Ceruloplasmin, Copper Toxicity and Wilson Disease

Chemical pathology Lab Tests

Sample

1. Venous blood is needed to prepare the serum.
2. The fresh serum is preferred.
3. Can store at 4 °C for 3 days.
4. Can keep at -20 °C for 4 weeks.

Precaution

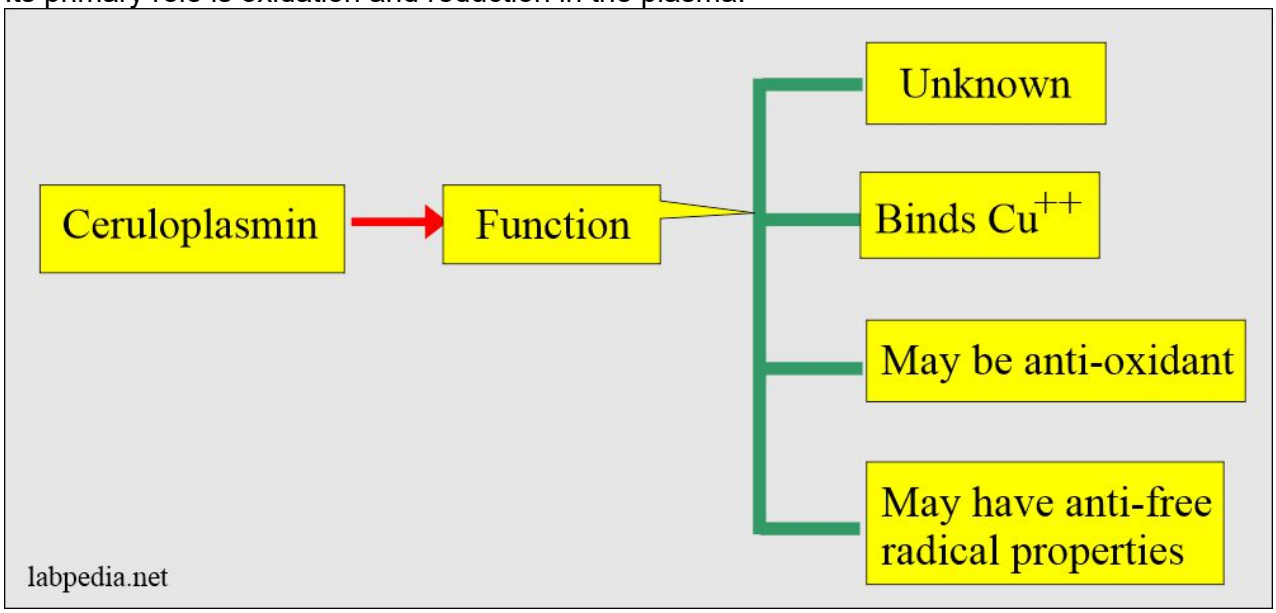
- Avoid lipemic and hemolyzed samples.

Purpose Of The Test (Indications)

