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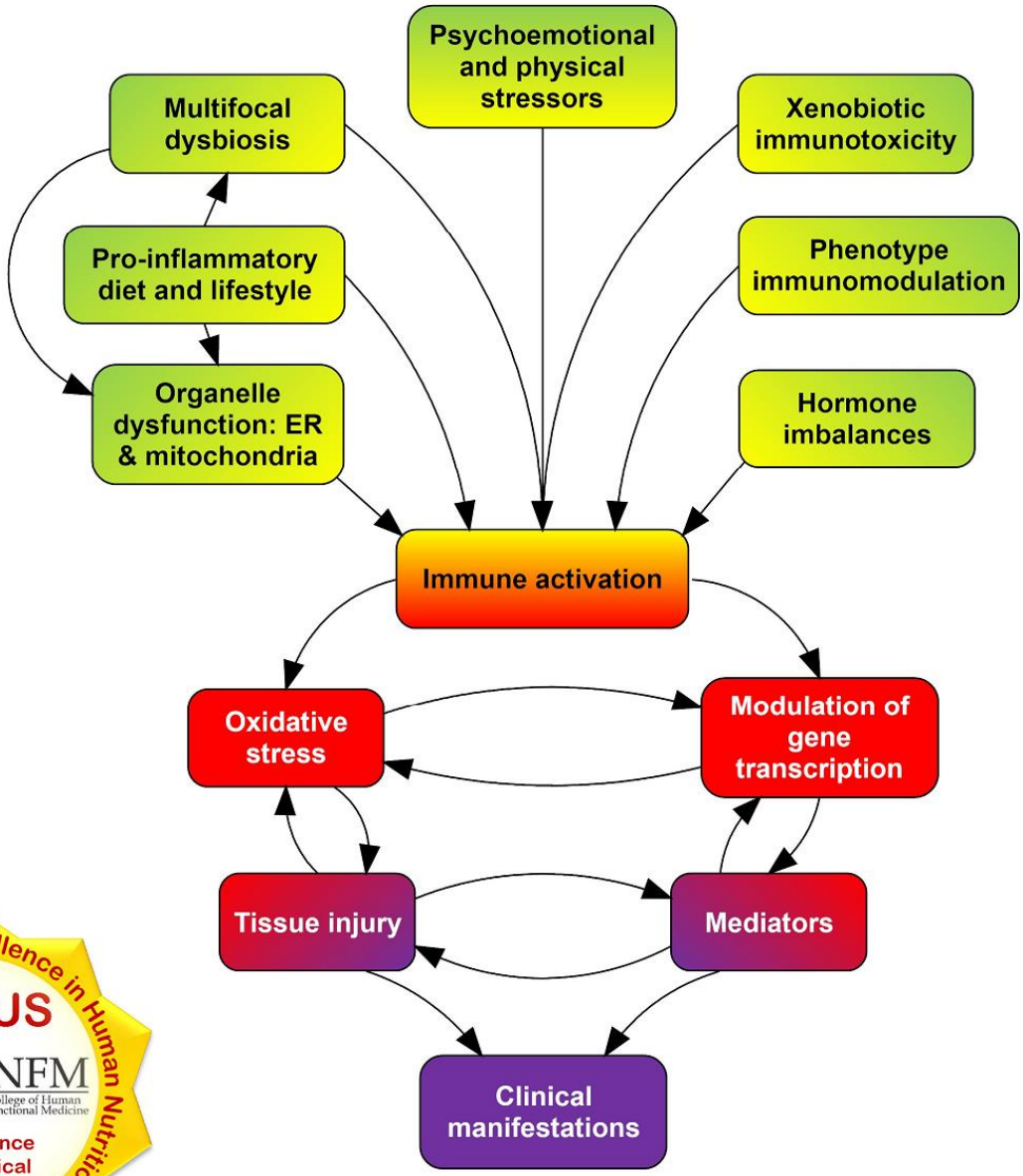

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Chapter 1:
Initial Considerations in Patient Assessment and Management:
An Overview of Key Concepts and Facts in Patient History, Physical Examination, Laboratory Interpretation, Risk Management and Clinical Approach, Common Clinical Considerations

Overview of this chapter

Reviewed herein are the three essential components of patient assessment:

1. History
2. Physical examination
3. Laboratory assessment

Additional concepts and perspectives are provided that will help facilitate risk management and promote and contextualize optimal patient care.

This chapter concludes with two new sections under the title of "Common Clinical Considerations", since these topics—hemochromatosis and hypothyroidism—are both commonly encountered in clinical practice and need to be considered in the routine evaluation of essentially all patients and especially those who present with disorders such as diabetes, depression, fatigue, and musculoskeletal pain. Previously, I had published these as separate chapters in various books, but—again—at this time I think these need to be integrated into basic/daily/routine clinical consideration.

Common Clinical Considerations: Hemochromatosis and Hypothyroidism

Iron Overload and Genetic Hemochromatosis:
Identification and Management

Introduction to Iron Overload

In its "classic" form, homozygous genetic hemochromatosis is noted in about 1 per 200-250 Caucasian persons, with a similar incidence among Hispanics. The incidence among persons of African descent is notably higher, reported as high as 1 per 80 among hospitalized African Americans. The heterozygous form of iron overload which is phenotypically milder occurs in as many as 1 per 7 (14% of total) persons; any disorder that is common in the general population will be even more common in a clinical population of symptomatic care-seeking patients, especially those with musculoskeletal disorders and complaints.[615]

Testing serum ferritin on a routine basis in clinical practice allows for the detection of iron deficiency (very common, even among non-anemic patients) and iron overload (quite common, especially among patients with joint pain, diabetes, heart failure, and liver disease as well as many other clinical manifestations—most common of which is asymptomaticity.

