Copper Deficiency

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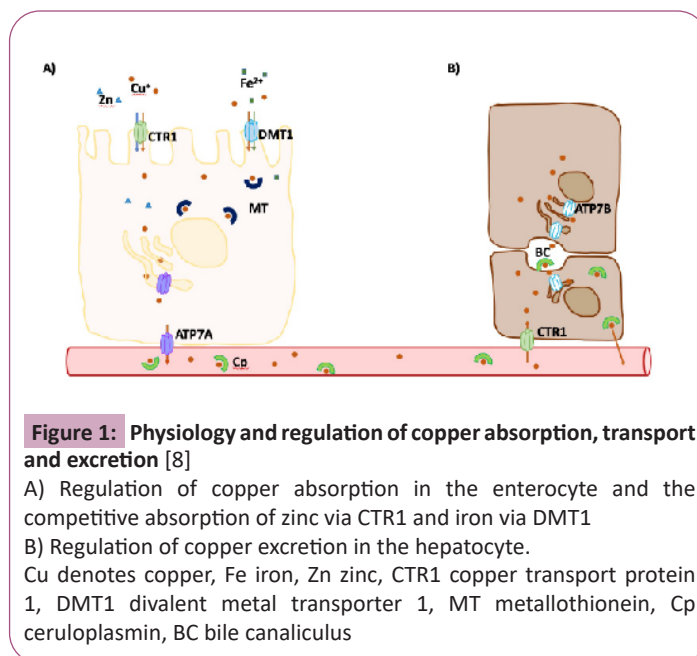E-mail: hofmannpatrick@bluewin.ch

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Abstract

Copper is an essential trace element serving as a cofactor for several pivotal enzymatic pathways for growth and metabolism. Copper deficiency can be caused by an impaired or insufficient uptake or increased demand. Symptoms of copper deficiency are nonspecific and include hematologic, neurologic and dermatologic alterations. Copper deficiency anaemia is most often macrocytic in combination with neutropenia. Diagnosis of copper deficiency is based on serum copper measurements and can be supported by serum ceruloplasmin and 24 h-urine copper excretion. Treatment depends on the underlying aetiology and generally includes oral copper replacement. Copper deficiency should be considered in any patient with unclear anaemia or neuropathy, especially in patients taking zinc supplements and in patients after gastrointestinal surgery.

Keywords: Copper deficiency; Zinc; Iron; Malnutrition; Ceruloplasmin; Macrocytic anemia; Neuropathy

Introduction

Physiology

Absorption: Food rich in Copper (Cu) are green vegetables, whole grains, seeds, nuts, mushrooms, milk and dark chocolate. The average dietary Cu intake is 0.5-1.5 mg per day [1,4]. The total amount of Cu reabsorbed from digestive fluids is 5-7 mg and only about 1 mg of Cu is excreted per day mainly through the hepatobiliary system [3]. Dietary Cu is absorbed in the stomach and duodenum through the transporter protein referred to as copper transport protein 1 (CTR1) and Divalent Metal Transporter 1 (DMT1). Before absorption, Cu must be reduced from the cupric (Cu^{2+}) state to the cuprous (Cu^+) state by cupric reductases located in the brush-border membrane [4]. The absorption rate increases during pregnancy and in patients with cancer [5]. Ferrous iron is also transported across the apical membrane by DMT1. During iron deprivation, the expression of DMT1 is upregulated, which increases Cu absorption [6,7]. In the enterocyte, Cu is bound to Metallothionein (MT) and glutathione and excreted into the portal blood stream on the basolateral side via the Cu-ATPase (ATP7A). Zinc is competitively absorbed via the CTR1 transporter and excessive zinc ingestion further upregulates MT, which also decreases Cu absorption [8] **(Figure 1)**.

Menkes disease, a rare X-linked recessive mutation in ATP7A is characterized by severe Cu deficiency, cognitive deficits, diminished growth and disease characteristic kinky hair [9].

