IRON ABSORPTION

10–20 mg iron

Fe-containing proteins in other tissues

Haemoglobin in RBCs

Storage as Ferritin (→ Haemosiderin)

Absorption partly regulated by iron stores

Transport bond to transferrin

Fig. 13. Absorption utilization iron stores contain on the
Dietary iron

Duodenum (average, 1–2 mg per day)

Utilization

Muscle (myoglobin) (300 mg)

Plasma transferrin (3 mg)

Utilization

Bone marrow (300 mg)

Circulating erythrocytes (hemoglobin) (1800 mg)

Storage iron

Liver parenchyma (1000 mg)

Reticuloendothelial macrophages (600 mg)

Sloughed mucosal cells
Desquamation
Menstruation
Other blood loss (average, 1–2 mg per day)

Iron loss
**FIGURE 1.** Major iron flows and their regulation by hepcidin and ferroportin. Iron in transferrin is indicated in blue, and iron in erythrocytes is in red. Hepcidin controls the iron flow into plasma by inducing the endocytosis and proteolysis of the iron exporter ferroportin (brown).
Proteine del metabolismo cellulare del ferro

- La ferritina è la principale proteina di deposito intracellulare del ferro. E' formata da 24 subunità di tipo H e di tipo L ed è in grado di legare fino a 4500 atomi di ferro.

- DMT1 è un co-trasportatore di cationi biivalenti e H⁺ espresso in molti tessuti (enterociti, cellule eritroidi, rene, polmone, cervello...).

- Ha un ruolo nell'assorbimento del ferro nel duodeno e nel meccanismo di rilascio del ferro dalla transferrina.

- L'espressione di DMT1 è indotta da carenza di ferro e sono state identificate diverse isoforme della proteina.
Transferrina (Tf)

- Proteina di trasporto del ferro
- Glicoproteina, mw 75.000 Da, sintesi epatica
- Unica catena polipeptidica, due siti di legame per Fe³⁺

NT e CT: domini N e C terminali; Fe siti di legame del ferro

Recettore della transferrina

Fig. 2  Schematic representation of the human transferrin receptor molecule.
- High mannose oligosaccharide; ⊗ Complex type oligosaccharide; --- Covalently bound fatty acid; ▲ Transferrin
Figure 2. The Transferrin Cycle.
Iron-laden transferrin (Fe₂-Tf) binds to transferrin receptors (TIR) on the surface of erythroid precursors. These complexes localize to clathrin-coated pits, which invaginate to form specialized endosomes. A proton pump decreases the pH within the endosomes, leading to conformational changes in proteins that result in the release of iron from transferrin. The iron transporter DMT1 moves iron across the endosomal membrane, to enter the cytoplasm. Meanwhile, transferrin (Apo-Tf) and transferrin receptors are recycled to the cell surface, where each can be used for further cycles of iron binding and iron uptake. In erythroid cells, most iron moves into mitochondria, where it is incorporated into protoporphyrin to make heme. In nonerythroid cells, iron is stored as ferritin and hemosiderin.

<table>
<thead>
<tr>
<th>Iron status</th>
<th>Iron (μmol/L)</th>
<th>Ferritin (μg/L)</th>
<th>TIBC (μmol/L)</th>
<th>TIBC saturation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference ranges</td>
<td>Males 14-32</td>
<td>15-350*</td>
<td>45-72</td>
<td>30-50</td>
</tr>
<tr>
<td></td>
<td>Females 10-28</td>
<td>8-500*</td>
<td>45-72</td>
<td>30-50</td>
</tr>
<tr>
<td>Physiological changes</td>
<td>Pregnancy Variable*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Premenstrual ↓</td>
<td>N</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Steroid contraceptives ↑</td>
<td>N</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Disease status</td>
<td>Iron deficiency ↓</td>
<td>↓</td>
<td>↑</td>
<td>&lt;30</td>
</tr>
<tr>
<td></td>
<td>Iron overload ↑</td>
<td>↑</td>
<td>N or ↓</td>
<td>up to 100</td>
</tr>
<tr>
<td></td>
<td>Infections, neoplasms ↓</td>
<td>↑ or N</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Hypoplastic anaemia ↑</td>
<td>↑ or N</td>
<td>N or ↓</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

N, Normal; ↑, Increased; ↓, Decreased
* A plasma ferritin below 20 μg/L suggests that the body's iron stores are depleted.
† See p. 178.
macropoiéti reticolonodoteli.

Mutazioni della ferroporzione causano accumulo di ferro nel Reato o nei
telastoci e nel eptacodi.

Espressa sulle membrane basolaterali dei telastoci, nei macropoieti,
indicavano.

