

Clinical conditions altering copper metabolism in humans^{1,2}

Donna Beshgetoor and Michael Hambidge

ABSTRACT Overt copper deficiency is not believed to be a widespread public health concern for most population groups. However, a variety of case studies suggest that under certain circumstances, clinical conditions may predispose individuals to the risk of copper deficiency or copper excess. Acquired copper deficiency has been documented in conditions predisposing to inadequate copper intakes, in prematurity, in malabsorption syndromes, and in conditions predisposing to excessive copper losses. In contrast, increases in copper concentrations have been reported in response to stress, inflammation, and infection; in Parkinson disease and diabetes mellitus; and in conditions involving an obstruction to bile flow. *Am J Clin Nutr* 1998;67(suppl):1017S–21S.

KEY WORDS Copper, acquired copper deficiency, prematurity, copper malabsorption, copper excess, humans, copper intake

INTRODUCTION

Although the essentiality of copper for mammals was clearly established during the 1920s and 1930s, human copper deficiency was not well described until the 1960s when Cordano and Graham (1–3) reported its development in severely malnourished infants treated with low-copper, milk-based diets. The recognition of Menkes syndrome as a genetic disorder affecting copper absorption provided new insights into the effects of severe copper deficiency in humans (4). Although overt copper deficiency is not believed to be a significant nutritional problem for many population groups (5), a variety of case studies over the past several decades suggests that copper metabolism may be altered under certain circumstances by specific clinical conditions.

CONDITIONS PREDISPOSING TO INADEQUATE COPPER INTAKES

Copper deficiency has been clearly documented in conditions predisposing to inadequate intakes of copper. Examples include the provision of prolonged, unsupplemented total parenteral nutrition (TPN), the provision of unmodified cow-milk-based diets to infants, and recuperation from malnutrition in infants. Acquired copper deficiency has occurred most frequently in patients undergoing long-term TPN. Before the use of TPN, there were actually no known reports of overt copper deficiency in adults. However, it has now been well established that unsupplemented TPN administration not only results in lower serum copper concentrations, elevated urinary copper output, and a net

negative copper balance (6, 7), but frequently leads to the development of overt symptoms of copper deficiency in both adults (8–15) and children (16–19). A daily parenteral requirement of 0.5–1.5 mg Cu for adults undergoing TPN has been recommended by the American Medical Association (20). However, balance studies by Shike et al (21) of patients receiving long-term TPN suggest that 0.3 mg Cu/d is a more appropriate recommendation for adult patients in stable conditions and that 0.2 mg Cu/d is a more suitable requirement for patients with cholestatic liver disease. Their studies also suggest recommendations for copper-depleted patients of 1 mg Cu/d for 2 wk followed by 0.5 mg/d and for infants of 0.2 mg Cu/d (7, 21).

It is surprising that 25 y after the first report of clinical copper deficiency in a patient maintained on total intravenous nutrition (16) and nearly 20 y after the American Medical Association (20) published recommendations for daily parenteral copper requirements, reports of copper deficiency resulting from TPN and from enteral nutrition continue to appear in the literature (15, 22). Such cases occur despite the fact that in this country, as well as in many other countries, copper is added to nutritional infusates. Furthermore, many infusates have near adequate concentrations of copper because of chance contamination (7). However, the continued incidence of TPN-related copper deficiency suggests the need for further research to enhance our understanding of how copper metabolism and requirements are likely altered by various disease states as well as by the intravenous infusion of nutrients.

The early introduction of unmodified cow milk as a primary nutrient source led to the development of copper deficiency, particularly in low-birth-weight and premature infants (23–26). Case studies by Levy et al (27) also described signs of copper deficiency in two 6-mo-old male infants who were neither premature nor seemingly malnourished, but fed cow milk since birth. These studies suggest that copper deficiency during the first year of life in infants fed a cow-milk-based diet may not be that uncommon and, unfortunately, may often go undiagnosed.

The work of Cordano (1–3) and Uauy (28, 29) has brought attention to the incidence of copper deficiency in association with protein-energy malnutrition (PEM). Copper nutriture proves to be especially problematic during the recovery stage of PEM, when growth is rapid. This rapid rate of growth is often confounded by increased copper requirements in these patients,

¹From the Section of Pediatric Nutrition and Center for Human Nutrition, University of Colorado School of Medicine, Denver.

