Ferritin

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GI for GPs

Faculty Disclosure

- **Faculty:** Marilyn Zeman
- **Relationships with commercial interests:**
  - **Grants/Research Support:** none
  - **Speakers Bureau/Honoraria:** none
  - **Consulting Fees:** none
  - **Other:** none

Objectives

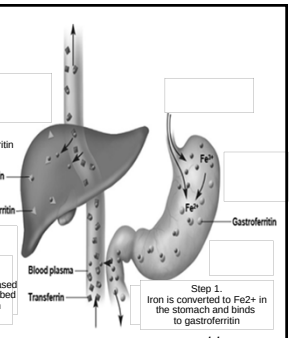
- Outline the causes and complications of hyperferritinemia and iron overload syndromes.
- Identify when an elevated ferritin suggests hereditary hemochromatosis and when treatment is required.

Iron absorption and distribution

Ferritin: an indirect measure of iron stores.

Transferrin iron saturation index (tsat): the amount of iron bound to transferrin.

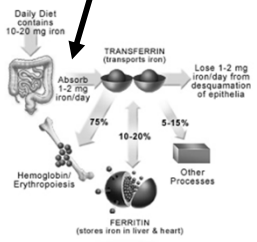
TIBC (total iron binding capacity): an indirect measure of transferrin in serum.



www.mhhe.com

Tsat= serum Fe/TIBC x 100

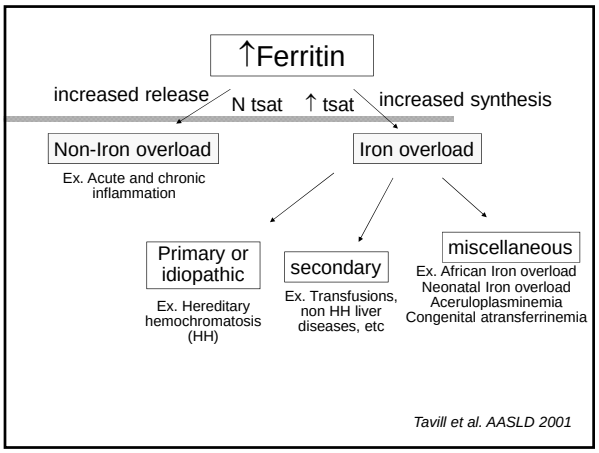
With Hereditary Hemochromatosis can absorb up to ~4 mg/day



no physiologic pathway for excretion of iron

↑ Absorption of iron → ↑ tsat → ↑ iron deposition in organs →↑ ferritin

www.cdc.com



Tavill et al. AASLD 2001

It is estimated that ~90% of patients with hyperferritinemia seen in routine medical practice do not have iron overload.

Adams & Barton, 2011

Spectrum of hyperferritinemia

Causes	Ferritin 300-1,000	Ferritin 1,000-5,000	Ferritin >10,000
Not iron overload	Metabolic syndrome/NAFLD Daily alcohol consumption Systemic inflammation Hyporegenerative anemias not treated by transfusion (CRF, marrow failure) Malignancy Unknown	Hereditary-hyperferritinemia cataract syndrome (HHCS) Alcoholic liver disease Viral hepatitis	Still's disease SLE Opportunistic infections in immunocompromised hosts Hemophagocytic Lymphohistiocytosis (HLH) Fulminant liver failure
Iron overload primary	Early hemochromatosis	Hemochromatosis Aceruloplasminemia Ferroportin mutations	
secondary		Secondary iron overload (transfusion related, ineffective erythropoiesis) Alcoholic liver disease Viral hepatitis	

adapted from Beaton & Adams, 2012

- Non-iron overload: ferritin tends to be acute, vary and <1000.
- If elevated ferritin not due to iron overload, treat condition not elevated ferritin.

Hyperferritinemia with iron overload

Iron indices in iron overload*

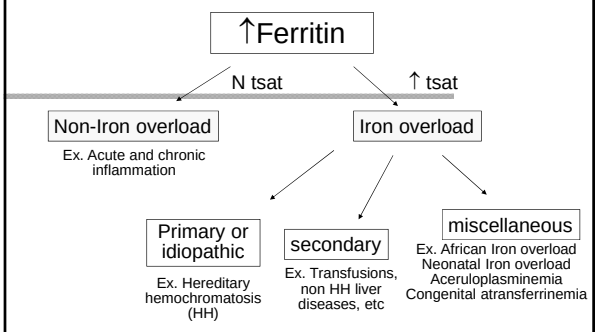
Transferrin saturation	*Sensitivity %*	*Specificity %*
≥ 45%	94	94
Ferritin	***Sensitivity %***	***Specificity %***
≥ 300 ug/L	50	88

