Hemochromatosis: Causes, Symptoms, Diagnosis and Treatment

Hemochromatosis refers to a group of conditions characterized by **excessive iron accumulation in parenchymal tissues** , leading to **progressive organ damage** due to **iron-induced oxidative stress** .

It is the **most common autosomal recessive disorder** in individuals of Northern European descent and a leading cause of **severe iron overload** .

Etiology and Classification

Hemochromatosis can be **hereditary** or **acquired** .

A. Hereditary Hemochromatosis (HH)

Characterized by **increased intestinal iron absorption** due to genetic mutations, leading to systemic iron overload.

Type	Gene Involved	Inheritance	Key Features
Type 1 (Classic HH)	HFE (C282Y and H63D mutations)	Autosomal recessive	Most common form
Type 2A (Juvenile)	HJV (hemojuvelin)	Autosomal recessive	Presents before age 30
Type 2B	HAMP (hepcidin gene)	Autosomal recessive	Severe early onset
Type 3	TFR2 (transferrin receptor 2)	Autosomal recessive	Less common
Type 4 (Ferroportin disease)	SLC40A1 (ferroportin)	Autosomal dominant	May cause macrophage iron accumulation

B. Acquired Iron Overload

Includes:

- **Chronic transfusions** (e.g., thalassemia major, sickle cell anemia)
- **Sideroblastic anemia**
- **Chronic liver disease**
- **Iron-loading anemias**

Pathophysiology

- **Normal iron stores** : ~3.5 g in men; ~2.5 g in women
- **Toxicity** develops when iron stores exceed ~10 g
- Iron is absorbed via the **duodenum** , primarily regulated by **hepcidin** , a liver-produced hormone

- **Hepcidin suppresses ferroportin** , an iron transporter; mutations in **HFE** , **hemojuvelin** , or **hepcidin** result in **reduced hepcidin levels** , increasing iron absorption

Organ Damage Mechanism:

- Excess iron catalyzes formation of **free hydroxyl radicals** (Fenton reaction)
- **Oxidative damage** to cellular components leads to:
  - Liver fibrosis and cirrhosis
  - Pancreatic ?-cell dysfunction (diabetes mellitus)
  - Cardiomyopathy
  - Pituitary and gonadal failure
  - Joint degeneration

Clinical Features

Most patients are **asymptomatic** in early stages (?75%).

Early Non-Specific Symptoms:

- **Fatigue** (most common, ~74%)
- **Arthralgia** , especially of hands (44%)
- **Impotence** or decreased libido (~45%)
- **"Iron Fist"** : Pain in the **2nd and 3rd MCP joints** (knuckles)—a specific early sign

Advanced Organ-Specific Manifestations:

Organ	Manifestations
Liver	Hepatomegaly, elevated LFTs, fibrosis, cirrhosis, ?HCC risk
Pancreas	Diabetes mellitus ("bronze diabetes")
Heart	Restrictive or dilated cardiomyopathy, arrhythmias
Skin	Hyperpigmentation (bronze or gray skin)
Gonads	Hypogonadotropic hypogonadism, infertility
Joints	Chronic arthropathy (often confused with RA)

Diagnosis

Initial Screening:

- **Transferrin saturation (TS%)** : >45% is suggestive
- **Serum ferritin** : >300 ng/mL in men; >200 ng/mL in women
  (Note: Elevated ferritin also occurs in inflammation and liver disease)

Confirmatory Testing:

- **HFE gene testing** for C282Y and H63D mutations
- **Liver biopsy** : if diagnosis is unclear or if assessing fibrosis
- **MRI** : to assess liver and cardiac iron concentration

Management

1. Phlebotomy (Therapeutic Venesection)

- **Mainstay of treatment**
- Weekly removal of 500 mL blood until ferritin <50 ng/mL
- Maintenance phlebotomy every 3–4 months thereafter
- Benefits: Prevents or slows cirrhosis, improves fatigue and skin changes
- Limitations: Does **not prevent hepatocellular carcinoma (HCC)**

2. Iron Chelation Therapy

- Used in patients **unable to undergo phlebotomy**
- Agents: **Deferoxamine** , **Deferasirox**

3. Lifestyle and Dietary Recommendations

- Avoid **iron supplements** , **vitamin C supplements** (enhance absorption)
- Moderate alcohol use—excessive alcohol potentiates liver damage
- Avoid uncooked seafood (risk of *Vibrio vulnificus* infection)

4. Monitoring

- Routine follow-up with **serum ferritin** , **transferrin saturation**
- **Liver ultrasound or AFP** screening for HCC in cirrhotic patients

High-Yield Facts

- **Most specific symptom** : Pain in the 2nd and 3rd MCP joints ("Iron Fist")
- **Best initial test** : Transferrin saturation
- **Most accurate test** : Genetic testing for HFE mutations
- **Definitive treatment** : Regular phlebotomy
- **Risk of HCC** : Persists even after iron depletion in cirrhotic patients

Mnemonic: “IRON FIST”

I : Increased iron
R : Restrictive cardiomyopathy
O : Organ damage (pancreas, liver, pituitary)
N : Noticed skin (bronze)
F : Fatigue
I : Impotence
S : Second and third MCP pain
T : Transferrin saturation ?