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Cite this as: *BMJ* 2015;351:h3692 doi: 10.1136/bmj.h3692

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor of medicine, Weill Cornell Medical College Qatar; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

RATIONAL TESTING

Interpreting raised serum ferritin levels

Marianna Koperdanova, Jonathan O Cullis

A 60 year old businessman attended his general practitioner after an insurance medical examination at which abnormal liver function tests had been noted (alanine aminotransferase 70 IU/L (normal range 10-40 IU/L) and γ -glutamyltransferase 120 IU/L (normal range 0-37 IU/L)). He was otherwise fit and well and not taking regular medication. His general practitioner noted that his full blood count and renal function were normal, and requested hepatitis B and C serology (which were negative) and serum ferritin level, which was 567 μ g/L (normal range 24-300 μ g/L).

What is the next investigation?

Ferritin is an intracellular iron storage protein and a marker of iron stores. Normal serum ferritin levels vary between laboratories but generally concentrations >300 μ g/L in men and postmenopausal women and >200 μ g/L in premenopausal women are regarded as elevated.¹ Low ferritin values provide absolute evidence of iron deficiency.² Raised levels often indicate iron overload, but they are not specific, as ferritin is an acute phase protein and is also released from damaged hepatocytes; thus levels are elevated in inflammatory disorders, liver disease, alcohol excess, or malignancy.³⁻⁴ Raised ferritin levels therefore require further investigation in primary care to determine if they truly represent iron overload. It is critical to consider two broad categories of causes:

- Raised ferritin without iron overload
- Raised ferritin due to iron overload.

These can usually be distinguished through clinical assessment and measurement of serum transferrin saturation.⁵

Raised ferritin without iron overload

Most patients (90%) with hyperferritinaemia will not have iron overload.^{6,7} Many conditions are associated with “reactive” high ferritin levels (box 1), and these may coexist (such as inflammation and hepatitis).⁸

Raised ferritin due to iron overload

Iron overload occurs when there is increased absorption of dietary iron, or after administration of iron or via blood transfusion.

Secondary iron overload—This may follow repeated blood transfusions, multiple infusions of intravenous iron (such as in people with renal failure and cancer patients who have been treated with repeated parenteral iron), or prolonged ingestion of iron supplements. It may occur in chronic anaemias with ineffective erythropoiesis (such as thalassaemia intermedia, sideroblastic anaemias, and chronic haemolytic anaemias). In such cases, those who have received >20 transfusions (for example, patients with sickle cell disease, β thalassaemia major, aplastic anaemia, or myelodysplasia) are at risk of iron overload and in the long term may develop cardiac, hepatic, or endocrine dysfunction. Secondary iron overload may also be due to porphyria cutanea tarda, a hepatic porphyria presenting with cutaneous photosensitivity and liver dysfunction due to hepatic iron deposition.

Primary iron overload (hereditary haemochromatosis)—This is iron accumulation due to inheritance of mutations in the HFE gene on chromosome 6. This autosomal recessive disorder is the commonest single gene disorder in northern European populations (estimated prevalence 0.4%), but is far less common in other populations.⁶ It causes excessive absorption of dietary iron, but is often asymptomatic and unrecognised in primary care.⁹⁻¹⁰ Associated morbidities (hepatic, endocrine, cardiac) are serious and preventable: timely diagnosis and treatment are important.

Clinical assessment in primary care

Initial clinical assessment of any patient with hyperferritinaemia should first consider reactive causes (box 2); if these are clearly present, further investigation may be unnecessary. An alcohol history is mandatory, as is assessment for liver disease. Check body mass index and blood pressure, as elevated ferritin levels in absence of

THE BOTTOM LINE

- Elevated ferritin levels are usually due to causes such as acute or chronic inflammation, chronic alcohol consumption, liver disease, renal failure, metabolic syndrome, or malignancy rather than iron overload
- Exclude these causes clinically or with initial tests such as full blood count, liver and renal function, and inflammatory markers (C reactive protein or erythrocyte sedimentation rate)
- A normal serum transferrin saturation (ideally fasting) usually excludes iron overload (where it is raised) and suggests a reactive cause for raised ferritin
- Unexplained serum ferritin values >1000 μ g/L warrant referral for further investigation
- Consider HFE mutation screen for hereditary haemochromatosis in individuals with elevated ferritin and a raised transferrin saturation >45%