²Address reprint requests to D Beshgetoor, Exercise and Nutritional Sciences, San Diego State University, San Diego, CA 92182-7251.

thus further predisposing them to copper deficiency unless adequate copper supplementation is prescribed.

For breast-fed infants exhibiting PEM, copper status may be jeopardized by early weaning. Under such circumstances, human milk is often replaced with alternate foods low in copper or with cow-milk-based feedings, frequently resulting in a high incidence of diarrhea. Although PEM has been shown to respond to cow-milk-based therapeutic regimens, the coexisting symptoms of copper deficiency are exacerbated by these traditional treatments.

One word of caution should be noted regarding copper deficiency secondary to PEM: low circulating concentrations of copper may not necessarily reflect copper deficiency per se. Rather, low circulating copper concentrations in PEM may be due to protein deficiency, which in turn results in decreased serum copper because ceruloplasmin synthesis in the liver is reduced.

PREMATURITY

It is likely that inadequate copper stores predispose premature infants to the risk of copper deficiency. Copper stores are especially important during development. As shown by the studies of Widdowson et al (30), fetal copper stores accumulate primarily during the last trimester of pregnancy. The net rate and timing of transfer of copper across the placenta from maternal stores determine the copper stores of the neonate at term. This store of copper, $\approx 15\text{--}17$ mg at term, is thought to provide a reserve that is available to the infant in early postnatal life, thus providing a level of protection against copper deficiency. However, premature infants are seemingly not afforded this level of protection because of reduced copper stores in the liver and increased copper requirements as a result of increased growth rates compared with full-term infants (31).

Studies in fetal and neonatal rodents suggest that additional developmental factors also determine the accumulation of copper by the liver (32) and that liver maturation is necessary to allow the release of copper to body tissues (33). This may be of particular relevance in premature infants. Serum copper concentrations in premature infants may not reach the concentrations of a full-term infant at delivery until the premature infant has attained an equivalent postconceptional age (34–36). Furthermore, small-for-gestational-age premature infants may have lower serum copper concentrations than either appropriate-for-gestational-age premature infants or full-term infants (37–39).

Little is known about how infants utilize hepatic copper stores accumulated in utero. It is possible that the high concentration of copper in fetal liver does not serve as a hepatic store of copper for physiologic needs but merely reflects limited biliary excretion of copper. The animal studies of Srai et al (40) suggest that at least some copper starts to be excreted soon after delivery. The current thought is that copper excreted in bile is not reabsorbed or is reabsorbed only to a small extent. It is not known whether this applies to all situations and, in particular, whether it is applicable to preterm or full-term infants.

CONDITIONS PREDISPOSING TO COPPER MALABSORPTION

Over the past several decades, case studies of acquired copper deficiency in clinical conditions causing decreased copper absorption secondary to malabsorption syndromes have been documented in the literature. In general, with the exception of

excessive intakes of zinc and iron, these cases of copper deficiency have been limited to a few isolated clinical situations. Pathogenic conditions include celiac disease, short bowel syndrome, cystic fibrosis, tropical and nontropical sprue, and diarrhea; postgastrectomy status; jejunoileal bypass surgery; and intakes of megadoses of zinc and iron (41).

One of the most important clinical factors that can predispose an individual to secondary copper malabsorption is an excessive intake of zinc. Because of similar physiochemical properties between copper and zinc, a high intake of zinc or high molar ratio of zinc to copper has long been recognized to interfere with copper metabolism. Zinc-induced copper deficiency has been reported clinically in conditions in which zinc was used therapeutically in the treatment of other diseases (41, 42). The increasing popularity of zinc supplementation within lay and food faddist populations has also resulted in several cases of copper deficiency secondary to zinc-copper antagonism. Manifestations of the deficiency include anemia, granulocytopenia, bone marrow abnormalities, elevated serum zinc concentrations, decreased serum copper concentrations, and decreased serum ceruloplasmin concentrations (43, 44). Although there has been some uncertainty about the mechanism of zinc-related copper deficiency, possible mechanisms include interference at the intestinal brush border, the induction of intestinal metallothionein (45), or the involvement of specific transporters (46).

