Elevated serum ferritin
What should GPs know?

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Background
Elevated serum ferritin is commonly encountered in general practice. Ninety percent of elevated serum ferritin is due to non-iron overload conditions, where venesection therapy is not the treatment of choice.

Objective
This article aims to outline the role of the Australian Red Cross Blood Service Therapeutic Venesection program, to clarify the interpretation of the HFE gene test and iron studies, and to describe the steps in evaluating a patient with elevated serum ferritin.

Discussion
After exclusion of hereditary haemochromatosis, investigation of elevated serum ferritin involves identifying alcohol consumption, metabolic syndrome, obesity, diabetes, liver disease, malignancy, infection or inflammation as causative factors. Referral to a gastroenterologist, haematologist or physician with an interest in iron overload is appropriate if serum ferritin is >1000 µg/L or if the cause of elevated serum ferritin is still unclear.

Keywords
haemochromatosis; venesection; iron

The Australian Red Cross Blood Service has experienced a growing number of referrals from general practitioners for therapeutic venesection for patients with elevated serum ferritin (SF) who do not meet the eligibility criteria of two HFE mutations or documented iron overload. Thirty-six percent of referrals to the Australian Red Cross Blood Service Therapeutic Venesection program in an 8 month period in 2011 were for patients with elevated SF and an HFE genotype not associated with iron overload.1 Venesection therapy, while the mainstay of treatment for iron overload due to hereditary haemochromatosis (HH), does not address the underlying reasons for elevated SF in patients without true iron overload.2

While there is interest in iron reduction therapy for cancer risk reduction,3 improvement of insulin sensitivity in metabolic syndrome4 and management of fatty liver disease not responding to lifestyle changes,5 the Australian Red Cross Blood Service Therapeutic Venesection program is currently restricted to patients meeting the criteria listed in Table 1, and who also meet the general eligibility criteria for volunteer blood donation.

Patients meeting therapeutic venesection criteria with contraindications to volunteer blood donation (eg. comorbid angina, hepatitis C, cerebrovascular disease) need to be referred elsewhere for therapeutic venesection. Options include private pathology providers, public hospitals, haematologists and some GPs.

In the absence of contraindications, patients with elevated SF who do not meet eligibility criteria for therapeutic venesection may become volunteer whole-blood donors every 12 weeks.

Potential harms of frequent venesection therapy for a person without true iron overload include development of iron deficiency anaemia, reinforcement of a suboptimal management strategy for a biochemical abnormality, perpetuation of the myth that a genetic condition affecting family members exists, and the general venesection risks of venous scarring, phlebitis and vasovagal episodes.

Table 1. Eligibility criteria for Australian Red Cross Blood Service Therapeutic Venesection program

- Evidence of hereditary haemochromatosis:
  - C282Y homozygosity
  - C282Y/H63D compound heterozygosity
- Clinical iron overload supported by FerriScan® MRI or liver biopsy
- Polycythaemia rubra vera
- Porphyria cutanea tarda
Iron metabolism

Approximately 75% of the body's 3–4 g total iron is bound within haemoglobin in red blood cells, 10–20% is stored in the protein ferritin and the remainder is found in the iron transport protein transferrin, as well as in myoglobin, cytochromes and as unbound serum iron. Synthesised by the liver, the hormone hepcidin regulates total body iron levels by controlling intestinal iron absorption. Under the strict control of hepcidin, daily iron losses of 1–2 mg from sloughed mucosal, gastrointestinal and skin cells of hepcidin, daily iron losses of 1–2 mg from dietary sources. Only 10% of daily dietary iron intake is absorbed.2

Iron overload

The human body lacks an iron excretion mechanism. Table 2 outlines circumstances in which iron overload can develop.

