LECTURE 12

PATHOPHYSIOLOGY OF METABOLIC DISORDERS OF AMINOACIDS, URIC ACID, IRON AND COPPER

Outline:

1. Protein homeostasis
2. Congenital disorders of amino-acids metabolism
3. Purine metabolism
4. Hyperuricemia
5. Iron and copper metabolism disorders

1. A short review of protein homeostasis
Proteins occupy a unique position in metabolism. Not only may they serve as sources of energy for the organism, but they constitute the most important raw materials out of which the complex structures of the body are built. While carbohydrates and fats are employed chiefly as fuels for the "protoplasmic fires," proteins, in the well balanced diet, serve mainly for purposes of synthesis. **Protein homeostasis** maintains proper intracellular balance by promoting protein folding and clearance mechanisms while minimizing the stress caused by the accumulation of misfolded and damaged proteins.

**General features**
1. Proteins represent principal constituents of organs and soft structures of the body.
2. Proteins include an enormous number of closely related, yet physiologically distinct groups of substances.
3. A liberal and continuous supply of proteins is needed throughout the "life" for growth, repair of tissues and organs, and other functions.

Functions
There is an enormous diversity of protein structure, made possible by the fact that proteins are made from 20 different building blocks, the amino acids. Because of their diverse structures, proteins have a great many different functions in cells and in the body. Some proteins are structural: collagen, for example, is a fibrous protein that provides strength in connective tissues (tendons and ligaments are composed predominantly of collagen). Many proteins are enzymes, which function as biological catalysts to cause specific chemical reactions to go faster. Antibodies are proteins, as are receptors on cell surfaces for regulatory molecules and transport carriers in the plasma (cell) membrane that move substances into or out of the cells. These and other types of molecules have specificity of function, a property of proteins because of their great diversity of structure. Protein structure is coded by the genes (DNA), using RNA as the intermediary.

2. Congenital disorders of amino acid metabolism
Amino acid disorders (AAs) are a group of rare inherited conditions, caused by missing or non-working enzymes. The symptoms and treatment vary between different amino acid disorders. They can also vary from person to person with the same amino acid disorder.

2.1 Inborn errors of amino acid metabolism: impaired synthesis and degradation.

2.1.1 Phenylketonuria (PKU)
Definition. PKU is an inherited, autosomal recessive disorder, caused by a deficiency in the production of the hepatic enzyme phenylalanine hydroxylase (PAH), needed to convert phenylalanine to tyrosine (Fig. 1). A lack of PAH results in the buildup of abnormally high phenylalanine levels in the blood and brain, and increased urinary elimination of phenylalanine and its catabolism products (phenylpyruvic, phenyllactic, and phenylacetic acids). Above normal levels of phenylalanine are toxic to the cells that make up the nervous system and causes irreversible damage.
Figure 1. Pathophysiology of phenylketonuria. Lack of phenylalanine hydroxylase blocks the transformation of phenylalanine into tyrosine. Unmetabolized phenylalanine is shunted into the pathway that leads to the formation of phenylketones. Excess phenylalanine also inhibits formation of melanin from tyrosine. (After Damjanov, 2000).

Clinical features.
Untreated PKU patients develop a broad range of symptoms related to severely impaired cognitive function, referred to as mental retardation. Phenylalanine causes irreversible brain damage because it inhibits neurotransmitter synthesis and amino acid transport → lack of neuronal development and defective myelin biosynthesis.
Other symptoms can include: extreme patterns of behavior, delayed speech development, seizures, characteristic body odors (as a result of a by-product of phenylalanine, phenylacetic acid) in their urine and sweat, and light body pigmentation. The light pigmentation is due to a lack of melanin (see Fig. 1), which normally colors the hair, skin and eyes. Melanin is made from the amino acid tyrosine, which is lacking in untreated cases of PKU.

Obs.! Babies do not show any visible symptoms of the disease for the first few months of life.
Diagnosis. PKU is usually diagnosed with a routine screening test (*Guthrie bacterial inhibition assay*). Newer diagnostic procedures (called mutation analysis and genotype determination) are able to identify the specific types of PAH gene mutations inherited by PKU infants.

