Copper

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Contribution:
Jessica Farebrother, from the OpeN-Global team, with Dr Daniela Hampel, OpeN-Global Expert Partner.

Dr Daniela Hampel, PhD
Project Scientist
USDA/ARS Western Human Nutrition Research Center
Department of Nutrition, University of California Davis

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Importance of copper for health

Copper is essential for human and animal life, though required in only trace amounts (1). Copper is a cofactor of several metalloenzymes that are oxidases for the reduction of molecular oxygen, e.g. the cytochrome c oxidase enzyme, the last enzyme in the electron transport chain (2). Copper is also critical for the use of dietary iron in the body, including the uptake of iron from the intestine, iron release from stores and the incorporation of iron into haemoglobin (2). Ferroxidases are cuproenzymes in the plasma, and function in ferrous iron oxidation that is needed to bind iron to transferrin (3).

Copper is a critical factor in the prevention of anaemia, and anaemia associated with hypochromic, microcytic erythrocytes is widely recognised (2). More recently, neuromuscular defects resembling

pernicious anaemic have responded to copper supplementation rather than administration of vitamin B12 (2, 4)

Table 1: Roles of cuproenzymes and effects of copper deficiency

Enzyme	**Function**	**Effect of copper deficiency**
Ceruloplasmin	Plasma multi-copper oxidase necessary for iron mobilisation	Iron-deficiency anaemia
Lysyl oxidase	Cross-links collagen and elastin	Weak-walled blood vessels
Dopamine-ß-hydroxylase	Catecholamine production	Neurological effects
Cytochrome *c* oxidase	Electron transport chain	Decreased ATP synthesis
Superoxide dismutase	Superoxide radical scavenger Prevents lipid peroxidation and membrane damage	Tissue damage

Copper is required for numerous body processes (2):

- Blood coagulation
- Control of blood pressure
- Cross-linking of connective tissue in bone, heart and arteries
- Antioxidant defence
- Energy transformation
- Myelination of brain and spinal column
- Reproduction
- Hormone synthesis.

Copper is absorbed mainly in the proximal part of the small intestine, followed by transport into the liver via the portal vein (1). The relative predictor of absorption is the copper content of the food consumed (2). Biliary excretion maintains plasma copper homeostasis, and urinary excretion is usually <0.1 mg/day over a wide range of dietary intakes (3). Homeostasis is influenced by interactions between other metals including zinc, iron, and molybdenum (3).

Foods high in copper include legumes, mushrooms, chocolate, nuts and seeds, and liver (2). Due to their relative abundance in the diet, bread, potatoes and tomatoes also make substantial copper contributions (2).

Risks of deficiency:

An inadequate copper intake has adverse effects on glucose and cholesterol metabolism, blood pressure control and heart function, immunity and bone mineralization (2). Low copper is associated with osteoporosis, also in infants and children (5, 6). It has been shown that copper administration can improve bone mineral density in post-menopausal women, though it is unknown whether the osteoporosis itself is due to copper deficiency (2).

Overt copper deficiency is rare in humans. Symptoms include normocytic, hypochromic anaemia, leucopoenia and neutropenia, and osteoporosis in children (3). The impact of diet may be particularly pronounced in neonates as digestive function and homeostatic regulation of biliary copper are immature (2).

Risks of excess:

Copper toxicity is relatively rare, since humans have evolved with precise homeostatic mechanisms for copper due to its reactivity (2). Copper exists almost always bound to proteins. People most at risk are those with a hereditary defect in copper homeostasis (Menkes' disease), characterised by a reduced copper uptake and placental copper transport (3). Those with Wilson's disease (see box) are also at higher risk of copper toxicity due to liver damage resulting from the disease (3).

Idiosyncratic copper toxicity is otherwise usually acute and has been associated with copper salts in supplements and drinking water (3); symptoms include gastrointestinal distress. Alternatively, exposure can be through metal fumes, bringing about an influenza-like syndrome (7).

Wilson's disease is a rare autosomal-recessive disorder of a copper-transporting ATPase resulting in abnormal copper storage (5). Its global prevalence is estimated to be 1:30,000 (8). The defect results in a failure to excrete copper effectively in bile, and an impaired incorporation of copper into ceruloplasmin. Thus, copper is deposited in various tissues including the liver causing cirrhosis, the brain leading to neurological symptoms, the kidneys, and the eyes causing damage. Chelation therapy is very effective however liver cirrhosis and neurological damage are permanent

Human biomarkers for measuring copper intake and status

Serum copper concentration reflects changes in both depleted and replete individuals and may have benefit as a biomarker (9). However, most copper in the body is bound to proteins: 65-71% is bound to ceruloplasmin, the glycoprotein enzyme involved in iron metabolism, and 15-19% to albumin (7).

Total ceruloplasmin reflects changes only in highly depleted individuals (9), and therefore may not have use as a population biomarker. Copper present free in serum and/or bound to amino acids may also be useful to measure; some reports suggest a link between an excessive free copper fraction and degenerative health effects due to oxidation and a depletion of antioxidant reserves (7, 10). Copper may also be assessed in human milk samples, which may be an accessible specimen in population studies involving lactating women and infants (11), and in plasma, though this method appears to be more infrequently used (9).

Other possibly biomarkers are plasma, platelet, and erythrocyte copper, and other proxy biomarkers including platelet and leucocyte cytochrome c oxidase, total glutathione and urinary pyridinoline (9). These biomarkers are not included here.

Methods

Atomic Absorption Spectrometry (AAS): Suitable for human serum, plasma, milk (12) and bones (13)

Instrument parameters are usually instrument-dependent. Example instrument parameters and temperature ramp for AAS described by (7).

*Inductively-coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS):*Suitable for plasma, serum, and milk samples for assessment of total copper (CDC SOP): https://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/CUSEZN_G_met_serum_elements.pdf)

Inductively-coupled plasma atomic emission spectrometry (ICP-AES): Suitable for

- Blood, serum, urine, cerebrospinal fluid (14)
- Milk (11)
- Hair (15)

Measurement of ceruloplasmin in serum or urine: Measurement can be conducted using a kit, e.g. by ThermoFisher Scientific *https://www.thermofisher.com/order/catalog/product/EIACPLC*

Confounding factors

Results should be interpreted with respect to factors that influence the concentration of copper in various body pools. Several physiological functions can affect copper content and the activity of ceruloplasmin in blood, including acute phase response to infection and inflammation, pregnancy and other hormonal perturbations, some carcinogens, and smoking (2). Circulating copper may be especially high during inflammation and may not represent cellular concentrations of cuproenzymes (2).

Accreditation schemes

Please see the OpeN-Global page on laboratory accreditation: https://open-global.kcl.ac.uk/accreditation/

Technical assistance

For questions on methods of copper assessment or for technical assistance, please contact the OpeN-Global team at https://open-global.kcl.ac.uk/contact/ or write to:

Dr Daniela Hampel, PhD, Project Scientist, https://nutrition.ucdavis.edu/people/daniela-hampel

USDA/ARS Western Human Nutrition Research Center
Department of Nutrition, University of California Davis

Email: dhampel@ucdavis.edu or daniela.hampel@ars.usda.gov

Useful links and further reading

US National Academies Press IOM Dietary reference intakes: Copper, 2006:
https://www.nap.edu/read/11537/chapter/34

Copper Alliance: https://copperalliance.org/benefits-of-copper/public-health/

Dietary copper and human health:
https://www.sciencedirect.com/science/article/pii/S0946672X16300207

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