An antagonistic interaction was also documented between iron and copper (47). Studies by Seely et al (48) in the early 1970s and more recent studies by Barclay et al (49) draw attention to the importance of copper-iron interactions, particularly in low-birth-weight infants. Low-birth-weight infants may be at risk of copper deficiency when they receive generous supplements of iron. Although plasma copper concentrations in low-birth-weight infants have been shown to be unaffected by iron supplementation (50), plasma copper is not an accurate means of assessing early risk of impaired copper utilization or copper deficiency in these infants. Barclay et al (49) suggest that erythrocyte superoxide dismutase activity is a more sensitive indicator of altered copper metabolism and of potential copper deficiency, particularly under these circumstances. Copper-iron interactions may also be of potential concern in pregnant women receiving high concentrations of supplemental iron from prescribed prenatal vitamin and mineral tablets. Because copper requirements are increased during pregnancy (41), excessively high iron concentrations could increase the risk of copper deficiency by interfering with the absorption of copper.

Malabsorption resulting from long-lasting enteropathies reportedly led to the development of hypocupremia in rare instances (51–53). Copper deficiency due to celiac disease has also been suggested by several case studies (54–56). Clinical symptoms include stunting, skin and hair depigmentation, pallor, vascular fragility, bone lesions, osteopenia, and, in some cases, low serum copper and ceruloplasmin concentrations, leukopenia, neutropenia, and anemia. The severe malabsorption that accompanies celiac disease is thought to be the mechanism leading to the depletion of copper stores and secondary copper deficiency (54). However, it is also possible that a failure to reabsorb biliary copper could contribute to the development of copper deficiency. This seems a less plausible mechanism, because earlier studies indicated that bile secretions are reduced in celiac disease as a result of impaired production of cholecystokinin and secretin (57).

Recent evidence has supported the earlier suggestion of Shahidi et al (58) and Cartwright and Wintrobe (59) that copper deficiency



is likely to occur in cystic fibrosis (60–62). Although several studies have reported normal copper status in cystic fibrosis patients (63–65), these investigators' conclusions were based solely on measurements of serum copper or ceruloplasmin concentrations, which may not be an accurate means of assessing copper status. Percival et al (62) proposed that the activities of two copper-requiring enzymes in neutrophils—superoxide dismutase and cytochrome-*c* oxidase—may be more sensitive indicators of copper status, particularly in cystic fibrosis and other conditions characterized by chronic infection and inflammation.

Perhaps the most important clinical condition resulting in the malabsorption of copper is infantile diarrhea. The studies of Cordano, Castillo-Duran, Uauy, and others (1–3, 23, 24, 66–70) have clearly documented the detrimental effects of infantile diarrhea on copper metabolism. The loss of copper in acute and protracted diarrhea is of particular concern in malnourished and premature infants, who are likely to already have altered mineral absorption and depleted mineral stores. Uauy et al (70) showed an association between copper deficiency in malnourished infants and the recurrence of episodes of acute diarrhea. However, further studies are needed to enhance our knowledge of the magnitude and duration of copper losses during both acute and protracted diarrhea. Isolated cases of acquired copper malabsorption have also been documented in patients undergoing jejunoileal bypass procedures for morbid obesity (71), in patients with a history of partial gastrectomy (72), and in patients with inflammatory bowel disease (11, 73).

CONDITIONS PREDISPOSING TO EXCESSIVE COPPER LOSSES

Excessive losses of copper can impair copper status under several clinical circumstances. The urinary loss of amino acid-bound copper could be at least a minor factor in TPN-related copper deficiency. Urinary losses of ceruloplasmin-bound copper likely play a significant role in predisposing patients with nephrotic syndrome to copper deficiency (74). Renal patients undergoing continuous ambulatory peritoneal dialysis may also experience excessive losses of ceruloplasmin-bound copper via dialysis exchanges (75). Excessive losses of copper via the skin can occur in burn patients (6, 76). Although ceruloplasmin generally responds as an acute-phase reactive protein after stress and trauma, Cunningham et al (77) reported an absence of this response in the early catabolic phase of severe burn trauma despite the administration of supplemental copper.

Chelating agents can increase copper excretion even when this is not the objective of treatment. Earlier studies by Keen et al (78) showed the detrimental effect of penicillamine therapy on copper metabolism in a rat model. In humans, penicillamine is used therapeutically to chelate endogenous copper and reduce potentially toxic concentrations of copper in persons with Wilson disease (79). However, several clinical reports suggest that the detrimental effects of penicillamine treatments shown in animal studies may also occur in humans (80).