La ferroporzione s'unico esportatore del ferro dalle cellule filomis.
Perossidasi: cerulolessamina e efezione
Regolazione del trasporto del ferro mediata dall'epcidina

L'epcidina è un peptide di 25 amminoacidi prodotto dal fegato. Si lega alla ferroporina causando l'interruzione e la degradazione, in questo modo diminuisce l'esporto del ferro dagli enterociti e dai macrofagi nella circolazione sanguigna. L'espressione dell'epcidina è indotta da eccesso di ferro e infiammazione (IL-6), e repressa da anemia e ipossia.
FIGURE 3. Hepcidin: the amino acid sequence and structure. The NH$_2$-terminal segment known to interact with ferroportin (193) is shaded in light red. The characteristic cysteines and their disulfide bonds are shown in yellow.
FIGURE 5. Regulation of hepcidin synthesis in hepatocytes. The major regulatory influences include iron-transferrin and iron stores (blue), inflammation (green), and erythroid activity (red).
Molecular pathways regulating hepcidin transcription. JAK-STAT3 and BMPR-SMAD are the two key pathways that regulate hepcidin promoter activity. Iron-related mediators are shown in blue, and iron sensors in red. The erythroid regulators are in green. The erythroid regulator (red) and its transcription pathways are not known.
Cytosol contains at least two proteins that respond to changes in iron concentration. They act as effector molecules controlling the translation of mRNAs, which are important in iron metabolism. These iron regulatory proteins (IRPs) bind to specific stem–loop structures on certain mRNAs. IRP-1 is the best defined of these proteins. It contains an Fe₄S₄ cubane group when the cellular concentration of iron is high. This prosthetic group endows IRP-1 so that it possesses an aconitase (see p. 554) activity. However, since neither citrate nor isocitrate is present in significant amounts in the cytosol, the activity is only a potential one. At low iron concentrations, the cubane structure collapses, dissociating from the protein and leaving an apoenzyme without catalytic activity. However, it can now bind to specific mRNA stem–loop structures, known as iron responsive elements (IREs) (see Figure 24.3). Seven mRNAs, encoding proteins with defined functions in iron metabolism, are known to contain IREs (see Table 24.1 for details). However, a search of human data bank sequences has revealed about 70 genes which contain IREs, emphasizing the important role of iron in many as yet to be identified metabolic processes. This is a field of rapidly expanding knowledge. Five of these mRNA have single 5′ stem–loop structures; two mRNAs have 3′ IREs. Transferrin receptor has five 3′ stem–loop structures whereas divalent metal transporter 1 (DMT 1) has only one. The binding of the 5′ and 3′ flanking IREs leads to different translational effects. In the iron-deprived state, binding to the 3′ IRE of transferrin receptor (see Figure 24.4) leads to stabilization of the mRNA with reduced turnover and, therefore, an increased number of receptor-specific RNA

![Diagram of aconitase](image)

**FIGURE 24.3**
Ironresponsive protein 1.
Dark colored circles represent iron atoms and open circles inorganic sulfur atoms.
Mechanisms of function are not yet fully defined.

The DMT1 and CDO14A1 motifs play a role in iron reductase. Single 3' UTR 1 motifs are present in the mRNA encoding the erythroid-specific ALAS2. The mRNA encoding the mitochondrial enzyme synthesizes enzymes. The mitochondrial electron transport chain degrades the mRNA. The expression of the regulatory protein interacts with the binding and degradation of the mRNA.

The 5' UTR interacts with the 3' UTR to regulate the translation of the protein.

Figure 4: Regulation of cellular iron metabolism.
Figure 5. Interplay between Systemic and Cellular Iron-Regulatory Systems

(Left) In hepcidin-producing cells (for example, hepatocytes), iron-regulatory proteins (IRPs) can influence Hepcidin gene regulation by modulating levels of transferrin receptor 1 (TfR1) and/or hypoxia-inducible factor 2α (HIF2α); the iron-responsive element (IRE)/IRP system may also impact on Hepcidin expression by changing intracellular iron levels (dashed line).

(Right) Ferroportin expression is regulated by both hepcidin and IRPs. Furthermore, IRPs can potentially exert a direct positive effect on iron uptake via divalent metal transporter 1 (DMT1) or TfR1, or an indirect negative effect via HIF2α repression.
FIGURE 1 | Sensing of transferrin-bound iron and regulation of hepcidin expression in hepatocytes. The iron-sensing process involves binding of transferrin-bound iron to Tfr1 causing a dissociation of Hfe from the Hfe/Tfr1 partnership, relocation of Hfe to Tfr2 and presumably the formation of a large membrane-bound complex composed of Hfe/Tfr2/Hjv and BMPRII and I. This hepatocyte-membrane complex activates transduction cascade involving the phosphorylation of the Smad1/5/8 and subsequent binding of common Smad4 protein to form a transcriptional complex which directly activates hepcidin transcription. The Bmp/Smad signaling is the central pathway for the regulation of hepcidin transcription. Lack of Hfe and other components of the membrane-bound complex severely impair the phosphorylation of Smad1/5/8 and consequently the transcription of hepcidin. Combined deficiency of Hfe and Tfr2 results in decreased Erk/Mapk signaling activity in the liver, implicating that additional or parallel signaling pathway to Bmp/Smad may be involved in the control of hepatic hepcidin transcription.
Table 1. Characteristics according to HH types.