*n=3011 C282Y/C282Y

Olynyk et al. NEJM. 1999

Must consider:

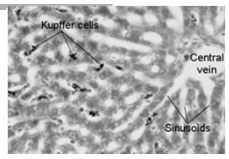
1. Ferritin is an acute phase reactant. In iron overload becomes abnormal only when loading has advanced to liver involvement.
2. Transferrin saturation is the ratio of serum Fe and transferrin, and therefore is impacted by situations which effect these variables, ex. alcohol ↑ Fe absorption→↑tsat. Chronic liver disease ↓ transferrin synthesis→↓transferrin (ie.TIBC)→↑tsat.



Tavill et al. AASLD 2001

Secondary Causes of Iron Overload

- Iron is deposited in Kupffer cells (macrophages of liver) and is mild.
- Kupffer cell iron loading is relatively innocuous (called hemosiderosis).



- When iron burden overwhelms ability of Kupffer cells to sequester iron, hepatocyte iron overload develops. *Piperno, 1998*
- …then, secondary iron overload can lead to liver disease, similar to that seen in primary iron overload.

Therefore can have iron overload without hepatic damage

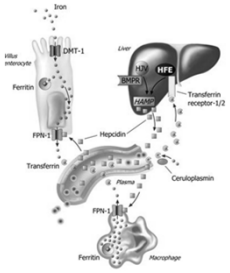
Secondary causes of iron overload

- Examples:
  - Iron loading anemias and transfusion:
    -thalassemia major
    -sideroblastic anemia
    -chronic hemolytic anemia
  - Dietary and transfusional iron overload
  - Chronic liver disease (alcohol, NASH, HCV, HBV)
  - Insulin resistance
  - Porphyria cutanous tarda

Treatment of hemosiderosis and secondary iron overload: treat condition. If not enough, remove iron with phlebotomy and/or iron chelation drugs depending on anemia and tolerability.

Primary/Idiopathic Causes of Iron Overload

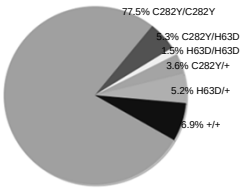
- Hereditary hemochromatosis
  - *HFE* related
    - C282Y/C282Y
    - C282Y/H63D
    - Other *HFE* mutation
  - Non-*HFE* related*
    - Hemojuvelin (*HJV*)
    - Transferrin receptor-2 (*TfR2*)
    - Ferroportin (*SLC40A1*)
    - Hepcidin (*HAMP*)
    - African iron overload



*account for <5% of cases encountered.

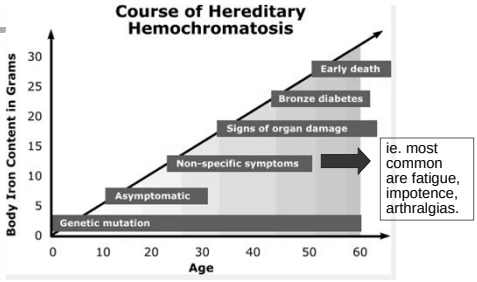
HFE- Hereditary Hemochromatosis

- Autosomal Recessive trait.
- HFE prevalence 1/150- 1/200 of Northern European descent.[1]
- Effect is unregulated increased Fe absorption from duodenum.
- Ferritin >1000 predicts presence of cirrhosis.[2]
- Individuals with asymptomatic HH and ferritin <1000 at low risk for developing signs and symptoms in the future.[3]



Hanson et al. 2001

1. Bacon. 2001; 2.Beaton et al. 2002; 3. Beutler et al. 2002



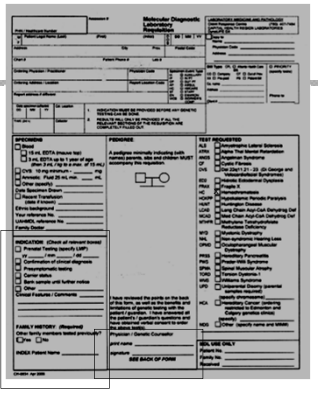
ie. symptoms and signs develop over decades. HH does not present with acute ↑ ferritin or acute ↑ in liver enzymes.

