Methods to determine hepatic iron content

AUTHOR: Maria Isabel Fiel, MD, FAASLD
SECTION EDITOR: Keith D Lindor, MD
DEPUTY EDITOR: Kristen M Robson, MD, MBA, FACG

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Jan 24, 2023.**

INTRODUCTION

Hereditary hemochromatosis, hematopoietic stem cell transplantation, myelodysplastic syndrome, chronic liver disease, dialysis, and blood transfusions for sickle cell disease and thalassemia can all cause iron to accumulate in the liver [1,2]. Iron overload is not just limited to the liver, but can also accumulate in other organs, particularly the heart and endocrine organs, resulting in end-organ damage and dysfunction [3]. Hemosiderosis is a commonly used term for iron accumulation in tissues from any cause. (See "Approach to the patient with suspected iron overload".)

Oxidative stress resulting in excess oxygen radicals and injury from tissue peroxidation are the main reasons why iron overload causes tissue damage [1,4]. Reducing the degree of iron overload is therefore paramount for most of these diseases to achieve successful treatment. Assessment of total body iron stores can be used to tailor titration of chelation therapy or phlebotomy in an attempt to reduce iron overload and its attendant complications [5]. Phlebotomy has been shown to slow the progression to cirrhosis in hereditary hemochromatosis, and it also reduces the risk of developing hepatocellular carcinoma [6]. Liver fibrosis may be reversible with phlebotomy therapy [7]. The risk of complications related to fibrosis and cirrhosis increases when there is significant iron overload, which is defined as hepatic iron concentration (HIC) greater than three times the upper limit of normal (greater than 90 micromol/g dry weight). Measurement of the HIC in liver tissue remains the reference method for evaluating the magnitude of body iron load. The term HIC was traditionally used for iron content in liver tissue as determined by chemical means. However, the terms HIC or liver

iron concentration have been applied for liver iron content using other non-invasive modalities [8,9]. Noninvasive imaging studies such as magnetic resonance imaging (MRI) are also used to evaluate for iron overload. (See 'Magnetic resonance imaging' below.)

Since the discovery of the *HFE* gene mutation (substitution by tyrosine for cysteine at amino acid 282; C282Y) and two other genetic mutations (aspartate for histidine [H63D] and cysteine for serine [S65C]), the diagnosis of hereditary hemochromatosis has become more straightforward [2]. Tests for the *HFE* gene are performed when serum ferritin and transferrin saturation are elevated. However, a small number of individuals with hereditary hemochromatosis may be missed with these genetic tests [3]. Non-HFE forms of hereditary hemochromatosis are related to mutations in genes involved in iron homeostasis other than HFE. These uncommon conditions are caused by defects that affect the hepcidin-ferroportin axis. Additionally, phenotypic penetrance in HFE hereditary hemochromatosis is variable with regard to the degree of iron overload and the risk of liver disease, fibrosis, and cirrhosis [10]. As a result, a positive genetic test does not ensure that iron overload had developed. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'Diagnostic criteria'.)

Determination of the tissue HIC is the most definitive proof of iron overload [11]. It can be used to estimate the total iron burden and the approximate amount of phlebotomy required for a patient with iron overload [1,12-14]. The HIC can also detect mild iron overload, which may be missed with less sensitive modalities [15]. An elevated serum ferritin level alone is often not adequate for estimating total iron burden, particularly if coexisting inflammation is present.

This topic will review the tests that can be done to determine hepatic iron content. The approach to a patient with suspected iron overload and the diagnosis of hereditary hemochromatosis are discussed separately. (See "Approach to the patient with suspected iron overload" and "Clinical manifestations and diagnosis of hereditary hemochromatosis".)

DISORDERS ASSOCIATED WITH HEPATIC IRON DEPOSITION

Several forms of liver disease are associated with hepatic iron deposition, including:

- **Hereditary hemochromatosis**: The first stage of fibrogenesis in hereditary hemochromatosis is believed to be iron deposition [4]. A ductular reaction characterized by a proliferation of the most terminal branches of the biliary tree precedes the development of fibrosis in patients with hereditary hemochromatosis [16]. Hepatocyte senescence and replicative arrest occur with iron overload and are positively correlated with the hepatic iron concentration (HIC). (See 'Hepatic iron concentration' below.)

- Non-HFE hereditary hemochromatosis: Different patterns of iron overload can be seen. Patients with these conditions typically have earlier disease onset as compared with HFE hereditary hemochromatosis. In addition, cardiac involvement and hypogonadism are more prevalent and liver fibrosis and cirrhosis are more commonly seen [17].

- **Alcohol-associated liver disease**: Mild hemosiderosis is found in more than half of patients with alcohol-associated liver disease, even in the absence of cirrhosis [18,19]. However, liver explants from patients with alcohol-related liver disease undergoing liver transplantation show a similar pattern of iron deposition as hereditary hemochromatosis [20].

- **Hepatitis C virus (HCV) infection**: Iron deposition is seen in patients with HCV once cirrhosis develops. In a study of patients with HCV who had paired liver biopsies, histologic progression (defined by increasing fibrosis and portal inflammation) was not associated with a significant increase in HIC. However, a significant increase in HIC was observed once cirrhosis had developed [21].

