Clinical Observation

Neurologic Dysfunction and Pancytopenia Secondary to Acquired Copper Deficiency Following Duodenal Switch: Case Report and Review of the Literature

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Financial disclosure: none declared.

The duodenal switch (DS) procedure is a type of restrictive-malabsorptive bariatric surgery that is typically reserved for severe morbidly obese people (body mass index >50 kg/m²) with obesity-related comorbidities, when diet, lifestyle changes, and pharmacologic therapy fail to achieve adequate weight loss. Patients who undergo the DS procedure are at risk for malabsorption, malnutrition, and nutrient deficiencies. Copper deficiency is a commonly reported long-term complication of Roux-en-Y gastric bypass (RYGB) surgery. However, data are limited on copper deficiency–associated complications and their treatment in DS patients. This article presents a case of a patient who developed hypocupremia with associated pancytopenia, myeloneuropathy, and leukoencephalopathy following DS and reviews the literature related to the pathophysiology of copper deficiency and copper replacement in bariatric surgery patients. When severe diarrhea was present, intravenous elemental copper 4 mg (as cupric chloride)/d in addition to daily oral copper gluconate was necessary to correct the hypocupremia and improve the hematologic indices and neurologic symptoms of copper deficiency. When diarrhea subsided, oral elemental copper 4 mg (as copper gluconate) 3 times daily maintained normal serum copper concentrations and avoided the relapse of severe neurologic dysfunction. Regular monitoring of serum copper and ceruloplasmin concentrations is recommended following DS surgery to detect any copper deficiency before irreversible neurologic damage occurs. Long-term copper supplementation is likely necessary to maintain normal copper status in DS patients. (*Nutr Clin Pract.* 2011;26:583-592)

Keywords: trace elements; micronutrients; nutritional status; nutritional assessment; obesity; copper; bariatric surgery

According to the Centers for Disease Control and Prevention (CDC), the self-reported adult obesity (body mass index [BMI] ≥30 kg/m²) in the United States increased from 25.6% in 2007 to 26.7% in 2009.[1] Morbid obesity is also increasing at a fast rate. From 2000–2005, the self-reported morbid obesity increased by 50% for people with a BMI >40 kg/m² and by 75% for those with a BMI >50 kg/m².[2] When diet, exercise, and medication therapy fail to achieve adequate weight loss in morbidly obese individuals, bariatric surgery may be indicated to induce weight loss and reduce obesity-related complications.[3] In 2008, the American Society for Metabolic and Bariatric Surgery reported that an estimated 220,000 morbidly obese individuals underwent bariatric surgery.[4] Bariatric surgeries are classified in 3 types of procedures: "restrictive," which involves stomach size reduction and includes laparoscopic adjustable gastric banding, vertical banded gastroplasty, and sleeve gastrectomy; "malabsorptive," which bypasses large segments of the small intestines and includes the jejunoileal bypass that is no longer practiced because of its associated common and serious complications; and "restrictive-malabsorptive," which combines both types of procedures and includes the Roux-en-Y gastric bypass (RYGB) and the duodenal switch (DS) or the biliopancreatic diversion (BPD) with or without DS.[5-8]

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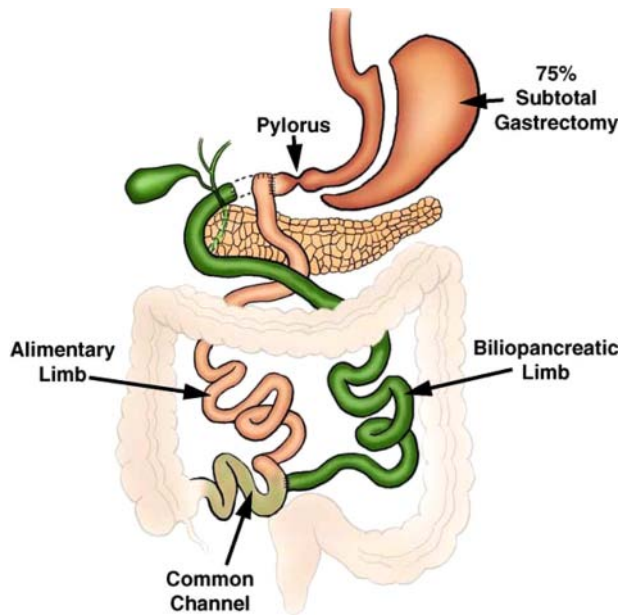
Figure 1. The duodenal switch procedure. Reprinted from Anthone GJ. The duodenal switch operation for morbid obesity. *Surg Clin North Am.* 2005;85(4):819-833. Copyright (2005), with permission from Elsevier.