Phenotypic expression of HFE-HH

	Genotype	Phenotype
Definite cause of iron overload	C282Y/C282Y	50% of women and 20% of men have normal ferritin and never require therapy. Disease rarely presents in people younger than 40 yr old. 50% penetrance.
Possible cause of iron overload	C282Y/H63D	Most have normal iron levels. Moderate iron overload can develop if other risks*. <1%penetrance.
Not cause of iron overload	C282Y/normal	10% of Caucasians. Most have normal iron levels. Rarely develop iron overload without other risks*.
	H63D/H63D	Most have normal iron but mutation may be associated with increased t sat levels. Iron overload depends on other risks*.
	H63D/normal	20% of Caucasians. Iron overload unlikely. If overload seen consider other causes.

*risks include alcohol, viral hepatitis, obesity, etc. *Gochee et al. 2002*

C282Y/C282Y in absence of elevated iron is not diagnostic for HH. It represents a genetic susceptibility to develop it in future.



Molecular Diagnostic Laboratory Requisition

SPECIMEN

FAMILY HISTORY

TEST REQUESTED

INDICATION

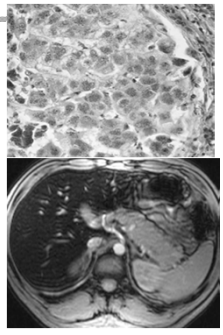
MOLECULAR DIAGNOSTIC LABORATORY

Alberta Health Services

INTERPRETATION

Diagnosis of iron overload and determination of cause

- History and blood work
- Genetics
- Liver biopsy
  - Iron in hepatocytes vs macrophages
  - Grade fibrosis
  - Determine Hepatic Iron Index (HII) (need to specify on path req.)
- MRI (FerriScan®)
- Quantitative phlebotomy



Quantitative phlebotomy

- 500 ml phlebotomy removes 200-250 g of mobilizable body iron and decreases serum ferritin ~25 ng/mL.
  - therefore if ferritin 1000, need 40 phlebotomies.
- Patient without significant iron overload cannot tolerate weekly phlebotomies
  - become deficient in 4-5 phlebotomies over 4-8 weeks.

Munoz et al. 2011

Summary- Common clinical scenario #1 (my approach)

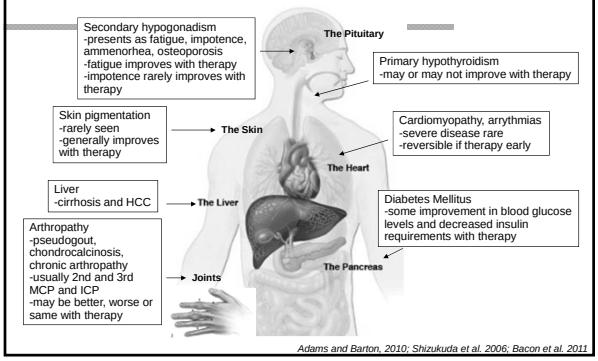
- 40 yr old obese man with DM, dyslipidemia, ALT 90, AST 80, ferritin 300. No previous blood work.
- Is this elevated ferritin from HH or metabolic syndrome?
- Approach:
  - Check tsat
    - ↑ tsat more consistent with HH but normal in metabolic syndrome.
  - Some would also suggest check ESR and CRP.
    - These could be up in inflammation but correlation with ferritin inconsistent.
  - Send genetic testing
    - Even if tsat normal, AASLD guidelines suggest testing. But even if HH genotype found, may not have phenotype.
  - Follow blood work with weight loss as first step.
    - Ferritin and liver tests do not vary with HH and would not improve with weight loss if due to HH.

Summary- common clinical scenario #2 (my approach)

- 40 yr old C282Y/H63D alcoholic with ALT 130, AST 100, ferritin 1000, tsat 60%
- Is this elevated ferritin and tsat from HH or alcoholism?
- Approach:
  - Follow blood work with alcohol abstinence.
    - If it because of alcohol use expect blood work to improve
  - Quantification of liver iron with biopsy, or alternatively with MRI or quantitative phlebotomy.
    - Liver biopsy could tell you if iron is in macrophages, hepatocytes or both. Only if iron is in hepatocytes would phlebotomy be needed. Biopsy can also tell you if evidence of fibrosis/cirrhosis, and can give quantification of iron.
    - MRI can also quantify iron load.
    - Quantitative phlebotomy (if unable to have biopsy or MRI). If patient becomes anemia within a few phlebotomies then not iron overload.