Hypothyroidism:
Clinical, Functional, and Practical Considerations

Introduction:

Due mostly to the allopathic medical profession's limited view of hypothyroidism, the condition has remained enigmatic, and both doctors and patients have been rendered ineffective in their ability to understand and treat this common clinical condition. In the following few pages, the illusion of complexity and incomprehensibility will be deflated. This chapter details the most important considerations in the assessment and treatment of various types of low thyroid function. As with the other chapters of the book, information will be presented in an outlined format.

[615] 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 & Rheumatism*: Official Journal of the American College of Rheumatology 1996; 39:1767-8

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.**[616,617,618,619,620,621,622]
- 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, hypopituarism, and hemochromatoic arthropathy.
- 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 disorders are common in all ethnic/racial populations

Genetic hemochromatosis is considered one of the most common hereditary disorders in the Caucasian population with a homozygote frequency of 1 per 200-250 (approx 0.5%) and a heterozygote frequency of about 1 in 7 (approx 14%); the condition is at least as common in other ethnic groups except that this predisposition toward iron overload is more common in Africans (as high as 1 in 20) and African-Americans (as high as about 1 in 80 in some series among hospitalized patients). Of course, the expected frequency would be even higher among symptomatic patients than among the general population. **Thus, for a clinician in full-time practice, the only reason for not appreciating this condition among one's patient population several times per year is because one is simply not sufficiently looking and testing for this condition.**

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, shows the best correlation with body iron stores and thus prognosis and need for treatment.

[616] Olynyk JK, Bacon BR. Hereditary hemochromatosis: detecting and correcting iron overload. *Postgrad Med* 1994; 96: 151-65
[617] Phatak PD, Cappuccio JD. Management of hereditary hemochromatosis. *Blood Rev* 1994; 8: 193-8
[618] Rouault TA. Hereditary hemochromatosis. *JAMA* 1993; 269: 3152-4
[619] Crosby WH. Hemochromatosis: current concepts and management. Hosp Pract 1987; 22:173-92
[620] Bloom PD, Gordeuk VR, MacPhail AP. HLA-linked hemochromatosis and other forms of iron overload. *Dermatol Clin* 1995; 13: 57-63
[621] Barton JC, Bertoli LF. Hemochromatosis: the genetic disorder of the twenty-first century. *Nat Med* 1996; 2: 394-5
[622] Lauffer, RB. *Iron and Your Heart*. New York: St. Martin's Press, 1991

Clinical presentations:

- **Many patients are asymptomatic.**
- **Most patients eventually present with a problem that is attributed to another disorder**:
  - Diabetes: Patients may present with diabetes, which is erroneously attributed to metabolic syndrome or type-2 diabetes.[623]
  - Musculoskeletal pain: Patients may present with joint pain that is erroneously attributed to osteoarthritis[624], rheumatoid arthritis[625], or some other musculoskeletal syndrome.[626]
  - Cardiomyopathy: Patients may present with heart failure that is written off as "idiopathic cardiomyopathy."[627]
  - Liver disease: Hemochromatosis liver disease resembles and exacerbates viral hepatitis, alcoholic hepatitis, and porphyria.
- 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, hyperbilirubenemia and jaundice,

- 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.

Conditions causally associated with iron overload

Primary/genetic disorders
1. Homozygous genetic hemochromatosis
2. Heterozygous genetic hemochromatosis
3. African iron overload
4. African-American hemochromatosis (African-American iron overload)
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

[623] "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, Mortaji AM, Loreal O, Paillard F, Brissot P, Deugnier Y. A new syndrome of liver iron overload with normal transferrin saturation. *Lancet*. 1997 Jan 11;349(9045):95-7

[624] Axford JS, Bomford A, Revell P, et al. Hip arthropathy in genetic hemochromatosis: radiographic and histologic features. *Arthritis Rheum* 1991; 34: 357-61

[625] Bensen et al. Hemochromatoic arthropathy mimicking rheumatoid arthritis. A case with subcutaneous nodules, tenosynovitis, and bursitis. *Arthritis Rheum* 1978; 21: 844-8

[626] Olynyk J, Hall P, et al. Screening for genetic hemochromatosis in a rheumatology clinic. *Australian and New Zealand Journal of Medicine* 1994; 24: 22-25

[627] [No authors listed] Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 31-1994. A 25-year-old man with the recent onset of diabetes mellitus and congestive heart failure. *N Engl J Med*. 1994 Aug 18;331(7):460-6

- '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.

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
- Symphysis 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

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.**[628,629]
- Cardiomyopathy:
- Hepatopathy: **Iron overload is one of the most important rule-outs in patients with liver disease.**[630] Liver biopsy is often indicated to assess condition and disease co-existence.
- Musculoskeletal disorders: **Patients with polyarthropathy should be tested for iron overload.**[631]
  - Degenerative arthritis or osteoarthritis
  - Pseudogout, calcium pyrophosphate dihydrate deposition disease
  - Rheumatoid arthritis[632]
  - Ankylosing spondylitis: The resemblance here is only superficial, related primarily to calcification of the intervertebral discs and ligaments.[633]
- Hyperthyroidism and hypothyroidism[634,635]
- Hypogonadotrophic hypogonadism: Erectile dysfunction in men, subfertility in women[636]
- Porphyria cutanea tarda: "Virtually all patients have increased iron stores; serum iron, iron saturation, and ferritin values."[637] **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 non-sensitive 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.