Figure 1: Physiology and regulation of copper absorption, transport and excretion [8]
A) Regulation of copper absorption in the enterocyte and the competitive absorption of zinc via CTR1 and iron via DMT1
B) Regulation of copper excretion in the hepatocyte.
Cu denotes copper, Fe iron, Zn zinc, CTR1 copper transport protein 1, DMT1 divalent metal transporter 1, MT metallothionein, Cp ceruloplasmin, BC bile canaliculus

Transport, Storage and Excretion: After entering the portal system, ceruloplasmin, albumin and macroglobulin are high affinity Cu binding proteins in the blood plasma. Ceruloplasmin transports over 90% of total serum Cu [10]. The liver acts as a storage organ and is central to the regulation and excretion of Cu. In the liver, Cu is linked to ceruloplasmin and excreted into the bloodstream and bile by ATP7B.In contrast to iron, Cu can be actively excreted and is highly regulated in the liver. In the autosomal recessive disorder

Aceruloplasminemia, reduced or absent ceruloplasmin levels impair iron excretion. The incorporation into the iron transport protein transferrin leads to iron accumulation, especially in the basal ganglia and liver, without relevant changes in Cu metabolism [11]. Cu excretion is regulated mainly in the liver via the biliary system and a small fraction of approximately 10% is excreted in the urine [12]. Under conditions of Cu excess, ATP7B traffics to the canalicular membrane and mediates Cu efflux for biliary excretion. Cu excreted in bile is complexed with bile salts and thus prevents reabsorption in the small intestine [13]. In Wilson's disease, the function of ATP7B is decreased, which leads to excessive Cu accumulation in the liver, heart, kidneys, eyes and central nervous system [9,15].

The Role of Cu in Health and Disease

Cu is an essential trace element serving as a cofactor in redox chemistry. There are several pivotal enzymatic pathways for growth and metabolism including the synthesis of hemoglobin, neurotransmitters, pigments and the electron transport chain [3]. A list of important Cu-dependent enzymes is provided in **Table 1**. Due to its high oxidative activity, Cu forms complexes with small cytosolic proteins called copper chaperones to avoid oxidative stress and damage to cell membranes, intracellular proteins and nucleic acid [16]. Ceruloplasmin synthesis is stimulated by the cytokines interleukin-1 and -6, and is therefore upregulated in inflammation, autoimmunity, infection and cancer [3]. Compared to normal tissue cells, tumor cells demonstrated higher copper concentrations [5]. Penicillamine, which limits the availability of Cu and increases its secretion by the kidney, has antineoplastic properties [17].

Table 1: Important Copper-dependent Enzymes [15].

Enzyme	Function
Amine oxidase	Inactivation of histamine, tyramine, dopamine
Blood clotting factor V and VIII	Blood coagulation
Cytochrome-c oxidase	Electron transport in mitochondria
Ceruloplasmin	Ferroxidase, Cu transport,
Cu/Zn Superoxide dismutase	Free radical detoxification
Dopamine-ß-monooxygenase	Catecholamine production
Diamine oxidase	Inactivation of histamine
Hephaestin	Iron absorption in enterocyte
Protein-lysine-6-oxidase	Cross-linking of collagen and elastin
Tyrosinase	Synthesis of melanin

Copper Deficiency

The recommended amount of Cu intake for adults is 1-2 mg per day, with higher doses recommended for pregnant woman and children [18,19]. Cu deficiency can be caused by an impaired or insufficient uptake (e.g., malnutrition, celiac disease, inflammatory bowel syndrome, short bowel syndrome, bariatric surgery) or increased demand during pregnancy or during periods of growth **(Table 2)**. Increased supply of enteral zinc is competitively absorbed via the CTR1 transporter and therefore impairs intracellular transport and basolateral excretion of Cu. This occurs by a zinc-mediated up regulation of MT [8]. Rare causes of excessive extra intestinal Cu loss are severe burn injuries and prolonged continuous hemofiltration [20,21].

Symptoms and clinical findings of Cu deficiency are nonspecific and the diagnostic delay is estimated to be over one year [22]. Manifestations of Cu deficiency can be divided into neurologic, hematologic and dermatologic alterations.

Hematologic: Cu deficiency leads to an inefficient myelopoiesis and hemoglobin synthesis through the impaired function of peroxidase enzymes. Anemia tends to be macrocytic, but can be micro-, or normocytic as well. This is often combined with leukopenia and particularly neutropenia [23]. Reactive thrombocytosis is common in copper deficiency [22,23] **(Figure 2)**. There are a few case reports in the literature on Cu deficiency presenting with isolated neutropenia, mainly in young patients with celiac disease [24,25]. The Cu-dependent enzyme hephaestin in the duodenum is required for adequate iron absorption. In non-resolving iron deficiency after enteral iron supplementation, copper deficiency should be considered [26]. In contrast, hepatic iron overload can occur in Cu deficiency and is caused by decreased ceruloplasmin, which is involved in hepatic iron excretion [27]. Bone marrow smear alterations include dysplastic erythropoiesis and ring sideroblasts reflecting the mitochondriopathy due to copper deficiency. Noteworthy, bone marrow morphology can be misinterpreted as myelodysplastic syndrome, sideroblastic anemia, aplastic anemia or severe hydroxycobalamin deficiency [25,28]. Hematologic symptoms of Cu deficiency normally occur in combination with other manifestations; however, cases of isolated macrocytic anemia are described in the literature and the precise pathophysiological mechanism is not yet fully understood [28].
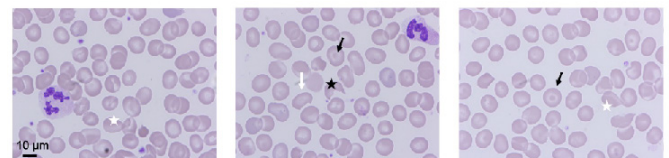
Figure 2: **Peripheral blood smear in a patient with copper deficiency** May-Giemsa stain. Peripheral blood smear show poikilocytosis and macrocytosis with dacrocytes (white star), stomatocytes (white arrow), target cells (black arrow) and fragmentocytes (black star)

