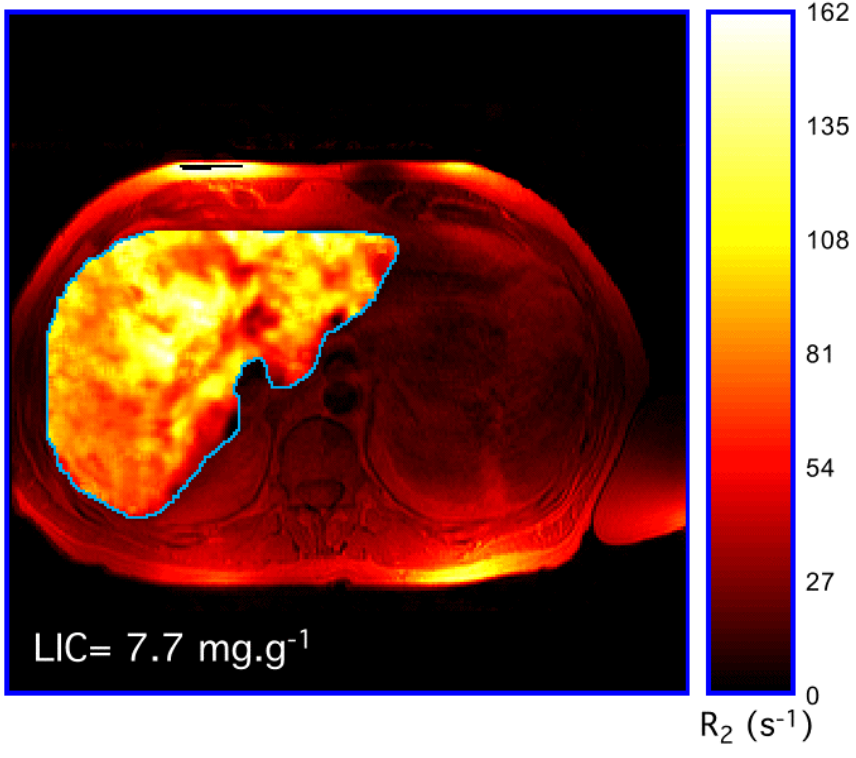
How can we use MRI to measure the concentration of iron in the liver?

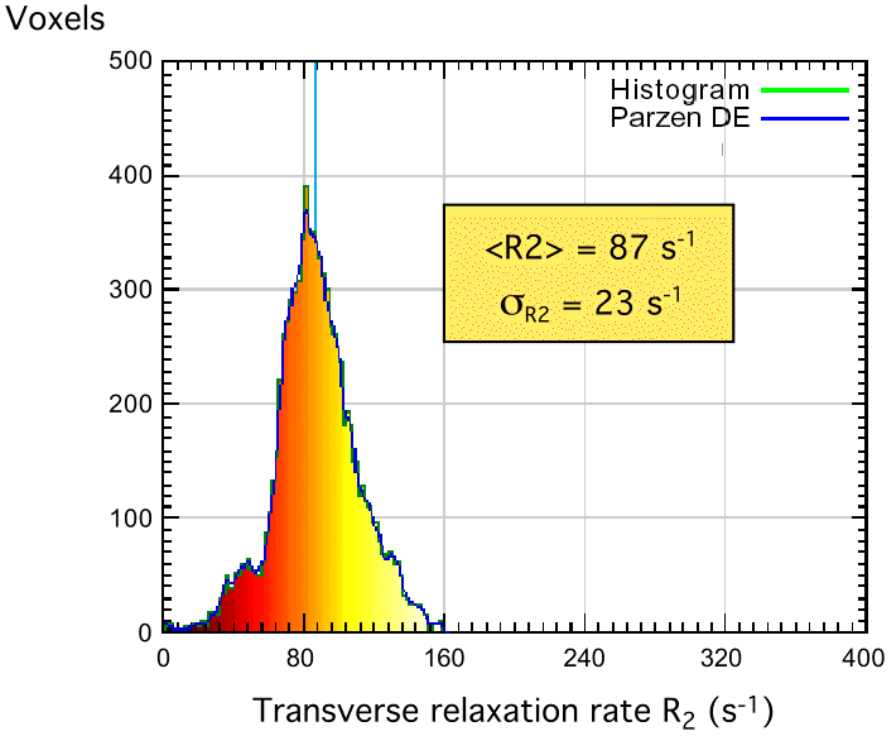
In a magnetic field, the rust particles in the liver become small magnets!