- **Nonalcoholic fatty liver disease (NAFLD)**: Iron deposition has been seen in NAFLD (picture 1). In two large series, hepatic iron was identified in 35 and 49 percent of patients with NAFLD, respectively [22,23]. In a series of patients with NAFLD and dysmetabolic iron overload syndrome attributed to metabolic abnormalities, the HIC was shown to reach up to 100 micromol/g dry weight [9,24,25]. Hepatic iron has been shown to be related to the development of fibrosis in NAFLD [4], and phlebotomy may improve serum indices in patients with NAFLD [26].

- **Cirrhosis**: Iron overload occurs in cirrhosis regardless of the cause. There is marked heterogeneity in iron distribution from one nodule to another. Because of this, measurements such as the HIC that are taken from liver biopsies may not be reliable or reflective of total iron stores [8,21]. As a result, assessment of hepatic iron in patients with cirrhosis should be interpreted based on histologic findings. Although there is increased iron deposition in noncirrhotic chronic liver disease, the HIC is typically <100 micromol/g dry weight [27].

- **Wilson disease**: Iron overload can be found in association with high copper and zinc levels in Wilson disease [28].

- **Porphyria cutanea tarda (PCT)**: Moderate to marked liver iron overload, whether tested for by serum markers or by HIC, may be seen in patients with PCT. In a cohort of patients with PCT, 19 percent were shown to be homozygous for C282Y and 7 percent heterozygous for C282Y mutation [29]. By comparison, only one percent of control

patients had an *HFE* mutation. Phlebotomy is the mainstay of treatment in PCT patients with heavy iron overload [30,31].

The causes of iron overload are discussed elsewhere. (See "Approach to the patient with suspected iron overload", section on 'Causes of iron overload'.)

HEPATIC IRON CONCENTRATION

Use of HIC in clinical practice — Determining the hepatic iron concentration (HIC) is rarely needed to make a definitive diagnosis of hereditary hemochromatosis due to the availability of genetic testing [5,32]. However, patients with hereditary hemochromatosis may undergo a liver biopsy to determine the severity of liver disease, in which case the HIC can also be determined to estimate total iron stores. Patients with a serum ferritin >1000 microg/L are at particular risk of advanced fibrosis and may benefit from a staging liver biopsy [5,33]. Studies suggest that the HIC is a reliable indicator of whole liver iron concentration, provided an adequate sample is available (≥1 mg dry weight) [34]. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'Diagnostic criteria'.)

Determining the HIC can also be used for a patient with a suspected genetic iron overload disorder but negative testing for the common genetic mutations: C282Y, H63D, and S65C [10]. However, alternative tests to determine hepatic iron stores (such as magnetic resonance imaging [MRI]) are less invasive. The HIC correlates well with T2-weighted MRI [35], but studies suggest that the sensitivity of MRI is variable [15], so if the suspicion for iron overload is high but an MRI is negative, calculation of the HIC may still be needed. (See 'Magnetic resonance imaging' below.)

Measurement — The HIC is determined using either a colorimetric method or atomic absorption spectrophotometry (AAS) [27]. AAS is the biochemical assay considered to be the reference method [36]. The tests can be performed using fresh liver tissue that has been desiccated or liver tissue removed from a formalin-fixed, paraffin-embedded (FFPE) specimen [27,34]. One study found that the iron content measurements were equivalent using fresh or FFPE tissue [37], while a second study found that FFPE tissue had approximately 23 percent more iron [38]. Dry liver weight taken from FFPE tissue, particularly when the dry weight is ≥0.4 mg, is as accurate as fresh tissue. FFPE to determine the HIC is particularly useful when no fresh tissue is available and the diagnosis of hemochromatosis is only made based on histology [39].

The HIC is usually reported as micrograms of iron per gram of dry liver weight. The value is then converted to micromoles of iron per gram by dividing by 56, which is the molecular weight of

iron [37].

As an example:

HIC = 1550 mcg/g dry ÷ 56 = 27.68 micromol/g dry liver weight

Interpretation — Normal HICs range from 10 to 35 micromol/g dry liver weight [40]. Values >71 micromol/g are considered to be liver iron overload [12]. The HIC is often higher in C282Y homozygotes than in C282Y/H63D compound heterozygotes [41]. In one study, the mean HIC was 13,563 +/- 10,400 mcg/g for C282Y homozygotes versus 7781 +/- 4954 mcg/g for compound heterozygotes [42]. The difference was seen in both patients with and without cirrhosis.

The severity of iron overload can be classified as follows [43]:

- Mild: HIC >70 to <99 micromol/g dry weight
- Moderate: HIC 99 to 200 micromol/g dry weight
- Severe: HIC ≥200 micromol/g dry weight

In patients with hereditary hemochromatosis, the HIC and serum ferritin level are linearly related to the amount of iron removed with phlebotomy (and as a result, total body iron stores) [12]. Changes in the HIC and ferritin levels can help estimate phlebotomy needs over time, though neither can accurately predict the phlebotomy requirements for a given patient at the time of initial diagnosis [12]. HIC is also predictive of total body iron stores in patients with thalassemia major [34,44].

In patients with hereditary hemochromatosis, the HIC is higher in patients with cirrhosis than in patients without cirrhosis [45]. In the absence of other chronic liver disease, cirrhosis typically develops once the HIC is over 250 to 300 micromol/g [46]. In one study, the HIC was 85 percent sensitive and 84 percent specific for predicting cirrhosis when a cutoff value of ≥283 micromol/g was used [45].

