Iron Overload

Primary/Genetic Hemochromatosis

Secondary Hemochromatosis

Description/pathophysiology:

- Hereditary iron overload disorders are now recognized as being among the most common genetic diseases in the human population.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\n- Iron overload is a phenotypic state to which a patient arrives by either genetic or environmental/iatrogenic routes. The severity of iron overload can range from moderate to severe.
- Excess iron catalyzes oxidative stress which damages body tissues and structures in which the iron is stored. In patients with genetic hemochromatosis, two problems exist simultaneously: 1) a disproportionately large amount of iron is absorbed from the gastrointestinal tract (i.e., these patients’ iron absorption is “too efficient”), and 2) iron is preferentially deposited in parenchymal tissues such as the heart, liver, pancreas, pituitary gland, and joints rather than being stored safely within the reticuloendothelial system. The deposition of excess iron in parenchymal tissues promotes destruction of these organs/tissues via oxidative mechanisms and subsequent tissue necrosis and fibrosis, leading to the protean manifestations of the disease dependent upon which organs are most affected in the individual patient: heart failure, hepatic fibrosis, hypoinsulinemic diabetes, hypopituitarism, and hemochromatotic arthropathy.\(^8\)
- Iron overload can be defined as a state of “iron toxicity” similar to mercury toxicity or poisoning with any other heavy metal or toxin, except that the mechanism is more related to the quantity of the iron rather than the unique characteristics or quality of iron itself. In other words, whereas the toxicity of mercury can be seen even when only small amounts of the metal are present, the toxicity of iron is directly related to the amount of the excess iron, rather than the inherent toxicity of the iron itself.

Iron overload and genetic hemochromatosis are not systemic autoimmune diseases, but are included in this text because they are very common in clinical practice and can mimic both osteoarthritis and systemic inflammatory arthritis.

Conditions associated with iron overload

- Primary/genetic disorders
  1. Homozygous genetic hemochromatosis
  2. Heterozygous genetic hemochromatosis
  3. African iron overload
  4. African-American hemochromatosis
  5. Non-HLA-linked hemochromatosis
  6. Juvenile hemochromatosis
  7. Neonatal hemochromatosis

- Secondary and metabolic disorders
  8. Dietary excess of iron
  9. Parenteral administration of iron in the form of iron injections and blood transfusions
  10. Porphyria cutanea tarda
  11. Portacaval shunt
  12. Hepatic cirrhosis, portal hypertension, and splenomegally
  13. AIDS
  14. Sudden infant death syndrome
  15. Alcoholism
  16. Metabolic syndrome

- Inherited red blood cell abnormalities ("iron-loading anemias", hemoglobinopathies)
  17. Alpha-thalassemia
  18. Beta-thalassemia
  19. Thalassemia intermedia
  20. Sideroblastic anemia
  21. Aplastic anemia
  22. Anemia associated with pyruvate kinase deficiency
  23. AC hemoglobinopathy
  24. AS hemoglobinopathy
  25. X-linked hypochromic anemia
  26. Pyridoxine-responsive anemia
  27. Atransferrinemia

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\(^3\) Rouault TA. Hereditary hemochromatosis. *JAMA* 1993; 269: 3152-4


\(^7\) Lauffer, RB. Iron and Your Heart. New York: St. Martin’s Press, 1991

\(^8\) Vasquez A. Musculoskeletal disorders and iron overload disease: comment on the American College of Rheumatology guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. *Arthritis Rheum* 1996 Oct;39(10):1767-8
Clinical presentations:

- Many patients are asymptomatic.
- Most patients eventually present with a problem that is attributed to another disorder:
  - Patients may present with diabetes, which is erroneously attributed to metabolic syndrome or type-2 diabetes.\(^9\)
  - Patients may present with joint pain that is erroneously attributed to osteoarthritis\(^10\), rheumatoid arthritis\(^11\), or some other musculoskeletal syndrome.\(^12\)
  - Patients may present with heart failure that is written off as “idiopathic cardiomyopathy.”\(^13\)
- Fatigue, lethargy, weakness
- Chronic abdominal pain
- Liver damage: hepatomegaly, elevated serum levels of liver enzymes and alkaline phosphatase, fibrosis and cirrhosis, hepatocellular carcinoma, or other findings such as hematemesis and melena, ascites, hyperbilirubinemia and jaundice, hypoalbuminemia, hepatic encephalopathy, clotting dysfunction, anemia, liver abscess, increased incidence of esophageal carcinoma.
- Abnormal glucose metabolism or diabetes mellitus: elevated glucose levels. Usually asymptomatic, yet can cause weight loss, polyuria, polyphagia, polydypsia.
- Musculoskeletal disorders: arthritis and arthralgia, generalized osteoporosis, bone pain, myalgia. Especially arthropathy of the hands and wrists, hips, and knees.
- Cardiac dysfunction: cardiomyopathy, arrhythmia, fibrillation, congestive heart failure; shortness of breath or dyspnea on exertion, fatigue.
- Cutaneous manifestations: ‘slate-gray’ or ashen coloration, increased pigmentation (‘tan’) of the skin, atrophy of the skin, ichthyosis, koilonychia, loss of body hair, increased incidence of malignant melanoma.
- Endocrine disorders: hypogonadotrophic hypogonadism, (autoimmune) hypothyroidism, hyperthyroidism; manifest as decreased libido, impotence, testicular atrophy, or sterility in males, amenorrhea or difficulty conceiving in females, loss of body hair.
- Susceptibility to increased frequency and severity of infections, especially infections due to *Yersinia enterocolitica*, *Vibrio vulnificus*, HIV, and *Mycobacterium tuberculosis*.
- Neurologic symptoms: blurred vision, sensorineural hearing loss, hyperactivity, dementia, attention deficit disorder, ataxia, lightheadedness, dizziness, anxiety, depression, tinnitus, confusion, lethargy, memory loss, disorientation, headaches and migraine headaches, personality changes, hallucinations, paranoia, chronic treatment-resistant psychiatric illness such as schizophrenia, compulsive disorders, bipolar affective disorder.

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### Musculoskeletal manifestations of iron overload

**Clinical findings may include:**
- Joint pain
- Bone pain
- Joint swelling
- Loss of motion
- Bursitis
- Tendonitis
- Tenosynovitis
- Subcutaneous nodules

**Sites of involvement**
- Metacarpophalangeal joints
- Wrist
- Hip
- Knee
- Shoulder
- Ankle
- Metatarsophalangeal joints
- Elbow
- Spine
- Sympyxis pubis
- Achilles tendon
- Plantar fascia

**Radiographic findings**
- Joint space narrowing
- Sclerosis
- Cysts
- Pseudocysts
- Osteophytes
- Hook-like osteophytes at the metacarpal heads (high specificity)
- Flattened or “squared-off” metacarpal heads
- Generalized osteopenia
- Generalized osteoporosis
- Chondrocalcinosis
- Subchondral cysts
- Carpal erosions
- Calcific tendonitis

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\(^{9}\) Most of the patients (95%) had one or more of the following conditions: obesity, hyperlipidaemia, abnormal glucose metabolism, or hypertension. INTERPRETATION: We have found a new non-HLA-linked iron-overload syndrome which suggests a link between iron excess and metabolic disorders.” Moirand R, Morajt AM, Lored O, Paillard P, Brisset P, Deugnier Y. A new syndrome of liver iron overload with normal transferrin saturation. *Lancet*. 1997 Jan 11;349(9045):95-7


• ‘Alcoholism’: Alcoholism can cause elevated liver enzymes and liver damage, and many iron overload patients are erroneously diagnosed as alcoholics despite their abstinence from alcohol when the clinician fails to consider iron overload as the cause for the hepatopathy.
• Any race, nationality, or ethnic background: Hereditary iron overload conditions have been identified in people of all ethnic backgrounds and nationalities. Secondary iron overload conditions can occur irrespective of genetic predisposition.
• Either gender: Iron overload conditions occur in both men and women
• A family history of, or suggestive of, a hereditary iron overload condition: family history of iron overload, hereditary anemia or iron-loading anemia, cardiac disorders or “heart disease”, arthritis, diabetes, neurologic disorders, liver disease, impotence, amenorrhea, sterility.