Box 1 | Causes of high ferritin without iron overload**Common**

- Liver disease (such as non-alcoholic steatohepatitis or viral hepatitis)
- Alcohol excess
- Acute and chronic inflammatory conditions
- Infections
- Malignancy
- Renal failure
- Metabolic syndrome

Less common

- Thyrotoxicosis
- Acute myocardial infarction

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Previous articles in this series

- ▶ Tests to predict imminent delivery in threatened preterm labour (BMJ 2015;350:h2183)
- ▶ Investigating intracerebral haemorrhage (BMJ 2015;350:h2484)
- ▶ Screening tests for tuberculosis before starting biological therapy (BMJ 2015;350:h1060)
- ▶ Investigating young adults with chronic diarrhoea in primary care (BMJ 2015;350:h573)
- ▶ Investigating sepsis with biomarkers (BMJ 2015;350:h254)

iron overload are increasingly recognised in patients with metabolic syndrome (obesity, type 2 diabetes, dyslipidaemia, and hypertension).^{11 12} Box 2 outlines other causes to be excluded.

First line tests

These include:

- Blood count and inflammatory markers (C reactive protein or erythrocyte sedimentation rate) to detect occult inflammatory disorders
- Serum creatinine and electrolytes for renal function
- Liver function tests—Abnormal results should prompt consideration of viral hepatitis screening and abdominal ultrasonography
- Blood glucose and lipid studies.

Transferrin saturation

If the cause of hyperferritinaemia is unclear, the most useful test to aid differentiation of true iron overload from other causes is the serum transferrin saturation.

Normal transferrin saturation

In patients with unexplained hyperferritinaemia, normal transferrin saturation (<45% in females, <50% in males) usually excludes conditions of iron overload, and reactive causes should be reconsidered.^{1 4} Ideally, transferrin saturation should be measured on a fasting morning sample, as serum iron levels undergo diurnal variation, and may rise with recent food ingestion, temporarily increasing transferrin saturation.¹³ Patients should also not be tested during acute illness, when iron levels may fall and misleadingly lower transferrin saturation.

Elevated transferrin saturation

In healthy adults, transferrin saturation >45% has a sensitivity of 94% and a positive predictive value of 6% for hereditary haemochromatosis.⁶ If the elevation is slight, consider repeating measurement on a fasting sample to eliminate effects of recent food. Generally, genetic mutation screening (for C282Y and H63D polymorphisms) for hereditary haemochromatosis should be offered according to local practice in patients with unexplained increased ferritin and transferrin saturation.¹⁴

Most (>80%) northern Europeans with hereditary haemochromatosis are C282Y homozygotes,¹⁵ with about 5% being C282Y/H63D compound heterozygotes (who are significantly less likely to develop iron overload).¹⁵ Clinical penetrance is variable, however,¹⁴ with possible influencing factors including menstruation, blood donation, dietary supplements, alcohol intake, and hepatitis. A study of primary care requests for laboratory estimation of serum ferritin suggests that targeting blood samples with raised ferritin levels (≥ 300 $\mu\text{g/L}$ in males, ≥ 200 $\mu\text{g/L}$ in females) and transferrin saturation levels (>50% males, >40% females) for HFE genotyping improves detection of C282Y homozygous hereditary haemochromatosis.¹⁰

What are the next steps?

- Patients with confirmed iron overload with ferritin >1000 $\mu\text{g/L}$ or abnormal liver function regardless of cause

Box 2 | Causes to be considered at first encounter with a patient with raised ferritin

Causes without iron overload

- Recent illness (such as acute infection)
- Alcohol intake
- Abnormal liver function, chronic liver disease, cirrhosis—Check liver function tests, consider liver ultrasound scan
- Viral hepatitis—Serology for hepatitis B and C
- Acute or chronic inflammatory conditions—Erythrocyte sedimentation rate or C reactive protein, or both
- Metabolic syndrome (obesity, type 2 diabetes, dyslipidaemia, hypertension)—Check body mass index, blood pressure, blood glucose, lipid studies
- Renal failure—Check renal function
- Malignancy (for example, weight loss, anorexia)—Imaging as appropriate