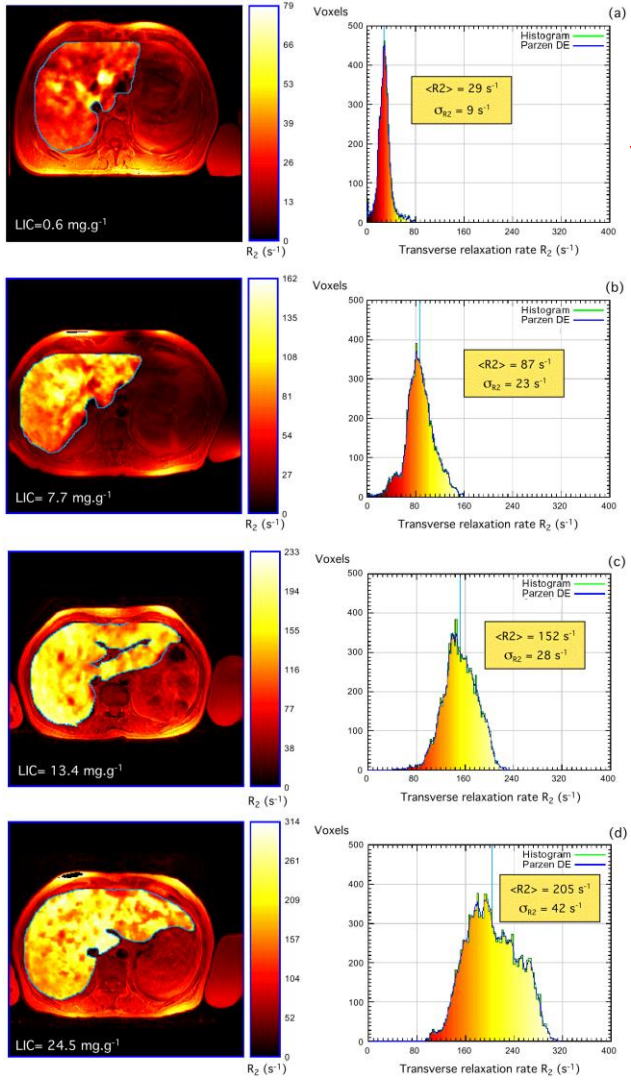
Transmission electron microscope image of iron loaded liver

FerriScan® - a way of using the MRI to sense the concentration of magnetic rust particles





FerriScan®



Normal iron

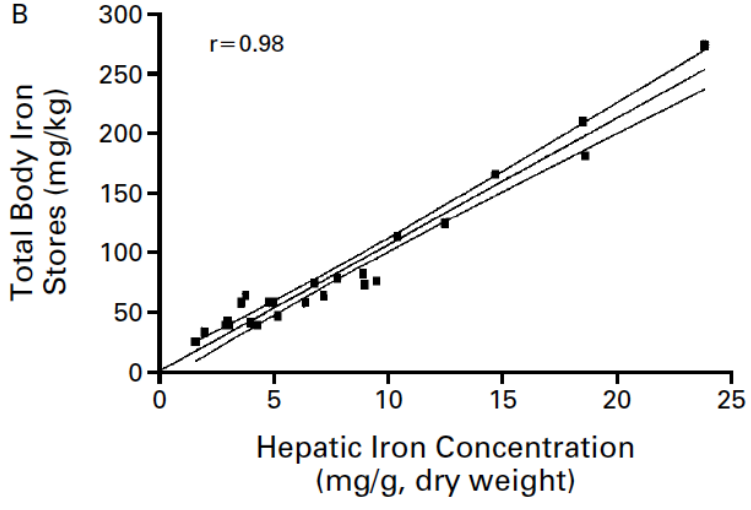
Very high iron

How can measuring liver iron concentration be useful in relation to sickle cell disease (and thalassaemia)?