Table 2: Causes of Copper Deficiency

Causes	
Decreased supply/increased demand	Anorexia/Malnutrition
	Pregnancy
	Growth
	Parenteral nutrition
	Hyperalimentation
Malabsorption	Celiac disease
	Inflammatory bowel disease
	Bariatric surgery
	Short bowel syndrome
	Zinc overdose
	Menkes syndrome
Extra intestinal loss	Burn injury
	Continuous hemofiltration

Neurologic: Neurologic manifestations can mimic hydroxycobalamin deficiency. Symptoms range from polyneuropathy, myelopathy, funicular myelosis to optic neuropathy [29,30]. In contrast to hematologic alterations of Cu deficiency, neurological symptoms tend to persist longer and can be irreversible. Patients usually present with initial symptoms of difficulties walking or synesthesia and parenthesis [31–33].

Dermatologic and cardiovascular: Defective keratinization and depigmentation of the skin and hair is caused by impaired tyrosinase and lysine-oxidase activity [34]. Cu deficiency has been linked to various cardiovascular disease, such as dilatative cardiomyopathy, atherosclerosis and myocardial infarction [35]. A potential role is attributed to homocysteine, a small, non-protein amino-acid. Homocysteine can chelate Cu and decrease its availability to antioxidative intracellular enzymes. These enzymes include superoxide dismutase leading to the formation of Reactive Oxygen Species (ROS), fibrosis, endothelial dysfunction and atherosclerosis [36].

Diagnosis, Treatment and Prevention

Normal blood Cu concentration ranges from 0.8-1.2 µg/ml (12.6-19 µmol/l) and Cu deficiency is diagnosed by serum Cu measurements [2]. Serum ceruloplasmin or the 24-h urine Cu excretion support the diagnosis and may provide further insights into the etiology or pathomechanism of the deficiency. Ceruloplasmin, an acute phase reactant, transporting approximately 95% of Cu in the serum, is upregulated during inflammation and may confound Cu measurements leading to falsely elevated levels. Screening for concomitant micronutrient deficiency (B9/B12, vitamin D/E, iron and zinc) is mandatory. The patient's history should focus on zinc-containing nutrient supplements and for zinc containing dental fixatives. In patients with symptoms or signs of malabsorption, endoscopy and serologic testing for celiac disease is required. The preferred route of administration is enteral because intravenous Cu, due to its oxidative potential, can lead to toxic side effects like copper hemolysis or liver necrosis [37]. Management of Cu deficiency depends on the severity of the deficiency. The guidelines recommend 2-8 mg per day until levels normalize. Hematologic abnormalities normally respond within two months after treatment initiation while neurologic and dermatologic symptoms may persist over the long term and can be irreversible [29,30,33,38].

In a retrospective study, 10% of patients who had undergone Roux-en-Y gastric bypass developed Cu deficiency.[39] The guidelines recommend regular screening and Cu supplementation of 1-2mg per day depending on the surgical procedure.[31] As patients usually take a multivitamin including trace elements, a ratio of 1mg additional Cu for every 10mg of elemental zinc is recommended to prevent Cu deficiency in patients after bariatric surgery [28,40].

Conclusion

In summary, copper deficiency is more frequent than previously recognized and represents an underdiagnosed micronutrient deficiency, probably due to the increasing number of bariatric surgery and renal replacement therapy. Copper deficiency should be considered in any patient with unclear anaemia or neuropathy, especially in patients taking zinc supplements and in patients after gastrointestinal surgery.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the work, authorship, and/or publication of this article.

Authors' Contributions

All authors were involved in designing and drafting this review article.

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