The laparoscopic RYGB is the most commonly performed bariatric surgery. It involves the construction of a small stomach pouch that is attached to a segment of the jejunum, thereby bypassing the duodenum and proximal jejunum.[5] The DS procedure is much less commonly performed and is reserved for severe morbidly obese individuals (BMI >50 kg/m²). It involves the resection of a large part (75%) of the stomach (restrictive), leaving a gastric sleeve of 100–200 mL, and the rearrangement of the small intestines (malabsorptive) in 2 limbs: (1) the alimentary limb (250 cm), which will carry the food and consists of the distal one-third of the small intestines that is attached to the small portion of the duodenum after it is transected 2–4 cm past the pylorus, and (2) the biliopancreatic limb, which will carry the pancreatic and liver secretions into the distal ileum. Both limbs join at the bottom end of the small intestines to form a "common channel" (100 cm) where food and digestive secretions mix together before entering the colon (Figure 1).[6-8] The bypass of the duodenum and jejunum significantly bypasses the absorption of proteins, carbohydrates, and most minerals and vitamins. Furthermore, less exposure to biliary secretions and pancreatic enzymes decreases the breakdown of proteins, carbohydrates, and fat. Because limited fat absorption occurs in the common channel, undigested fat enters the colon and causes diarrhea. The shorter the common channel, the more likely are the complications of diarrhea, malabsorption, protein-calorie

malnutrition, and vitamin and mineral deficiencies. Revision or reversal of the DS may be considered in patients who develop intractable diarrhea and severe malnutrition, and who do not respond to dietary or pharmacologic interventions.[9,10]

Patient Case

A 58-year-old man presented to our hospital on April 29, 2010, with severe fatigue, confusion, progressive neuropathies, ataxia, and gradual weight loss over the past year (30 kg weight loss beyond his maintenance body weight of 100 kg). The patient's past medical history was significant for severe morbid obesity (baseline body weight = 160 kg; BMI = 55 kg/m²) with comorbidities, including obstructive sleep apnea, type 2 diabetes mellitus, hypertension (all of which have resolved), and gastroesophageal reflux disease. His past surgical history was significant for the DS procedure, with appendectomy and cholecystectomy in June 2001. According to the surgical report, the patient had about 120 mL of remaining stomach volume, an alimentary limb of 200 cm, and a common channel of 100 cm. The patient's home medications included omeprazole, hydrochlorothiazide/losartan, and oral nutrient supplements of calcium, vitamin D, vitamin C, iron, and vitamin A. The patient had been consuming a regular diet until a week before this presentation when he began to have decreased appetite with reduced oral intake.

According to the medical history obtained from the patient and caregiver, the patient had bilateral numbness in his legs and thighs that first started about 2–3 years after his bariatric surgery in the lateral aspect of his left foot and toes and then slowly spread to the remainder of the left foot and then the right foot. These symptoms slowly progressed with time up to his thighs along with weakness and inability to lift his feet, difficulties of movement and ambulation, and lack of sensation. Over the past 6–12 months, the patient had noticed difficulties in flexing his hands and inability to write with his right hand. He also had significant trouble maintaining his balance that recently necessitated the use of a cane, wheeled walker, wheelchair, or a power scooter. His caregiver described his voice as becoming weaker with lack of emotional ability. Since these symptoms began, the patient had undergone multiple clinical workups at outside hospitals and was diagnosed with neuropathy of unidentified etiology.

On physical exam, the patient was ill appearing with clinical signs of cachexia and malnutrition. He was hypothermic (rectal temperature 30.7°C) and hypoglycemic (serum glucose concentrations 60 mg/dL; normal range, 73–110 mg/dL). His hospital course progressed to worsening weakness and altered mental status, with progressive motor neuropathies, discoordination, confusion,