Transfusional iron overload

- Patients receiving multiple blood transfusions are at risk of iron overload
- One unit of red cells delivers approx 200 - 250 mg of iron to the body
- The human body generally has no natural mechanism for excreting iron
- Iron chelation therapy is necessary to prevent iron-related tissue damage

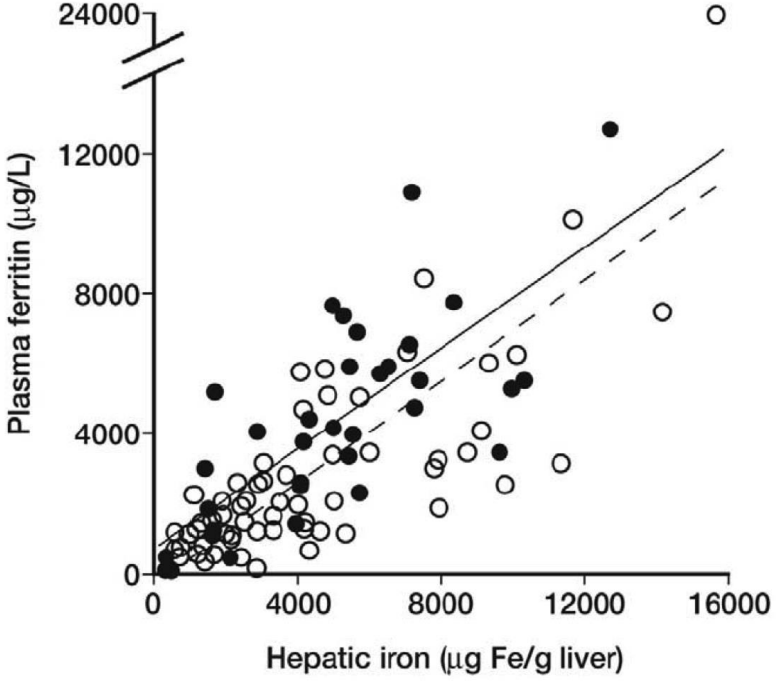
LIC is a reliable measure of total body iron stores (TBIS) in patients with thalassaemia major



There is a very strong correlation between LIC and total body iron stores in thalassaemia major patients

Angelucci et al (2000) N Eng J Med 343, 327

Is serum ferritin a reliable indicator of LIC?

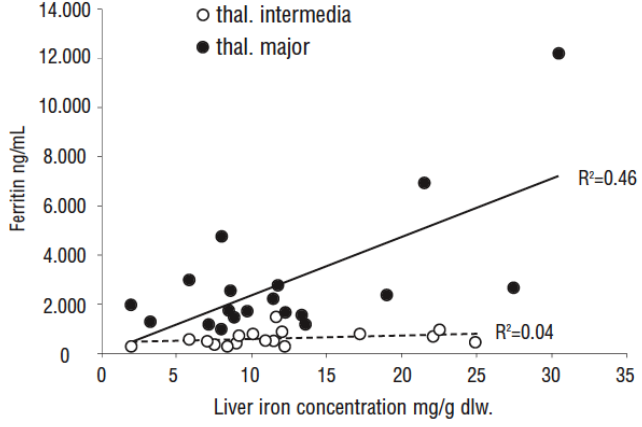


- There is a weak correlation between SF and LIC in the population of thalassaemia major (o) and sickle cell anaemia patients (•)
- For individuals, SF is an unreliable indicator of LIC and TBIS

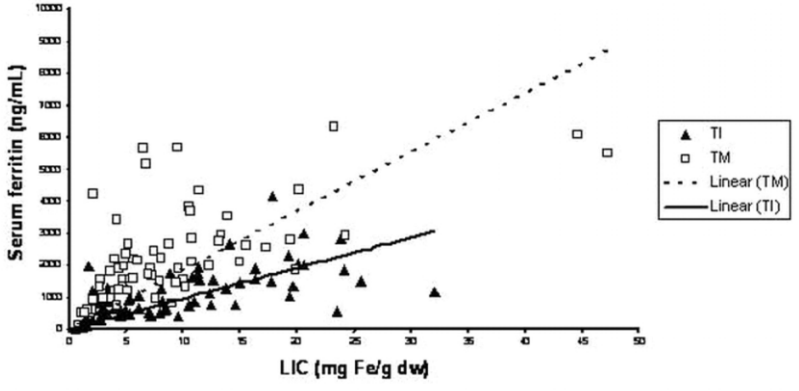
Brittenham et al, Am J Hematol 1993: 42, 81-85.