Causes with iron overload

- Iron supplements, intravenous iron, transfusion history
- Anaemia or known haematological conditions—Full blood count, blood film, haemoglobinopathy studies
- Hereditary haemochromatosis (fatigue, lethargy, arthralgia, diabetes, loss of libido, impotence, amenorrhoea, right upper quadrant abdominal pain, hepatomegaly, cirrhosis, chondrocalcinosis, skin hyperpigmentation, heart failure)
- Family history of iron overload
- Porphyria cutanea tarda (cutaneous photosensitivity)

- Refer to a hepatologist, as this degree of elevation is more likely to be due to serious underlying pathology.⁸
- Patients with positive HFE mutation results
 - Refer for further assessment and therapy. Venesection is the mainstay of management in patients with iron overload, aiming to reach and maintain ferritin concentrations <50 $\mu\text{g/L}$.¹⁴ Combined genetic testing and iron studies would also be offered to siblings.¹⁵
- Patients with suspected primary iron overload (that is, raised transferrin saturation, other clinical features suggestive of haemochromatosis) who lack the common HFE genotypes
 - Refer for direct assessment of iron stores, such as magnetic resonance imaging or liver biopsy.¹⁵ Screening for other genes implicated in hereditary haemochromatosis may be considered in such patients if increased iron stores are confirmed and other hepatic and haematological disorders are excluded.
- Patients with secondary iron overload (for example, due to inherited or acquired anaemia)
 - Consider iron chelation. Phlebotomy cannot be used to remove excess iron in secondary iron overload except in patients who have received transfusions during curative therapy for haematological malignancies.
- Patients with mildly increased ferritin levels (300–1000 $\mu\text{g/L}$) in whom iron overload is unlikely (that is, normal transferrin saturation) and other causes

(such as liver disease, inflammatory disorders) are not evident

- Consider interventions as deemed appropriate to reduce ferritin concentrations (alcohol abstinence, improved glycaemic control, weight reduction, and lowering triglyceride concentrations). We suggest re-checking serum ferritin (and other relevant tests) three to four months after these interventions.

Outcome

The patient’s fasting serum transferrin saturation was 40%, and an abdominal ultrasound scan showed fatty change within the liver. He admitted to drinking 35 units of alcohol a week. The chronic alcohol consumption was believed to be the cause of the hyperferritinaemia, and there was no evidence of iron overload. Lifestyle advice and alcohol abstinence were advised, and liver function and ferritin measurements had normalised on repeat testing three months later.

10-MINUTE CONSULTATION

Bariatric surgery

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Cite this as: *BMJ* 2015;351:h3802 doi: 10.1136/bmj.h3802

This is part of a series of occasional articles on common problems in primary care. *The BMJ* welcomes contributions from GPs.

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Previous articles in this series

- ▶ Nipple discharge (*BMJ* 2015;351:h3123)
- ▶ Gradual loss of vision in adults (*BMJ* 2015;350:h2093)
- ▶ Foot drop (*BMJ* 2015;350:h1736)
- ▶ High INR on warfarin (*BMJ* 2015;350:h1282)
- ▶ Teenagers with back pain (*BMJ* 2015;350:h1275)

An obese 34 year old man with a body mass index of 37.4, type 2 diabetes, and hypertension presents wanting advice on weight loss. He is concerned about his lack of progress despite adhering to a six month primary care led weight loss regime. He has heard of weight loss surgery being offered by the NHS and wants to know if he is eligible.

What you should cover

- Ask the patient about what weight loss measures he has tried so far. For example:
 - How has he modified his diet and physical activity?
 - Has he tried weight support or management programmes?
- Check dates of any prescriptions issued for drug interventions.
- Check attendance (current or future) at a tier 3 weight management service, which may affect eligibility for bariatric surgery in England (table).¹
- Assess whether any clinically beneficial weight loss has been achieved. As this is not defined in the guidelines, we suggest the following:
 - *Objective improvements*—Body mass index, waist circumference, improved blood pressure control, better glycaemic control.
 - *Subjective improvements*—Energy levels, mobility, general health and wellbeing.
- Assess eligibility for surgery (table).
- Assess the patient for comorbidities that may affect his eligibility for surgery, including cardiovascular, respiratory, kidney, or liver disease.