HEPATIC IRON INDEX

The hepatic iron index (HII) is calculated from the hepatic iron concentration by dividing the quantitative iron in micromoles per gram of dry liver weight by the patient's age. Prior to the discovery of the *HFE* gene mutation, an HII of >1.9 was considered to be diagnostic for hereditary hemochromatosis [6]. However, the HII has been shown to be elevated even in those without the *HFE* genetic mutation [47].

A simple semiquantitative grading system for the amount of iron deposition (0 to 3) in liver biopsies based on iron staining has shown good correlation with the HII in patients with hereditary hemochromatosis [48]. In one study, a score of 1+ corresponded to an HII ≤1.9, a score of 2+ with an HII score of >2, and a score of 3+ correlated with an HII ≥4.4 (up to 8.3) [48].

OTHER METHODS TO DETERMINE IRON OVERLOAD

Other methods to evaluate iron overload include serum iron indices, magnetic resonance imaging (MRI), and histologic evaluation of liver biopsy specimens.

Iron indices — Serum ferritin and transferrin saturation levels are the values most commonly used to determine iron overload [5]. However, increased levels of serum ferritin can be caused by a variety of inflammatory states, metabolic disorders, neoplastic processes, diabetes, nonalcoholic fatty liver disease, and alcohol liver injury, and do not necessarily quantitatively reflect body iron content [2].

Magnetic resonance imaging — Noninvasive imaging studies such as magnetic resonance imaging (MRI) using T2 and R2 (FerriScan) measurements have become increasingly accurate for determining hepatic iron deposition and quantifying its severity (image 1) [49-53]. Liver iron concentration (LIC, estimated by MRI) that is >3 to 7 mg Fe/g dry weight (equivalent to approximately 53 to 125 micromol/g dry weight) indicates hepatic iron overload. The indications for and diagnostic accuracy of MRI in the evaluation of patients with suspected iron overload is discussed separately [15]. (See "Approach to the patient with suspected iron overload", section on 'Noninvasive imaging (MRI)'.)

The noninvasive reference standard for measurement of liver iron concentration is the biomagnetic liver susceptometry (BLS) using a superconducting quantum interference device (SQUID), which measures magnetic susceptibility, a quantitative property of tissue. When iron is present, the magnetic susceptibility of the liver is altered. Despite the advantages of the SQUID biomagnetometer, this system is available in only a few centers worldwide [54]. MRI-based quantitative susceptibility mapping (QSM) and confounder-corrected R2 mapping of the liver to estimate liver iron concentration has been shown to correlate with SQUID-BLS [54]. Because of correlation with SQUID, the MRI-based QSM shows promise as a more accessible method to determine liver iron concentration.

Liver biopsy — Liver biopsies remain the reference standard for measuring HIC [8]. In patients with hereditary hemochromatosis (HH) biopsies are typically performed to stage the degree of fibrosis, assess hepatic damage, and sometimes to quantify the HIC [11]. In addition, liver

biopsy can identify both the pattern and grade of liver iron deposition [48,55]. Liver biopsy can also identify other concurrent pathology, such as fatty liver disease and other metabolic disorders [27]. (See "Clinical manifestations and diagnosis of hereditary hemochromatosis", section on 'Liver biopsy for selected patients'.)

Liver biopsy specimens may be processed routinely, embedded in paraffin, and stained with hematoxylin-eosin, Masson trichrome, and a Perls' Prussian blue stain. The Prussian blue stain will highlight the degree and pattern of distribution of iron deposition (picture 2) [27].

Early in the course of hereditary hemochromatosis, there is a decreasing gradient of parenchymal iron distribution from periportal to centrilobular areas (seen in >93 percent of patients) (picture 3) [56]. The pattern is not specific for the C282Y *HFE* gene mutation [55].

Several scoring systems for hepatic iron deposition have been developed. Although not validated, the most commonly used are the Scheuer method and its modified version because of their simplicity [57]. The score is based on the percentage of hepatocytes with iron, and ranges from 0 to 4. Other scoring systems that have been developed are the Deugnier and Turlin, Rowe, Sindram and Marx, Conn, and Brissot systems [27]. Deugnier's histological scoring system correlates with measurement of the HIC [36]. There is also a modification of the histological scoring system for iron overload by Sindram and Marx that includes the size of iron granules to reach a final score. When this system was used in one study, there was a strong correlation between histologic score and HIC [58].

SUMMARY

- The role for hepatic iron concentration (HIC) and hepatic iron index (HII) determination has greatly diminished since genetic testing for hereditary hemochromatosis has become widely available. Determining the HIC is rarely needed to make a definitive diagnosis of hereditary hemochromatosis. However, patients with hereditary hemochromatosis may undergo liver biopsy to determine the severity of liver disease, in which case the HIC can also be determined to estimate total iron stores. The HIC appears to be a reliable indicator of whole liver iron concentration, provided an adequate sample is available (≥1 mg dry weight). (See 'Use of HIC in clinical practice' above.)