Serum ferritin in thalassaemia major and intermedia

- Serum ferritin has almost no sensitivity or specificity for iron stores in thalassemia intermedia

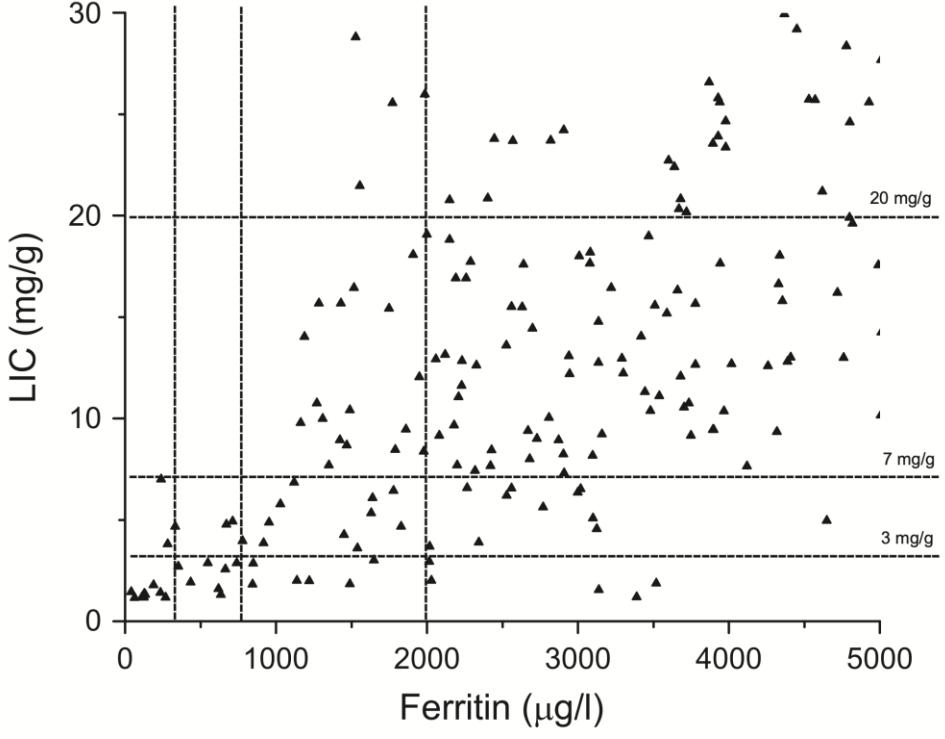


Origa et al, Haematologica 2007: 92, 583-588.



Taher et al, Haematologica 2008: 93, 1584-5.

Relationship of LIC to serum ferritin in SCD

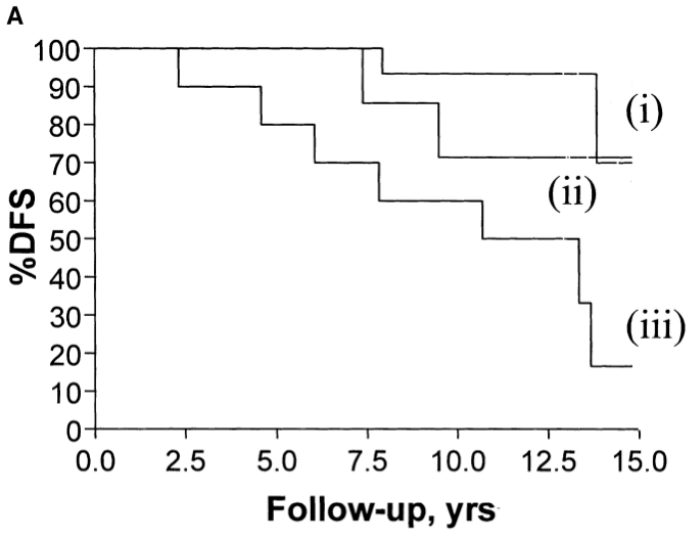


Coates and Wood (2017) Br J Haematol, 177: 703.

Why is it important to control total body iron stores?