**Differential diagnoses:**

- **Diabetes mellitus:** Remember that the classic presentation of hemochromatosis is “bronze diabetes with cirrhosis.” All patients with diabetes should be tested for iron overload.14,15
- **Cardiomyopathy:**
- **Hepatopathy:** Iron overload is one of the most important rule-outs in patients with liver disease.16
- Liver biopsy is often indicated to assess condition and disease co-existence.
- **Musculoskeletal disorders:** Patients with polyarthropathy should be tested for iron overload.17,18
  - Degenerative arthritis or osteoarthritis
  - Pseudogout, calcium pyrophosphate dihydrate deposition disease
  - Rheumatoid arthritis
  - Ankylosing spondylitis: The resemblance here is only superficial, related primarily to calcification of the intervertebral discs and ligaments.20
- **Hypogonadotrophic hypogonadism:** impotence in men, subfertility in women21
- **Hyperthyroidism and hypothyroidism**22,23
- **Porphyria cutanea tarda:** “Virtually all patients have increased iron stores; serum iron, iron saturation, and ferritin values.”24 All patients with porphyria cutanea tarda must be tested for iron overload.

**Clinical assessment:**

- **History/subjective:**
  - The manifestations of the condition are so protean that history is generally nonsensitive and non-specific for the disorder. Rarely, a patient will mention that a relative was diagnosed with iron overload or that a relative had an unusual heart or liver disease, and this clue may lead to a diagnosis of iron overload in unsuspecting family members.

### Rationale for screening all patients:

1. Hereditary iron-accumulation disorders occur in a large percentage of the population.
2. Persons with the disease usually have no symptoms.
3. Clinical manifestations are often indicative of irreversible organ damage or organ failure.
4. Iron overload can cause death if not treated early.
5. Early treatment ensures normal life expectancy.
6. Therefore, early detection (before the onset of symptoms and organ damage) requires screening asymptomatic patients.

**Test of choice:** serum ferritin, because it shows the best correlation with body iron stores and thus prognosis and need for treatment

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17. Msellat AM, Fornasier VL, Fox IH. Arthropathy as the major clinical indicator of occult iron storage disease. *JAMA* 1977; 238: 1825-8
23. “Virtually all patients have increased iron stores; serum iron, iron saturation, and ferritin values.” Rich MW. Porphyria cutanea tarda. Don’t forget to look at the urine. *Postgrad Med.* 1999;105: 208-10, 213-4
• **Physical examination/objective:**
  - The classic presentation of the fully developed disease is “bronze diabetes with arthritis and cirrhosis.”
  - Physical examination should be specific for the patient’s complaint(s) of arthritis, cardiomyopathy, diabetes, etc.

• **Imaging & laboratory assessments:**
  - Routine screening with serum ferritin for iron overload among all patients should be the standard of care in clinical practice.
    - “In view of the high prevalence of hereditary hemochromatosis, its dire consequences when untreated, and its treatability, screening for the disorder should be performed routinely.”
    - “Screening for hemochromatosis is both feasible and cost-effective, and we recommend its use in patients seeking medical care.”
    - “The high gene frequency in the general population warrants routine screening tests in asymptomatic healthy young adults.”
    - "CONCLUSIONS: Primary iron overload occurs in African Americans… Clinicians should look for this condition.”
  - Imaging: The radiographic findings are nearly identical to those of osteoarthritis, except more joints are typically involved and that the distribution is typically symmetric (both due to the systemic/metabolic nature of the disease). Hook-like osteophytes at the metacarpal heads—with the “hooks” pointing proximally (rather than distally, as in rheumatoid arthritis) may be the only finding that could be called pathognomonic. Flattened or “squared-off” metacarpal heads are also seen. See previous table labeled “Musculoskeletal manifestations of iron overload” for more details.
  - Laboratory evaluation: Serum ferritin is the test of choice when looking for primary iron overload, secondary iron overload, and/or iron deficiency and should be a component of each new patient’s evaluation, just as are CBC and the chemistry/metabolic panel.
    - **Ferritin:** Routine use of serum ferritin is the most reasonable and cost-effective means for diagnosing this condition in symptomatic and asymptomatic patients. Elevations of ferritin (i.e., >200 mcg/L in women and >300 mcg/L in men) need to be retested along with CRP (to rule out false elevation due to excessive inflammation) before making the presumptive diagnosis of iron overload. In the absence of significant inflammation, ferritin values >200 mcg/L in women and >300 mcg/L in men indicate iron overload and the need for treatment/phlebotomy regardless of the absence of symptoms or end-stage complications. Another benefit to the use of serum ferritin is the frequent detection of iron deficiency.
    - **Transferrin saturation:** good test for detecting genetic hemochromatosis before iron overload has occurred; values greater than 40% should be repeated in conjunction with a measurement of serum ferritin.
    - **CRP:** should be relatively normal as iron overload is not inflammatory, per se. If the ferritin is elevated and the CRP is markedly elevated, then inflammatory and hepatocentric diseases must be considered, namely advanced cancer, viral hepatitis or other hepatopathy, and alcoholic liver disease. If the ferritin is elevated and the CRP is normal, then the most likely diagnosis is iron overload, which should be confirmed either with liver biopsy or diagnostic/therapeutic phlebotomy.
    - **CBC:** may show anemia, but the findings here are nonspecific
    - **Chemistry panel:** may show evidence of diabetes and hepatopathy