- Determining the HIC can be used for a patient with a suspected genetic iron overload disorder but with negative testing for the common genetic mutations: C282Y, H63D, and S65C. However, alternative tests to determine hepatic iron stores (such as magnetic

resonance imaging) are less invasive. (See 'Use of HIC in clinical practice' above and 'Magnetic resonance imaging' above.)

- The HIC is usually reported as micrograms of iron per gram of dry liver weight. The value is then converted to micromoles of iron per gram by dividing by 56, which is the molecular weight of iron. (See 'Measurement' above.)

  The severity of iron overload can be classified as follows:

  - Mild: HIC >70 to <99 micromol/g dry weight
  - Moderate: HIC 99 to 200 micromol/g dry weight
  - Severe: HIC ≥200 micromol/g dry weight

- The HII is calculated from the HIC by dividing the quantitative iron in micromoles per gram of dry weight by the patient's age. Prior to the discovery of the *HFE* gene mutation, an HII of >1.9 was considered to be diagnostic for hereditary hemochromatosis. However, the HII can be elevated even in patients without the *HFE* genetic mutation. (See 'Hepatic iron index' above.)

- Other methods to evaluate iron overload include serum iron indices, magnetic resonance imaging, and histologic evaluation of liver biopsy specimens. (See 'Other methods to determine iron overload' above.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Bruce Bacon, MD, who contributed to an earlier version of this topic review.

REFERENCES

1. Brissot P, Troadec MB, Bardou-Jacquet E, et al. Current approach to hemochromatosis. Blood Rev 2008; 22:195.
2. Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. Gastroenterology 2010; 139:393.
3. Bardou-Jacquet E, Ben Ali Z, Beaumont-Epinette MP, et al. Non-HFE hemochromatosis: pathophysiological and diagnostic aspects. Clin Res Hepatol Gastroenterol 2014; 38:143.

4. O'Brien J, Powell LW. Non-alcoholic fatty liver disease: is iron relevant? Hepatol Int 2012; 6:332.
5. Bacon BR, Adams PC, Kowdley KV, et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011; 54:328.
6. Kowdley KV, Trainer TD, Saltzman JR, et al. Utility of hepatic iron index in American patients with hereditary hemochromatosis: a multicenter study. Gastroenterology 1997; 113:1270.
7. Nadakkavukaran IM, Gan EK, Olynyk JK. Screening for hereditary haemochromatosis. Pathology 2012; 44:148.
8. Brittenham GM. Reference method for measurement of the hepatic iron concentration. Am J Hematol 2015; 90:85.
9. Britton L, Bridle K, Reiling J, et al. Hepatic iron concentration correlates with insulin sensitivity in nonalcoholic fatty liver disease. Hepatol Commun 2018; 2:644.
10. Bacon BR, Britton RS. Clinical penetrance of hereditary hemochromatosis. N Engl J Med 2008; 358:291.
11. Bacon BR. Measurement of hepatic iron concentration. Clin Gastroenterol Hepatol 2015; 13:64.
12. Olynyk JK, Luxon BA, Britton RS, Bacon BR. Hepatic iron concentration in hereditary hemochromatosis does not saturate or accurately predict phlebotomy requirements. Am J Gastroenterol 1998; 93:346.
13. Salgia RJ, Brown K. Diagnosis and management of hereditary hemochromatosis. Clin Liver Dis 2015; 19:187.
14. Ali S, Pimentel JD, Munoz J, et al. Iron overload in allogeneic hematopoietic stem cell transplant recipients. Arch Pathol Lab Med 2012; 136:532.
15. Sarigianni M, Liakos A, Vlachaki E, et al. Accuracy of magnetic resonance imaging in diagnosis of liver iron overload: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2015; 13:55.
16. Wood MJ, Gadd VL, Powell LW, et al. Ductular reaction in hereditary hemochromatosis: the link between hepatocyte senescence and fibrosis progression. Hepatology 2014; 59:848.
17. Sandhu K, Flintoff K, Chatfield MD, et al. Phenotypic analysis of hemochromatosis subtypes reveals variations in severity of iron overload and clinical disease. Blood 2018; 132:101.
18. Jakobovits AW, Morgan MY, Sherlock S. Hepatic siderosis in alcoholics. Dig Dis Sci 1979; 24:305.