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[628] Czink E, Tamas G. Screening for idiopathic hemochromatosis among diabetic patients. *Diabetes Care* 1991; 14: 929-30
[629] Phelps G, Chapman I, Hall P, Braund W, Mackinnon M. Prevalence of genetic haemochromatosis among diabetic patients. *Lancet* 1989; 2: 233-4
[630] Herrera JL. Abnormal liver enzyme levels: clinical evaluation in asymptomatic patients. *Postgrad Med* 1993; 93: 119-32
[631] M'Seffar AM, Fornasier VL, Fox IH. Arthropathy as the major clinical indicator of occult iron storage disease. *JAMA* 1977; 238: 1825-8
[632] Bensen WG, Laskin CA, Little HA, Fam AG. Hemochromatoic arthropathy mimicking rheumatoid arthritis. *Arthritis Rheum* 1978; 21: 844-8
[633] Bywaters EGL, Hamilton EBD, Williams R. The spine in idiopathic hemochromatosis. *Ann Rheum Dis* 1971; 30: 453-65
[634] Edwards CQ, Kelly TM, Ellwein G, Kushner JP. Thyroid disease in hemochromatosis. Increased incidence in homozygous men. *Arch Intern Med* 1983 Oct;143(10):1890-3
[635] Phillips G Jr, Becker B, Keller VA, Hartman J 4th. Hypothyroidism in adults with sickle cell anemia. *Am J Med* 1992 May;92(5):567-70
[636] Tweed MJ, Roland JM. Haemochromatosis as an endocrine cause of subfertility. *BMJ*. 1998 Mar 21;316(7135):915-6 bmj.bmjjournals.com/cgi/content/full/316/7135/915
[637] "Virtually all patients have increased iron stores; serum iron, iron saturation, and ferritin values." Rich MW. Porphyria cutanea tarda. *Postgrad Med*. 1999;105: 208-10, 213-4

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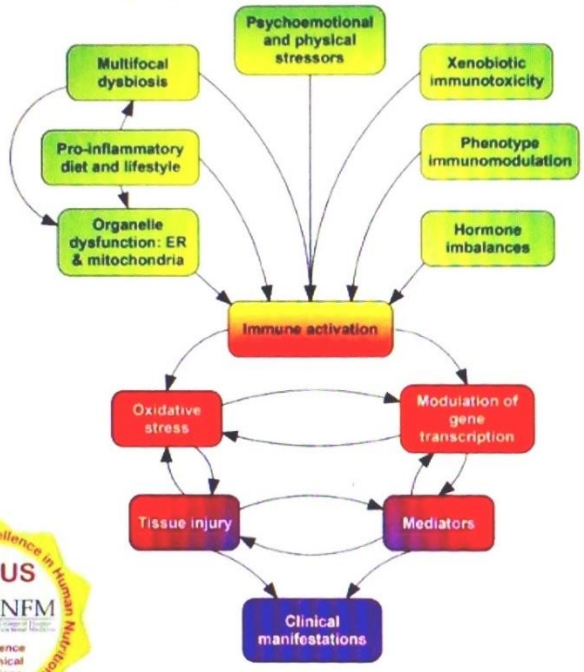