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**Chapter 18: Iron Overload and Genetic Hemochromatosis**

- **Thyroid assessment:** may show hyperthyroidism or hypothyroidism, both of which are more common in patients with iron overload.
- **Bone marrow biopsy:** unnecessary and archaic in this setting, now that serum ferritin is widely available.
- **Liver biopsy:** traditionally considered the “gold standard” for diagnosing iron overload but is now clearly unnecessary for the diagnosis, which can be established by monitoring the response to therapeutic phlebotomy, which is the treatment of choice. Life-saving diagnostic and therapeutic phlebotomy should never be delayed or denied for lack of liver biopsy in patients with laboratory indicators of iron overload.
- **Genetic testing, such as for the HFE mutation** is a waste of time and money in most clinical situations; these tests should be reserved for research purposes. The only value these tests may have in clinical practice is that of supporting a diagnosis in a patient with elevated serum ferritin who refuses biopsy, liver MRI, or phlebotomy; however, a negative result is meaningless if the ferritin is high and the clinical picture is compatible with iron overload. If the diagnosis is established, genetic relatives must be tested.

**Guide to Patient Management Based on Iron Status**

<table>
<thead>
<tr>
<th>Screen asymptomatic patients.</th>
<th>Follow-up abnormal laboratory results. (high serum iron, elevated liver enzymes, high blood glucose, etc.)</th>
<th>Screen high-risk and symptomatic patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assess iron status with transferrin saturation and serum ferritin.</strong> Use fasting morning specimen.</td>
<td><strong>IRON-DEFICIENCY</strong> serum ferritin:&lt;10-15 in women, &lt;20 in men, transferrin saturation:&lt;16%</td>
<td><strong>POSSIBLE SEVERE IRON OVERLOAD</strong> transferrin saturation: &gt;40% and/or serum ferritin: &gt;200 in women; &gt;200 in men</td>
</tr>
<tr>
<td>In adults with no obvious cause of blood loss: Assume pathologic gastrointestinal bleeding until proven otherwise. Simply testing for occult blood in the stool is insufficient. Refer for complete (endoscopic) evaluation.</td>
<td><strong>&quot;HEALTHY IRON STATUS&quot;</strong> transferrin saturation: 25-30% serum ferritin: 30-70</td>
<td><strong>PROBABLE SEVERE IRON OVERLOAD</strong> Ferritin &gt;200 in women, or Ferritin &gt;300 in men. Confirm with diagnostic phlebotomy, or liver biopsy, or MRI.</td>
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<tr>
<td></td>
<td>Periodically assess iron status as part of routine health assessment. Consider assessment for impending iron deficiency. Consider periodic blood donation and low-iron diet to maintain healthy iron status.</td>
<td>Refer as needed (usually gastroenterologist, hematologist, or internist) for phlebotomy therapy and/or deferoxamine chelation.</td>
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<td><strong>&quot;MODERATE IRON OVERLOAD&quot;</strong> transferrin saturation: &gt;33-45% serum ferritin: 80-160</td>
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<td></td>
<td>No treatment is mandatory. Periodically assess iron status as part of routine health assessment. Consider low-iron diet and regular blood donation to reduce risk of cancer and myocardial infarction.</td>
<td>Second assessment suggests &quot;healthy iron status&quot; or &quot;moderate iron overload&quot;: Average results and/or reassess within 1 month, or periodically assess iron status as part of routine health assessment.</td>
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30 "Therapeutic phlebotomy is used to remove excess iron and maintain low normal body iron stores, and it should be initiated in men with serum ferritin levels of 300 microg/L or more and in women with serum ferritin levels of 200 microg/L or more, regardless of the presence or absence of symptoms." Barton JC, McDonnell SM, Adams PC, Brissot P, Powell LW, Edwards CQ, Cook JD, Kowdley KV. Management of hemochromatosis. Hemochromatosis Management Working Group. *Ann Intern Med*. 1998 Dec 1;129(11):932-9

