Nutrition Information Brief—Copper

Nutrient

Copper (Cu; atomic number, 29; average atomic weight, 63.546) constitutes ∼70 ppm of the Earth's crust. The electronic configuration of copper ([Ar] $3d^{10}4s^1$) allows it to exist in 2 oxidation states in biological systems (i.e., Cu^{2+} and Cu^{1+}), which underlies its primary physiological function as a redox catalyst in various metabolic reactions. Due to its high redox potential, excess copper is toxic. The essentiality of copper for humans and animals has been recognized for nearly a century. Although less common in humans, copper deficiency is the leading nutritional deficiency disease among agricultural animals worldwide. The RDA for copper for adults is 900 μg/d. The human body contains ∼100 mg of Cu, with ∼75% of the total in skeleton and muscle tissue, whereas the liver, brain, blood, heart, and kidney contain most of the remainder (1). Higher copper concentrations likely reflect elevated metabolic activity, because copper is a required cofactor for cytochrome c oxidase, the terminal complex in the electron transport chain. Copper is also an essential cofactor for several other oxidases that function in the regulation of blood coagulation and blood pressure control, cross-linking of connective tissues, energy transformation, myelination of brain and spinal cord, reproduction, and hormone synthesis (2). Copper is also required for maintenance of iron homeostasis, which is perhaps best reflected by the 2 multicopper ferroxidases, hephaestin and ceruloplasmin (CP) (3).

Deficiencies

Copper depletion adversely affects cholesterol and glucose metabolism, blood pressure control and heart function, immunity, and mitigation of oxidative stress. Importantly, some of these deficiency symptoms have only been described in experimental animal models of copper deficiency (3). Moreover, copper-deficient children are at increased risk for developing osteoporosis, exemplifying the critical role that copper plays in bone development and mineralization. Although dietary copper insufficiency has been infrequently described, low intakes may occur with malnutrition (e.g., poverty, anorexia nervosa) or in malabsorptive disorders (e.g., Crohn disease, celiac disease). Copper depletion also occurs in the rare genetic disorder Menkes disease (MD). Impaired absorption of dietary copper due to mutations in *ATP7A* (encoding ATPase copper transporting alpha) underlies MD. Copper deficiency may also occur due to excessive losses, as seen in severe burn patients or those with chronic kidney disease on dialysis, and after gastric bypass surgery for morbid obesity. Excessive zinc intake can also cause copper depletion (likely by impairing copper absorption). Symptoms of copper deficiency include ataxia, anemia, neutropenia, immune dysfunction, and increased LDL/HDL cholesterol ratio (4, 5).

Moderate to severe copper deficiency is typified by decrements in serum copper and CP activity (6). CP carries most circulating copper; thus, changes in blood copper likely reflect changes in CP concentrations. Using serum Cu and CP activity as bioindicators of copper status is, however, complicated because infection and inflammation, pregnancy, and some cancers can increase serum copper content and CP activity. Blood copper may thus be elevated during inflammation. Moreover, plasma copper may not accurately reflect copper concentrations in liver and other organs, as demonstrated by work in experimental animals. Detecting more subtle copper depletion is also challenging, because sensitive and specific bioindicators of copper nutritional status have not been identified (7). This is an important area for further experimentation because mild (or subclinical) copper deficiency may occur more frequently than once thought in the United States (8) and possibly be associated with pathophysiologic outcomes.

Diet Recommendations

Dietary reference intakes for copper were established in 2001 (9) and summarized in 2006 (10), although these recommendations were based on quite limited experimental data. Adequate Intake levels were established for infants 0–6 mo (200 μg/d) and 7–12 mo (220 μg/d) of age. Established RDAs increase with age (all in μg/d; for males and females): 340, 1–3 y; 440, 4–8 y; 700, 9–13 y; 890, 14–18 y; and 900, 19–70+ y. Recommended intakes increase in pregnancy (1000 μg/d) and lactation (1300 μg/d). Upper tolerable intake levels (ULs) have also been established for copper, varying from 1000 μg/d at 1–3 y to 10,000 μg/d in adults (19–70+ y), with liver damage as a selecting criterion. Copper consumption data acquired through NHANES 2012 suggest that ∼25% of the US population does not meet the RDA (11). Interestingly, copper intake recommendations for adults are higher in the United Kingdom (1200 μg/d), the European Union (1300–1600 μg/d), and Australia/New Zealand (1700 μg/d), suggesting that the US RDA may be low. Human balance studies support a copper requirement for adults between 0.8 and 2.4 mg/d, but methodologic limitations preclude a precise estimate of dietary copper requirements (6). The average estimated copper intake in the United States meets (or exceeds) current dietary recommendations (12). However, if the US RDA were raised to meet minimum European Union guidelines of 1300 μg/d, ∼70% of Americans would fail to meet the RDA for copper (according to NHANES 2012 data). Establishing copper RDAs is also complicated

by the fact that accurately assessing copper intakes is quite challenging.

