Iron overload: diagnosis and monitoring

M.HASHEMIEH,M.

Pediatric hematologist

Professor of Shaheed Beheshti University of Medical Science

Iron overload

- Iron overload occurs as a result of red blood cell transfusions or increased absorption of iron through the gastrointestinal (GI) tract.

- Both of these occur in thalassaemias.

- Iron accumulation is toxic to many tissues, causing heart failure, cirrhosis, liver cancer, growth retardation and multiple endocrine abnormalities.

Distribution and consequences of transfusional iron overload

- In iron overload, transferrin becomes saturated and iron species that are not bound to transferrin are present in plasma (plasma non-transferrin bound iron, or NTBI).
- The distribution of NTBI uptake is thought to involve calcium channels.
- Myocardial muscle, endocrine tissue and hepatocytes take up NTBI rapidly.
- This iron is then stored as ferritin or haemosiderin.

- The myocardial iron overload can induce heart failure from cardiomyopathy 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, namely 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 serious complications.

- Chelation therapy aims to balance the rate of iron accumulation from blood transfusion by increasing iron excretion in urine and /or faeces with chelators.

- Because iron is also required for essential physiological purposes, a key challenge of chelation therapy is to balance the benefits of chelation therapy with the unwanted effects of excessive chelation.

- Careful dose adjustment is necessary to avoid excess chelation as iron levels fall.

- The second major challenge in chelation therapy is to achieve regular adherence to treatment regimens throughout life, as even short periods of treatment interruption can have damaging effects.

- Monitoring of Iron Overload is essential in establishing effective iron chelation regimes, tailored to individuals' specific needs.

Monitoring of Iron Overload

Serum ferritin

- Serum ferritin (SF) generally correlates with body iron stores, and is relatively easy and inexpensive to determine repeatedly.

- A decreasing trend in SF is good evidence of decreasing body iron burden but absence of a decreasing trend does not exclude a decreasing iron burden.

- However, an increasing SF trend implies an increasing iron burden but may also be due to inflammation or tissue damage, so clinical judgment must be used to interpret these trends.

- Studies have identified a significantly lower risk of cardiac disease and death in at least two-thirds of cases where serum ferritin levels have been maintained below 2,500 µg/l over a period of a decade or more (Olivieri et al., 1994).

- Observations with larger patient numbers show that maintenance of an even lower serum ferritin of 1,000 µg/l may be associated with additional clinical advantages (Borgna-Pignatti et al., 2004)

limitations of serum ferritin measurements

- SF must be performed in a laboratory that has established how to dilute samples with high values.
- SF measures do not always predict body iron or trends in body iron accurately.
- In TM, variation in body iron stores accounts for only 57% of the variability in serum ferritin (Brittenham et al., 1993).
- This variability is in part because inflammation increases serum ferritin, and partly because the distribution of liver iron between macrophages (Kupffer cells) and hepatocytes in the liver has a major impact on serum ferritin.

PRACTICAL POINT

- A sudden increase in serum ferritin should prompt a search for hepatitis, other infections, or inflammatory conditions.

- A lack of fall in SF with chelation does not therefore necessarily prove that the patient is a ‘non responder’ to the chelation regime.

- The relationship between body iron and SF is not always linear, particularly in the context of inflammation or tissue damage (Adamkiewicz et al., 2009).
- Body iron can fall considerably from a high starting point (e.g. liver iron concentration >30 mg/g dry weight) before a change in ferritin is clear.
- Below 3000 µg/l SF values are influenced mainly by iron stores in the macrophage system, whereas above 3000 µg/l they are determined increasingly by ferritin leakage from hepatocytes (Davis et al., 2004; Worwood et al., 1980).

Liver iron concentration (LIC) measurement

- Normal LIC values are up to 1.8 mg/g dry weight (wt), with levels of up to 7 mg/g dry wt seen in some non-thalassaemic populations without apparent adverse effects.
- Sustained high LIC (above 15-20 mg/g dry wt) have been lined to worsening prognosis, liver fibrosis progression or liver function abnormalities.
- 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 hence cardiac risk reliably, and myocardial iron may be found in some patients despite currently well controlled LIC.

- LIC is the most reliable indicator of body iron load, which can be derived from the following formula:
- Total body iron stores in mg iron /kg body wt = 10.6 x the LIC (in mg/g dry wt)
- Sequential measurement of LIC is the best way to determine whether body iron is increasing or decreasing with time (iron balance).

- LIC determination should be considered for those patients whose serum ferritin levels deviate from expected trends (i.e. those with suspected co-existing hepatitis, or patients on chelation regimens with variable or uncertain responses), as this may reduce the risk of giving either inadequate or excessive doses of chelation therapy.
- Assessment of LIC may be particularly useful when new chelating regimes are being used.

- At high levels of SF (>4000 µg/l), the relationship to LIC is not linear and patients may show a fall in LIC (negative iron balance) without a clear trend in SF in the first 6-12 months.
- When a patient fails to show a fall in SF over several months the change in LIC can identify whether the current regime is adequate or need to be modified

Methods for measuring LIC

- Biopsy: an invasive procedure
- Magnetic biosusceptometry (SQUID):Current methodology requires liquid helium which is very expensive.Furthermore, the SQUID apparatus needs to be in an environment away from paramagnetic forces (e.g. lifts, cars) which is often impractical.
- MRI:The most widely used methods for LIC determination.

myocardial T2*

- The utility of myocardial T2* (mT2*) MRI was originally identified on the basis of shortened T2* values <20 ms in patients with decreased left ventricular ejection fraction (LVEF) (Anderson et al., 2001).
- The risk of developing heart failure increases with T2* values <10 ms, which are associated with a 160 fold increased risk of heart failure in the next 12 months (Kirk et al., 2009).
- Indirect non-linear relationship with myocardial iron

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.
- Methodology requires standardization worldwide

Monitoring of other organ function

- With improved MRI imaging, other endocrine organs have also been evaluated.
- It is of interest, that there is generally a close correlation between iron deposition in the heart and deposition in endocrine tissues, such as those of the pituitary and pancreas (Noetzli et al., 2009; Au et al., 2008).
- This supports the notion of shared uptake mechanisms for NTBI in heart and endocrine systems and supports clinical observations of shared risks in cardiac and endocrine systems once iron begins to escape from the liver.

24h Urinary iron estimation

- Measurement of the urinary iron excretion has been used in assessing the effect on iron excretion by deferoxamine (about half of total iron excreted in urine) or deferiprone (over 80% of iron excreted in urine), but is not useful in patients treated with deferasirox, as nearly all the iron is excreted in faeces.