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>Gene Product Function</th>
<th>Gene Inheritance</th>
<th>Phenotype</th>
<th>Number</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH</td>
<td></td>
<td></td>
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</tbody>
</table>

**Table 1.** Characteristics according to HH types.
Figure 3. Schema of the HFE protein – transmembrane consisting of three extracellular alpha domains. Wild-type HFE binds to transferrin receptor reducing its affinity for iron-bound (holo)transferrin and thereby modulating iron entry into the cell via receptor-mediated endocytosis. The C282Y mutation disrupts a disulphide bond which prevents β2-microglobulin binding and subsequent cell surface expression. Disabled within the cell, mutant HFE is unable to interact with transferrin receptor and influence iron uptake.
Figure 1. Normal (A) and hemochromatosis (B) conditions. A1: HFE, HJV, and TFR modulates hepcidin synthesis by hepatocytes; A2: normal hepcidin levels; A3: hepcidin ferroportin interaction with internalization and ferroportin degradation in enterocytes; A4 normal iron absorption. B1: HFE or HJV or TFR2 gene mutations alter hepcidin synthesis modulation; B2: lower hepcidin levels; B3: decreased hepcidin-ferroportin interaction and increased ferroportin activity; B4: iron overload observed in types 1, 2 and hemochromatosis. TFR2: transferrin receptor 2; TFR1: transferrin receptor 1, HFE: HFI protein; HJV: hemojuvelin.
Acute porphyrias are a group of rare metabolic disorders that can cause a wide range of symptoms, from mild to life-threatening. They are caused by deficiencies in specific enzymes that are involved in heme biosynthesis. The clinical manifestations can vary widely, but they often include pain, neurological symptoms, and psychiatric symptoms. The diagnosis is typically made through a combination of clinical symptoms and laboratory tests. Treatment often involves the use of supportive care and medication to manage symptoms. An acute attack begins with minor behavioral changes, which can escalate to confusion, delirium, and seizures.

Figure 1: Porphyrias and heme biosynthesis

<table>
<thead>
<tr>
<th>Pyrrolase</th>
<th>Protoporphyrin IX</th>
<th>Protoporphyrinogen IX</th>
<th>Protoporphyrinogen III</th>
<th>Protoporphyrinogen III</th>
<th>Protoporphyrinogen III</th>
<th>Protoporphyrinogen III</th>
</tr>
</thead>
<tbody>
<tr>
<td>deaminase</td>
<td>deaminase</td>
<td>deaminase</td>
<td>deaminase</td>
<td>deaminase</td>
<td>deaminase</td>
<td>deaminase</td>
</tr>
<tr>
<td>6-aminolevulinic acid</td>
<td>6-aminolevulinic acid</td>
<td>6-aminolevulinic acid</td>
<td>6-aminolevulinic acid</td>
<td>6-aminolevulinic acid</td>
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<td>6-aminolevulinic acid</td>
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<tr>
<td>Corrinoid pyrrolcoporphyrin</td>
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<td>Corrinoid pyrrolcoporphyrin</td>
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<td>Corrinoid pyrrolcoporphyrin</td>
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<td>Uroporphyrinogen</td>
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<tr>
<td>Uroporphyrinogen III</td>
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<td>Uroporphyrinogen III</td>
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<td>Uroporphyrinogen III</td>
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<td>Uroporphyrinogen III</td>
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<td>Uroporphyrinogen III</td>
<td>Uroporphyrinogen III</td>
<td>Uroporphyrinogen III</td>
</tr>
</tbody>
</table>

