# *The Highs and Lows of Ferritin*

**Sharon E. Card, MD, MSc, FRCPC**
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A ferritin test is often ordered to clarify iron status. It frequently has its results confounded by its other major role as an acute phase reactant.[1]

## *How do I investigate low ferritin levels?*

The investigation of low ferritin starts through a knowledge of the regulation of iron.[2] Ferritin is a protein that stores iron in the body. Approximately 1 mg of iron per day is absorbed, primarily in the duodenum and the upper jejunum. Iron is transported by transferrin and is stored as ferritin. Body iron stores are assiduously conserved and normally have a close correlation with ferritin. About 1 mg of ferritin is lost daily, from shedding of GI, genitourinary and skin cells. Menstruation results in the additional loss of about 1 mg of iron a day.

## *How is iron storage and transport measured?*

Serum iron is the amount of available iron in the blood, but is not a reliable measure of iron stores. Its value is influenced by:

- diurnal variation,
- malignancy,
- inflammatory conditions,
- myocardial ischemia,
- chemotherapy and
- iron supplements.

### Angelina's Fatigue

- Angelina, 25, is a long-distance runner who presents with fatigue. She was previously running 5 km easily, but now she has to stop at 4 km
- Her menses are regular, but heavy
- Review of her history identifies no other symptoms and no other bleeding sites
- Her physical examination is normal
- Her laboratory investigations reveal:
  - Mean corpuscular hemoglobin (MCH): 32.5 pg (27.0 pg to 32.0 pg)
  - White blood cell count (WBC): 7.30 (4.00$^{9}$/L to 11.00 10^$^{g}$/L)
  - Platelets: 431 (150$^{9}$/L to 400 10^$^{g}$/L)
  - Hemoglobin = 135 (110$^{g}$/L to 160$^{g}$/L)
  - Mean corpuscular volume MCV): 96.4 fl (79.0 fl to 99.0 fl)
  - Ferritin = 13 mg (20mg/L-120 mg/L)

**What's wrong with Angelina?**
**Go to page 55 to find out.**

Total iron binding capacity (TIBC) refers to the aggregate binding sites of all the transferrin in circulation.

Normal saturation is between 20% and 45% of the iron binding sites of transferrin filled. Saturation refers to the ability of the binding sites to soak-up more iron.

Ferritin is the storage form of iron. Bone marrow iron stores are currently the gold standard for iron stores, but they are rarely needed.

**Table 1**

**Diagnostic usefulness of ferritin for iron deficiency[4]**

| Serum ferritin | | Likelihood ratio | Diagnostic impact |
|---|---|---|---|
| Very positive | < 15 mmol/L | 52 | Rule in |
| Moderately positive | 15 mmol/L to 34 mmol/L | 4.8 | Intermediate high |
| Neutral | 35 mmol/L to 64 mmol/L | 1 | Indeterminate |
| Moderately negative | 65 mmol/L to 94 mmol/L | 0.39 | Intermediate low |
| Extremely negative | ≥ 95 mmol/L | 0.08 | Rule out |

**Table 2**

**Causes of failure of bodily response to oral iron and appropriate solutions**

| | |
|---|---|
| Ongoing blood loss | Fix the leak |
| Failure to take medication | Try a lower dose<br>Take with meals<br>Try a different preparation |
| Wrong diagnosis | Thalassemia<br>Sideroblastic anemia |
| Malabsorption | Celiac disease |
| Mixed deficiency | B12<br>Folate |
| Damaged marrow | Lack of erythropoietin, otherwise depleted marrow cannot respond well |
| Slow-release preparation | If released past the duodenum, the upper jejunum will not be as effective |

## *How do these lab tests help?*

Storage iron depletion (*ie.*, lack of bone marrow iron stores, low ferritin) occurs first, without compromise of the iron supply for erythropoiesis. With iron-deficient erythropoiesis, TIBC increases because the body recognizes the lack of iron stores and tries to compensate for it. As a result, serum iron drops and since per cent saturation is purely a ratio of serum fe/TIBC, it too will drop. Below 15% saturation, transferrin saturation circulating cells become microcytic and hypochromic. The hemoglobin changes last. If baseline hemoglobin is in the upper normal range, a patient must lose 20% to 30% of body iron before anemia is diagnosed from an iron deficiency.[1] Classic iron deficiency anemia is represented by:

1) Small, depleted cells (low mean corpuscular volume. Low mean corpuscular hemoglobin is a classic, but late sign of iron deficiency)
2) Low serum iron is influenced by other factors, so it is a poor indicator of iron deficiency
3) High TIBC as the body is good at trying to increase the transport of iron
4) A low per cent saturation
5) Low ferritin is the most indicative test in an otherwise healthy individual. If equivocal, the other tests are needed (Table 1).

## *How do I treat low ferritin?*

It is important to determine the cause. In post-menopausal women or in men, occult gastrointestinal bleeding, including malignancies, must be considered and evaluated. Iron treatment can almost always be oral; however, if the patient is not responding, consider parenteral after considering potential causes, as in Table 2.

### Back to Angelina

- Angelina's results fit with iron depletion, without anemia
- Consider iron supplementation for greater exercise performance, especially if the iron loss is ongoing (menorrhagia)[5]

## *Causes of iron overload*

An inevitable response to increased body iron entry, due to fixed losses is iron overload (Table 3). Increasing iron absorption to 1.5 mg per day, will accumulate 5.5 g of iron every decade and 33 g in 60 years (Figure 1), which is the amount usually found in patients with clinically detected hereditary hemochromatosis (HH).[6] With no obvious cause for elevated ferritin (*i.e.,* transfusions, anemia), the diagnostic dilemma is generally HH vs. alcohol-induced liver disease. It is important for a physician to not discount HH in those with apparent excessive alcohol consumption, as cirrhosis is more common in patients with the HH phenotype who have heavy alcohol intake.

## *When to think HH?*

HH is an autosomal recessive disorder of the iron metabolism, resulting in excessive iron overload and subsequent tissue iron deposition. Several presentations should prompt the investigation for HH, particularly if there is a suggestive feature, such as family history or atypical age. Keep in mind that anything that can be infiltrated will be. The following can all be manifestations of HH:

- Type 2 diabetes mellitus ,
- cardiac arrhythmias,
- liver failure,
- hepatomegaly,
- cirrhosis,
- elevated liver enzyme levels,
- hepatocellular carcinoma,
- arthritis,
- hypogonadism and
- changes in skin pigmentation.[7,8]

### Meet Adam

- Adam, 65, has Type 2 diabetes mellitus
- His brother has just been diagnosed with an iron problem
- Adam has no new symptoms and his physical examination is unremarkable
- His laboratory investigations reveal:
  - Hemoglobin 150 g/L (110 g/L to 160 g/L)
  - Normal white blood cells
  - Normal platelet count
  - Liver enzymes are normal
  - Ferritin 900 µg/L (20 µg/L to 120 µg/L)
  - Fasting transferrin saturation is 80%

**For more on Adam go to page 56**

**Dr. Card** is an Associate Professor, Division of General Internal Medicine, University of Saskatchewan, Department of Internal Medicine, Royal University Hospital, Saskatoon, Saskatchewan.