Table 1. Laboratory Parameters

Laboratory Tests (Normal Range)	Blood Levels With Corresponding Collection Dates						
	4/30/2010	5/28/2010	7/7/2010	10/1/2010	1/12/2011	2/4/2011	4/1/2011
Copper (0.7–1.4 mcg/mL)	0.2	0.7	0.5	0.6	0.8	0.9	0.7
Ceruloplasmin (16–36 mg/dL)	5	14.7	10.9	13.6	16.9	17.5	13.2
Zinc (0.5–1.5 mcg/mL)	0.4	0.6	0.6			0.6	0.6
Albumin (3.5–4.9 g/dL)	2.8	2.9	2.7	1.8	3.8	4.3	4.2
WBC (4–10 k/mm^3)	2.4	3.1	3.4	2.4	3.3	4.7	4.9
Hemoglobin (13.5–17 g/dL)	10.4	9.6	10.3	9.6	10	10.8	11.5
Hematocrit (40–50%)	32.7	31.5	32.8	30.4	33.3	34.3	37.7
Platelet count (150–400 k/mm^3)	118	201	219	45	236	214	226
RBC (4.4–5.7 m/mm^3)	3.44	3.49	3.85	3.23	4.2	4.4	4.88
MCV (79–99 fl)	94.9	90.1	85.3	94.2	79.3	78.1	77.3

MCV, mean corpuscular volume; RBC, red blood cell count; WBC, white blood cell count.

delirium, and lack of arousal to voice and noxious stimuli. The patient's neurologic exam was suggestive of a myeloneuropathy with motor predominance, leukoencephalopathy, and optic neuropathy.

Outside reports of electromyogram (EMG) and nerve conduction studies from December 2009 showed evidence of severe axonal polyneuropathy (motor greater than sensory) that involved the lower more than the upper extremities. The active denervation and neurogenic motor units that were seen in the distal extremities suggested a chronic, length-dependent process but without evidence of myopathy, widespread denervation to suggest motor neuron disease, or lumbosacral radiculopathy.

During the patient's hospital stay, additional workups included a head computed tomography (CT) without contrast that showed no definite acute intracranial abnormality. A head magnetic resonance imaging (MRI) showed diffuse white matter disease, primarily in the subcortical white matter following pyramidal tracts without evidence for stroke. Electroencephalography (EEG) was consistent with mild to moderate diffuse encephalopathy with no seizures or epileptiform discharges. Abdominal ultrasound showed diffuse fatty infiltration of the liver. Chest CT showed no evidence of malignancy within the thorax or pneumonia.

Further clinical workups showed normal tests for all of the following: anti-double-stranded DNA immunofixation; serum protein electrophoresis; antinuclear antibody; anti-Sm, anti-double-stranded DNA, anti-RNP, anti-Ro, anti-La, antiendomysial, and anti-glutaminase antibodies; erythrocyte sedimentation rate; creatine kinase; aldolase; oral glucose tolerance; urine protein electrophoresis; serum-free light chains; thyroid stimulation hormone; lactate dehydrogenase; ammonia; C-reactive protein; homocysteine; fasting lipid panel; urine analysis; rapid plasma reagin; varicella zoster virus;

cytomegalovirus; and human immunodeficiency virus. Hepatitis B surface antibody and hepatitis C antibody were nonreactive. Cerebrospinal fluid cultures were all negative. Serum alanine aminotransferase and aspartate aminotransferase were elevated denoting transaminitis. Prothrombin time, the international normalized ratio, and partial thromboplastin time were all elevated.

Further blood workup showed copper and zinc deficiencies, hypoalbuminemia, anemia, neutropenia, thrombocytopenia, and low iron levels (Tables 1 and 2). Serum copper concentrations were 0.2 mcg/mL (normal range, 0.7–1.4 mcg/mL) and ceruloplasmin at 5 mg/dL (normal range, 16–36 mg/dL). At baseline, serum concentrations of vitamin A (retinol; 151 mcg/L [normal range, 325–780 mcg/L]), vitamin E (α tocopherol; 4.3 mg/L [normal range, 5.5–17 mg/L]), and 25-hydroxyvitamin D (8 ng/mL [normal range, 25–80 ng/mL]) were all decreased. Baseline blood concentrations of red blood cell vitamin B_1 (100 nmol/L [normal range, 80–150 nmol/L]), vitamin B_6 [11 mcg/L [normal range, 5–50 mcg/L]), folic acid (11 ng/mL [deficient <0.3 ng/mL]), vitamin B_{12} (603 pg/mL [normal range, 211–911 pg/mL]), and methylmalonic acid (0.11 μmol/L [normal ≤0.4 μmol/L]) were all normal.