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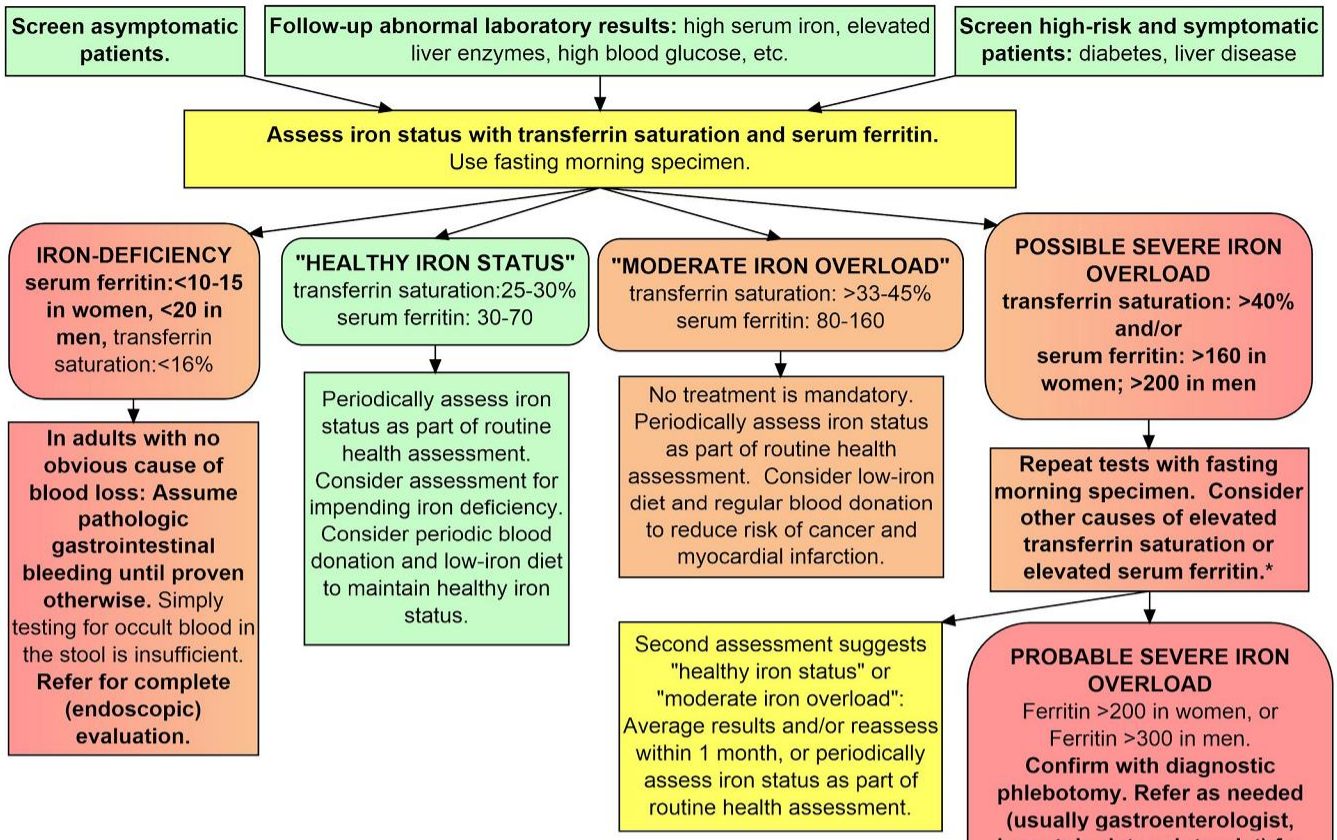
- **Physical examination/objective**:
  - The classic presentation of the fully developed disease is "bronze diabetes with arthritis and cirrhosis."
  - Physical examination should be specific for the patient's complaint(s) of arthritis, cardiomyopathy, diabetes, etc.
- **Imaging & laboratory assessments**:
  - **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."[638]
    - "Screening for hemochromatosis is both feasible and cost-effective, and we recommend its use in patients seeking medical care."[639]
    - "The high gene frequency in the general population warrants routine screening tests in asymptomatic healthy young adults."[640]
    - "Primary iron overload occurs in African Americans… Clinicians should look for this condition."[641]
  - 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. Transferrin saturation is a common test used for the detection of genetic hemochromatosis in research studies because it measures both iron levels but also disordered iron handling; this is why this test is best used in research screening of large populations. For clinicians, serum ferritin is very obviously the superior lab test for iron overload and 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*. Guidelines for screening for genetic hemochromatosis advocate the transferrin saturation test because it is a more sensitive assessment (compared to serum ferritin) for the hemochromatosis genotype which manifests phenotypically not simply as increased iron absorption and accumulation but also as an abnormality in iron handling which preferentially alters the transferrin saturation value, which is the ratio of serum iron to serum transferrin; the former rises due to increased iron absorption while the latter declines due to impaired hepatic synthetic function secondary to the preferential intraparenchymal deposition of iron in genetic hemochromatosis. Thus, genetic hemochromatosis is not simply a disorder characterized by increased iron absorption; it is also a disorder of iron handling/metabolism wherein iron is stored intracellularly in tissue parenchyma rather than (as in non-GH persons) in the reticuloendothelial system.
    - **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**.[642] Another benefit to the use of serum ferritin is the frequent detection of iron deficiency

[638] Fairbanks VF. Laboratory testing for iron status. *Hosp Pract* (Off Ed) 1991 Suppl 3:17-24
[639] Balan V, Baldus W, Fairbanks V, et al. Screening for hemochromatosis: a cost-effectiveness study based on 12, 258 patients. *Gastroenterology* 1994; 107: 453-9
[640] Gushusrt TP, Triest WE. Diagnosis and management of precirrhotic hemochromatosis. *W Virginia Med J* 1990; 86: 91-5
[641] Wurapa RK, Gordeuk VR, Brittenham GM, Khiyami A, Schechter GP, Edwards CQ. Primary iron overload in African Americans. *Am J Med.* 1996 Jul;101(1):9-18
[642] 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

Interpretation of iron status based on serum ferritin (in descending order)