Prognosis and treatment.
A *phenylalanine-restricted diet* (but not eliminated it altogether, since phenylalanine is essential for living), if started early and maintained for life, allows for normal development. Dietary restrictions started after 2 to 3 years of age may control extreme hyperactivity and seizures and raise the child's eventual intelligence quotient (IQ) but do not reverse intellectual disability. Recent evidence suggests that some intellectually disabled adults with PKU (born before newborn screening tests were available) may function better when they follow the PKU diet. Meat, milk, or other common natural sources of proteins, are forbidden, due to their high content in phenylalanine. Instead, a variety of processed foods, which are specially manufactured to be phenylalanine-free, associated with low-protein natural foods, such as fruits, vegetables, and restricted amounts of certain grain cereals, can be eaten. Special nutritional products, including infant formula without phenylalanine, are also available. Future treatments may include cell transplantation and gene therapy.

2.1.2 Alkaptonuria
Definition. Alkaptonuria (ochronosis) is a *rare autosomal recessive disease* caused by *mutations in the gene that encodes homogentisic acid oxidase (HGAO)*. This enzyme deficiency blocks the metabolism of phenylalanine and leads to the *accumulation of homogentisic acid in collagen rich connective tissue, tendons, and cartilage*, imparting to these tissues a blue-black pigmentation (ochronosis) most evident in the ears, nose, and cheeks.

![Pathophysiology of alkaptonuria](image)

**Figure 2. Pathophysiology of alkaptonuria.** Deficiency in homogentisic acid oxidase (HGAO) impairs the conversion of homogentisic acid (HGA, also called alkaptone) to maleyl acetoacetateleads to accumulation of homogentisic acid and benzoquinone acetic acid (BQA).
Some is eliminated in the urine and rest is deposited in the connective tissues where it is toxic and is harmful to the bones and the cartilages. (After, Muhammad Nafees & Muhammad Muazzam, 2007).

Clinical features.
The most serious consequences of ochronosis, however, stem from deposits of the pigment in the articular cartilages of the joints. In some obscure manner, the pigmentation causes the cartilage to lose its normal resiliency and become brittle and fibrillated. Excretion of homogentisic acid causes the urine to darken upon standing (oxidation). The metabolic defect is present from birth, but the degenerative arthropathy develops slowly and usually does not become clinically evident until the thirties.

Prognosis.
Although it is not lifethreatening, it may be severely crippling. The disability may be as extreme as that encountered in the severe forms of osteoarthritis of the elderly, but in alkaptonuria the arthropathy occurs at a much earlier age.

2.1.3 Albinism
Definition. Albinism comprises a group of hereditary disorders associated with hypopigmentation due to a defect in melanin biosynthesis. The most common form is oculocutaneous albinism (OCA), an autosomal recessive disorder characterized by deficiency of melanin in the skin, hair follicles, and eyes.

Clinical features.
There are two major types of OCA:

1. Tyrosinase-positive OCA (type 1): the most common type in both whites and blacks. The biochemical defect is unknown. Infants are born with complete albinism, but pigmentation increases with age.

2. Tyrosinase-negative OCA (type 2): the second most common type of OCA. It is characterized by complete absence of tyrosinase.

   - Tyrosinase converts tyrosine to form melanin ➔ these patients lack melanin and exhibit snow-white hair, pink skin, blue eyes, and red pupils. These patients suffer from photophobia, strabismus, nystagmus, and decreased visual acuity.
   - The incidence of squamous cell carcinoma is also increased.

2.1.4 Cystinosis
Definition. An inherited autosomal recessive disorder characterized by the widespread deposition of the amino acid cystine in cells due to a defect in
**cystine transport.** Cystine normally forms after protein degradation and *is transported from structures called lysosomes into the cytoplasm.* Lysosomes are membrane-bound compartments within cells that break down certain nutrients such as fats, proteins, and carbohydrates. Lysosomes are the primary digestive unit within cells. Some enzymes within lysosomes break down (metabolize) these nutrients, while other enzymes transport the leftover metabolic products (such as cystine) out of the lysosome. *The lack of such a specific transporter causes cystine to accumulate in lysosomes in cells throughout the body.* Cystine forms crystals (crystallizes) in many types of cells and slowly damages affected organs. Cystinosis is therefore a *lysosomal storage disease.*

**Clinical features.**
There are three types of cystinosis:

1. The classic **nephropathic type** of cystinosis.
2. The **intermediate cystinosis**, which has the same features as the nephropathic type but is much slower in its progression.
3. The **ocular cystinosis**, which has the typical eye findings but NO systemic disease.