- Free iron (labile iron) causes tissue damage
- Tissue iron deposits are a source of free iron
- The liver is the primary site of iron storage
- If liver iron storage capacity is exceeded, iron is deposited in other tissues of the body including the heart
- Iron deposits in the heart are associated with heart failure
- Excess iron in the liver can induce fibrosis and cirrhosis

LIC and long-term prognosis in thalassaemia major



32 thalassaemia major patients followed for median period of 13.6 years after single biopsy LIC measurement

Telfer et al (2000) *BJH* 110: 971-977

LIC (mg Fe/g dw)	13 year Cardiac Disease Free Survival	Number Patients	Group
< 7	93.3% (SE 6.4)	15	(i)
7 – 15	71.4% (SE 17.1)	7	(ii)
> 15	50.0% (SE 15.8)	10	(iii)

Cardiac iron loading in SCD is rare

- Several studies show that extrahepatic consequences, particularly endocrine and cardiac effects of iron overload, are lower or more delayed in SCD than in thalassemia major [1].

- While rare, iron cardiomyopathy is detectable in about 2.5% of chronically transfused SCD patients [2].

1. Porter and Garbowski (2013) Hematology, 2013: 447.
2. Meloni, et al. (2014) American Journal of Hematology, 89: 678.

LIC thresholds and associated risks Transfusional Iron Overload (thalassaemia)

LIC threshold (mg Fe/g dry weight)	Clinical relevance
1.8	Upper 95% of normal
3.2	Suggested lower limit of optimal range for LICs for chelation therapy in transfusional iron overload[1]
7.0	Suggested upper limit of optimal range for LICs for transfusional iron overload and threshold for increased risk of iron-induced complications[1]
15.0	Threshold for greatly increased risk for cardiac disease and early death in patients with transfusional iron overload[1]

1. Olivieri and Brittenham, Blood. 1997;89:739-61.

LIC thresholds and clinical relevance Non-Transfusion-Dependent Thalassemia

LIC threshold (mg Fe/g dry weight)	Clinical relevance
1.8	Upper 95% of normal
3.0	Threshold below which deferasirox treatment for NTDT patients should be interrupted[1]
5.0	Threshold above which iron chelation therapy with deferasirox can be considered for patients with NTDT[1]
15.0	Baseline LIC above which increase of deferasirox dose to 20 mg/kg/day should be considered after first 4 weeks of therapy for NTDT patients[1].

1. FDA (2013) Exjade Label: FDA Reference ID: 3393658.

Why is measurement of liver iron concentration (LIC) important?

- A patient's LIC value is the best measure of total body iron stores
- A patient's LIC value enables better informed decisions on when to
  - Initiate chelation therapy
  - Increase chelation dose
  - Decrease chelation dose
  - Change mode of chelator delivery (e.g. iv mode)

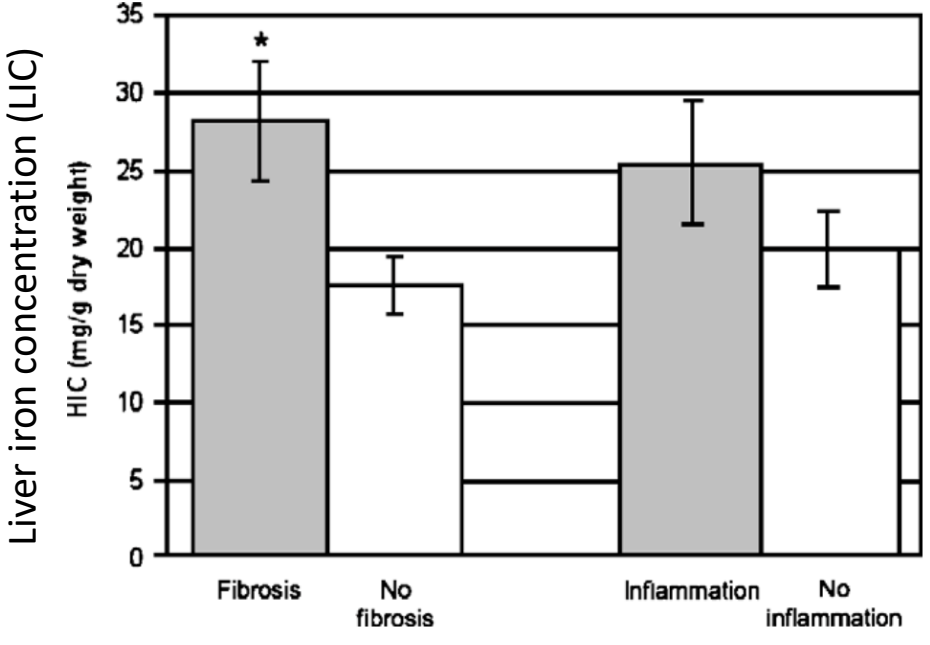
Are there any LIC thresholds specific to SCD?