Assessment of iron overload relies on surrogate markers, including serum tests (transferrin saturation, serum ferritin), noninvasive magnetic resonance imaging (MRI) scans for hepatic iron concentration (FerriScan®), liver biopsy and serum tests (transferrin concentration (FerriScan®), liver biopsy and serum tests (transferrin saturation).6 Accurate diagnosis of a patient's total body iron stores can be calculated from the volume of blood removed during weekly venesections. Removal of 4 g or more of iron (16 weekly venesections) without developing iron deficiency anaemia indicates iron overload.6

Hereditary haemochromatosis

Hereditary haemochromatosis is an autosomal recessive condition of progressive iron overload, usually due to homozygosity for the C282Y mutation in the HFE gene. This mutation causes inappropriately increased intestinal iron absorption at a rate 2–3 times greater than normal.8 Similar to type 1 diabetes being a metabolic condition of glucose homeostasis due to insulin deficiency, HH is a metabolic condition of iron homeostasis due to hepcidin deficiency.9 Approximately 1 in 200 people of Caucasian race are homozygous for the C282Y mutation. This mutation has much higher penetrance than the H63D mutation. C282Y homozygotes have a high risk of developing total body iron overload whereas C282Y/ H63D compound heterozygotes have much lower risk.6,10 Even if H63D homozygotes develop elevated serum iron indices, they are unlikely to develop total body iron overload.10,11

C282Y homozygosity confers risk of the multi-organ consequences of iron overload, including liver fibrosis, liver cirrhosis, hepatocellular carcinoma, cardiac arrhythmias, cardiomyopathy, diabetes, arthropathy, hypogonadism and skin hyperpigmentation. Organ damage can be averted with early diagnosis and appropriate venesection therapy, but this is challenging due to the variable, subtle and nonspecific symptoms in early disease.

Whereas the HFE gene test indicates the risk of eventually developing iron overload, iron studies indicate if iron overload is currently present. The HFE gene test is performed once, whereas iron studies are performed every time an assessment of current iron overload is required (Table 3). A typical schedule of venesections for a patient with HH and iron overload is presented in Table 4.

Iron studies

Accurate diagnosis of a patient's total body iron stores requires careful interpretation of iron studies (Table 9). Serum iron exhibits diurnal variation14 and the ideal specimen for iron studies is a fasting morning sample where oral iron supplementation has been withheld for at least 24 hours before testing.13

The most useful tests in the evaluation of iron overload due to HH are transferrin saturation and serum ferritin.15 Transferrin saturation >45% is sensitive and fairly specific for diagnosing HH, with increasing specificity when the threshold is increased to >55%. Serum ferritin is most useful in monitoring venesection regimen and venesection response in patients already diagnosed with HH.

Serum ferritin

While low SF is a sensitive and specific indicator of low total body iron stores, elevated SF is sensitive but very nonspecific for iron overload. While a normal SF rules out iron overload, only 10% of cases of elevated SF are due to iron overload (Figure 1). Chronic alcohol consumption, metabolic syndrome, obesity, diabetes, malignancy, infection and inflammatory conditions explain 90% of causes of elevated SF.6,16

Elevations of SF in the range 300–1000 µg/L are common, and often reflect the presence of the previously listed conditions. Mild elevations below 1000 µg/L are “tolerable” and in the absence of HH, the risk of hepatic iron overload is exceedingly low.17 Australian studies have shown a link between alcohol consumption and elevated SF, with beer more so than spirits or wine causing increases in SF.

Table 2. Causes of iron overload

<table>
<thead>
<tr>
<th>Mechanism of iron overload</th>
<th>Example</th>
</tr>
</thead>
</table>
| Inappropriately increased intestinal iron absorption | • Hereditary haemochromatosis  
  • HFE-haemochromatosis  
  • Type 1: HFE mutation (HFE gene)  
  • Non-HFE haemochromatosis (rare)  
  • type 2A: haemojuvelin mutation (HJV gene)  
  • type 2B: hepcidin mutation (HAMP gene)  
  • type 3: transferrin receptor 2 mutation (TIR2 gene)  
  • type 4: ferroportin mutation (FPN1 gene) |

| Transfusional iron overload 1 unit packed red cells = 250 mg iron | • Multiple transfusions to treat anaemia due to:  
  • red cell aplasia (congenital or acquired)  
  • haemoglobinopathies  
  • myelodysplastic syndrome, leukaemia  
  • cancer or chemotherapy for cancer  
  • severe haemorrhage in haemophilia/surgery/trauma |

| Iron-loading anaemias | • α-thalassaemia  
  • β-thalassaemia  
  • Chronic haemolytic anaemias  
  • Congenital sideroblastic anaemia  
  • Congenital dyserythropoietic anaemia |

| Hepatocellular chronic liver disease | • Alcoholic liver disease  
  • Hepatitis B or C  
  • Nonalcoholic steatohepatitis |

| Excess parenteral iron | • Excess IM or IV iron |
Elevated serum ferritin – what should GPs know?