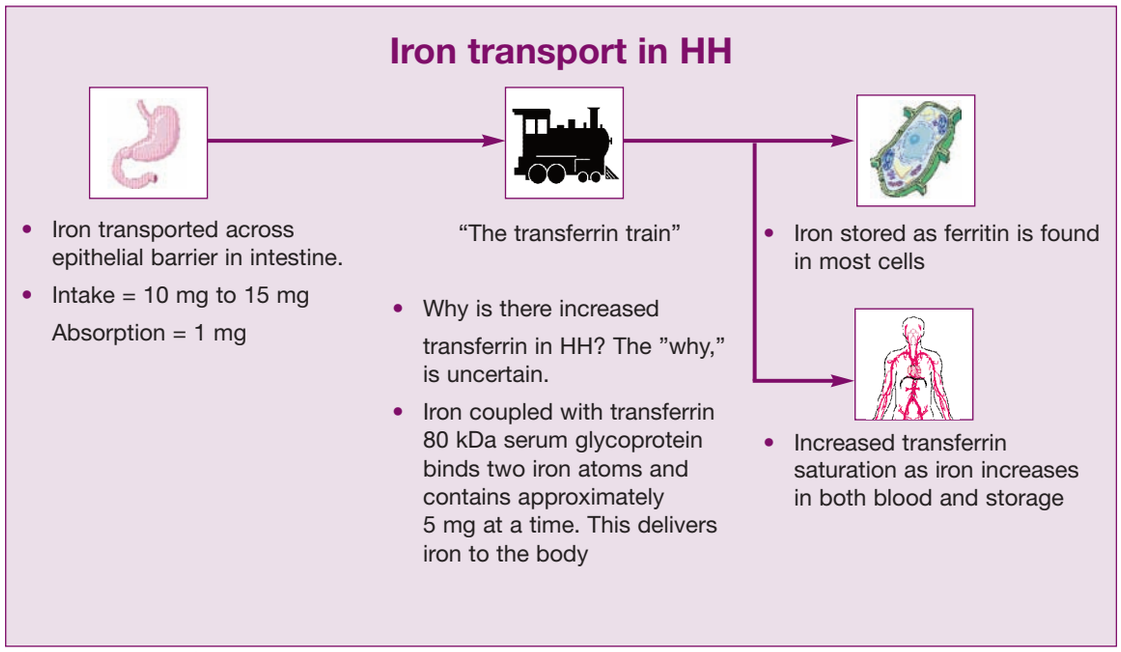


Figure 1. Iron transport in HH

## More on Adam

- Adam should have further investigations for hereditary hemochromatosis, either a genetics or a liver biopsy
- A specialty consultation is reasonable at this point

## Take-home message

1. Low ferritin means deficient iron stores. In a healthy person, ferritin alone will diagnose iron deficiency
2. To diagnose iron deficiency in the face of other inflammatory conditions a combination of iron studies is needed
3. Screening for iron overload should start with ferritin and fasting transferrin saturation

## *Lab tests in hereditary HH*

Because of the nature of the absorptive defect, even with reduced iron stores, the transferrin saturation is elevated (Figure 1). There is lack of consensus as to a cut off level to consider abnormal. Abnormal levels are quoted as ≥ 60% in men and ≥ 50% in women, vs. > 45% in both genders.[7,8] Lowering the cutoff to 45% increases sensitivity, but reduces specificity. Overnight fasting avoids circadian or postprandial variations, decreasing false-positive rates. A ferritin level of ≥ 200 µg/L in women and ≥ 300 µg/L in men would be considered suggestive particularly with a percentage saturation > 55%.[8]

There is no general agreement about diagnostic criteria, but someone with a high ferritin but a low percent saturation is very unlikely to have HH. However, individuals with both a high ferritin and a high per cent saturation should be further evaluated.

**Table 3**
**Causes of iron overload**

| Primary iron overload | Secondary iron overload |
|---|---|
| 1) Hereditary HH<br>2) C282Y HFE mutation<br>3) H63D HFE mutation<br>4) Other gene mutations | 1) Iron-loading anemias +/- transfusion<br>- Anemic with excess iron<br>- Thalassemia major<br>- Chronic hemolytic anemia<br>2) Dietary iron overload<br>3) Chronic liver disease<br>- hepatitis B and hepatitis C<br>- Alcohol-induced liver disease<br>- *Porphyria cutanea tarda*<br>- Fatty liver disease |

The definitive test for the diagnosis of iron overload is a liver biopsy. Genetic testing is available for HH and may obviate the need for biopsy. A specialty consultation is generally needed at this point.

## *How do I treat a patient with high ferritin?*

Treatment is dependent on the cause. Chelation is recommeded for transfusional overload and phlebotomy for HH. Specialist involvement is generally needed. GPs need to be aware of the increased susceptibility to infection with HH patients.

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