The age of onset, symptoms, and severity of cystinosis can vary greatly from one person to another. The **kidneys and eyes** are the two organs most often affected.

**Nephropathic cystinosis** presents in infancy and is the most common and severe form. Early detection and prompt treatment is critical in slowing the development and progression of symptoms associated with cystinosis. Individuals with nephropathic or intermediate cystinosis ultimately require a kidney transplant.

**Non-nephropathic cystinosis** only affects the **corneas of the eyes**, leading to **photophobia** (excess sensitivity of the eye to light), between mid-childhood.

**2.2 Inherited defects of membrane transport**
Specific membrane transporters mediate the passage of amino acids across cellular membranes. *Mutations in transporter molecules* cause disorders of the heart, muscle, brain, and endocrine and sensory organs. The most common inherited defects impairing the transport of selected amino acids that can present in adults are presented below.

**2.2.1 Cystinuria**
**Definition.** Cystinuria is an *autosomal recessive disorder* caused by **defective transporters in the apical brush border of proximal renal tubule and small**
intestinal cells. It is characterized by impaired reabsorption and excessive urinary excretion of the dibasic amino acids: lysine, arginine, ornithine, and cystine). Because cystine is poorly soluble, its excess excretion predisposes to the formation of renal, ureteral, and bladder stones. Such stones are responsible for the signs and symptoms of the disorder.

Clinical features.

Cystine stones account for 1–2% of all urinary tract calculi but are the most common cause of stones in children. Stone formation usually manifests in the second or third decade but may occur in the first year of life. Symptoms and signs are those typical of urolithiasis: hematuria, flank pain, renal colic, obstructive uropathy, and infection. Recurrent urolithiasis may lead to progressive renal insufficiency.

Diagnosis and management.

Cystinuria is suspected after observing typical hexagonal crystals in the sediment of acidified, concentrated, chilled urine. Quantitative urine amino acid analysis confirms the diagnosis of cystinuria by showing selective over excretion of cystine, lysine, arginine, and ornithine.

Management is aimed at preventing cystine crystal formation by increasing urinary volume (up to 5–7 L/day is optimal) and by maintaining an alkaline urine pH (with bicarbonate or potassium citrate). Occasional patients progress to renal failure and require kidney transplantation.

2.2.2 Dibasic aminoaciduria

Definition. Dibasic aminoaciduria is an autosomal recessive disorder, characterized by a defect in renal tubular reabsorption of the three dibasic amino acids: lysine, arginine, and ornithine but NOT cystine. There are two variants:

1. Type I presents as profound mental retardation WITHOUT hyperammonemia or protein intolerance. Heterozygotes have modest dibasic amino aciduria.

2. Type II (the common form) also known as lysinuric protein intolerance (LPI) is a defective intestinal transport of dibasic amino acids as well as exaggerated renal losses. The transport defect affects basolateral rather than luminal membrane transport and is associated with impairment of the urea cycle. Homozygotes have protein intolerance, hyperammonemia, and failure to thrive. Heterozygotes do not have amino aciduria.

Clinical features. Manifestations are related to the losses of ornithine, arginine, and lysine. Affected patients present in childhood with hepatosplenomegaly,
protein intolerance, and episodic ammonia intoxication. Older patients may present with severe osteoporosis, impairment of kidney function, or interstitial changes in the lungs. Plasma concentrations of lysine, arginine, and ornithine are reduced, whereas urinary excretion of lysine and orotic acid are increased. Hyperammonemia may develop after the ingestion of protein loads or with infections, probably because of insufficient amounts of arginine and ornithine to maintain proper function of the urea cycle. Treatment consists of dietary protein restriction and supplementation of citrulline, a neutral amino acid that fuels the urea cycle when metabolized to arginine and ornithine. Pulmonary disease responds to glucocorticoids or bronchoalveolar lavage in some patients.

2.2.3 Hartnup disease
Definition. Hartnup disease is an autosomal recessive disorder characterized by pellagra-like skin lesions, variable neurologic manifestations, and neutral and aromatic aminoaciduria. Disease is caused by a defective gene, which has been located on the long arm of chromosome 11, which encodes transport for sodium-depandant amino acids. Alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, glutamine, asparagine, and histidine are excreted in urine in quantities 5–10 times greater than normal, and intestinal transport of these same amino acids is defective.