19. Harrison-Findik DD. Role of alcohol in the regulation of iron metabolism. World J Gastroenterol 2007; 13:4925.
20. Fierro-Fine A, Guerin L, Hicsasmaz H, Brown KE. Clinical Factors Associated with Hepatocellular Iron Deposition in End-stage Liver Disease. J Clin Transl Hepatol 2020; 8:231.
21. Larson AM, Taylor SL, Bauermeister D, et al. Pilot study of the relationship between histologic progression and hepatic iron concentration in chronic hepatitis C. J Clin Gastroenterol 2003; 37:406.
22. Nelson JE, Wilson L, Brunt EM, et al. Relationship between the pattern of hepatic iron deposition and histological severity in nonalcoholic fatty liver disease. Hepatology 2011; 53:448.
23. Valenti L, Fracanzani AL, Bugianesi E, et al. HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with nonalcoholic fatty liver disease. Gastroenterology 2010; 138:905.
24. Turlin B, Mendler MH, Moirand R, et al. Histologic features of the liver in insulin resistance-associated iron overload. A study of 139 patients. Am J Clin Pathol 2001; 116:263.
25. Britton LJ, Subramaniam VN, Crawford DH. Iron and non-alcoholic fatty liver disease. World J Gastroenterol 2016; 22:8112.
26. Aigner E, Theurl I, Theurl M, et al. Pathways underlying iron accumulation in human nonalcoholic fatty liver disease. Am J Clin Nutr 2008; 87:1374.
27. Deugnier Y, Turlin B. Pathology of hepatic iron overload. Semin Liver Dis 2011; 31:260.
28. Boaru SG, Merle U, Uerlings R, et al. Laser ablation inductively coupled plasma mass spectrometry imaging of metals in experimental and clinical Wilson's disease. J Cell Mol Med 2015; 19:806.
29. Bulaj ZJ, Phillips JD, Ajioka RS, et al. Hemochromatosis genes and other factors contributing to the pathogenesis of porphyria cutanea tarda. Blood 2000; 95:1565.
30. Aarsand AK, Boman H, Sandberg S. Familial and sporadic porphyria cutanea tarda: characterization and diagnostic strategies. Clin Chem 2009; 55:795.
31. Liu LU, Phillips J, Bonkovsky H. Porphyria Cutanea Tarda, Type II. In: GeneReviews, Pagon R A, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Dolan CR, Fong CT, S mith R (Eds), University of Washington, Seattle 2013.
32. Olynyk JK, Trinder D, Ramm GA, et al. Hereditary hemochromatosis in the post-HFE era. Hepatology 2008; 48:991.
33. European Association For The Study Of The Liver. EASL clinical practice guidelines for HFE hemochromatosis. J Hepatol 2010; 53:3.

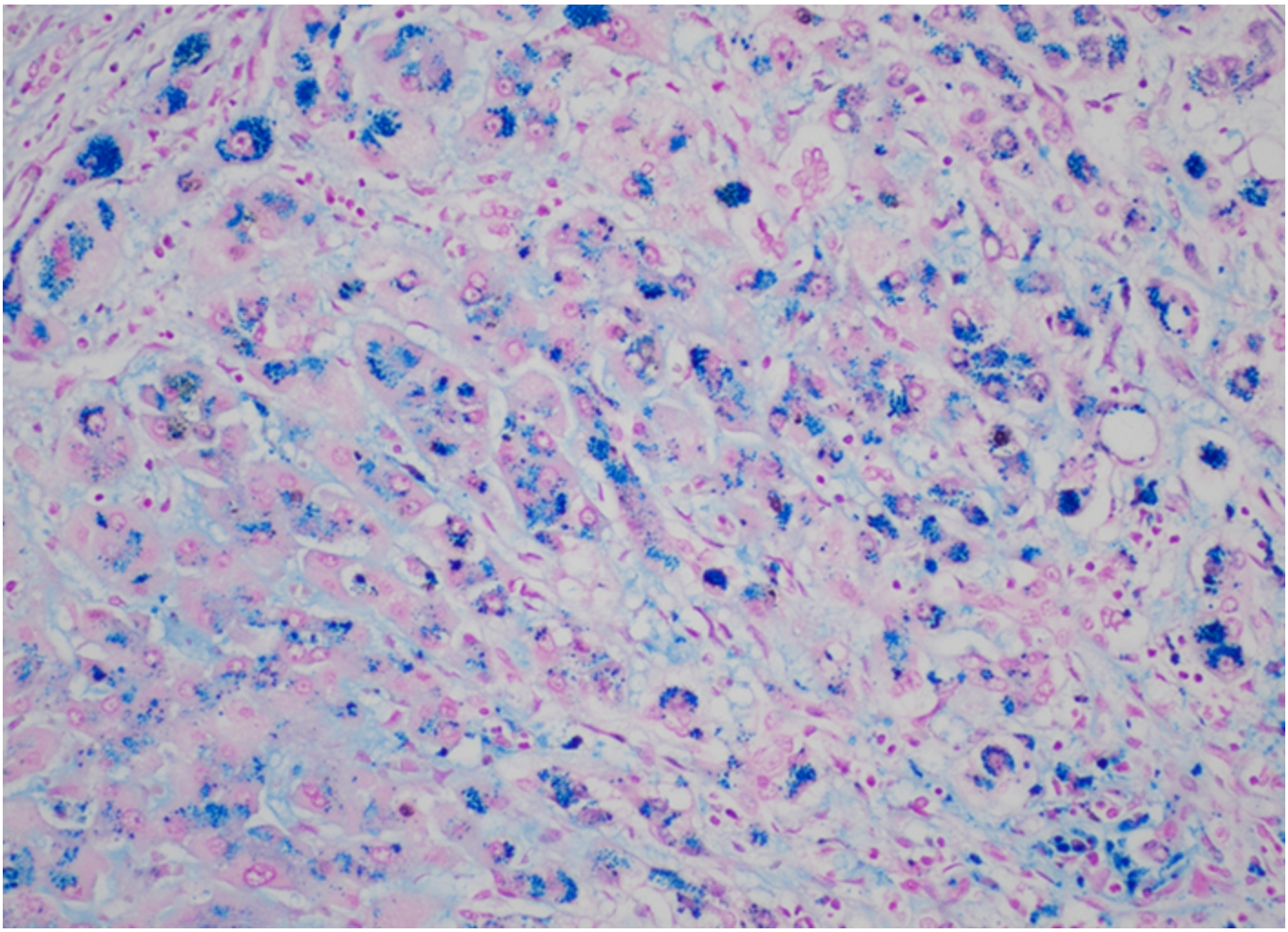
34. Urru SA, Tandurella I, Capasso M, et al. Reproducibility of liver iron concentration measured on a biopsy sample: a validation study in vivo. Am J Hematol 2015; 90:87.
35. Gandon Y, Olivié D, Guyader D, et al. Non-invasive assessment of hepatic iron stores by MRI. Lancet 2004; 363:357.
36. Deugnier Y, Margules S, Brissot P, et al. Comparative study between biochemical and histological methods and image analysis in liver iron overload. J Clin Pathol 1982; 35:45.
37. Olynyk JK, O'Neill R, Britton RS, Bacon BR. Determination of hepatic iron concentration in fresh and paraffin-embedded tissue: diagnostic implications. Gastroenterology 1994; 106:674.
38. Butensky E, Fischer R, Hudes M, et al. Variability in hepatic iron concentration in percutaneous needle biopsy specimens from patients with transfusional hemosiderosis. Am J Clin Pathol 2005; 123:146.
39. Beilby JP, Prins AW, Swanson NR. Determination of hepatic iron concentration in fresh and paraffin-embedded tissue. Clin Chem 1999; 45:573.
40. Brissot P, Bourel M, Herry D, et al. Assessment of liver iron content in 271 patients: a reevaluation of direct and indirect methods. Gastroenterology 1981; 80:557.
41. Bacon BR, Olynyk JK, Brunt EM, et al. HFE genotype in patients with hemochromatosis and other liver diseases. Ann Intern Med 1999; 130:953.
42. Cheng R, Barton JC, Morrison ED, et al. Differences in hepatic phenotype between hemochromatosis patients with HFE C282Y homozygosity and other HFE genotypes. J Clin Gastroenterol 2009; 43:569.
43. Adams P, Brissot P, Powell LW. EASL International Consensus Conference on Haemochromatosis. J Hepatol 2000; 33:485.
44. Angelucci E, Brittenham GM, McLaren CE, et al. Hepatic iron concentration and total body iron stores in thalassemia major. N Engl J Med 2000; 343:327.
45. Adams PC. Is there a threshold of hepatic iron concentration that leads to cirrhosis in C282Y hemochromatosis? Am J Gastroenterol 2001; 96:567.
46. Powell LW, Dixon JL, Ramm GA, et al. Screening for hemochromatosis in asymptomatic subjects with or without a family history. Arch Intern Med 2006; 166:294.
47. Cotler SJ, Bronner MP, Press RD, et al. End-stage liver disease without hemochromatosis associated with elevated hepatic iron index. J Hepatol 1998; 29:257.
48. Nash S, Marconi S, Sikorska K, et al. Role of liver biopsy in the diagnosis of hepatic iron overload in the era of genetic testing. Am J Clin Pathol 2002; 118:73.