Table 3. Advice based on HFE genotype and serum ferritin

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Prevalence in Caucasian Australians</th>
<th>Advice if serum ferritin is normal</th>
<th>Advice if serum ferritin is elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk HFE genotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest risk</td>
<td>1 in 188</td>
<td>• Increased risk of future iron overload</td>
<td>• Begin venesections – candidate for therapeutic venesection</td>
</tr>
<tr>
<td>C282Y homozygous</td>
<td></td>
<td>• Check iron studies every 1–5 years</td>
<td>• Family members need testing¹³</td>
</tr>
<tr>
<td>Lower risk</td>
<td>1 in 46</td>
<td>• Family members need testing¹³</td>
<td>• SF &gt;1000 µg/L: refer to gastroenterologist, haematologist or physician with an interest in iron overload</td>
</tr>
<tr>
<td>C282Y/H63D compound heterozygous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk HFE genotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H63D homozygous</td>
<td>1 in 49</td>
<td>• Check iron studies every 1–5 years</td>
<td>• Not a candidate for therapeutic venesection but can become a volunteer blood donor if no contraindications exist</td>
</tr>
<tr>
<td>C282Y carrier</td>
<td>1 in 8</td>
<td>• No further follow up needed¹³</td>
<td>• Look for another cause of elevated SF apart from HH, especially alcohol consumption, metabolic syndrome, obesity, liver disease and inflammation</td>
</tr>
<tr>
<td>H63D carrier</td>
<td>1 in 4</td>
<td></td>
<td>• Consider non-HFE haemochromatosis</td>
</tr>
<tr>
<td>No mutations</td>
<td>3 in 5</td>
<td></td>
<td>• Family members don’t need testing¹³</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• SF &gt;1000 µg/L: refer to gastroenterologist, haematologist or physician with an interest in iron overload</td>
</tr>
</tbody>
</table>

Table 4. Venesection schedule

<table>
<thead>
<tr>
<th>Iron unloading phase, target serum ferritin ~50 µg/L</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Weekly venesection of ~7 mL/kg (maximum 550 mL) whole blood</td>
<td></td>
</tr>
<tr>
<td>• Ensure pre-venesection haemoglobin &gt;120 g/L</td>
<td></td>
</tr>
<tr>
<td>• Monitor Hb and SF</td>
<td></td>
</tr>
<tr>
<td>– Hb: is it safe to remove more blood? Delay for 1 week if pre-venesection Hb &lt;120 g/L</td>
<td></td>
</tr>
<tr>
<td>– SF: is it safe to remove more iron? Monitor SF every 4–6 venesections, more often as SF approaches 100 µg/L</td>
<td></td>
</tr>
<tr>
<td>• It may take many months or even years to unload excess iron</td>
<td></td>
</tr>
<tr>
<td>• Oral vitamin B12 and folate supplements support erythropoiesis during frequent venesections</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifelong maintenance phase, target SF ~50–100 µg/L</td>
<td></td>
</tr>
<tr>
<td>• Venesections to maintain SF ~50–100 µg/L</td>
<td></td>
</tr>
<tr>
<td>• Highly variable between individuals, often in the range 2–6 venesections per year</td>
<td></td>
</tr>
<tr>
<td>• Monitor SF at least every 12 months</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Interpretation of iron studies