The patient was diagnosed with severe copper deficiency complicated by pancytopenia and neurologic dysfunction. A copper replacement regimen was initiated with intravenous elemental copper 2.4 mg (as cupric chloride)/d (total dose mixed in 100 mL of 0.9% sodium chloride and infused over 2 hours) for 7 days and thereafter converted to oral elemental copper 4 mg (as copper gluconate) twice daily along with intravenous elemental copper 2.4 mg (as cupric chloride) once weekly. After 9 days of hospital stay, serum copper concentrations increased to 0.6 mcg/mL. Although the patient's clinical status stabilized, he continued with weakness and poor proprioception in his distal upper extremities and bilateral

Table 2. Iron Studies

Laboratory Tests (Normal Range)	Blood Levels With Corresponding Collection Dates			
	5/5/2010	7/7/2010	10/11/2010	1/24/2011
Iron (33–150 mcg/dL)	14	50	42	46
IBC (220–440 mcg/dL)	242	264	277	407
TSAT (20%–50%)	5.8	18.9	15.2	11.3
Ferritin (18–320 ng/mL)	402.8	436	271.4	93

IBC, iron binding capacity; TSAT, percent transferrin saturation.

weakness in his lower extremities, and his mental status continued to fluctuate. He was discharged to a subacute rehabilitation facility with a plan to follow up as an out-patient with the neurology clinic. His copper supplementation regimen upon discharge consisted of oral elemental copper 4 mg (as copper gluconate) twice daily with intravenous elemental copper 2.4 mg (as cupric chloride) once weekly. Home oral copper supplementation was later increased to elemental copper 4 mg (as copper gluconate) 3 times daily.

On October 1, 2010, the patient was readmitted to the inpatient general medicine service for mental status changes, progressive generalized weakness, functional impairment, anasarca, and severe diarrhea (up to 8 loose stools per day). With regard to his diarrhea, tests for celiac disease and *Clostridium difficile* infection were negative. Stools were also negative for fecal leukocytes or white blood cells. The patient was therefore started on parenteral nutrition (PN) on October 5, 2010, due to malabsorption and malnutrition. His PN was initially supplemented with elemental copper 2 mg (as cupric chloride)/d. The parenteral copper dose was thereafter increased to 3 mg and then 4 mg/d in PN because of persistently low serum copper concentrations. Oral copper supplementation was continued with elemental copper 4 mg (as copper gluconate) 3 times daily. Considering the patient's impaired activities, functional deficits, and gait dysfunction, he was transferred to the inpatient physical therapy and rehabilitation service. With rehabilitation and treatment, the patient's cognition noticeably improved. He regained more control of his fingers and was able to ambulate with a walker. After 3 weeks of rehabilitation, the patient was discharged from the hospital on daily home PN that provided elemental copper 4 mg (as cupric chloride)/d. Oral elemental copper 4 mg (as gluconate) 3 times daily was also continued.

On November 9, 2010, the patient was seen in the surgery clinic in follow-up to his continued diarrhea. He was started on pancreatic enzyme supplementation (Creon, pancrelipase delayed-release oral capsules; Abbott Laboratories, Abbott Park, IL) that consisted of 2 capsules (each capsule provides lipase 24,000 USP units, protease 76,000 USP units, and amylase 120,000 USP units) orally 3 times daily with meals. The plan was to consider revising the DS if diarrhea and malabsorption did not resolve with pancreatic enzyme therapy. Following several days of pancreatic enzyme supplementation, the patient reported that his diarrhea decreased to 2–3 stools daily and was therefore continued on the same pancreatic enzyme therapy.

On December 12, 2010, the patient was readmitted to the hospital for fluid overload with 1+ bilateral lower extremity edema to the knees and orthopnea. He was diagnosed with pulmonary edema and diastolic heart failure. Given his decreased diarrhea and improved dietary intake and nutrition status, PN was discontinued, and the patient was discharged home on his previous oral copper gluconate maintenance regimen.

On January 25, 2011, the patient was seen in follow-up in the neuromuscular disorders clinic. He had increased energy and appetite. His neurological exam showed significant improvement, with normal mental status, strength coordination, and reflexes. He was able to do most activities of daily living, although he still had some difficulties with balance and was using a walker or scooter for ambulation. His hematological parameters and serum copper concentrations were maintained within the normal range. Figure 2 depicts the daily copper intake and corresponding serum copper concentrations during the patient's follow-up period.