49. Banerjee R, Pavlides M, Tunnicliffe EM, et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. J Hepatol 2014; 60:69.
50. Wood JC. Estimating tissue iron burden: current status and future prospects. Br J Haematol 2015; 170:15.
51. St Pierre TG, El-Beshlawy A, Elalfy M, et al. Multicenter validation of spin-density projection-assisted R2-MRI for the noninvasive measurement of liver iron concentration. Magn Reson Med 2014; 71:2215.
52. Paisant A, d'Assignies G, Bannier E, et al. MRI for the measurement of liver iron content, and for the diagnosis and follow-up of iron overload disorders. Presse Med 2017; 46:e279.
53. Hernando D, Zhao R, Yuan Q, et al. Multicenter Reproducibility of Liver Iron Quantification with 1.5-T and 3.0-T MRI. Radiology 2023; 306:e213256.
54. Sharma SD, Fischer R, Schoennagel BP, et al. MRI-based quantitative susceptibility mapping (QSM) and R2* mapping of liver iron overload: Comparison with SQUID-based biomagnetic liver susceptometry. Magn Reson Med 2017; 78:264.
55. Brunt EM, Olynyk JK, Britton RS, et al. Histological evaluation of iron in liver biopsies: relationship to HFE mutations. Am J Gastroenterol 2000; 95:1788.
56. Deugnier YM, Loréal O, Turlin B, et al. Liver pathology in genetic hemochromatosis: a review of 135 homozygous cases and their bioclinical correlations. Gastroenterology 1992; 102:2050.
57. SCHEUER PJ, WILLIAMS R, MUIR AR. Hepatic pathology in relatives of patients with haemochromatosis. J Pathol Bacteriol 1962; 84:53.
58. Tavassoli H, Mahjoub F, Jahanzad E, et al. Introducing a new histologic scoring system for iron deposition in liver of thalassemic patients, compared with atomic absorption spectrometry. Exp Toxicol Pathol 2015; 67:365.