Progression of iron overload in SCD

- Olivieri (2001) obtained 42 biopsy specimens from 20 patients with SCD (mean age, 15.7 years) who received transfusions.
- Both liver iron concentration and the presence of fibrosis by histology were obtained from the biopsy specimens.
- Liver iron concentration in patients in whom fibrosis was observed varied from **8.9** to 37.7 mg Fe / g dw.
- Olivieri noted that the lower threshold of 8.9 mg Fe/g dw was similar to the threshold of 7 mg Fe/g dw seen for thalassaemia major patients.

Olivieri (2001) Semin Hematol, 38: 57.

Association of liver fibrosis with LIC in SCD (USA)

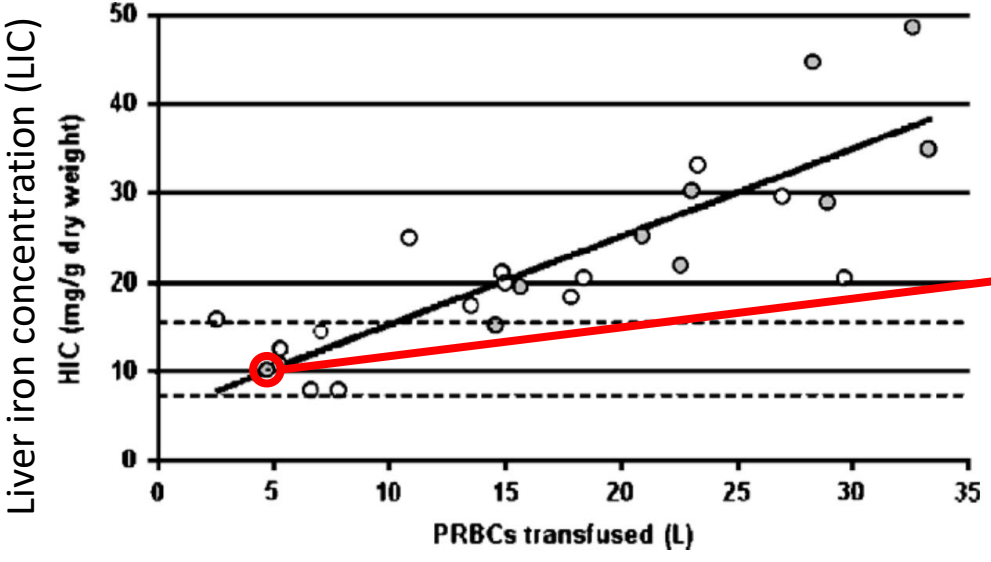


- Children with SCD (n=27)
- Mean age 11.0 ± 3.3 years
- Chelation naïve
- All negative for HIV, Hep B, Hep C
- Chronic transfusion therapy
- Mean duration transfusion 50 ± 27 mnths
- Total vol of transfusions 17.4 ± 9.6 L

- LIC measured from biopsy
- Fibrosis assessed from biopsy

Brown, et al. (2009) J Pediatric Hematol Oncol, 31: 309.