Clinical manifestations result from nutritional deficiency of the essential amino acid tryptophan, caused by its intestinal and renal malabsorption, and of niacin, which derives in part from tryptophan metabolism. Only a small fraction of patients with the chemical findings of this disorder develop a pellagra-like syndrome, implying that manifestations depend on other factors in addition to the transport defect.

The neurologic and psychiatric manifestations range from attacks of cerebellar ataxia ➔ mild emotional lability ➔ frank delirium, and they are usually accompanied by exacerbations of the erythematous, eczematoid skin rash. Fever, sunlight, stress, and sulfonamide therapy provoke clinical relapses.

Treatment is directed at niacin repletion and includes a high-protein diet and daily nicotinamide or niacin supplementation.

3. Purine metabolism
Purines are key components of cellular energy systems (eg, ATP, NAD), signaling (eg, GTP, cAMP, cGMP), and, along with pyrimidines, RNA and DNA
production. Purines and pyrimidines may be synthesized de novo or recycled by a salvage pathway from normal catabolism. Purines can be synthesized de novo in cells (Fig. 3). The initial and rate-limiting step of this biosynthetic process is the conversion of phosphoribosylpyrophosphate (PRPP) to 5′-phosphoribosylamine. This step is catalyzed by the enzyme amidophosphoribosyltransferase, and it is regulated by the concentrations of nucleoside monophosphates and PRPP. Adenylic acid (AMP) and guanylic acid (GMP) are feedback inhibitors of the enzyme. Under normal conditions, depletion of PRPP decreases the rate of purine biosynthesis de novo, and elevation of PRPP is associated with an increased rate of purine biosynthesis.

The first branch point in the pathway leading to the de novo synthesis of AMP and GMP (see Fig. 3) occurs with the synthesis of inosinic acid (IMP). IMP is used to form AMP and GMP, and these steps may be governed by the intracellular concentration of guanylic acid triphosphate (GTP). GTP is a substrate of adenylosuccinate synthetase and an inhibitor of IMP dehydrogenase. As IMP is formed, it is used for the synthesis of xanthyllic acid, GMP, guanylic acid diphosphate, and GTP. As GTP reaches a critical concentration in the cell, it may increase the activity of adenylosuccinate synthetase, allowing IMP to be effectively used in the synthesis of AMP. When accelerated purine biosynthesis results in the production of surplus IMP, there is a rapid conversion of the excess ribonucleotide to uric acid rather than a continued expansion of the pools of adenyl and guanyl nucleotides.

Nucleotide breakdown is regulated in a complex manner. Regulation of nucleotide degradation is critically controlled by AMP deaminase and 5′-nucleotidase activities. Release of inhibition of AMP deaminase results in accelerated production of uric acid. Regulation of dephosphorylation is complex, involving three soluble 5′-nucleotidase activities. The nucleosides formed by nucleotidase reactions are converted to the bases adenine, guanine, or hypoxanthine. These bases can be “salvaged” by reconversion to nucleosides catalyzed by purine nucleoside phosphorylase activity (hypoxanthine and guanine) or conjugated with PRPP to form ribonucleotides by phosphoribosyltransferase activities. If not salvaged, they are degraded to uric acid.

Exogenous purines also significantly contribute to the total body urate pool. The magnitude of this contribution depends on the amount and type of purine in the diet, but it is often considerable.

The final catabolism product of purines is uric acid (Normal values: 1,5-6 mg% in women; 2,5-7,5 mg% in males). Urinary uric acid excretion accounts for only part of the daily disposition of uric acid, however.
4. Hyperuricemia
Approximately two thirds of total body urate is produced endogenously, while the remaining one third is accounted for by dietary purines. Approximately 70% of the urate produced daily is excreted by the kidneys, while the rest is eliminated by the intestines.

Hyperuricemia (elevated uric acid level in plasma) may occur because of decreased excretion (underexcretion), increased production (overproduction), or a combination of these two mechanisms.