Discussion

Copper Homeostasis

Copper is a trace metal that is involved in several enzymatic and metabolic functions (Table 3).[11] The dietary reference intake (DRI) for copper in adults (nonpregnant, nonlactating) is 0.9 mg/d, with the typical U.S. diet providing copper 2–5 mg/d.[12,13] Copper-rich foods include whole grains, nuts, cereals, beans, organ meats (especially liver), shellfish, oysters, and dark green leafy vegetables. About 30%–40% of copper is absorbed throughout the small intestines, with a smaller proportion absorbed in the stomach. The acidic milieu of the stomach is favorable
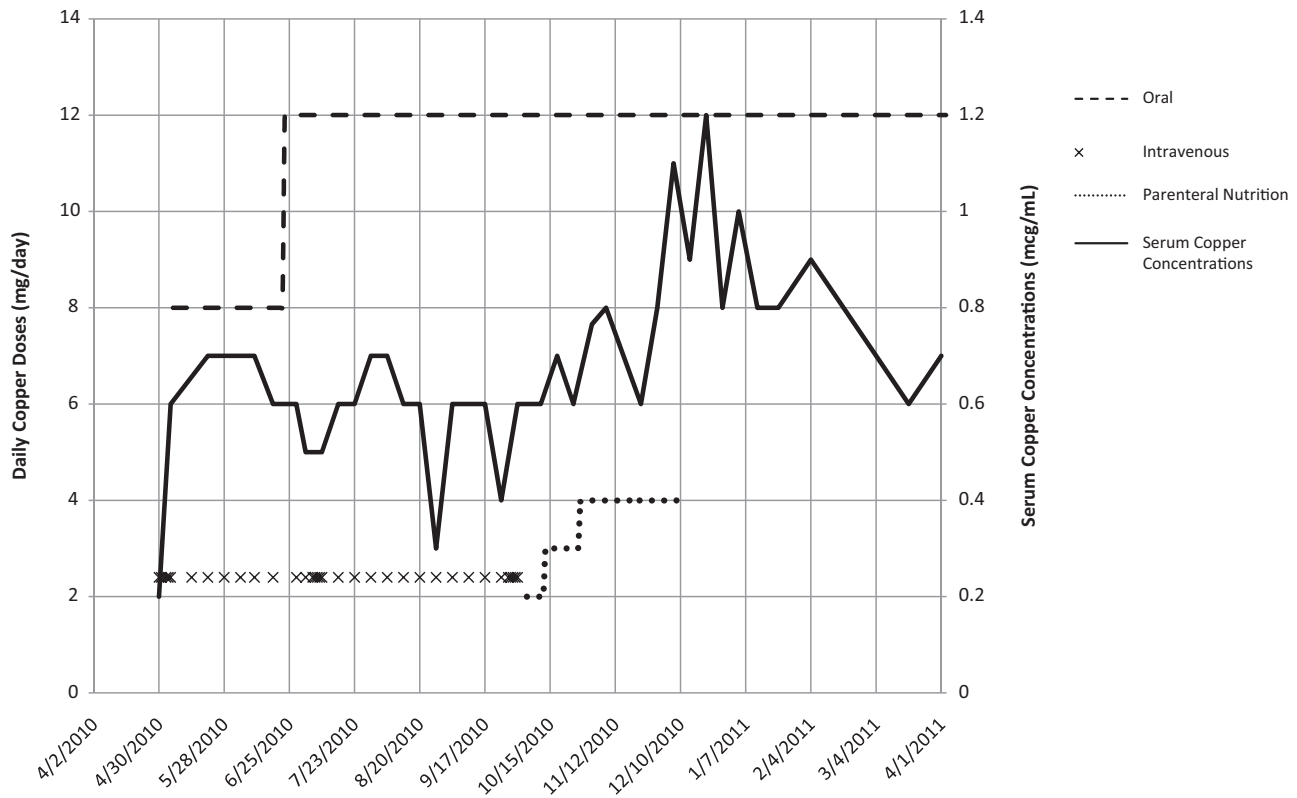
Figure 2.   Daily copper doses and serum copper concentrations.

Table 3.   Examples of Physiologic Functions of Copper-Dependent Enzymes[11, 25]

Copper-Dependent Enzymes	Physiologic Functions
Amine oxidases	Primary amines deamination
Catechol oxidase	Melanin synthesis
Cytochrome-c oxidase	Adenosine triphosphate synthesis, electron transport
Dopamine-β monooxygenase	Dopamine to norepinephrine conversion
Ferroxidases I and II (ceruloplasmin)	Ferrous iron oxidation and mobilization
Lysyl oxidase	Elastin and collagen cross-linking, formation of connective tissue
Peptidylglycine monooxygenase	Bioactive peptides synthesis, α-amidation of neuropeptides
Phenylalanine hydroxylase	Phenylalanine oxidation to tyrosine
Superoxide dismutase	Free radical scavenging
Tyrosinase	Melanin synthesis from tyrosine

for releasing copper from food complexes, which facilitates its absorption in the proximal duodenum. However, as intestinal pH increases, a smaller proportion of copper is solubilized and absorbed. Therefore, copper absorption is at its highest in the upper small bowel and at its lowest in the ileum.[14]