Association of LIC with volume of PRBCs transfused during chronic transfusion regime



Greyed circles = fibrosis present

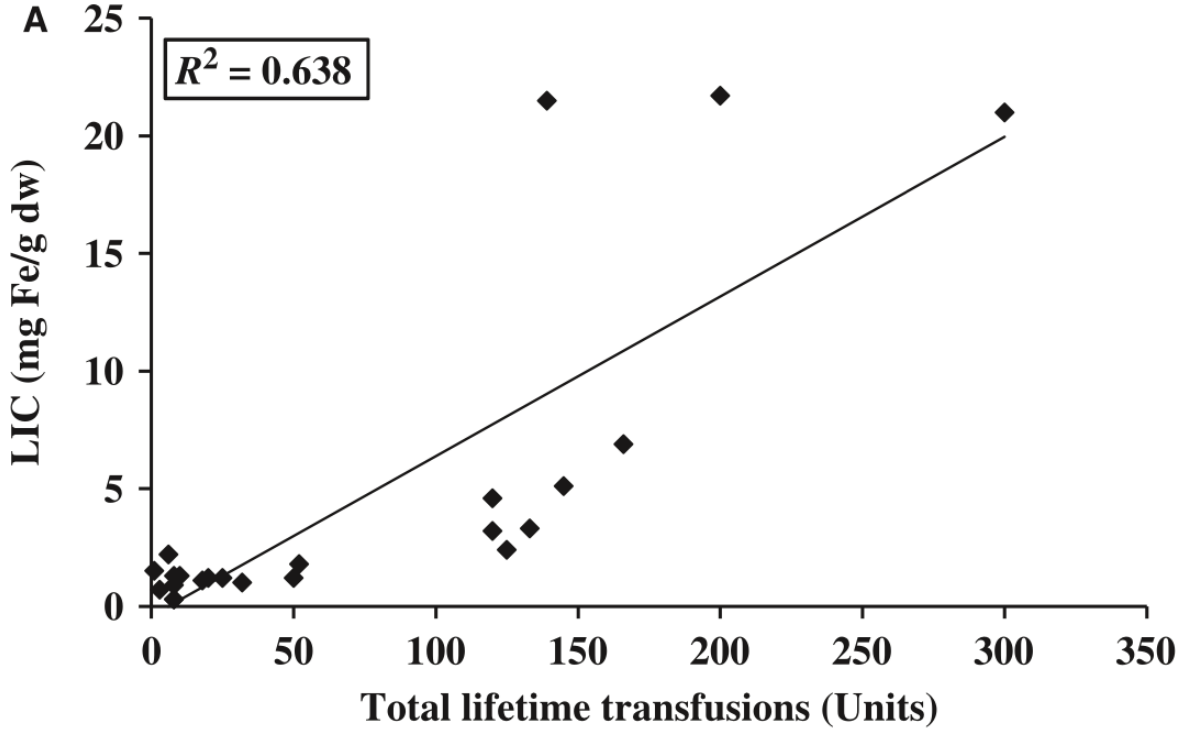
Fibrosis first seen at about 10 mg Fe/g dw

Threshold very similar to that found by Olivieri (2001)

Brown, et al. (2009) J Pediatric Hematol Oncol, 31: 309.

Is LIC always associated with number of transfusions received in SCD?