**Establishing the diagnosis:** Any one of the following three is sufficient:

- Diagnostic liver biopsy shows heavy iron deposits
- Characteristic laboratory findings (ferritin >200 in women or >300 in men) and the ability to resist intractable anemia with serial/weekly phlebotomies
- Characteristic MRI of liver and the ability to tolerate serial/weekly phlebotomies

**Complications:**

- Patients diagnosed and effectively treated before the onset of signs and symptoms have normal life expectancy.
- The most common causes of premature mortality in undiagnosed and untreated patients are related to heart failure, liver failure, infections and/or complications of diabetes.

**Clinical management:**

- Treatment for severe iron overload is iron-removal therapy. Since blood is high in iron, the removal of blood—therapeutic phlebotomy—is the treatment of choice. Deferoxamine chelation can be administered to patients who refuse or cannot withstand phlebotomy (i.e., patients with cardiomyopathy, severe anemia, hypoproteinemia) but is much less effective, much more expensive, and with side effects such as neurotoxicity. Adjunctive nutritional and lifestyle modifications are no substitute for iron-removal therapy, and weekly phlebotomy is the treatment of choice.

**Treatments:**

- **Medical standard:** Iron-removal is accomplished by weekly phlebotomy of 1-2 units (250-500 mL of blood, each of which removes 250 mg of iron), and deferoxamine chelation is used in patients who cannot tolerate phlebotomy. Complications of the disease, such as arthritis, heart failure, hypogonadism, and diabetes are treated appropriately. Cirrhotic patients must be monitored for hepatoma with twice-yearly liver ultrasound and measurement of serum alpha-fetoprotein. Always, when a hereditary iron overload disorder is diagnosed, all (first-degree) blood relatives must be screened for iron overload.
  
- **Diet modifications:** These are no substitute for iron-removal therapy with phlebotomy and are weak in their effectiveness by comparison.
  - Decrease consumption of foods and nutritional supplements which are significant sources of iron: Iron supplements, iron-fortified foods and supplements, liver, beef, pork, lamb.
  - Increase consumption of foods that will decrease intestinal absorption of iron from ingested food: tannins in tea, phytates (in whole-grain products, bran, legumes, nuts, and seeds), soy protein, egg, calcium supplements.
  - Ensure adequate protein intake to replace protein lost during phlebotomy.
  - Decrease consumption of excess ascorbic acid (vitamin C); high-dose vitamin C supplementation is clearly contraindicated.32
  - Alcohol consumption should be avoided because ethanol exacerbates liver damage and increases iron absorption from the gut.
  - **Silymarin:** Milk thistle has proved benefit in an animal model of iron overload33 and is probably suitable for use in patients with iron overload, particularly given its ability to reverse cirrhosis.34
  - **Antioxidant supplementation (excluding high-dose ascorbate):** Oxidative stress is increased and antioxidant reserves are decreased in patients with iron overload.
  - **Coenzyme Q10:** CoQ-10 probably has a role in the treatment of hemochromatotic cardiomyopathy given its safety and efficacy in other cardiomyopathies.