Food Sources

Copper absorption occurs mainly in the upper small intestine. Recent studies in humans using radioisotope tracers suggest that fractional absorption of dietary copper is ~50% over a range of intakes (0.7–6 mg/d) (13). Dietary factors, including iron (14), vitamin C, and zinc, have been reported to exert adverse effects on the bioavailability of copper. Local conditions (e.g., copper content of soil) lead to variations in copper content in various foods. Copper exposure can also occur from tap water (e.g., from copper plumbing). Although accurate assessment of food copper content is technically challenging, some rich sources have been identified, including shellfish, seeds and nuts, organ meats, wheat-bran cereals, whole-grain products, and chocolate.

Clinical Uses

Copper is used clinically mainly to replete copper-deficient individuals. Copper gluconate, cupric sulfate or oxide, or copper–amino acid chelates are most frequently used in supplements. The relative bioavailability of these different chemical forms of copper has, however, not been extensively investigated (15). Various supplements contain a few micrograms of copper up to 15 mg (which exceeds the UL for adults) (16). Copper supplementation of at least 2 mg/d is recommended for Roux-en-Y gastric bypass patients (17). Supplemental copper should be cautiously administered to infants, as toxicity risks are elevated because homeostatic regulation of copper absorption and biliary excretion is not yet fully functional. Moreover, patients with conditions that increase risk for copper toxicosis, including Wilson disease (WD) and biliary cirrhosis and atresia, should avoid taking supplemental copper.

Toxicity

Copper toxicosis is rare in humans and other mammals because excess copper can be excreted. Biliary copper excretion is mediated by ATPase copper transporting beta (ATP7B). Mutations in *ATP7B* underlie the rare genetic copper-loading disorder WD. Excess copper is likely to increase oxidative stress, resulting in tissue/organ damage. The liver may be the initial organ affected, given that absorbed copper travels there first via the portal blood circulation. Copper supplementation of adults with 10 mg cupric gluconate daily for 3 mo did not result in notable copper toxicity, but higher intakes (30 mg/d) in 1 individual resulted in acute liver failure (18). A UL of 10 mg/d has been established, mainly to avoid liver damage in susceptible individuals (10). Those at increased risk for copper toxicity include neonates and infants, as well as individuals with WD or other disorders in which biliary copper excretion is impaired.

Recent Research

Copper has recently been implicated in conditions of disturbed lipid homeostasis (11, 19). For example, in an analysis of US NHANES data, increases in serum copper were positively associated with elevation of total cholesterol, LDL cholesterol, and HDL cholesterol in women (20). Moreover, most prominently in women and middle-aged individuals, high circulating copper increased risk for developing nonalcoholic fatty liver disease (21). It is hoped that mechanisms by which high (or low) copper interferes with normal lipid homeostasis will be elucidated in future investigations. Another worthy area of future scientific pursuit relates to copper and neurodegenerative disorders. Conflicting reports of the effects of low and high copper on these disorders complicate interpretation of previous investigations. Also, whether copper accumulation plays a primary or secondary role in disease pathogenesis has yet to be established. Interestingly, copper imbalance in neurodegenerative diseases often occurs concurrently with perturbations in zinc homeostasis (22). Because excess zinc intake can induce copper deficiency and both metals interact with the same ligands, future research should focus on understanding the pathophysiologic implications of these interactions in these (and potentially other) disease states. Furthermore, dietary copper insufficiency may be more common than previously thought in the United States (8), and the current RDAs for copper may be low (6, 8). More extensive human balance studies (which also consider copper losses) and identification of more sensitive bioindicators of copper status may lead to reconsideration of copper intake recommendations in the future. Additional advancements in understanding the relation between copper and development of common chronic diseases in humans also likely await the discovery of new and improved copper nutrition-related biomarkers.

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Abbreviations used: CP, ceruloplasmin; Cu, copper; MD, Menkes disease; UL, upper tolerable intake level; WD, Wilson disease.

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