Thank you

Complications of HFE-HH



Adams and Barton, 2010; Shizukuda et al. 2006; Bacon et al. 2011

Liver complications of HFE-HH

Liver fibrosis in 5-20%[1]

↓

Cirrhosis in 2-6%[1]

>60 g/d alcohol increases risk of cancer by 9 fold[2]

↓

20 fold increased lifetime risk
4% annual incidence rate[3]

Hepatocellular cancer in 30-50% cirrhotics
Death from cirrhosis complications 20%[4]

- Risk factors for HCC include cirrhosis, severity, advanced age, alcoholism, smoking, HBV/HCV infection.
- Phlebotomy can reverse fibrosis but does not reverse cirrhosis and does not decrease risk of cancer.

1. Powell et al. 2006; 2. Fletcher et al. 2002; 3. Harrison & Bacon, 2005; 4. Adams, 1997

Genetic Hemochromatosis

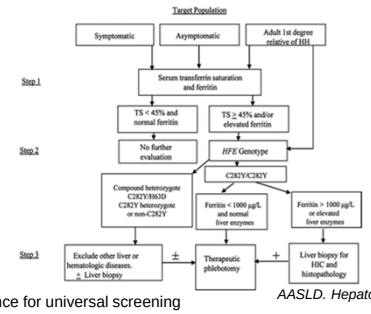
	Adult ("classical") hemochromatosis		Juvenile hemochromatosis	
HH type	Type I	Type III	Type IIA	Type IIB
Protein	HFE	TfR2	Hemojuvelin	Hepcidin
Gene	HFE	TfR2	HJV	HAMP
Transmission	AR	AR	AR	AR
Frequency	Frequent	Limited cases	Limited families	Very rare
Ethnic background	North European	Southern European, Japanese	Southern European	Southern European
Clinical findings	Ubiquitous	Ubiquitous	Heart failure, hypogonadism	Ubiquitous

Adapted from Anguilar-Martinez et al. 2005

Other Causes of Hereditary Hyperferritinemia

Disease	Inheritance	Clinical
Ferroportin disease	AD	Anemia, minimal if any iron overload
Hereditary Hyperferritinemia-Cataract Syndrome	AD	Early bilateral cataracts, no iron overload
Hypotransferritinemia	AR	Severe anemia, iron overload
Aceruloplasminemia	AR	Anemia, neurological symptoms, iron overload
DMT1 disease	AR	Anemia, neurological symptoms, iron overload
African iron overload	?	Iron overload
Neonatal hemochromatosis	?	Liver failure, iron overload

American Association for the Study of Liver Disease (AASLD) screening guidelines for Hereditary Hemochromatosis



No evidence for universal screening

AASLD. Hepatology 54(1),2011

Treatment of iron overload

- Iron depletion improves quantity and quality of life
- Phlebotomy
  - Tsat usually remains elevated until iron stores are depleted.
  - Ferritin may fluctuate and eventually falls.
  - In HH, some, especially women, may never reaccumulate iron after phlebotomy to depletion.

Crosby et al. 1986

Hereditary hemochromatosis
One phlebotomy (removal of 500 mL blood) weekly or biweekly
Check hematocrit/hemoglobin prior to each phlebotomy.
Allow hematocrit/hemoglobin to fall by no more than 20% of prior level
Check serum ferritin level every 10-12 phlebotomies
Stop frequent phlebotomy when serum ferritin reaches 50-100 μg/L
Continue phlebotomy at intervals to keep serum ferritin between 50 and 100 μg/L

AASLD. Hepatology 54(1),2011

Treatment of iron overload continued

- Iron chelating drugs (2nd line if phlebotomy not an option)
  - Deferoxamine: poor compliance in HH
  - Deferasirox, deferiprone: need more studies in HH
- Dietary management
  - No need to avoid meat
  - Limit intake of supplement of vitamin C to 500 mg/d
  - Avoid iron supplementation
  - Avoid alcohol
  - Avoid shellfish (vibrio vulnificus, Yersinia enterocolitica, listeria infections have been documented, as they are "iron-loving" organisms)

Adams & Barton, 2010

Summary

- Ferritin is a maker of iron stores, but may be falsely elevated in infection/inflammation.
  - Especially if acute, fluctuating, <1000 ng/mL
- Transferrin saturation more specific marker of iron overload.
- Genetic iron overload seen with C282Y/C282Y and possibly C282Y/H63D
  - Penetrance is low and having genetic susceptibility does not mean somebody will develop disease.
  - Consider other risk factors for iron overload in other genotypes and try to eliminate these risk factors.

Summary

- In HH iron overload, symptoms and abnormal liver tests develop over decades.
- Iron overload diagnosed by liver biopsy, MRI, quantitative phlebotomy.
- Phlebotomy treatment only indicated in those with diagnosed hepatic iron overload.
- If phlebotomy not an option or not tolerated, iron chelation drugs are an option.