Topic 3614 Version 25.0

GRAPHICS

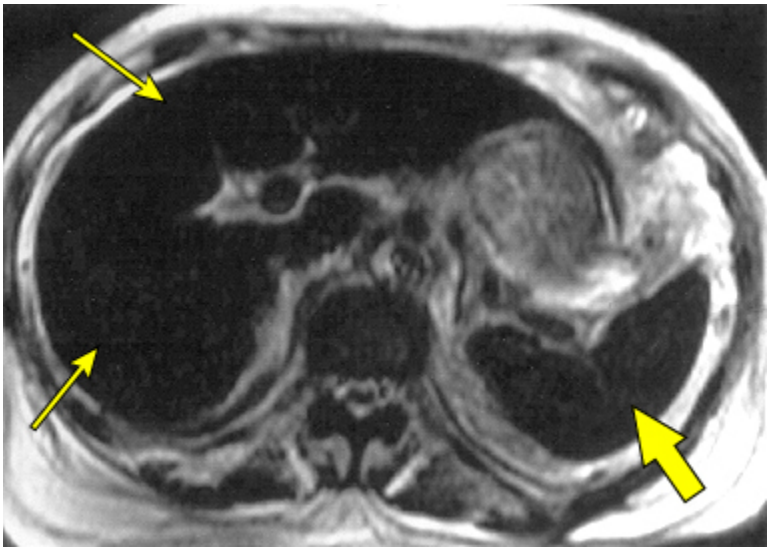
Iron overload in nonalcohol-associated fatty liver disease



There are fine to coarse blue granules in the cytoplasm of hepatocytes corresponding to deposits of iron. Note that these are associated with vacuoles, representing steatosis. (Perls' Prussian blue stain, original magnification ×400.)

Graphic 103741 Version 2.0

Hemochromatosis on magnetic resonance imaging

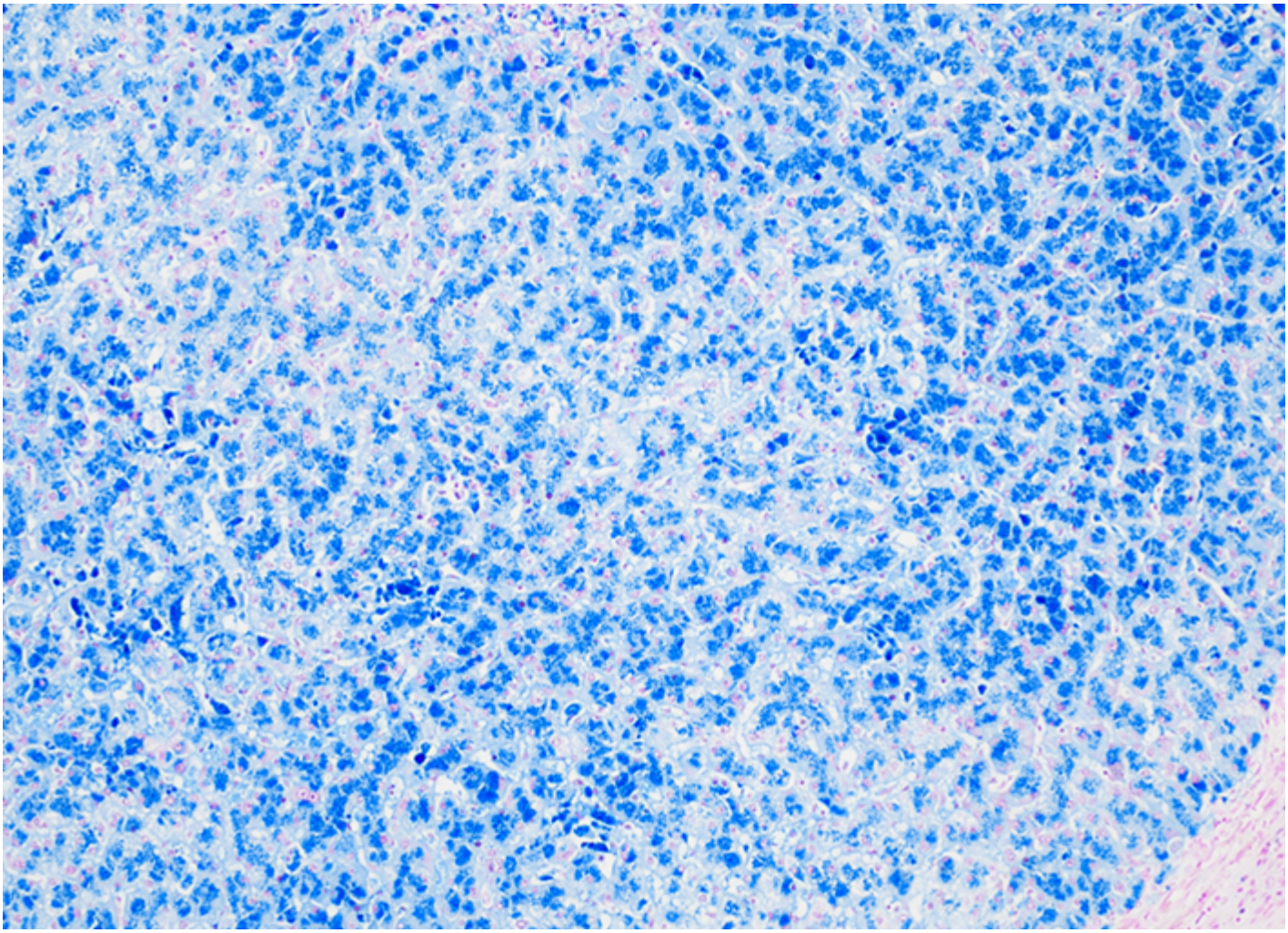


72-year-old female with hemochromatosis suggested by MRI. T1-weighted images show a black hypointense liver characteristic of iron overload (arrows) and a similar low intensity of the spleen (thick arrow).

