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 noniron 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 syndrome[4] 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 found 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.[6]

Synthesised by the liver, the hormone hepcidin regulates total body iron levels by controlling intestinal iron absorption.[7] Under the strict control of hepcidin, daily iron losses of 1–2 mg from sloughed mucosal, gastrointestinal and skin cells are accurately offset by daily absorption 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 quantitative phlebotomy.[2,6]

Whole blood contains 250 mg iron per 500 mL. In HH, 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 are at highest risk of developing total body iron overload whereas C282Y/H63D compound heterozygotes have much lower risk.[8,10] 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*.

Table 2. Causes of iron overload

Mechanism of iron overload	Example
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 (TfR2 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

Iron studies

Accurate diagnosis of a patient's total body iron stores requires careful interpretation of iron studies (*Table 5*). Serum iron exhibits diurnal variation[14] 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 requirement 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'[6] 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

Table 3. Advice based on HFE genotype and serum ferritin

Genotype	Prevalence in Caucasian Australians[11,12]	Advice if serum ferritin is normal	Advice if serum ferritin is elevated
High risk HFE genotypes			
Highest risk C282Y homozygous	1 in 188	• Increased risk of future iron overload • Check iron studies every 1–5 years • Family members need testing[13]	• Begin venesections – candidate for therapeutic venesection • Family members need testing[13] • SF >1000 µg/L: refer to gastroenterologist, haematologist or physician with an interest in iron overload
Lower risk C282Y/H63D compound heterozygous	1 in 46		
Low risk HFE genotypes			
H63D homozygous	1 in 49	• Check iron studies every 1–5 years	• Not a candidate for therapeutic venesection but can become a volunteer blood donor if no contraindications exist • Look for another cause of elevated SF apart from HH, especially alcohol consumption, metabolic syndrome, obesity, liver disease and inflammation • Consider non-HFE haemochromatosis • Family members don't need testing[13] • SF >1000 µg/L: refer to gastroenterologist, haematologist or physician with an interest in iron overload
C282Y carrier H63D carrier No mutations	1 in 8 1 in 4 3 in 5	• No further follow up needed[13]	

Table 4. Venesection schedule

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

in ferritin secretion by the liver.[18] Chronic daily consumption of two or more standard drinks might explain elevated SF.[19] Repeat SF testing after a period of alcohol abstinence can clarify the contribution of a patient's alcohol intake on their elevated SF.

Table 5. Interpretation of iron studies

Iron study test name	Explanation	Iron as an analogy to money	Abnormal values (vary from laboratory-to-laboratory)	
			Suggestive of low iron stores	Suggestive of high iron stores
Serum iron	Unbound serum iron	'Loose change in your pocket'	<10 µmol/L	>30 µmol/L
Total iron binding capacity	Ability to bind even more iron	'Greediness for more money'	>70 µmol/L	<45 µmol/L
Transferrin saturation	• Iron absorbed from duodenum bound to a transport protein • One molecule of transferrin binds two atoms of iron	'Money kept in your wallet'	<16%	>45%
Serum ferritin	• Iron within a storage protein • One molecule of ferritin binds 4500 atoms of iron	'The savings you have in your bank'	<30 µg/L	• >200 µg/L pre-menopausal women • >300 µg/L men and postmenopausal women • >1000 µg/L refer to gastroenterologist, haematologist or physician with an interest in iron overload

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-reative protein (CRP), erythrocyte sedimenation 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: www.transfusion.com.au/high_ferritin
- 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:

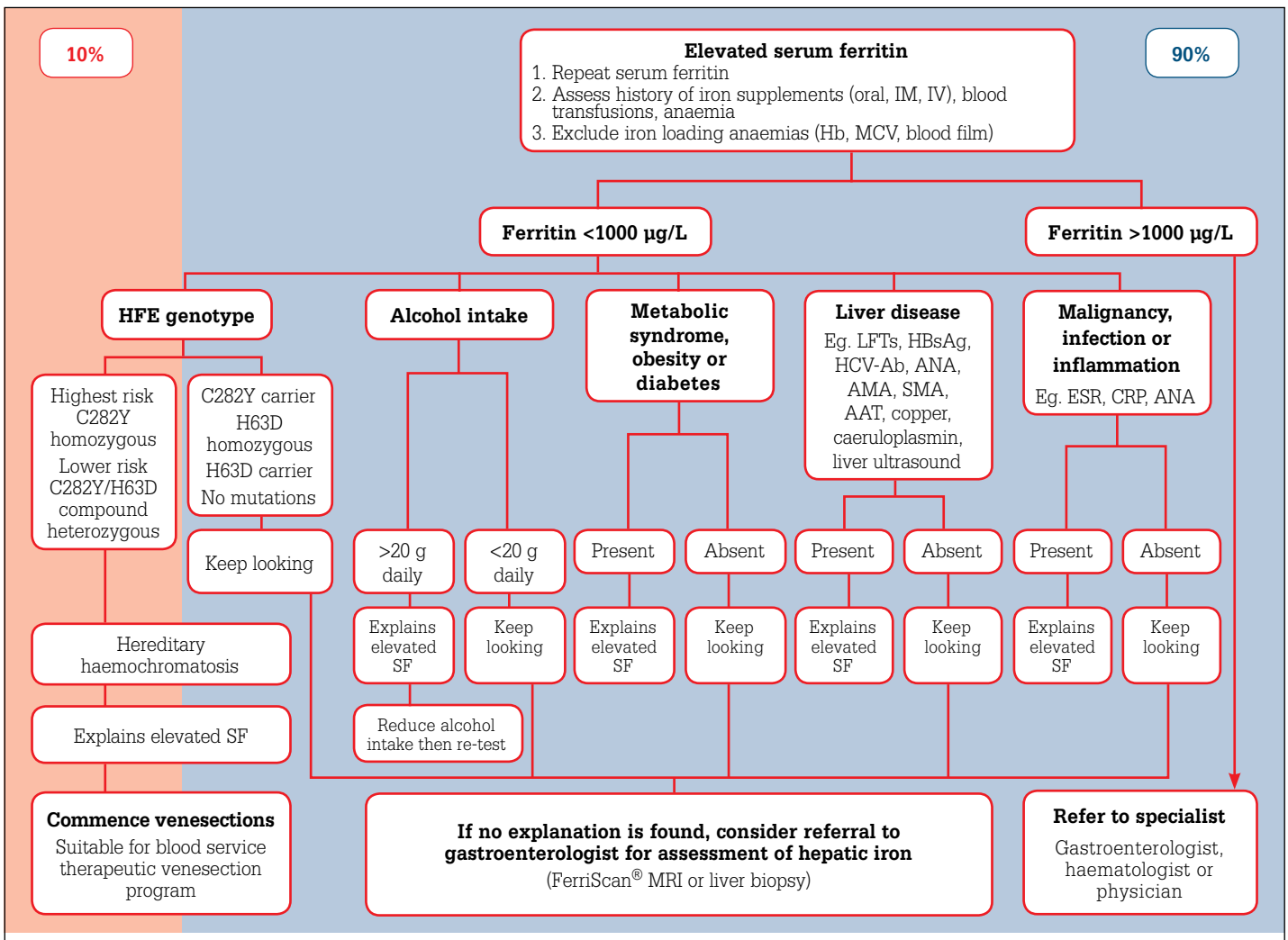

Figure 1. Algorithm for the investigation and management of elevated serum ferritin in general practice

Table 6. Comparison between elevated serum ferritin in haemochromatosis and in metabolic syndrome

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

www.gesa.org.au/files/editor_upload/File/Professional/Haemochromatosis.pdf

- FerriScan®: www.resonancehealth.com.

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