Other iatrogenic factors may increase copper losses. Prolonged treatment with the glucocorticoid dexamethasone has been shown to interfere with copper metabolism in premature infants (39). As discussed previously, this may confound an already precarious copper status in these infants. Copper deficiency was also reported in an otherwise healthy woman consuming a normal diet but who consumed ≤ 15 antacid tablets per

day for a prolonged period (81). Antacids contain oxides that can precipitate cupric salts at an alkaline pH. Thus, the ingestion of a large number of antacids can induce secondary copper deficiency by reducing the bioavailability of dietary copper (5). It is likely that several other medications affect copper metabolism as well (5, 82); however, to date, little is known about the interactions between dietary copper and various drugs. Such information will be vital in determining copper requirements in clinical circumstances in which medications are an important component of treatment.

CONDITIONS PREDISPOSING TO COPPER EXCESS

It is well known that concentrations of serum ceruloplasmin and copper are increased during conditions of stress. Increases in copper concentrations have been cited in response to inflammation and infections and in various chronic diseases such as arthritis and neoplasia (6). As an acute-phase reactant, ceruloplasmin may be elevated in response to a variety of circumstances and may be responsible for up to threefold elevations in serum copper concentrations (45). However, it is beyond the scope of this review to describe all such situations.

Several chronic diseases reportedly result in elevations in copper concentrations. Pall et al (83) reported elevated concentrations of copper in cerebrospinal fluid in patients with Parkinson disease. The cause of the increased copper concentrations remains unknown, although results suggest that the copper abnormality was not due to nonspecific leakage across the blood-brain barrier or out of neural cells. The study suggests a possible role for copper-catalyzed oxidative mechanisms in the etiology of Parkinson disease and has opened the door to discussion of the possibility of a relation between oxidant properties of copper and the neurologic damage that occurs in Parkinson disease.


Clinical studies of type 1 and type 2 diabetes have shown alterations in copper metabolism in these diseases (84–86). The results of these studies have been inconsistent, however, with both normal and increased plasma and serum copper concentrations reported. Increased concentrations of plasma copper were observed in diabetic subjects with complications of retinopathy, hypertension, macrovascular disease, or a combination of all three (84). It is not yet known whether the abnormalities in copper metabolism noted in these subjects are a consequence of the disease per se or whether they play a role in the progression of the disease (87). Although alterations in tissue concentrations of copper have not been documented in studies of diabetes in humans, studies in animal models have reported increased tissue copper concentrations in diabetes (87). The results of these studies suggest altered copper transport at the intestinal brush border in diabetic animals.

Other conditions predisposing to copper excess typically involve obstructions to bile flow. Copper (and manganese) are distinct among the trace elements in that their primary route of excretion is via bile. Therefore, if bile excretion is impaired, copper excretion is in turn compromised. This is of concern in clinical circumstances associated with biliary stasis and in other conditions, such as Wilson disease, in which biliary copper excretion is impaired. Examples of such conditions include primary biliary cirrhosis, obstructive hepatobiliary disease, extrahepatic biliary atresia, neonatal hepatitis, choledochal cysts, and α_1 -antitrypsin deficiency (88–91). Primary biliary cirrhosis, often used as a prototype for investigations of copper retention in cholestasis, is char-



acterized by an abnormal accumulation of copper in the liver. Studies of primary biliary cirrhosis suggest that the accumulation of liver copper is potentially hepatotoxic, with concentrations in the range of those observed in Wilson disease (88).

Elevated concentrations of hepatic copper are also seen in extrahepatic biliary atresia (91). These elevated concentrations do not approach those reached in Wilson disease or in Indian childhood cirrhosis, however. Thus, it is not certain whether the concentrations are elevated enough to be hepatotoxic.

A related area of concern is that of hepatic copper concentrations in cholestatic liver disease secondary to intravenous nutrition. To our knowledge, no studies of copper metabolism under these clinical conditions have been published. Yet cholestasis is not an infrequent complication in infants maintained for prolonged periods on TPN, particularly infants with short bowel syndrome. Therefore, it is important to understand the ramifications of trace element supplementation on cholestasis resulting from TPN. Additional research is needed to determine the effects of the intravenous administration of inorganic copper salts on the systemic circulation, on peripheral tissues, and on the infusate solution. 

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