

PaLMS (PATHOLOGY NORTH) TRACE ELEMENTS FACT SHEET

COPPER

Introduction

Atomic mass 63.5. Found in nature as the metal and as sulphide ores. Copper is an essential micronutrient for most plants and animals. Copper is a catalytic component of numerous enzymes and is also a structural component of many important proteins. Because of copper's wide distribution in food, diet-related copper deficiency is unlikely in all but the most extreme situations. However, copper deficiency may arise in the following situations predominantly related to impaired absorption or increased loss:

- Chronic diarrhoea.
- Malabsorption syndromes including coeliac disease, cystic fibrosis and short bowel syndrome.
- Foregut surgery, including gastrectomy.
- High doses of zinc supplementation (interferes with copper absorption).
- Premature infants fed formula lacking sufficient copper.
- Chronic peritoneal dialysis.
- Total parenteral nutrition with inadequate supplementation.
- Menkes' disease (a rare x-linked genetic defect characterised by impaired intestinal absorption of copper and likely abnormalities in intracellular copper transport. Presents in the first few months of life).

Toxicity may be seen with ingestions of supplements or contamination of diet and water supplies (including those used to prepare dialysis fluids). Copper toxicity may also be seen in the autosomal recessive condition, Wilson's disease. Wilson's disease results from a genetic mutation that causes a reduction in the rate of caeruloplasmin synthesis leading to decreased excretion of copper into the biliary system and reduced incorporation of copper into caeruloplasmin. These defects lead to accumulation of toxic levels of copper, initially in the liver, then in other tissues of the body.

Exposure

Daily requirements for copper are of the order of 2mg. Exposure to copper that leads to a significant level of circulating free copper can produce a haemolytic anaemia and renal damage. Ingestion of caustic copper containing solutions or water can cause nausea, vomiting, diarrhoea, melaena, haematemesis and shock. Longer-term exposure to copper can result in liver damage.

Absorption

Copper is absorbed actively from the small bowel in a competitive process with other trace metals, but especially with zinc. Once absorbed copper is transported to the liver bound to albumin and amino acids.

Distribution

Copper is incorporated into proteins, especially caeruloplasmin, in the liver. Copper is present in many enzyme systems as an essential co-factor or as a part of a functional enzyme group. Plasma copper is low at birth and increases to adult levels by about six months.

Excretion

Copper is normally primarily excreted to the bile. When the copper burden is high there is significant renal excretion.

Pathology

The clinical manifestations of copper deficiency are predominantly haematological and neurological. There may be impaired iron insertion into haemoglobin resulting in anaemia (usually hypochromic and normocytic) and leukopenia as well as ataxia, neuropathy, cognitive deficits. There may also be osteoporosis. Abnormal ECG and GTT, elevated cholesterol and urate and the development of a hypercoagulatable state have been reported with copper deficiency.

Clinical manifestations of severe acute toxicity include hepatic necrosis, coma, haemolysis, renal failure, hypotension, and even death. Mild gastrointestinal symptoms such as nausea, vomiting and abdominal pain can occur in less acute and less serious toxic conditions.

The presentation of Wilson's disease is highly variable, but most commonly presents between the ages of 6 and 30 years with hepatic or neurological dysfunction. Hepatic complications may include anything from asymptomatic abnormalities of liver function tests through to chronic hepatitis, portal hypertension, and even acute liver failure. The neurological features may include Parkinsonism, dystonia, cerebellar dysfunction, or pyramidal signs. Patients with neurological manifestations almost always have some chronic liver disease, although it may be asymptomatic. Kayser-Fleischer rings in the cornea may also be seen on slit-lamp examination or even clinically visible in some cases.

Monitoring

About 90% of plasma copper is bound to caeruloplasmin (a glycoprotein synthesised by the liver). A number of factors can increase caeruloplasmin concentration independent of copper status. Foremost among these factors are high oestrogen levels (from either endogenous or exogenous sources) and the acute-phase response. An elevation of serum caeruloplasmin will secondarily increase total plasma copper. These factors need to be taken into consideration when interpreting the serum copper and caeruloplasmin results.

Free copper can be estimated by determining caeruloplasmin and serum copper.

Caeruloplasmin (g/L) x 50.4 = Bound Copper (umol/L).

Free copper = total copper – bound copper.

Normal free copper concentrations are expected to be in the range 3-5 umol/L.

In situations of acute toxicity, serum copper concentrations will be high but caeruloplasmin levels remain normal.

In Wilson's disease there is a decreased caeruloplasmin. Therefore, despite increased total body copper stores, the serum copper concentration is often decreased. The proportion of copper not bound to caeruloplasmin is often appreciably increased.

Urine copper (24-hour) is a good indicator of acute and chronic copper accumulation. A 24-hour urine copper is elevated in acute toxicity and in Wilson's disease. Urinary copper decreases in deficiency, but the change from an already low basal level is small.

Penicillamine challenge and, moreover, liver biopsy provide tests of greater specificity for Wilson's disease diagnosis in atypical cases. The American Association for Liver Diseases has published guidelines for the diagnosis of Wilson's disease (Roberts EA, Schilsky ML. AASLD practice guidelines: A practice guideline on Wilson disease. Hepatology 2003;37:1475-1492).

Treatment

Copper supplementation should resolve the clinical signs of deficiency within weeks to months. Penicillamine chelation is recommended for treatment of Wilson's disease. Determining urine copper content monitors efficacy of the chelation. The chelation removes zinc as well as copper so the patients zinc status should be monitored.

Analysis

Copper in the various sample matrices is determined by inductively coupled plasma – mass spectrometry.

For further information please contact Ross Wenzel, PaLMS Trace Elements on (02) 9926 7682 or email rwenzel@nsccahs.nsw.health.gov.au.

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