Copper crossing of the intestinal apical membranes is mainly facilitated by the copper transporter Ctr1 located on the luminal surface, although passive copper diffusion may also occur especially with high copper intake.[15-18] The presence of metalloreductases and other transporters in the brush-border membrane may also play a role in copper absorption.[13,18-20] Copper absorption occurs primarily via rate-limiting active transport mechanisms.[15] Although the absolute amount of copper absorbed increases directly with the dose, the relative bioavailability of copper decreases with increasing dose.[21,22] With dietary copper intake at 7.5 mg/d, only 12% is absorbed, whereas copper 0.8 mg/d and 1.7 mg/d resulted in 56% and 36% of copper absorbed, respectively.[22] Copper is then stored inside the enterocyte by combining with the intracellular cytoplasmic protein metallothionein until it interacts with the copper-transporting ATPase enzyme for transfer into the systemic circulation.[23]

Once in the bloodstream, copper binds to albumin and is transported to the portal blood, where it undergoes enterohepatic recycling. Total body copper is estimated at 100 mg in adults, with the liver storing the majority of body copper. A downregulation effect of copper release by the liver has been postulated, which may play a role in preventing copper loading when excessive copper intake occurs.[16] In the liver, small copper fractions are used for the synthesis of ceruloplasmin and other copper proteins. Ceruloplasmin is the major copper transporter that binds and transports 7 copper atoms per molecule in the blood. It has a biological half-life of about 7 days, whereas the more labile copper-bound albumin has a much shorter half-life of 10 minutes. Copper is primarily eliminated via the bile, with more than 95% of oral copper found in the feces, leaving only about 1%–5% of copper to be excreted in the urine. However, biliary copper is strongly bound to bile, which makes it poorly bioavailable.[13] There appears to be a direct relationship between copper intake and copper excretion, which further helps regulate body copper homeostasis.[22]

Bariatric Surgery and Copper Deficiency

Copper deficiency has been typically reported in malabsorption syndromes (eg, small bowel resections, chronic diarrhea, short bowel syndrome) as a result of decreased intestinal absorption.[11] With the increased number of bariatric surgeries performed, cases of copper deficiency have been more frequently reported in patients who underwent different bariatric surgery procedures, mainly with RYGB,[24-34] with limited information available on copper deficiency and treatment following DS. In a 3-year follow-up study of 64 morbidly obese individuals who underwent BPD, asymptomatic but significant decreases from baseline in serum copper concentrations were detected at 6 months and up to 3 years after BPD despite oral elemental copper supplementation of 4 mg/d. The percentage of patients with low serum copper concentrations significantly increased from 23% at 6 months to 70% at 3 years after BPD as compared to baseline ($P < .05$).[35] In another 5-year follow study that compared serum copper and zinc concentrations in patients who underwent RYGB (n = 52) or BPD (n = 89), hypocupremia and hypozincemia occurred more frequently in BPD as compared to RYGB patients. Average serum copper concentrations progressively decreased in BPD patients, reaching their lowest levels 24 months following BPD surgery. However, no hematologic or neurologic complications were reported with hypocupremia.[36]

Predisposing factors to copper deficiency following bariatric surgery are mainly related to decreased copper intake and absorption and increased losses. Reduced dietary copper intake due to reduced gastric volume, changes in gastrointestinal pH, bypass of small bowel segments, and diarrhea, along with cell mass breakdown