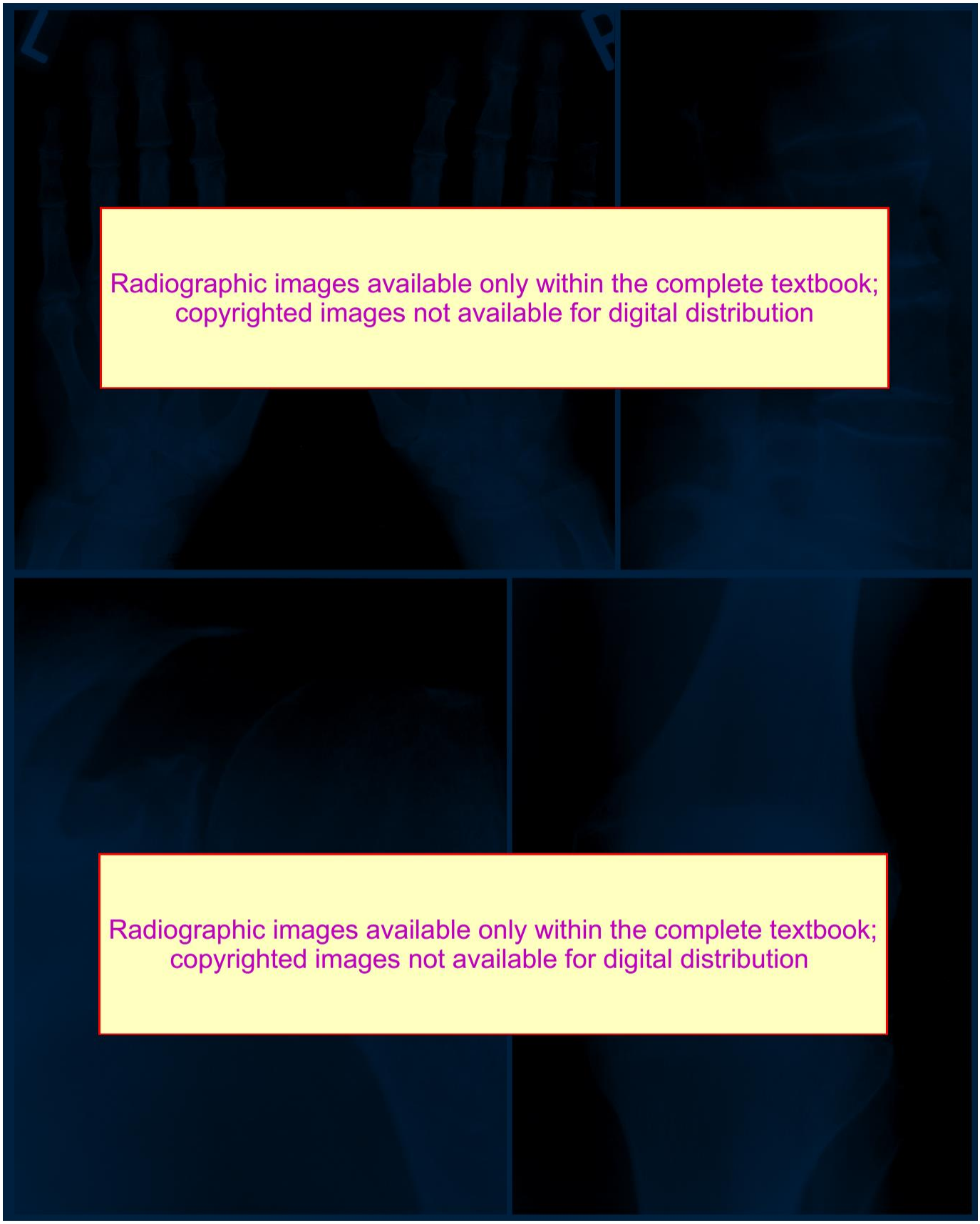
Ferritin	Categorization and management
≥ 800 mcg/L	Practically diagnostic of severe iron overload[643]: Repeat tests; rule out inflammation or occult pathology. Initiate phlebotomy and consider liver biopsy or MRI.
≥ 300 mcg/L	Probable iron overload; clear predisposition to iron accumulation[644]: Repeat tests; rule out inflammation or occult pathology. In men, initiate phlebotomy and consider liver biopsy or MRI.[645]
≥ 200 mcg/L	*In women*: Probable iron overload; clear predisposition to iron accumulation[646]: Repeat tests, rule out inflammation or occult pathology. In women, initiate phlebotomy and consider liver biopsy or MRI.[647] *In men*: High-normal *unhealthy* iron status with increased risk of myocardial infarction[648]: Rule out inflammation or occult pathology. No follow-up is mandated, yet blood donation and/or abstention from dietary iron are recommended preventative healthcare measures.
≥ 160 mcg/L	*In women*: Abnormal iron status[649]: Repeat tests, rule out inflammation or occult pathology. Consider phlebotomy and liver biopsy or MRI.
≥80-120 mcg/L	High-normal unhealthy iron status[650,651]: No follow-up is mandated; blood donation and abstention from dietary iron are suggested preventative healthcare measures. A subset of patients with restless leg syndrome (RLS, a condition also causally associated with intestinal bacterial overgrowth dysbiosis) have impaired transport of iron into the brain and therefore require slightly elevated ferritin/iron levels (up to 120) to enhance cerebral iron uptake.
40-70 mcg/L	**Optimal iron status for most people**[652,653]
< 20 mcg/L	Iron deficiency: Search for occult gastrointestinal blood loss with endoscopy or imaging assessments in adults; refer to gastroenterologist.[654,655]

[643] Milman N, Albeck MJ. Distinction between homozygous and heterozygous subjects with hemochromatosis using iron status markers and receiver operating characteristic (ROC) analysis. *Eur J Clin Biochem* 1995; 33: 95-8. See also Milman N. Iron status markers in hereditary hemochromatosis: distinction between individuals being homozygous and heterozygous for the hemochromatosis allele. *Eur J Haematol* 1991;47:292-8
[644] Olynyk JK, Bacon BR. Hereditary hemochromatosis: detecting and correcting iron overload. *Postgrad Med* 1994;96: 151-65
[645] "Therapeutic phlebotomy is used to remove excess iron and maintain low normal body iron stores, … 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
[646] Barton JC, Edwards CQ, Bertoli LF, Shroyer TW, Hudson SL. Iron overload in African Americans. *Am J Med* 1995; 99: 616-23
[647] Barton JC, McDonnell SM, Adams PC, et al. Management of hemochromatosis. *Ann Intern Med.* 1998 Dec 1;129(11):932-9
[648] Salonen JT, Nyyssonen K, Korpela H,et al. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation* 1992; 86: 803-11
[649] Nicoll D. Therapeutic drug monitoring and laboratory reference ranges. In: Tierney LM, et al. *Current Medical Diagnosis and Treatment.* Appleton and Lange, 1996: 1442
[650] Lauffer, RB. *Iron and Your Heart*. New York: St. Martin's Press, 1991: 79-8, 83-88, 162
[651] Sullivan JL. Iron and the sex difference in heart disease risk. *Lancet.* 1981 Jun 13;1(8233):1293-4
[652] Lauffer, RB. *Iron and Your Heart*. New York: St. Martin's Press, 1991: 79-8, 83-88, 162
[653] Vasquez A. High body iron stores: causes, effects, diagnosis, and treatment. *Nutritional Perspectives* 1994; 17: 13, 15-7, 19, 21, 28 and Vasquez A. Men's Health: Iron in men: why men store this nutrient in their bodies and the harm that it does. *MEN Magazine* 1997; Jan:11,21-23 vix.com/menmag/alexiron.htm
[654] Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. *N Engl J Med.* 1993;329(23):1691-5
[655] "Endoscopy revealed a clinically important lesion in 23 (12%) of 186 patients. … CONCLUSIONS: Endoscopy yields important findings in premenopausal women with iron deficiency anemia, which should not be attributed solely to menstrual blood loss." Bini EJ, Micale PL, Weinshel EH. Evaluation of the gastrointestinal tract in premenopausal women with iron deficiency anemia. *Am J Med.* 1998 Oct;105(4):281-6