1. This is an acute-phase protein.
2. This test is done to diagnose Wilson's disease.

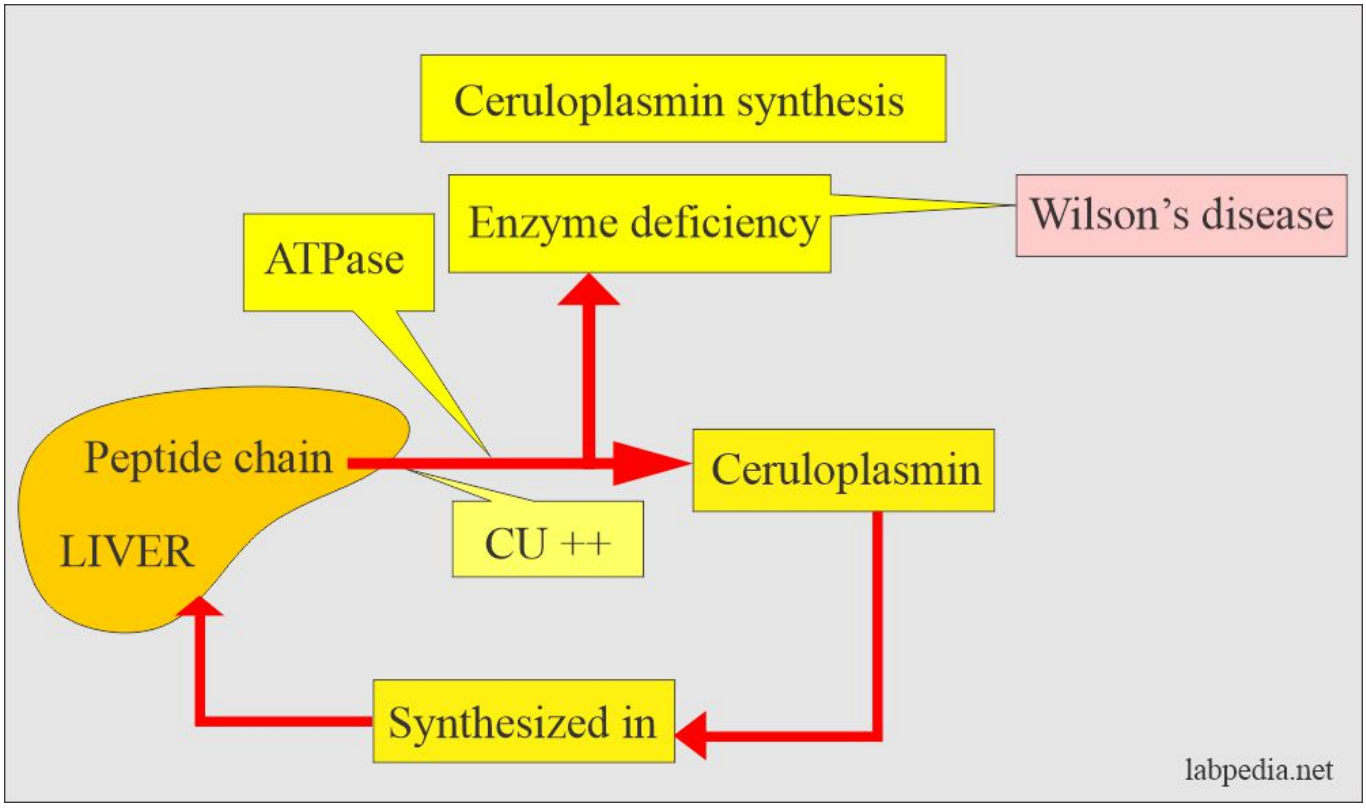
Pathophysiology

1. Ceruloplasmin is alpha-2 globulin.
    1. It contains 95% of the serum copper and gives it a blue color.
    2. In the case of increased Ceruloplasmin, there is a greenish tint of the plasma.
    3. Its primary role is oxidation and reduction in the plasma.



