IRON OVERLOAD

DR.Baghersalimi

1400

IRON OVERLOAD

- Iron overload is inevitable in thalassemia major and intermedia
- Blood transfusion being the major cause of iron overload in TM and increased GI absorption being more important in TI
- Human body lacks a mechanism to excrete excess iron
- Iron accumulation is toxic to many tissues, causing heart failure, cirrhosis, liver cancer, growth retardation and endocrine abnormalities

IRON OVERLOAD

- Chelation therapy aims to balance the rate of iron accumulation by increasing iron excretion in urine /stool with chelators
- A key challenge is to balance the benefits of chelation therapy with side effects of excessive chelation
- The second major challenge is to achieve regular adherence to treatment throughout life
- Even short periods of treatment interruption can have damaging effects
- Convenience and tolerability of drugs , psychological well being and family and institutional support impact on adherence and outcomes.

The Rate of Iron Loading

Blood transfusion

- A unit of PC contains 200 mg of iron
- According to the routine transfusion scheme, this is equivalent to 116-232 mg of iron/ kg Wt/year
- Regular blood transfusion therapy therefore increases iron stores to many times
- In TM, the iron absorbed from GI is small

The Rate of Iron Loading

Increased gastrointestinal absorption of iron

- Normal GI iron absorption is about 1-2 mg/day
- In TI, iron absorption increases several-fold
- Transfusion to keep the pre-transfusion Hb > 9 g/dl have been prevent such expansion
- In TM with poorly transfused, absorption rises to 3-5 mg/day or more, or additional 1-2 g of iron loading per year

The Rate of Iron Loading

Table 1. Iron loading rates in the absence of chelation.

PATIENTS WEIGHT	20 kg	35 kg	50 kg	65 kg
Pure red cell volume ml/ year	2,000-4,000	3,500-7,000	5,000-10,000	6,500-13,000
Yearly iron loading (g)	2.3-4.6	4.1-8.2	5.8-11.6	7.5-15.1
Daily Iron loading (mg)	6.3-12.6	11.2-22.5	15.9-31.8	20.5-41.4

Toxicity from Iron Overload

Mechanisms of iron toxicity

- Iron is highly reactive and, generates harmful free radicals
- These can damage lipid membranes, organelles and DNA, causing cell death and fibrosis
- In health, iron is 'kept safe' by binding to molecules such as transferrin,
- In TM the capacity to bind iron is exceeded
- The resulting 'free iron', damages many tissues unless treated by iron chelation therapy
- Free iron also increases the risk of infections and neoplasia

Toxicity from Iron Overload

Distribution and consequences of iron overload

- In iron overload, transferrin becomes saturated and iron are present in plasma (NTBI)
- The distribution of NTBI is different from transferrin uptake
- Organ damage in TM reflects the pattern of tissue iron uptake from NTBI
- Some tissue are spared such as skeletal muscle, **BUT:**
- Myocardial muscle, endocrine tissue and hepatocytes take up NTBI rapidly
- This iron is then stored as ferritin or hemosiderin

Toxicity from Iron Overload

- The myocardial iron overload can induce heart failure in patients without chelation in as early as the second decade of life
- Iron overload also causes pituitary damage, leading to hypogonadism, growth retardation and delayed puberty
- Endocrine complications such as diabetes mellitus, hypothyroidism and hypoparathyroidism are also seen
- Liver disease with fibrosis and eventually cirrhosis and hepatocellular carcinoma, particularly if concomitant chronic viral hepatitis is present, are also seen

Monitoring of Iron Overload

Serum ferritin

Why measure serum ferritin?

- Serum ferritin (SF) generally correlates with body iron stores,
- and is relatively easy and inexpensive to determine repeatedly.
- Serum ferritin is most useful in identifying trends.
- Decreasing trend in SF is evidence of decreasing body iron

But:

- Absence of a decreasing trend does not exclude a decreasing iron burden
- Increasing SF trend implies an increasing iron burden but:
- May also be due to inflammation or tissue damage

Monitoring of Iron Overload

Why measure serum ferritin?

- Long term control of SF is also a useful guide to the risk of complications from iron overload
- There is an association between the control of ferritin and prognosis
- There is a significantly lower risk of cardiac disease and death where ferritin <2,500 over a period of a decade or more
- Maintenance of an even lower ferritin of 1,000 may have additional clinical advantages

Monitoring of Iron Overload

What are the limitations of serum ferritin measurements?

- SF measures do not always predict body iron or trends
- In TM, variation in body iron accounts for only 57% of the variability in serum ferritin .
- This variability is in part because inflammation increases serum ferritin, and partly because the distribution of liver iron between macrophages and hepatocytes has impact on serum ferritin.
- A sudden increase in ferritin should prompt a search for hepatitis, other infections, or inflammatory conditions.
- A lack of fall in SF with chelation does not therefore prove that the patient is a 'non responder'

Monitoring of Iron Overload

What are the limitations of serum ferritin measurements?

- Body iron can fall considerably from a high starting point before a change in ferritin is clear
- The relationship between ferritin and body iron stores may also vary depending on the chelator used and by duration of chelation therapy

Table 2. Use of serum ferritin for monitoring chelation treatment.