4.1 Metabolic hyperuricemia (overproduction)
Definition: increased production of uric acid.
Pathogenesis:
1. Activation of de novo synthesis of purins, via:
   - Phosphoribosylpyrophosphate synthetase superactivity: a X-linked, recessive disorder causes purine overproduction. Excess purine is degraded, resulting in hyperuricemia and gout and neurologic and developmental abnormalities.
2. Decreased intracellular level of AMP and GMP: due to decreased feedback inhibition of amidophosphoribosyltransferase
3. Decreased reutilization of purines within the “salvage pathway” via:
   - deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT): Lesch-Nyhan syndrome (rare, X-linked, recessive disorder); degree of deficiency (and hence manifestations) vary with the specific mutation. HPRT deficiency results in failure of the salvage pathway for hypoxanthine and guanine. These purines are instead degraded to uric acid. Additionally, a decrease in inositol monophosphate and guanosyl monophosphate leads to an increase in conversion of 5-phosphoribosyl-1-pyrophosphate (PRPP) to 5-phosphoribosylamine, which further exacerbates uric acid overproduction. Hyperuricemia predisposes to gout and its complications.
4. Increased turnover of nucleic acids → secondary hyperuricemia from:
   - carcinomas, lympho- and myeloproliferative disorders (tumor lysis syndrome)
   - hemolytic anemias
   - polycythemia (polycythemia vera).

4.2 Renal hyperuricemia (underexcretion)
Underexcretion accounts for most causes of hyperuricemia. Urate handling by the kidneys involves filtration at the glomerulus (98%), reabsorption in proximal tubes (presecretory reabsorption), secretion (approximately 10% of the filtrated urate is eliminated), and, finally, postsecretory reabsorption, within the distal tubes.
Consequently, altered uric acid excretion can result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption.
While decreased urate filtration may not cause primary hyperuricemia, it can contribute to the hyperuricemia of renal insufficiency.
Decreased tubular secretion of urate occurs in patients with acidosis (eg, diabetic ketoacidosis, ethanol or salicylate intoxication, starvation ketosis). The organic acids that accumulate in these conditions compete with urate for tubular secretion.
Finally, enhanced reabsorption of uric acid distal to the site of secretion is the mechanism thought to be responsible for the hyperuricemia observed with diuretic therapy and diabetes insipidus.

4.3 Combined mechanisms (underexcretion and overproduction) of hyperuricemia
The most common cause under this group is alcohol consumption, which results in accelerated hepatic breakdown of ATP and the generation of organic acids that compete with urate for tubular secretion. Enzymatic defects such as glycogenoses type I and aldolase-B deficiency are other causes of hyperuricemia that result from a combination of overproduction and underexcretion.

4.4 Gout
Definition: Gout is a metabolic disease characterized by hyperuricemia (>7 mg/dL) and deposition of urate crystals (tophus) in various sites, most often joints, subcutaneous soft tissues, and kidneys. It is a common disease inherited as a multifactorial trait: 20% patients have a family history of gout. Males are affected preferentially (male-to-female ratio, 9:1) and its onset is in the 20- to 40-year-old age group.

The metatarsophalangeal joint of the great toe is the most often involved joint, accounting for the term podagra (“foot-trap”). Ankle, knee, wrist, and elbow are also often involved. The disease may be monoarticular or polyarticular.

N.B. Tophus = aggregates of monosodium urate (MSU) crystals, which typically elicit a foreign body reaction with numerous multinucleated giant cells and mononuclear histiocytes surrounding the crystals. Tophi can develop in various locations, commonly the fingers, hands, feet, and around the olecranon or Achilles tendon. Tophi can also develop in the kidneys and other organs and under the skin. Patients with osteoarthritic Heberden nodes may develop tophi in the nodes. This development occurs most often in elderly women taking diuretics. Normally painless, tophi, especially in the olecranon bursae, can become acutely inflamed and painful. Tophi may even erupt through the skin, discharging chalky masses of urate crystals. Tophi may eventually cause deformities. In properly fixed tissue (i.e., in 100% alcohol because uric acids are eluted from tissues by water-containing fixative, such as formalin), the uric acid crystals appear birefringent under polarized light.

Risk factors
Hyperuricemia is found in approximately 15% of all adults, but only 10% of these develop attacks of gout. The disease is obviously multifactorial and has a hereditary basis, but some preventable and treatable factors may influence its occurrence and precipitate the attacks. These risk factors include:
- Obesity and hyperlipidemia
- Hypertension
- Alcoholism
- Drugs, such as diuretics (e.g., thiazides), cyclosporine, ethambutol, etc.