Bariatric surgery eligibility criteria in England (as defined by NICE guideline)¹

Body mass index	Extra eligibility criteria	6 month NSI requirement*
≥27.5	Asian origin and recent onset T2DM	No
≥30	Recent onset T2DM	No
≥35	Obesity related comorbidity†	Yes
≥40	None	Yes
≥50	None	No

- Check that he does not have uncontrolled alcohol or drug dependency—ask about alcohol and drug use, check medical records, and administer AUDIT-C questionnaire to screen for alcohol misuse if concerns exist.²

What you should do

- Outline the available surgical options:
 - There are two main types of surgery, almost always done via keyhole (laparoscopic) surgery: one that restricts how much can be eaten (restrictive) and one that limits absorption from the gut (malabsorptive).
 - Commonly offered procedures include sleeve gastrectomy (restrictive), gastric banding (restrictive), and gastric bypass (combination of restrictive and malabsorptive).
 - Surgery may involve a stay in hospital of up to a few days.
 - Each type of surgery has its own specific complications, and the surgical team will explain these in greater detail, but direct the patient to appropriate online resources.^{3 4}
- Discuss possible benefits of surgery⁵:
 - *Weight loss*—On average 25% loss of body weight, depending on the procedure (bypass ~30%, banding ~18%). Warn that weight loss may be transient, with some weight gain recurring after two years.
 - *Some comorbidities may improve*—However, this is not inevitable. For example, type 2 diabetes may require less or no insulin, obstructive sleep apnoea may not require nocturnal continuous

THE BOTTOM LINE

- Refer patients for bariatric surgery if they have body mass index >35 with associated obesity conditions (type 2 diabetes, hypertension, obstructive sleep apnoea) and have failed to control their weight with non-surgical efforts
- Consider referral at a lower body mass index if the patient is of Asian origin, has new onset type 2 diabetes, or both



LIFE IN VIEW/SPL

- positive airway pressure, lipid profile may improve (although patients may still need a statin if they have concurrent ischaemic heart disease), and hypertension may be better controlled.
 - *Lower mortality*—29-40% lower risk of death from any cause compared with no surgery.
 - *Better quality of life*—Studies show overall improvement, with greater improvement in physical functioning than in mental state.
- Discuss the short term postoperative risks:
 - Perioperative mortality is low (<0.3%) and depends on the type of operation (bypass > banding) and patient related factors (comorbidities, age).
 - Complication (4-25%) and reoperation rates (22-26%) vary depending on operation type and patient related factors (history of thromboembolism, obstructive sleep apnoea, extremes of body mass index, or impaired functional status).⁵
 - Encourage the patient to find out more himself and offer sources of information.
- Discuss long term postoperative complications:
 - Following a successful operation and recovery, patients may still experience complications including nutritional deficiencies (iron, vitamin B₁₂, folic acid, vitamin D), which require lifelong monitoring and replacement when needed.
 - Patients will not be able to eat the same amount and type of food as before. This is difficult to predict. They will have to see what works best for them, although they will be given advice and support by the specialist team.
- For gastric banding, failure rates of 30-50% are common and revision surgery is not routinely offered on the NHS.
- Warn patients who have had or are having bypass about the risk of dumping syndrome (postprandial feeling of faintness, sweating, and palpitations that may be accompanied by bloating, nausea, and diarrhoea caused by rapid movement of food, especially sugar, from the stomach into the duodenum), hypoglycaemic events, and lower alcohol tolerances.
- Excess skin can result from weight loss, and its removal is not offered on the NHS.
- The surgical team will discuss operation type specific complications with them.
- Impress on the patient the need for long term follow-up. This includes regular follow-up for at least two years with the surgical team and a lifelong commitment to annual monitoring with the GP, with review of symptoms and complications, weight, nutrition, and mineral and vitamin concentrations, with replacement treatment if necessary.
- If potentially eligible, and the patient remains keen, refer him for bariatric surgery. The patient has the ultimate responsibility to decide about his care, but remind him that eligibility decisions also lie with the surgical team. In this case, the patient would be eligible as he meets all the criteria
- Provide written information. The Patient.co.uk and NHS Choices websites offer detailed information for patients about the entire process,^{3 4} empowering them to make informed treatment decisions.