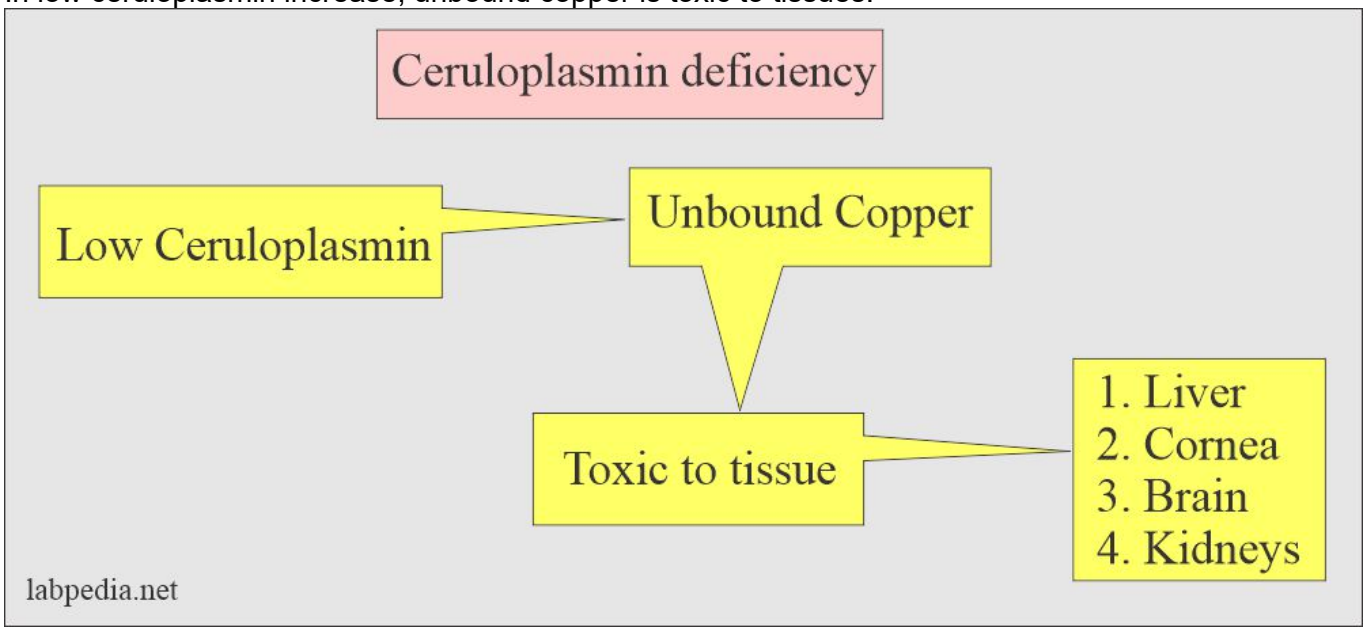
Ceruloplasmin functions

2. Ceruloplasmin will bind copper for transport in the blood.
3. Ceruloplasmin is synthesized in the liver.



Ceruloplasmin synthesis and deficiency

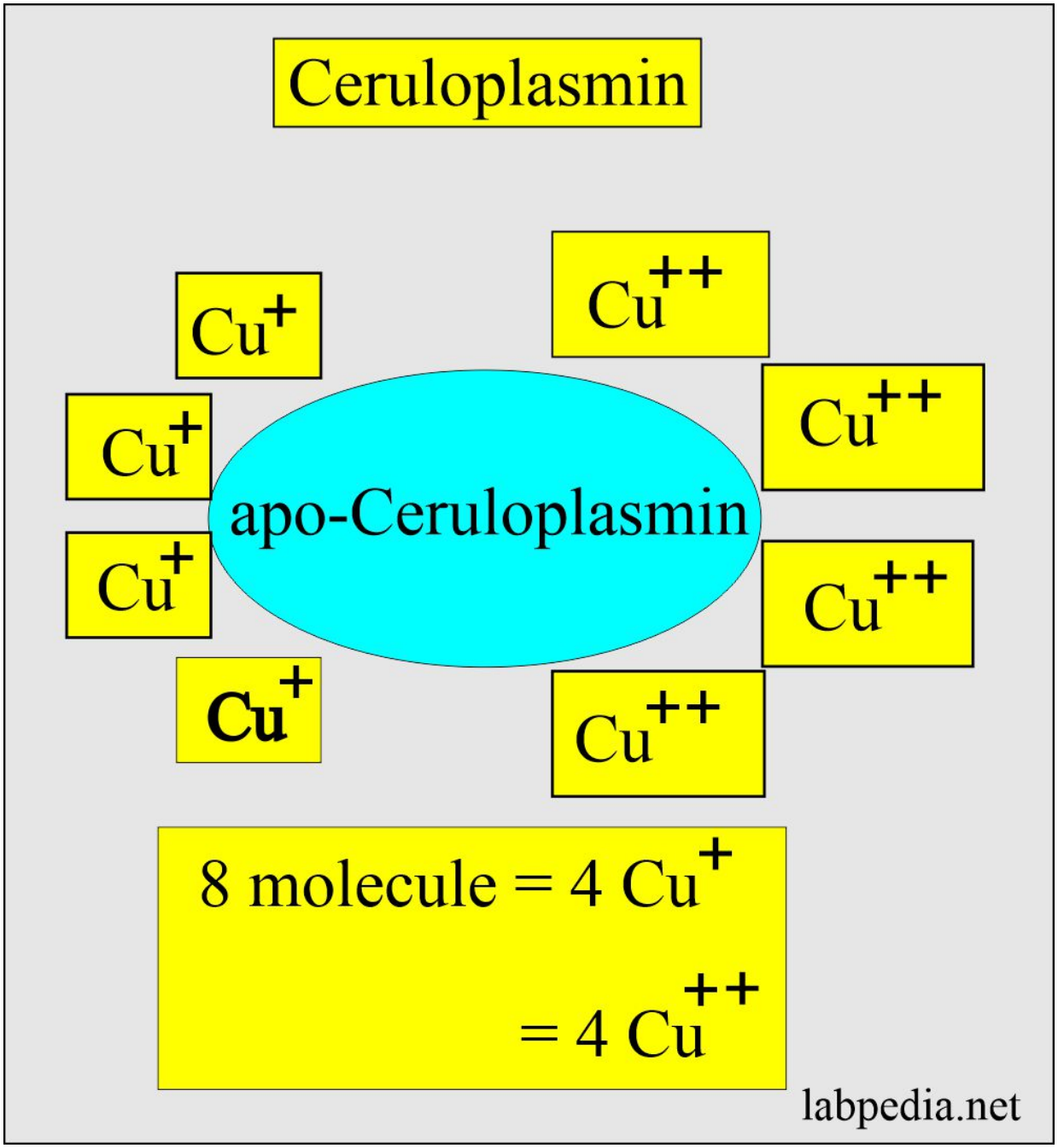
4. Wilson's disease is an inherited disorder where its level is decreased.
5. In low ceruloplasmin increase, unbound copper is toxic to tissues.



Ceruloplasmin deficiency

Copper metabolism:

1. Copper is absorbed from the gastrointestinal system from the food.
    1. Excess copper is excreted into the bile by the Ceruloplasmin, which is produced by the liver.
    2. In the case of deficiency of Ceruloplasmin, copper accumulates in the body.
    3. Ceruloplasmin is a copper-containing protein that accounts for more than 95% of the copper found in the plasma.