In addition to cardiac arrest, a common cause of death, porphyrias can also present with neurological symptoms. These symptoms may include pain, muscle weakness, and psychiatric symptoms. The diagnosis is typically made through a combination of clinical symptoms and laboratory tests. Treatment often involves the use of supportive care and medication to manage symptoms. An acute attack begins with minor behavioral changes, which can escalate to confusion, delirium, and seizures.
<table>
<thead>
<tr>
<th>Site of Overproduction</th>
<th>Enzyme Defect</th>
<th>Inheritance</th>
<th>Gene and Mutations</th>
<th>Characteristics of Polyphosphatasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td></td>
<td>autosomal recessive</td>
<td>227 mutations in the ADPase gene (9 bp)</td>
<td>Lethal polyphosphatemia, hepatic failure, skeletal and ocular defects</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td>autosomal recessive</td>
<td>75 mutations in the UROS gene (34 bp)</td>
<td>Lethal polyphosphatemia, hepatic failure, skeletal and ocular defects</td>
</tr>
<tr>
<td>Severe disease</td>
<td></td>
<td>autosomal recessive</td>
<td>10 X on chromosome 11.22</td>
<td>Lethal polyphosphatemia, hepatic failure, skeletal and ocular defects</td>
</tr>
<tr>
<td>Acute disease</td>
<td></td>
<td>autosomal recessive</td>
<td>15 X on chromosome 11.22</td>
<td>Lethal polyphosphatemia, hepatic failure, skeletal and ocular defects</td>
</tr>
<tr>
<td>Acute disease</td>
<td></td>
<td>autosomal recessive</td>
<td>45 X on chromosome 11.22</td>
<td>Lethal polyphosphatemia, hepatic failure, skeletal and ocular defects</td>
</tr>
<tr>
<td>Acute disease</td>
<td></td>
<td>autosomal recessive</td>
<td>55 X on chromosome 11.22</td>
<td>Lethal polyphosphatemia, hepatic failure, skeletal and ocular defects</td>
</tr>
<tr>
<td>Acute disease</td>
<td></td>
<td>autosomal recessive</td>
<td>65 X on chromosome 11.22</td>
<td>Lethal polyphosphatemia, hepatic failure, skeletal and ocular defects</td>
</tr>
</tbody>
</table>

The activity of the disease should be followed up for increased sympathetic activity and are associated with sepsis, hypertension, and ischemia, which are signs of sepsis, hypertension, and ischemia. Pain in the back or in the extremities is frequently common and severe, mimicking acute abdominal crisis, usually followed by vomiting and constipation—often resistant to treatment.

Table 2: Enzymatic Deficiency
PORFIRIE

ERITROPOIETICHE
(ECCESIVA PRODUZIONE DI PORFIRINE NEL MIDollo OSSEO)

molto rare

\( \uparrow \) PORFIRINE nei globuli rossi
accumulo PORFIRINE nella pelle
\( \rightarrow \) FOTOSENSIBILITÀ

\( \downarrow \) ACQUISITE

\( \rightarrow \) Avelenamento Piombo
\( \rightarrow \) Deficienza Fe
\( \rightarrow \) Zn-Protoporfin

\( \rightarrow \) DOLORI ADDOMINALI ACUTI
\( \rightarrow \) VOMITO
\( \rightarrow \) NEUROPAatie PERIFERICHE
\( \rightarrow \) DISTURBI MENTALI
\( \rightarrow \) FOTOSENSIBILITÀ (in alcuni tipi)

EPATICHE

MANIFESTAZIONI ACUTE

per accumulo di [ALA e PBG]

effetto NEUROTOSICO
itiociti, causata dall'inibizione operata dal piombo di un certo numero di enzimi e fanno parte della via biosintetica della glicogenina (Fig. 2). Un segno clinico è rappresentato dalla comparsa di un segno blu delle gengive.

Il piombo si misura nel sangue intero o nelle urine (Tab. 1). L'esecuzione può essere facilitata usando qualunque agente chelante, come NaCaEDTA, dimercaprol o N-etil penicillammina, ma per ridurre gli accumuli nelle ossa può rendersi necessario un trattamento prolungato.

**mercurio**

Avvelenamento da mercurio può essere uto o cronico ed è correlato all'esposizione a fumi di mercurio allo stato elementare, sali inorganici o a forme organiche come il metilmercurio. Il mercurio metallico è tossico se ingerito, ma i fumi di mercurio danno tossicità acuta.

I sintomi sono tosse, respiratoria e dolore metallico in bocca.

I sali mercuriosi, soprattutto il calome, sono noti per causare intossicazioni oriche per assorbimento attraverso la cute di polveri e altre forme, ma sono meno tossici dei sali mercurici, come il cloro di mercurio, molto tossico se ingerito.

I sintomi sono: nausea e vomito, emorragia muscolare, sintomi al SNC e danni renali.

La diagnosi si esegue in base alla misurazione delle concentrazioni di mercurio nel sangue e nelle urine (Tab. 1). Un monitoraggio a lungo termine dell'esposizione, che può rendersi necessario per coloro che lavorano con amalgami dentali, si

---

**Nota clinica**

Spesso associato in passato con l'omicidio, l'avvelenamento da arsenico può essere ancora incontrato sotto forma di malattia industriale. Le caratteristiche sono: dolori addominali, mal di testa, confusione, neuropatia periferica e coma.

---

**Avvelenamento da metalli**

- I metalli pesanti costituiscono una causa insidiosa di malattie gastrointestinali, rene e neurologiche.
- Misurazioni dei livelli nel sangue e nelle urine sono utilizzati nella diagnosi di avvelenamento.
- Il trattamento delle esposizioni acute si esegue con agenti chelanti.