following significant weight loss, are contributing factors to copper deficiency in bariatric surgery patients. Furthermore, acid secretion is almost absent in the remaining stomach sleeve,[37] therefore decreasing free copper availability for absorption. Another major limiting factor to copper absorption in DS patients is the bypass of the duodenum and jejunum, the main sites for copper absorption. This leaves the alimentary limb with the common channel as the remaining sites where copper can be absorbed. However, little free copper is typically absorbed in the ileum because of the high intraluminal pH and the formation of mostly insoluble cupric hydroxide and basic cupric salts.[14] In 1 clinical study, there was no correlation between the length of the common channel and serum copper concentrations in BDP patients.[36] Furthermore, it is unknown if ileal adaptation to increasing copper absorption occurs in humans following intestinal bypass surgery, similar to the intestinal adaptation that occurs following small bowel resections. In an animal study that involved a 50% resection of the proximal (starting 3 cm distal to the ligament of Treitz) and distal (down to 15 cm from the ileocecal valve) small bowel, there was a significant ileal adaptation with increased mucosal growth and copper concentrations in the ileal mucosa but not in the duodenum or midgut.[38] In animal models of RYGB, intraluminal nutrients stimulated intestinal adaptation (increased intestinal width, villus height, crypt depth, and proliferation) in the alimentary limb, whereas glucagon-like peptide-2 (GLP-2) stimulated to a lesser extent biliary limb adaptation.[39] Therefore, a possible combination of ileal adaptation, upregulation of copper absorption,[40] and mobilization of liver copper reserves[16] are plausible mechanisms to understand the delayed appearance of copper deficiency in patients who undergo bariatric surgery. It can be then postulated that the adaptation of the alimentary limb and the common channel may possibly allow sufficient copper absorption to maintain normal serum copper concentrations in patients with DS. However, this postulated mechanism requires evaluation.

Biochemical Signs and Clinical Manifestations of Copper Deficiency

Biochemical signs of copper deficiency are reflected in serum copper and ceruloplasmin concentrations below the normal range. Severe copper deficiency may present as pancytopenia (neutropenia, thrombocytopenia, iron-resistant hypochromic normocytic or macrocytic anemia) and/or neurologic dysfunction that may include peripheral neuropathy, myelopathy, spastic gait, ataxia, optic neuropathy, encephalopathy, central nervous system demyelination, polyradiculoneuropathy, and rhombencephalopathy.[41-48] Hypotonia and increased infection risk

have also been reported, as well as bone abnormalities such as osteoporosis, separation of epiphyses, and fractures of ribs and long bones, especially in children.[11]

Typically, the neurologic manifestations related to severe copper deficiency appear after years of longstanding copper depletion in patients who underwent bariatric surgery.[36,48] The earliest neurologic changes are typically related to vitamin B_1 deficiency, whereas the delayed complications that affect the spinal cord and peripheral nerves are mostly related to copper and/or vitamin B_{12} deficiencies.[45,48,49] In a study of 20 adult patients who underwent partial gastrectomy, a mean of 20.7 years elapsed before the detection of copper deficiency, although no correlation was found from the time of gastric resection to the decreased serum copper and ceruloplasmin concentrations.[44] To the contrary, early-onset copper deficiency at 14 months following RYGB bypass surgery has been reported,[34] which makes the prediction of the onset of hypocupremia difficult across the diverse patient populations who undergo bariatric surgery. Slow and subclinical copper deficiency likely occurs before clinical symptoms of severe copper deficiency become apparent. Interindividual variation is likely when considering differences in baseline nutrition status, copper intake, and the type of bariatric surgery performed.

Copper Supplementation and Patient Outcomes

The goals of copper supplementation in a copper-deficient patient are to treat the associated clinical signs and symptoms, normalize serum copper concentrations, restore body copper stores, and prevent future deficiency or relapse. However, the optimal copper dosing to treat the neurologic manifestations in acquired copper deficiency secondary to bariatric surgery is largely empirical. Furthermore, the correlation between serum copper concentrations, tissue copper stores, and neurologic recovery is unknown. Therefore, copper dosing should be individualized based on clinical response and changes in serum copper and ceruloplasmin concentrations.

Oral and/or enteral elemental copper intake of 2–10 mg with or without intravenous copper supplementation has been used to correct copper deficiencies in gastric bypass patients.[24,25,28,30,34,50,51] In our report, oral elemental copper 4 mg (as copper gluconate) 3 times daily successfully maintained normal serum copper and ceruloplasmin concentrations and prevented relapse. Copper gluconate is a commonly used oral copper supplement, but its optimal dosing and duration to correct copper deficiency are unknown. Because copper gluconate is highly soluble, it is prone to binding by complexing agents (eg, dietary fibers, fructose) in the intestinal tract.[15,52] This may require higher copper gluconate doses and extended duration of therapy for adequate copper repletion. In a small study of

7 healthy adult volunteers, copper gluconate supplementation at 10 mg/d for 12 weeks resulted in no significant increase in serum copper concentrations as compared to baseline.[52] However, the study is limited by its small sample size and its enrollment of healthy volunteers, who may have different absorptive patterns as compared to gastric bypass patients. Another oral copper salt form, copper acetate, has also been used to correct copper deficiency.[43,53] In a patient who developed myelopathy secondary to copper deficiency following vertical banded gastroplasty, elemental copper 4 mg (as copper acetate)/d with additional elemental copper 2 mg/d from an oral multivitamin/multitrace element supplement improved the neurological symptoms and corrected the hematological parameters of copper deficiency.[53]