Ceruloplasmin structure

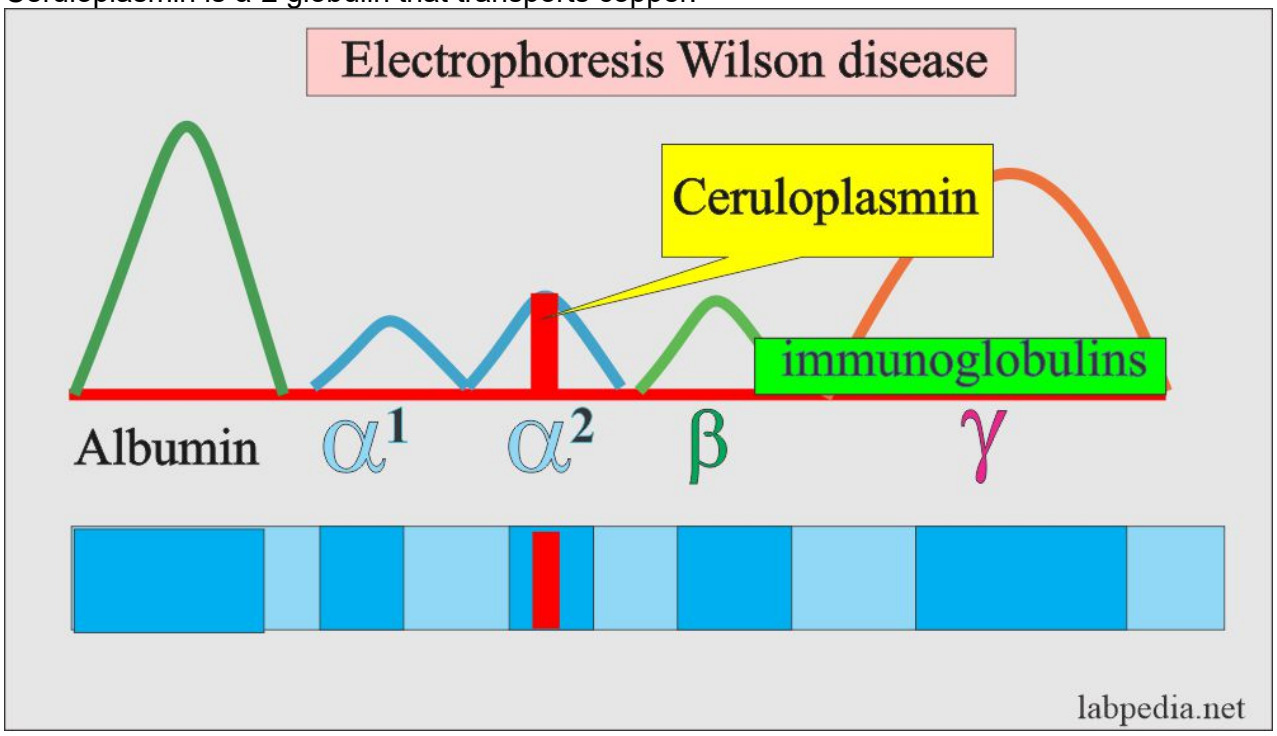
2. **Copper functions** are the development of:
    1. Nerves.
    2. Bones. Copper maintains healthy bones. It prevents osteoporosis.
    3. Skin pigments.
    4. Collagen.
    5. It helps the immune system.
    6. It contributes to iron absorption.
    7. It prevents cardiovascular diseases.
    8. It prevents osteoporosis.
3. Copper is a metal component of various enzymes:
    1. Cytochrome oxidase.
    2. Superoxide dismutase.
    3. Tyrosinase.
4. Copper can deposit in:
    1. Eye.

2. Liver.
3. Brain.
4. Kidneys.
    1. Hemolysis, necrosis, and other cellular changes may be caused by lipid peroxidation, a known toxic effect of copper.
    2. Urinary copper excretion is increased.

Wilson's Disease:

Pathophysiology:

1. Wilson's disease is a familial disorder of copper metabolism, and it is transmitted as an autosomal recessive trait.
2. This is also known as hepatolenticular degeneration and progressive lenticular degeneration.
3. Worldwide it is 1 in 30,000 people.
4. Most people diagnosed are between the ages of 5 to 35 years (another reference 8 to 30 years), but maybe seen in younger and older people (another source = This disease occurs from 6 to 40 years).
    1. The symptoms do not appear before the age of 6 years.
5. This is a rare genetic disease where there is an accumulation of copper (copper toxicity).
    1. It is inherited as an autosomal recessive trait.
        1. Patient inherent one defective gene from one of the couples.
    2. There is a decrease in copper-containing Ceruloplasmin in the liver.
    3. There is impairment of the excretion of the copper from the liver.
        1. Copper starts accumulating in the brain and liver.
    4. Ceruloplasmin level may be as low as **<20 mg/dL**.
    5. Albumin-bound and free copper levels are increased, but total serum copper is low because of low Ceruloplasmin.
6. It can be controlled if diagnosed before the deposition of copper in tissue.
7. There is an accumulation of copper in the liver, kidney, brain, and cornea.
8. **Pathogenesis of Wilson disease:**
    1. Wilson's disease is characterized by the inability of the liver to make a normal quantity of Ceruloplasmin.
    2. Ceruloplasmin is α-2 globulin that transports copper.