Guide to Patient Management Based on Iron Status:

- Deficiency: Adult patients with iron deficiency must generally be presumed to have occult gastrointestinal blood loss and should therefore be referred for gastrointestinal endoscopy; this is consistent with the standard of care in medicine.
- Optimal: Ferritin levels between 40-70 mcg/L are generally optimal for most men and women; up to 120 mcg/L is reasonable for subsets of patients with restless leg syndrome, perhaps also those with recalcitrant depression and/or Parkinsonian features to allow sufficient iron entry into the brain for maximal dopamine production.
- Excess: Levels greater than 200 mcg/L in a woman or 300 mcg/L in a man are suggestive of iron overload and/or tendency toward accumulation and are physiologically unnecessary and medically unjustifiable, particularly as increased iron stores correlate with increased cancer mortality, increased cardiovascular mortality, and increased all-cause mortality.
- Overload: Diagnosis and treatment for iron overload can occur simultaneously with diagnostic/therapeutic phlebotomy. Genetic testing and liver biopsy are generally inefficient expenditures of financial and medial resources; genetic testing is largely irrelevant in the presence of the hemochromatosis phenotype (i.e., otherwise inexplicable iron accumulation) while liver biopsy exposes the patient to unnecessary treatment delays, risk, and expenses. Identification of idiopathic or genotropic iron overload requires testing of genetic relatives.



Musculoskeletal findings in genetic hemochromatosis: The only specific finding is the retrograde hook-like osteophytes at the metacarpal heads; other findings of intervertebral disc calcification, osteophytosis of the humeral head, and meniscal chondrocalcinosis are nonspecific and therefore easily nondiagnosed or misdiagnosed. Images here are respectfully used with kind permissions of Dr Manfred Harth and *Journal of Rheumatology* (hands and knee) and Dr JD Macfarlane and *Journal of Bone and Joint Surgery* (spine and shoulder) per personal correspondence, written permission, and provision of radiographs.

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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

To the Editor:

The recent clinical guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms, proposed by the American College of Rheumatology (1), provide useful information and a good review for clinicians. However, there is one important omission in these guidelines. Nowhere in the guidelines is hemochromatosis mentioned. Such a prevalent and potentially life-threatening disease certainly deserves to be considered in the evaluation of patients with musculoskeletal disorders.

Hereditary hemochromatosis is now thought to be the most common genetic disorder in the white population (2). Approximately 1 in 250 persons is homozygous for this disorder and will develop the characteristic clinical manifestations such as diabetes, cardiomyopathy, liver disease, endocrine dysfunction, and, most notable for this discussion, arthropathy or other musculoskeletal disorders (2). Although hereditary iron overload disorders have traditionally been thought of as occurring exclusively in whites, recent research by Barton et al (3) indicates that approximately 1 in 67 African-Americans is affected by an etiologically distinct and severe form of iron overload. Hereditary iron overload disorders have been detected in persons of every ethnic background.

Arthropathy affects up to 80% of iron-overloaded patients and is often the only manifestation of this disease (4). Joint pain is a common and early symptom of iron overload, and "bone pain" has also been described as a common initial complaint (5). Clinically and radiographically, hemochromatoic arthropathy can resemble osteoarthritis, calcium pyrophosphate dihydrate deposition disease, pseudogout, rheumatoid arthritis, ankylosing spondylitis, or generalized osteopenia with osteoporotic fractures (4,6,7). Since iron overload can cause such a wide array of musculoskeletal manifestations and because definitive clinical differentiation of iron overload from other arthropathies is very difficult, patients with peripheral arthropathy should be screened for iron overload. Indeed, recent research by Olynyk et al (8) indicates that the prevalence of iron overload is 5 times higher in patients with peripheral arthropathy than in the general population. Therefore, screening of patients with peripheral arthropathy for the possible presence of iron overload is justified.

Thus, since iron overload affects such a large portion of the population and arthropathy is a common manifestation of this disorder, patients with musculoskeletal symptoms should be screened for iron overload (4,8). The current literature suggests that everyone should be screened for iron overload even if there are no symptoms (8–10).

