Copper

Atomic number 29
Atomic weight 63.55

Collection

Serum/Plasma	2 mL	Plastic container No anticoagulant / Heparin
Urine	20 mL	Sterile Universal
Tissue Specimens	See instructions on Trace Elements Home Page.	

Reference ranges

			Reference
Serum/plasma	µmol/L	7.9-25.1	1,2
Blood	µmol/L	9.8-27.7	3-5
Urine	µmol/L	0.3	6,11
	µmol/24 h	Less than 0.7	
	nmol/mmol creatinine	16.4-76.2	
	µmol/mol creatinine	Male 28 (95th percentile) Female 44 (95th percentile)	11
Liver	µg/g dry weight	Less than 55	9,10

Notes

Age	Serum/plasma
0-4 months	1.4-7.2
4-<6 months	3.9-17.3
6months -<9 years	11.1-27.4
9-<13 years	11.2-23.7
13-<19 years	9.1-22.5

Wilson's disease:	
penicillamine challenge - Urine	
pre dose	greater than 1.8 µmol/24 h
post dose	greater than 25 µmol/24 hr
Liver	
greater than 250	

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Clinical

Copper (Cu) is an essential element, but is potentially toxic when present in excess, owing to its ability to participate in free radical formation. Cu homeostasis is primarily controlled at the level of excretion: the minimum daily intake that is recommended by the WHO is 1.3mg/d (= 20 µmol/d).[1] Most diets satisfy this requirement owing to the ubiquitous presence of Cu. Under normal circumstances, about 30-40% of ingested copper is believed to be absorbed in the small intestine primarily as cuprous ion (Cu^{+}) via the luminal plasma membrane transporter, CTR1 (SLC31A1)[2, 3]: The transporter, which exists as a homotrimer, works in concert with intestinal reductases[4], including DCytb, a putative Fe^{3+} reductase. Once transported across the membrane, metallochaperones including CCS, Cox 17 and Atox1 deliver copper to target proteins (in organelles/compartments). Small amount of absorption has also been documented to take place in the stomach owing to release of Cu within the acidic milieu.

The presence of CTR1 at the basolateral membrane (via cell-surface labelling) in Caco-2 cells (a model for enterocytes), has however, questioned the absorptive mechanism.[5] Similar basolateral observations have also been made in renal cells and hepatocytes. Mechanisms other than CTR1 are thus believed to operate at the intestinal level. The divalent metal transporter, DMT1, which transports ferrous iron, has been postulated to also import copper,[6] but its precise role in Cu transport remains controversial. Recent investigations indicate that CTR2 (homologous to CTR1) may also play a role in Cu transport.[7,8] Efflux

of Cu across the baso-lateral membrane of intestinal enterocytes is energy dependent and governed by the protein ATP7A.

Once in the liver, the primary early storage site, Cu homeostasis is governed by the activity of ATP7B, which facilitates: (a) biliary copper transport, possibly via interaction with the protein MURR1 (COMMD1) and (b) caeruloplasmin synthesis within the trans-Golgi network (TGN). Excess copper is thus excreted in the bile with only small amounts being found in urine, unless renal damage is present, or substances which bind copper are excreted.

Cu is an integral component of enzymes that are involved in various biological functions, including antioxidant defense, iron and catecholamine metabolism, connective tissue development, neuropeptide synthesis and immune function. Caeruloplasmin, a glycoprotein synthesized in the liver, has the capacity to bind 6 – 8 atoms of Cu per molecule- and accounts for 95% of the Cu present in the plasma. The function of caeruloplasmin is still unclear, but it is important in iron metabolism as a ferroxidase. It is an acute phase protein and can (as with copper) increase greatly in response to infection, injury, chronic inflammatory conditions or steroid hormones (pregnancy, certain contraceptive pills and oestrogen therapy).

Deficiency

Copper deficiency can present as microcytic, hypochromic anaemia with marked neutropenia: the anaemia is only correctable by copper supplementation. Children and neonates on diets deficient in copper have ineffective collagen synthesis, and may develop nerve damage and/or bone disease. As the liver contains substantial stores of copper, frank clinical copper deficiency is unusual, but has been reported in malnourished children and in adults on long term parenteral nutrition without adequate supplementation.[9] Reduced copper absorption is also common in diarrhoea and when zinc intake is increased, due to competitive absorption at the intestinal level.

Subclinical copper deficiency may be more widespread than previously thought and has been suggested as a risk factor for cardiovascular disease,[10] through reduced antioxidant activity altered lipoprotein and catecholamine metabolism and vascular changes.