Courtesy of Martina Morrin, MD.

Graphic 56593 Version 4.0

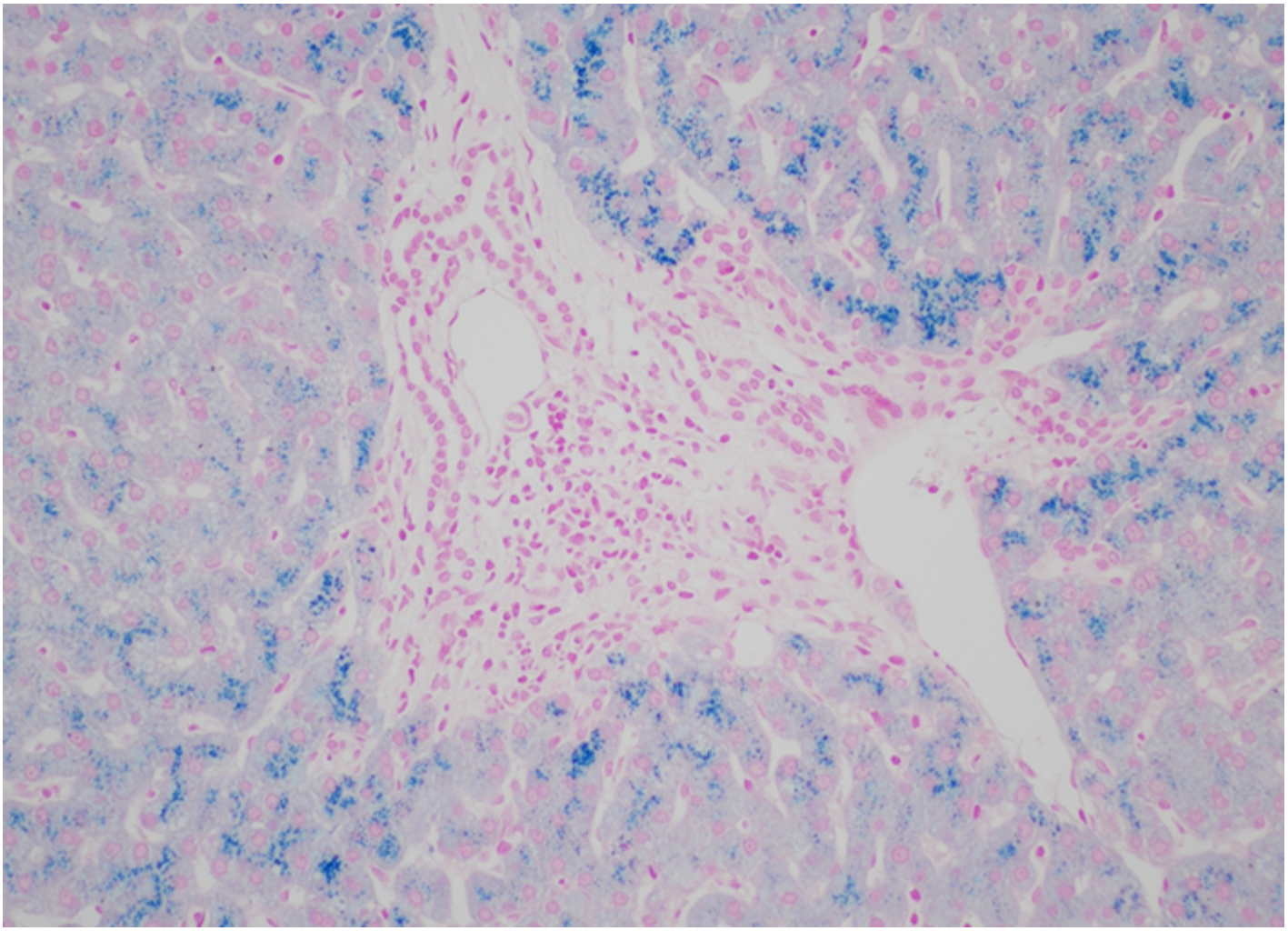
Iron overload in hereditary hemochromatosis



There is diffuse deposition of coarse iron granules (++++) involving the hepatic parenchyma, the reticuloendothelial system (Kupffer cells and portal macrophages), and endothelial cells. The typical decreasing gradient from periportal to centrilobular zones initially seen in this disease is not apparent due to the panlobular involvement by iron in this case. (Perls' Prussian blue stain, original magnification ×400.)

Graphic 103742 Version 2.0

Hepatic iron distribution in hereditary hemochromatosis



Early in the course of hereditary hemochromatosis, there is a decreasing gradient of parenchymal iron distribution from periportal to centrilobular areas. (Prussian blue stain.)

Graphic 105340 Version 2.0

Contributor Disclosures

Maria Isabel Fiel, MD, FAASLD No relevant financial relationship(s) with ineligible companies to disclose. **Keith D Lindor, MD** Consultant/Advisory Boards: Pliant [DSMB member]. All of the relevant financial relationships listed have been mitigated. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→