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1. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines: Guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. Arthritis Rheum 39:1–8, 1996
2. Olynyk JK, Bacon BR: Hereditary hemochromatosis: detecting and correcting iron overload. Postgrad Med 96:151–165, 1994
3. Barton JC, Edwards CQ, Bertoli LF, Shroyer TW, Hudson SL: Iron overload in African Americans. Am J Med 99:616–623, 1995
4. Faraawi R, Harth M, Kertesz A, Bell D: Arthritis in hemochromatosis. J Rheumatol 20:448–452, 1993
5. Adams PC, Kertesz AE, Valberg LS: Clinical presentation of hemochromatosis: a changing scene. Am J Med 90:445–449, 1991
6. Bywaters EGL, Hamilton EBD, Williams R: The spine in idiopathic hemochromatosis. Ann Rheum Dis 30:453–465, 1971
7. Eyres KS, McCloskey EV, Fern ED, Rogers S, Beneton M, Aaron JE, Kanis JA: Osteoporotic fractures: an unusual presentation of hemochromatosis. Bone 13:431–433, 1992
8. Olynyk J, Hall P, Ahern M, Kwiatek R, Mackinnon M: Screening for hemochromatosis in a rheumatology clinic. Aust N Z J Med 24:22–25, 1994
9. Baer DM, Simmons JL, Staples RL, Runmore GJ, Morton CJ: Hemochromatosis screening in asymptomatic ambulatory men 30 years of age and older. Am J Med 98:464–468, 1995
10. Adams PC, Gregor JC, Kertesz AE, Valberg LS: Screening blood donors for hereditary hemochromatosis: decision analysis model based on a 30-year database. Gastroenterology 109:177–188, 1995

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comment on the American College of Rheumatology guidelines
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- 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 hepatic 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
- 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.[656] **Life-saving diagnostic and therapeutic phlebotomy should never be denied or delayed for lack of liver biopsy in patients with laboratory indicators of iron overload**.[657]
- Genetic testing, such as for the HFE mutation: This is a waste of time and money in most clinical situations; these tests should be reserved for research purposes and for evaluation of affected relatives—especially children—of index cases. 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.

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.

Initiation of therapeutic phlebotomy is based on serum ferritin and does not require liver biopsy

"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 et al. Management of hemochromatosis. *Ann Intern Med.* 1998 Dec

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.
- When a hereditary iron overload disorder is diagnosed, all (first-degree) blood relatives must be screened for iron overload.

[656] "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;129:932-9

[657] Sullivan JL, as quoted in Crawford R, ed. "The debate." In: *Ironic Blood: information on iron overload*. West Palm Beach: Iron Overload Diseases Association. 1996; 16 (2)

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.[658]
  - 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 overload[659] and is probably suitable for use in patients with iron overload, particularly given its ability to reverse cirrhosis.[660] More recently, silybin has been shown to chelate iron in the gastrointestinal tract and reduce its absorption; the more important finding here is that silybin is safe for patients with hemochromatosis.
  - Iron-chelating potential of silybin in patients with hereditary hemochromatosis (*Eur J Clin Nutr* 2010 Oct[661]): "Milk thistle contains silybin, which is a potential iron chelator. … In this crossover study, on three separate occasions, 10 patients who were homozygous for the C282Y mutation in the HFE gene (and fully treated)

1726.6±346.8 versus tea 2099.3±223.3; P<0.05). In conclusion, silybin has the potential to reduce iron absorption, and this deserves further investigation, as silybin could be an adjunct in the treatment of hemochromatosis."

- 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 hemochromatoic cardiomyopathy given its safety and efficacy in other cardiomyopathies.[662,663,664,665,666,667,668,669]

Musculoskeletal disorders and iron overload disease—reminder to review the previous article on page 57

"Approximately one and a 250 persons is homozygous for this disorder and will develop the characteristic clinical manifestations such as diabetes, cardiomyopathy, liver disease, endocrine dysfunction, and, most notable for this discussion, arthropathy or other musculoskeletal disorders. ... The current literature suggests that everyone should be screened for iron overload, regardless of the presence or absence of symptoms."

Vasquez A. *Arthritis Rheum.* 1996 Oct

[658] Mclarlan et al. Congestive cardiomyopathy and hemochromatosis: rapid progression possibly accelerated by excessive ingestion of ascorbic acid. *Aust NZ J Med* 1982;12:187-8
[659] "CONCLUSIONS: Oral administration of silybin protects against iron-induced hepatic toxicity in vivo. This effect seems to be caused by the prominent antioxidant activity of this compound." Pietrangelo A, et al. Antioxidant activity of silybin in vivo during long-term iron overload in rats. *Gastroenterology.* 1995 Dec;109(6):1941-9
[660] Salmi et al. Effect of silymarin and chemical, functional, and morphological alterations of the liver. A double-blind controlled study. *Scand J Gastroenterol* 1982;17:517-21
[661] Hutchinson et al. The iron-chelating potential of silybin in patients with hereditary haemochromatosis. *Eur J Clin Nutr.* 2010 Oct;64(10):1239-41
[662] Greenberg S, Frishman WH. Co-enzyme Q-10: a new drug for cardiovascular disease. *J Clin Pharmacol* 1990; 30: 596-608
[663] Langsjoen PH, Langsjoen PH, Folkers K. Long-term efficacy and safety of coenzyme Q-10 therapy for idiopathic dilated cardiomyopathy. *Am J Cardiol* 1990; 65: 521-3
[664] Manzoli U, Rossi E, Littarru GP, et al. Coenzyme Q-10 in dilated cardiomyopathy. *Int J Tiss Reac* 1990; 12: 173-8
[665] Langsjoen et al. Pronounced increase of survival of patients with cardiomyopathy when treated with coenzyme Q-10 and conventional therapy. *Int J Tiss Reac* 1990;12:163-8
[666] Folkers K. Heart failure is a dominant deficiency of coenzyme Q-10 and challenges for future clinical research on CoQ-10. *Clin Investig* 1993; 71: s51-s54
[667] Folkers K, et al. Therapy with coenzyme Q-10 of patients in heart failure who are eligible or ineligible for a transplant. *Biochem Biophys Res Commun* 1992;182:247-53
[668] Mortensen SA, et al. Coenzyme Q-10: clinical benefits with biochemical correlates suggesting a scientific breakthrough.... *Int J Tiss Reac* 1990;12:155-62
[669] Langsjoen PH, Langsjoen PH, Folkers K. A six-year clinical study of therapy of cardiomyopathy with coenzyme Q-10. *Int J Tiss Reac* 1990; 12: 169-71