Menkes ‘steely hair’ disease, is the result of mutations in the X-linked gene ATP7A,[11] which encodes a Cu-transporting P-type ATPase. The disease is characterized by a failure of copper transport across the intestinal mucosa. Although copper levels are low in brain and liver, copper accumulates in many tissues of the body. The intake into cells appears to be normal but there is defective utilisation intracellularly. The condition is therefore one of functional copper deficiency as a result of impaired function of copper dependent enzymes. Patients show mental retardation, depigmentation, severe anaemia, hypotonia and scorbutic changes in bone. Serum copper and caeruloplasmin concentrations are extremely low; treatment with copper histidine is however, not always effective. Diagnosis of this disorder can be

confirmed by measuring the accumulation of copper in cultured fibroblasts from skin biopsy, or prenatally, by measuring the copper content of chorionic villi in the first trimester.

Toxicity

Wilson's disease (WD; hepatolenticular degeneration) is an autosomal recessive disorder caused by loss of function mutations in the copper transport gene ATP7B.[12] The frequency of this condition is in the order of 1 in 30,000 live births. Although over 500 distinct mutations have been identified, some are common to particular populations only (e.g. H1069Q in Europeans). As copper cannot be excreted via the bile, or incorporated into caeruloplasmin, it accumulates in the liver and ultimately in extrahepatic tissue (e.g. lenticular nuclei), resulting in hepatic (cirrhosis) and neurological manifestations. Kayser Fleischer (KF) rings are present in majority of patients with neurological manifestation. The apo-caeruloplasmin that is present in plasma is rapidly degraded - and as a result the copper carrying capacity is reduced.

The classical presentation is of adults with progressive neurological symptoms, low serum concentrations of copper and caeruloplasmin, raised urinary copper excretion, and characteristic copper deposits in the corneas (Kayser-Fleischer rings). Children and adolescents frequently present with a variety of hepatic symptoms including fulminant hepatic failure.

Depending on the stage of the disorder, plasma copper may be normal or even increased. Similarly, caeruloplasmin, may be normal as a result of acute phase response. Measurement of the liver copper content or of the urinary output of copper following a penicillamine challenge may be necessary to diagnose difficult cases.

Acute ingestion of copper (e.g. as a salt) produces nausea, vomiting, diarrhoea and hypotension. Individuals with glucose 6 phosphate deficiency are at increased risk of haematological effects. In situations of acute toxicity, serum copper concentration will be high, but the caeruloplasmin concentration will be normal. Chronic poisoning with copper leads to gross hepatic copper overload with severe liver disease and could be fatal. Indian childhood cirrhosis (ICC) has been ascribed to increased Cu intake through storage of milk in copper yielding vessels. ICC-like conditions have however, been documented in children of non-Indian origin,[13] indicating a genetic component being responsible for the copper loading and hepatotoxicity. Liver copper content in such cases can exceed that found in overload due to Wilson's disease, but the storage mechanisms and histological appearances are different.

Laboratory Indices of Copper Status

The standard first line investigation is usually the serum copper and caeruloplasmin and the basal urinary copper excretion. Copper deficiency may however be masked by normal/increased caeruloplasmin as part of an 'acute phase' response to infection, injury or chronic inflammatory disease. The degree of such a response should thus be considered. An increase in caeruloplasmin following copper supplementation may be a method for confirming deficiency. Furthermore, in neonates, serum copper

and caeruloplasmin levels are low and rise during the early weeks of life, reaching adult levels after 1 to 2 years. This makes the diagnosis of Wilson's disease difficult during the first six months. Copper concentrations which fail to rise above 5 µmol/L after the first few weeks may indicate copper deficiency.

'Free' or non- caeruloplasmin bound copper is a parameter that is still utilised by some clinicians for diagnosis of WD. It can be calculated based on the serum copper and caeruloplasmin measurements; this parameter is however dependent on adequacies of the methodologies in use for Cu and caeruloplasmin. 'Free Cu' concentration increases as Wilson's disease progresses, but is raised in other liver disorders too (e.g. chronic cholestasis).

Measuring urinary copper excretion before and during administration of 2 x 500 mg oral doses of penicillamine at 12 hour intervals can help to distinguish children with Wilson's disease (over 25 µmol/24h post-penicillamine)[14] from those with liver disease due to other causes.

Although investigators have utilised measurements of activities of various Cu containing enzymes (e.g. erythrocyte SOD, Glutathione peroxidase), their importance as useful biomarkers for ascertaining copper status remains questionable. LFT's, haematological indices as well as ophthalmic examination are useful tests in diagnosis of WD.

Determination of copper content and/or the histological examination of a needle biopsy of liver are frequently the standard value for establishing the diagnosis of WD. However, it is noteworthy that biliary impairment (and thus reduced Cu excretion) exists in other liver conditions, such as primary biliary cirrhosis and biliary atresia. The ^{65}Cu uptake test (where other investigations are equivocal) as well as genetics (mutation detection) are further tests that maybe applied to individuals and more so to family studies.

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