ADVANTAGES	DISADVANTAGES
Easy to assess repeatedly	Indirect estimate of iron burden
Inexpensive	Increased by inflammation
Trend identification possible with repeat samples	Cannot determine iron balance directly
Long term control linked to outcome	Non-linear response to iron load at high
Useful for dose adjustment as iron levels fall	Absence of decrease doesn't exclude response
	Relationship to iron load varies with chelator
	Relationship to LIC differs in different diseases

Liver iron concentration (LIC) measurement

Why monitoring liver iron concentration?
– To identify whether body iron is adequately controlled

- Adequate control of LIC is linked to hepatic as well as extrahepatic
- Normal LIC values are up to 1.8 mg/g dry wt, with levels of up to 7 mg/g dry wt seen in some population
- High LIC (> 15-20 mg/g dry wt) have been linked to worsening prognosis, liver fibrosis or liver function abnormalities .
- However, the relationship between LIC and extra-hepatic iron is complicated by chelation therapy as iron tends to be accumulate initially in the liver and later in the heart but also is removed more rapidly from the liver than the heart by chelation therapy
- Thus, in patients receiving chelation therapy, whilst high LIC increases the risk of cardiac iron overload, the measurement of LIC will not predict myocardial iron, and myocardial iron may be found despite well controlled LIC.

Liver iron concentration (LIC) measurement

Why monitoring liver iron concentration?
– To determine iron balance: is body iron increasing or decreasing on current therapy?

- LIC is the most reliable indicator of body iron load
- Total body iron stores in mg iron /kg body wt = 10.6 x LIC
- Sequential LIC measurement is the best way to determine iron balance
- LIC determination should be considered for those patients whose serum ferritin levels deviate from expected trends

Liver iron concentration (LIC) measurement

Why monitoring liver iron concentration?

– To determine iron balance: is body iron increasing or decreasing on current therapy?

- At high levels of SF (>4000), the relationship to LIC is not linear and patients may show a fall in LIC without a clear trend in SF in the first 6-12 months

Methods for measuring LIC

Biopsy

- Biopsy is an invasive procedure . Inadequate sample size (or uneven distribution of iron, particularly in the presence of cirrhosis , may give misleading results however. Biopsy also allows the evaluation of liver histology

SQUID Superconducting quantum interference device is very expensive

MRI

- Are now becoming the most widely used for LIC determination.
- The first widely used technique was the T2* technique
- Unfortunately T2* can underestimate LIC by two-fold. Therefore may underestimate LIC
- The R2 technique have acceptable linearity up to LIC values of about 30 mg/g dry wt

Myocardial iron estimation: MRI T2*

- The risk of developing heart failure increases with T2* values <10 ms, and associated with a 160 fold increased risk of heart failure in the next 12 months
- This risk increases progressively with T2* values <10
- Risk may be less in patients taking regular chelation
- In patients with severe cardiac iron load (T2* <10 ms), no patients developed heart failure over a 2 years period while on iron chelation therapy

Medical Imaging Center

Date	20140929
Admission Number	930707026
Name	FOROOGH POORBORZO
Date of Birth	19910101
Height (cm)	151
Weight (kg)	45
Sex	Female

Dear Dr. Baghersalimi

Technique

ECG gated cardiac MR images were obtained for T2 calculation. Short axis images were prepared in different sequences.*
T2 and "Iron Load" values were calculated by "CMR Tools" software.*

Findings

Organ	T2* (ms)	Loading (mg/g/dw)
Heart	22.66	
Liver	2.06	6.643281

Interpretation

Cardiac Iron Load: ***Normal***
Hepatic Iron Load: ***Moderate***

with Best Regards

S Akhlaghpoor MD
Radiologist

A Shirkavand
Physicist

Guidelines for Iron Assessment

Myocardial Loading	Myocardial T2* (ms)
Normal	>20
Mild	14-20
Moderate	10-14
Severe*	<10

Hepatic Loading	Hepatic T2* (ms)	Dry Weight
Normal	>6.3	<2
Mild	2.8-6.3	2-5
Moderate	1.4-2.7	5-10
Severe	<1.4	>10

** In 89% of patients with heart failure, cardiac T2* is <10ms.*

آدرس : تهران ، خیابان سعادت آباد ، خیابان بیست و پنجم (شهید قره تپه ای) ، پلاک ۰۵
تلفن : ۸۸۶۸۷۹۷۰ ، ۸۸۶۸۶۵۸۴ ، ۸۸۶۸۴۷۰۶ ، ۸۸۶۸۶۵۷۳ فکس : ۸۸۶۸۷۹۶۶
No.5 , 25th St ., Saadat - Abad Ave., Tehran , Iran .
Tel: 88687970 , 88686584 , 88684706 Fax:88687966

Table 4. MRI T2* method to assess myocardial iron.

ADVANTAGES	DISADVANTAGES
Rapidly assessed iron content in myocardial septum	Indirect non-linear relationship with myocardial iron
Reproducible method	Requires a validated centre with dedicated methods
Linked to heart iron (reciprocal relationship)	Technically demanding
Potential to measure heart function at same visit	Methodology requires standardisation worldwide
Potential to measure LIC at same visit	Does not predict liver body iron overload
Linked to LVEF at time of measurement	Requires continuous quality assurance such as regular phantom scanning
Linked to risk of heart failure in next year	

Cardiac function

- Sequential monitoring of LVEF has been shown to identify patients at high risk of developing clinical heart failure
- When LVEF fell below reference values, there was a 35-fold increased risk of clinical heart failure and death, with a median interval to progression of 3.5 years, allowing time for intensification of chelation therapy
- This approach required a method for determination of LVEF (such as MRI),
- Echocardiography is too operator-dependent for this purpose
- Also, there is a need to identify high risk patients before there is a decline in LVEF
- MRI T2* can achieve this and has additional predictive value

Monitoring of other organ function

- There has been recent interest in using MRI for identifying iron damage to the endocrine system
- There is good correlation between MRI findings (loss of pituitary volume) and pituitary damage
- With improved MRI imaging, other endocrine organs have also been evaluated
- It is of interest, that there is a close correlation between iron deposition in the heart and deposition in endocrine tissues, such as pituitary and pancreas.

THANK YOU