the wave of abnormal brain function—cortical spreading depression—that typifies migraine and which promotes its exacerbation; cortical spreading depression (CSD) leads to elaboration of the inflammatory and destructive enzyme MMP9 which causes leakiness of the BBB and subsequent brain edema (secondary to protein and water entry into the brain) and increased brain entry of substances from the blood, such as peripherally derived proinflammatory cytokines.[8,9] Brain edema in migraine is associated with and likely contributes to reduced brain perfusion (ie, reduced blood flow).[10] Very importantly, enhanced glutaminergic neurotransmission is itself sufficient to induce cortical spreading depression in experimental models. In an insightful article published in 2014 that supports the model that I have proposed, Malkov et al[11] showed that cortical spreading depression is caused by elaboration of reactive oxygen species (ROS, free radicals) and that these initiate "metabolic collapse" in brain cells.

All of these components are interconnected and thus the terms and components become (ultimately/practically) conceptually synonymous

Since microglial activation causes astrocyte activation, these terms can be summarized as glial activation. Microglial activation triggers formation of QUIN, which along with glutamate from astrocyte activation, causes stimulation of the NMDA receptor, promoting excitation of neurons. Since glial activation causes neuronal excitation, we can generally state that glial activation is synonymous with hyperexcitation of neurons, which segues into excitotoxic death of neurons and neurodegeneration. Persistent and prolonged hyperexcitation of neurons causes these neurons to strengthen their connections with each other, leading to facilitated pain perception, called central sensitization, as noted in **migraine**, **fibromyalgia**, and **complex regional pain syndrome**. Microglial activation—via release of nitric oxide (NO·) —causes mitochondrial dysfunction and additional glutamate release, causing the combination of metabolic impairment (e.g., reduced ATP formation) and increased metabolic demand, because activation of the NMDA receptor by glutamate and QUIN imposes increased metabolic demand on the neuron cells as they must control the resulting influx of calcium, which if not controlled will promote additional inflammation, impairment, and neuronal cell death.

5. Pain route—the covering of the brain is sensitive to metabolic and inflammatory changes within the brain, and interprets the inflammatory substances as pain signals: The trigeminal nerve (cranial nerve V, #5) receives transmissions from nerve endings surrounding the blood vessels of the membrane surrounding the brain (pia mater) and inside of the skull (dura mater). Recall as previously discussed and cited that the blood-brain barrier becomes more permeable when the brain is inflamed, thereby promoting passage/diffusion of inflammatory mediators from the brain to nearby neurons that receive noxious stimuli and convert the reception of those substances into nerve impulses received and interpreted as pain signals (nociception). While sensory innervation of the supratentorial dura mater membrane is via small meningeal branches of the trigeminal nerve, the innervation for the infratentorial dura mater is via upper cervical nerves, thereby establishing a bidirectional relationship between neck pain (and other subconscious neurologic inputs) and intracranial stimuli and structures.
6. Pain sensitization: As more pain signals are received, the brain facilitates the reception of these messages and thereby becomes more sensitive to the reception of pain; this is called central sensitization, and is greatly facilitated by brain inflammation and mitochondrial impairment.
7. Blood vessel dilation and constriction, and the role of serotonin-1D receptors: Metabolic impairment can trigger vasodilation, while inflammatory mediators promote vasoconstriction; both vasodilation and vasoconstriction have been noted in migraine.
8. Nuances in the contribution of various factors leads to different clinical presentations (e.g., migraine headaches vs cluster headaches); however, in the main primary headache conditions—migraine and cluster—the main themes of mitochondrial dysfunction and brain inflammation dominate the causal pathophysiology and therefore guide treatment: The model presented and used here is that cluster headache is simply a variant of migraine headache, with secondary rather than primary causes of the underlying mitochondrial dysfunction, and with a greater contribution by psychoemotional stress, muscle

[8] Moskowitz MA. Genes, proteases, cortical spreading depression and migraine: impact on pathophysiology and treatment. *Funct Neurol.* 2007 Jul-Sep;22(3):133-6
[9] Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. *J Am Geriatr Soc.* 2002 Dec;50(12):2041-56
[10] For evidence of brain edema (with associated hypoperfusion) in patients with migraine: Kim et al . Recurrent stereid-responsive cerebral vasogenic edema in status migrainosus and persistent aura. *Cephalalgia.* 2015 Jul;35:728-34. See also: Bereczki et al. Cortical spreading edema in persistent visual migraine aura. *Headache.* 2008 Sep;48:1226-9
[11] Malkov et al. Reactive oxygen species initiate a metabolic collapse in hippocampal slices: potential trigger of cortical spreading depression. *J Cereb Blood Flow Metab.* 2014 Sep;34(9):1540-9