Clinical features
- **Acute gouty arthritis** usually begins with sudden onset of pain (often nocturnal). The pain becomes progressively more severe, usually over a few hours, and is often excruciating. **Swelling, warmth, redness, and exquisite tenderness** may suggest infection. The overlying skin may become tense, warm, shiny, and red or purplish. **Fever, tachycardia, chills, and malaise** sometimes occur. The first few attacks usually affect only a single joint and last only a few days. Later attacks may affect several joints simultaneously or sequentially and persist up to 3 wk if untreated.
- Attacks tend to recur at unpredictable times. The intervals between the attacks (called intercritical intervals) are often long but tend to become shorter as the disease progresses.
- In severe, long-standing hyperuricemia, **MSU crystals** may be deposited in the kidney parenchyma. At the acid pH of urine, urate precipitates readily as small platelike or irregular crystals that may aggregate to form gravel or stones, which may obstruct urine outflow. Renal calculi represent the most important extrarticular complication (found in 10% of cases).

Classification:
1. **Primary gout** is idiopathic (i.e., unrelated to a known cause or disease). It accounts for 90% of all cases of gout. Hyperuricemia results most often from an impaired urinary excretion of urates and less often because of overproduction.
2. **Secondary gout** is a complication of other diseases or their treatment. Hyperuricemia can occur because of:
   - Overproduction of uric acid from nucleic acids.
   - Underexcretion of uric acid in the kidneys, as seen in patients who have end-stage kidney disease.

Pathophysiology.
Urate levels can be elevated because of:
1. **Decreased renal excretion**: the most common cause of hyperuricemia.
   - It may be hereditary
   - it may occur in patients receiving diuretics and in those with diseases that decrease GFR.
- Ethanol increases purine catabolism in the liver and increases the formation of lactic acid, which blocks urate secretion by the renal tubules.
- Lead poisoning and cyclosporine, usually in the higher doses given to transplant patients, damage renal tubules, leading to urate retention.

2. Increased production of urate may be caused by:
   - increased nucleoprotein turnover in hematologic conditions (eg, lymphoma, leukemia, hemolytic anemia)
   - conditions with increased rates of cellular proliferation and cell death (eg, psoriasis, cytotoxic cancer therapy, radiation therapy)
   - it may also occur as a primary hereditary abnormality and in obesity, because urate production correlates with body surface area. In most cases, the cause of urate overproduction is unknown, but a few cases are attributable to enzyme abnormalities.

3. Increased intake of purine-rich foods (eg, liver, kidney, anchovies, asparagus, consommé, herring, meat gravies and broths, mushrooms, mussels, sardines, sweetbreads) can contribute to hyperuricemia. However, a strict low-purine diet lowers serum urate by only about 1 mg/dL.

Deposition of urate crystals in the joints may cause an acute or chronic inflammation of the affected joint. Acute attacks of gout arthropathy begin with the deposition of insoluble uric acid crystals in tissues. These crystals activate complement, which generates chemotactic fragments, attracting neutrophils into the area.

Chronic gout arthropathy results from massive aggregates of uric acids, which form nodular masses protruding into the joint and eroding the joint surfaces of the bones (chronic tophaceous gout).

4.5 Pseudogout or chondrocalcinosis, is a common joint disease caused by deposition of calcium pyrophosphate dihydrate (CPPD) crystals. Most often, it is asymptomatic, but it may simulate gout and osteoarthritis. X-ray signs of pseudogout may be seen in 5% of 70 year olds and in more than 50% of those older than 90 years of age. However, only a minority of these people will develop signs of arthritis, which may resemble gout or osteoarthritis.

Diagnosis is made by finding linear calcifications in the articular cartilage and by identifying CPPD crystals in the joint fluid. These crystals are rod shaped or rhomboid and are birefringent under polarizing light.
5. Iron and copper metabolic disorders

5.1 Hereditary hemochromatosis
Definition. Hereditary hemochromatosis is an **autosomal recessive disease caused by a mutation of a gene encoding the protein that regulates the absorption of iron in the intestine**. There are **4 types** of hereditary hemochromatosis (types 1 through 4), depending on the gene that is mutated.

Pathophysiology
The mechanism for iron overload is **increased iron absorption from the GI tract** → **chronic deposition of iron in the tissues**. **Hepcidin**, a liver-derived peptide, is the critical control mechanism for iron absorption. Hepcidin is normally up-regulated when iron stores are elevated and, through its inhibitory effect on ferroportin (see chapter “Red blood cells disorders”), it **prevents excessive iron absorption and storage**. All 4 types of hemochromatosis present the same pathogenic basis: lack of **hepcidin synthesis or activity**, and key clinical features. It is considered that tissue injury results from **reactive free hydroxyl radicals generated when iron deposition in tissues catalyzes their formation**. Other mechanisms may affect particular organs (eg, skin hyperpigmentation can result from increased melanin as well as iron accumulation).