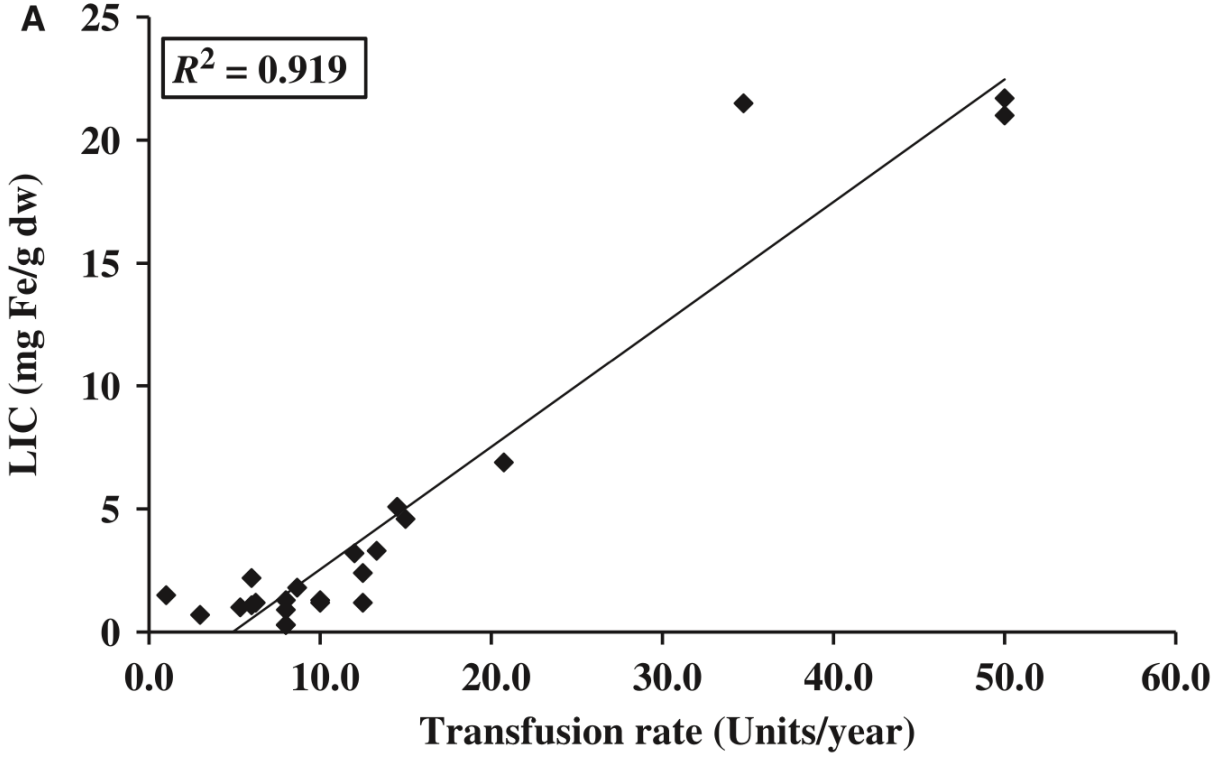
Association of LIC with units transfused in non-chelated SCD patients (Lebanon)



Correlation not as good as the USA chronic transfusion study

Inati, et al. (2009) Eur J Haematol, 83: 565.

LIC more closely associated with RATE of transfusion



LIC rises when transfusion rate >10 units/year

Implies spontaneous iron losses of up to 0.11 mg/kg/d (urinary?)

Inati, et al. (2009) Eur J Haematol, 83: 565.

What is the situation with iron overload and SCD in Africa?

Reasons for blood transfusions in SCD in Africa

- Chronic blood transfusion programmes either as prophylaxis or treatment are not common in Nigeria. (Odunlade et al, 2017))
- Most children with SCD in Nigeria receive episodic blood transfusions as needed for the treatment of severe anaemia associated with infections, especially malaria. (Odunlade et al, 2017))
- Transfusion is mainly used for acute anaemic complications in Africa, especially in children who suffer from infections such as malaria, splenic sequestration or acute hemolysis. (Diop and Pirenne, 2021)

Odunlade, et al. (2017) Pediatric Hematol Oncol J, 2: 35.
Diop and Pirenne (2021) Transfusion Clinique et Biologique, 28: 143.

Studies of iron status among SCD children in Nigeria

Source	Age range	No SCD children in study	Conclusions
Jeyakumar et al (1987)	<10	24	High prevalence of Fe deficiency
Akodu et al (2013) Olufemi et al (2021)	up to 5	97	High ferritin in SCD => higher iron content in RES
Odunlade et al (2017)	1 - 15	48	High ferritin in SCD => excessive iron in RES*

Odunlade and colleagues note:

- High ferritin may be a false positive elevation secondary to inflammation.
- LIC measurement by MRI planned for future studies

Jeyakumar, et al. (1987) J Trop Pediatrics (1980), 33: 326.
Akodu, et al. (2013) Anemia, 2013: 254765.
Olufemi, et al. (2021) African Health Sciences, 21: 753.
Odunlade, et al. (2017) Pediatric Hematol Oncol J, 2: 35.

Summary

- Liver iron concentration can be used to
  - Assess total body iron stores;
  - Identify patients at risk of iron-related morbidity and mortality;
  - Make better informed decisions on when to initiate chelation therapy, and when to increase or decrease chelation dose;
  - Assess the risk of the presence of liver fibrosis;

- Liver iron concentration (LIC) can be non-invasively measured using MRI scanners.

THE UNIVERSITY OF WESTERN AUSTRALIA

Thank you for joining the webinar today

Tim St Pierre

Tim.StPierre@uwa.edu.au

Webinar 13th September 2023

ARISE

African Research And Innovative Initiative For Sickle Cell Education