Ceruloplasmin electrophoresis

3. The etiology is unknown; there is excessive deposition of copper in various tissues, and it ultimately produces damage to the basal ganglia of the brain and liver tissue.
4. Kidneys may also be affected by producing amino aciduria.
5. Copper is also deposited in the cornea producing a zone of discoloration called the Kayser-Fleischer ring.

9. **Clinical presentation:**
10. The patient has symptoms of:
    1. About 30% to 50% develop liver symptoms.
        1. About 30% to 40% develop neurological symptoms.
        2. About 20% to 30% develop psychiatric abnormalities like schizophrenia.
        3. Few patients develop Coom's negative hemolytic anemia.
        4. Children are usually seen with liver symptoms. Mostly there is chronic hepatitis.
        5. Macronodular cirrhosis develops later and is usually found in late age patients group.
        6. Some patients present with minimal active or non-active cirrhosis.
    2. Neurological symptoms start from the basal ganglia area (lentiform nucleus) of the brain, and it consists of:
        1. Varying degree of incoordination.
        2. Tremors.
        3. Spasticity.
        4. Rigidity.
        5. Dysarthria (speech problems)
        6. There may be flapping tremors.
    3. There is fatigue, lack of appetite, and pain abdomen.
    4. Hepatitis.
    5. Cirrhosis.
    6. Recurrent neuromuscular incoordination.
        1. Uncontrolled movements or muscle stiffness.
    7. Swallowing problems.
    8. Green brown discoloration in the cornea due to the deposition of copper (Kayser-Fleischer rings).
    9. Urinary copper excretion is increased.
11. Early detection is the key to control the disease.
12. Ceruloplasmin is an acute-phase protein, so that it will be raised in infections, stress, and pregnancy.

The normal level of Ceruloplasmin

Source 1

1. Adult = 23 to 50 mg/dL.
2. Neonates = 2 to 13 mg/dL.
3. >7 years = 20 to 54 mg/dL

Source 2

Age	Level mg/dL
1 day to 3 months	5 to 18
6 to 12 months	33 to 43
13 to 36 months	26 to 55
4 to 5 years	27 to 56
6 to 7 years	24 to 48
>7 years	20 to 54

Adult	18 to 45
During pregnancy	Gradually raise and a peak of 2 to 3 of normal

For conversion to SI unit x 10 = mg /L

Treatment:

1. This disease is treated by giving the copper chelating agent (penicillamine) or zinc acetate.

Diagnosis:

1. **Clinical diagnostic** features are:
    1. Kayser-Fleischer ring. It may be clear on the gross eye or sometimes needed slit-lamp examination.
    2. Liver cirrhosis.
    3. Neurological features.
2. **Laboratory findings:**
    1. There is increased urinary excretion of copper, >40 µg/24 hours, and usually is >100 µg/24 hours.
    2. Advise serum or plasma copper levels.
        1. Hepatic copper is raised >210 to 250 µg (dry liver).
    3. Ceruloplasmin level. This is low <20 mg/dL.
        1. <5 mg/dL is diagnostic.
    4. Hemolytic anemia is Coombs negative.
    5. Measurement of superoxide dismutase and cytochrome with oxidase in platelets or leukocytes helps assess copper status.

The complication of Wilson's disease:

1. Scarring of the liver (cirrhosis).
2. Liver failure.
3. Persistent neurological disease.
4. Kidney diseases.
5. Psychological problems.
6. Blood problems like anemia and jaundice.

The Increased Level Is Seen In:

1. Acute inflammatory diseases.
2. Pregnancy.
3. Thyrotoxicosis.
4. Malignancies.
5. Autoimmune diseases (Rheumatoid arthritis).
6. Copper intoxication.
7. Biliary Cirrhosis.

The Decreased Level Is Seen In:

1. Wilson's disease.
2. In early infancy age before six months.
3. Sprue.
4. Kwashiorkor.
5. Nephrotic syndrome.
6. Starvation.
7. The inherited defect of production of alpha 2 globulin.