Clinical features
In the classical form it is known as **“bronze diabetes with cirrhosis”**. Clinical findings resulting from the accumulation of iron in various organs include:
- **Cirrhosis** of the liver. The liver is dark brown (“pigmentary cirrhosis”) because of the accumulation of hemosiderin in liver cells, bile ducts, and Kupffer cells. 20-30% of patients with cirrhosis develop hepatocellular carcinoma.
- **Glucose intolerance or diabetes mellitus**
- **Hyperpigmentation of the skin**
- **Arthritis**
- **Cardiomyopathy with heart failure. Together with cirrhosis, it is the most common cause of death in these patients!**
- **Endocrine gland atrophy**. Atrophy occurs at a variable rate and involves the **thyroid** (hypothyroidism), **testes** (erectile dysfunction), **pituitary** (gonadism).

**N.B.**! Because symptoms may be delayed until iron accumulation is excessive (10-20 g), hemochromatosis may not be recognized until later in life. In women, clinical manifestations are
uncommon before menopause because iron loss due to menses (and sometimes pregnancy and childbirth) tends to offset iron accumulation.

Diagnosis: elevated serum ferritin level and elevated transferrin saturation, and is confirmed by a gene assay.

5.2 Copper deficiency and toxicity

5.2.1 Wilson disease
Definition. Also known as hepatolenticular degeneration, Wilson disease is an inherited copper toxicity leading to accumulation of copper in the liver and other organs.

Pathophysiology
The genetic defect impairs copper transport:
- decreased copper secretion into the bile ➔ copper overload ➔ accumulation in the liver, which begins at birth.
- interfering with incorporation of copper into the copper protein ceruloplasmin ➔ decreased serum levels of ceruloplasmin.

Clinical features are related to the deposition of excessive amounts of copper in various organs and include the following:
- Liver disease: It begins as fatty liver ➔ acute and chronic hepatitis ➔ cirrhosis. Increased amounts of copper in liver biopsy are typically found; accordingly, the liver biopsy is important for the diagnosis of this disease.
- Neurologic symptoms: These include motor disturbances (resembling Parkinson disease: including any combination of tremors, dystonia, dysarthria, dysphagia, chorea, drooling, and incoordination) and behavioral changes requiring psychiatric treatment. Copper accumulates in the basal ganglia ➔ neurotoxic changes, which are most prominent in the putamen.
- Eye lesions: Deposits of iron around the rim of the cornea and edge of the iris lead to the formation of a green or brown Kayser–Fleischer ring.
- Kidney changes: These lead to proteinuria, aminoaciduria, and phosphaturia and are evidence of renal tubular injury. Renal changes are related to osteomalacia.
- Hemolytic episodes: These occur in 15% of patients and are related to copper toxicity.

Diagnosis of Wilson disease is based on correlating clinical and laboratory findings. Typical laboratory findings include the following:
- Increased concentration of copper in liver tissue, usually obtained by biopsy
- Decreased serum ceruloplasmin
- Increased urinary copper excretion.

5.2.2 Copper deficiency

5.2.2.1 Acquired copper deficiency
Under normal conditions (genetic mechanisms controlling copper metabolism), dietary deficiency rarely causes clinically significant copper deficiency.

Causes:
- severe childhood protein deficiency,
- persistent infantile diarrhea (usually associated with a diet limited to milk),
- severe malabsorption (as in sprue),
- excessive zinc intake.

Clinical features: neutropenia, impaired bone calcification, myelopathy, neuropathy, and hypochromic anemia NOT responsive to iron supplements.

Diagnosis is based on low serum levels of copper and ceruloplasmin, although these tests are not always reliable.

5.2.2.2 Inherited Copper Deficiency (Menkes Syndrome)
Occurs in male infants who inherit a mutant X-linked gene and leads to deficiency of copper in the liver, serum, and essential copper proteins, including cytochrome-c oxidase, ceruloplasmin, and lysyl oxidase.

Symptoms: severe intellectual disability, vomiting, diarrhea, protein-losing enteropathy.

References:
3. Harrison’s Principles of Internal Medicine, 18th Edition. Chapter 359. Inherited Defects of Membrane Transport