<table>
<thead>
<tr>
<th>Iron study test name</th>
<th>Explanation</th>
<th>Iron as an analogy to money</th>
<th>Abnormal values (vary from laboratory-to-laboratory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>Unbound serum iron</td>
<td>‘Loose change in your pocket’</td>
<td>Suggestive of low iron stores: &lt;10 µmol/L</td>
</tr>
<tr>
<td>Total iron binding capacity</td>
<td>Ability to bind even more iron</td>
<td>‘Greediness for more money’</td>
<td>Suggestive of low iron stores: &gt;70 µmol/L</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Iron absorbed from duodenum bound to a transport protein</td>
<td>‘Money kept in your wallet’</td>
<td>Suggestive of low iron stores: &lt;16%</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>Iron within a storage protein</td>
<td>‘The savings you have in your bank’</td>
<td>Suggestive of low iron stores: &lt;30 µg/L</td>
</tr>
<tr>
<td></td>
<td>One molecule of ferritin binds 4500 atoms of iron</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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There exists a well-established link between elevated SF, metabolic syndrome and fatty liver.20,21 With the Australian prevalence of metabolic syndrome being 1 in 3,22 the high pre-test probability of ‘metabolic hyperferritinaemia’ is important to consider when evaluating patients with elevated SF. Features which may discriminate elevated SF due to HH from metabolic hyperferritinaemia are listed in Table 6. Liver disease is a cause of elevated SF. Injured hepatocytes leak ferritin into the serum, so in liver disease, SF can be considered as another type of liver function test (LFT), along with the transaminases (alanine transaminase [ALT], aspartate aminotransferase [AST]) and gamma-glutamyl transferase (GGT). Some causes of liver disease are associated with increased hepatic iron concentration (hepatitis B, hepatitis C, alcoholic liver disease, HH) so elevated SF with abnormal LFTs usually requires further investigation.23 Malignancy, infection and inflammatory conditions may all cause elevated SF. Normal screening tests for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and antinuclear antibody (ANA) can help exclude the presence of these conditions.

Specialist review is mandatory if SF exceeds 1000 µg/L due to the increased risk of fibrosis and cirrhosis above this threshold. However, in the absence of C282Y homozygosity, hepatic iron concentration is usually normal or only mildly elevated and fatty liver, hepatitis B, hepatitis C and alcoholic liver disease may be found.17,24

**Key points**

- Of all HFE genotypes, only C282Y homozygotes have a high risk of hepatic iron overload.
- Once HH has been excluded in a patient with elevated SF, assess for potential causes including chronic alcohol consumption, metabolic syndrome, obesity, diabetes, liver disease, malignancy, infection and inflammation.
- If SF >1000 µg/L, refer to a gastroenterologist, haematologist or physician with an interest in iron overload.
- If SF <1000 µg/L, address reversible causes and repeat iron studies.
- Encourage voluntary blood donation every 12 weeks.

**Further information**

- Australian Red Cross Blood Service App (which provides real-time processing of referrals and current information regarding patients who do not meet eligibility criteria): http://highferritin.transfusion.com.au
- Haemochromatosis Australia resources for GPs: www.haemochromatosis.org.au/GPResources.htm
- GESA haemochromatosis clinical practice guidelines:

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**Figure 1. Algorithm for the investigation and management of elevated serum ferritin in general practice**
Table 6. Comparison between elevated serum ferritin in haemochromatosis and in metabolic syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Elevated serum ferritin due to hereditary haemochromatosis</th>
<th>Metabolic hyperferritinaemia due to metabolic syndrome/fatty liver/insulin resistance/diabetes/obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>C282Y homozygous</td>
<td>Not C282Y homozygous</td>
</tr>
<tr>
<td>Ancestry</td>
<td>Usually Caucasian</td>
<td>Variable</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Usually &gt;45%</td>
<td>Usually normal (20–45%)</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hepcidin levels (not commercially available)</td>
<td>Reduced hepcidin levels</td>
<td>Normal or elevated hepcidin levels</td>
</tr>
<tr>
<td>Serum ferritin over time</td>
<td>Progressively more elevated</td>
<td>Fluctuations from one test to another</td>
</tr>
<tr>
<td>Total body iron levels</td>
<td>Raised</td>
<td>Normal</td>
</tr>
<tr>
<td>Response to weekly 500 mL venesections</td>
<td>Patient tolerates &gt;16 weekly venesections without becoming anaemic</td>
<td>Patient becomes anaemic after &lt;16 weekly venesections</td>
</tr>
<tr>
<td>Hepatic iron concentration</td>
<td>(FerriScan® MRI or liver biopsy)</td>
<td>Normal</td>
</tr>
<tr>
<td>Pattern of iron deposition on liver biopsy</td>
<td>Parenchymal deposition in hepatocytes</td>
<td>Nonparenchymal deposition in sinusoidal and Kupffer cells</td>
</tr>
<tr>
<td>Management</td>
<td>• Iron depletion</td>
<td>• Lifestyle modifications</td>
</tr>
<tr>
<td></td>
<td>– venesections</td>
<td>– weight control</td>
</tr>
<tr>
<td></td>
<td>– iron chelation therapy</td>
<td>– correction of insulin resistance</td>
</tr>
</tbody>
</table>


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