In patients with malabsorption, intravenous cupric chloride has been used for copper repletion. The initial intravenous copper dosing regimen used in our patient was based on previous reports of copper supplementation in 2 patients with severely low serum copper and ceruloplasmin concentrations following bariatric surgery.[24] One 53-year-old patient presented 21 years after RYGB with abnormal gait, painful paresthesias in lower extremities, neutropenia, and anemia. The other 58-year-old patient presented 10 years after an unspecified bariatric surgery with anemia, neutropenia, ataxia, numbness, paresthesias in lower extremities and hands, and wheelchair dependence. Initially, intravenous copper 2.4 mg/d was given for 6 days to both patients and then changed to once-weekly infusion along with oral elemental copper 8 mg (as copper gluconate)/d for 21 weeks, followed by 7 weeks of only oral copper supplementation. In the first patient, hematologic parameters and serum copper concentrations normalized and the paresthesias improved after 1 month of copper supplementation. However, there was no improvement in lower extremity vibratory sensations and proprioception. In the second patient, hematologic parameters normalized within 1 week of copper supplementation, and the light touch sensation gradually improved over several weeks. However, it was not until 7 months after copper repletion that the patient could walk without assistance.[24] In our patient case, weekly doses of intravenous copper 2.4 mg in addition to oral elemental copper 8 mg (as copper gluconate)/d marginally corrected serum copper concentrations and were not associated with significant clinical improvement. However, intravenous elemental copper 4 mg (as cupric chloride)/d in PN in addition to oral elemental copper 12 mg (as copper gluconate)/d divided into 3 doses maintained normal serum copper and ceruloplasmin concentrations and significantly improved the hematologic parameters and neurologic symptoms.

In summary, hematologic abnormalities appear to recover first in response to copper supplementation,[44] although clinical relapse may occur with inadequate copper

intake.[53] This is similar to our patient case when blood indices were first to respond to improved copper status, but neurologic symptoms relapsed after initial improvement. Higher copper doses were required until significant neurologic improvement and stabilization were observed. However, despite normalization of serum copper and ceruloplasmin concentrations, neurologic manifestations may only partially improve or stabilize rather than fully recover.[24,48-51,54]

Coexisting Micronutrient Deficiencies

Severe copper and/or vitamin B_{12} deficiencies have similar neurologic manifestations and may coexist in bariatric surgery patients.[33,45,46,50,53,55] Both copper and vitamin B_{12} deficiencies should be ruled out and corrected as necessary. In DS patients, vitamin B_1 deficiency resulting in peripheral neuropathy[49] and vitamin A deficiency resulting in night blindness have been reported.[56] Other water-soluble (vitamin C, folate) and fat-soluble (vitamins D, E, and K) vitamin deficiencies may also occur and should be ruled out.[9,24,45,48,49,57,58] Furthermore, copper and zinc deficiencies may coexist and are prevalent following DS.[35,36,53] However, high zinc intake has shown to decrease copper absorption and result in copper defciency.[41,43,50,59,60] A possible mechanism by which zinc inhibits copper absorption is by inducing the intestinal metallothionein that sequesters copper inside the intestinal cells, and copper will get eliminated in the stools when enterocytes are desquamated.[61] Because endogenous zinc primarily undergoes fecal elimination via small intestinal mucosa and pancreatic secretions,[62,63] intravenous zinc supplementation could theoretically inhibit copper absorption by indirectly allowing more intestinal zinc delivery, although it is unknown how these interactions may play out in DS patients. Regardless, in cases of simultaneous copper and zinc deficiencies, the intravenous route should preferably be used for the supplementation of both trace metals. Intravenous copper is available in the forms of cupric chloride (0.4 mg elemental copper/mL in 1.07 mg cupric chloride salt) and cupric sulfate (0.4 mg elemental copper/mL in 1.57 mg cupric sulfate salt).[64] Intravenous zinc is available as zinc chloride (1 mg elemental zinc/mL in 2.09 mg zinc chloride salt) and zinc sulfate (1 mg elemental/mL zinc in 4.39 mg zinc sulfate salt).[65] If the oral route is used, oral copper and zinc supplements should be administered at distant times as possible, although the optimal separation time to avoid competitive inhibition of absorption is unknown, and the interaction between copper and zinc may not be completely avoided.[66]

Other metal (calcium, magnesium, iron, selenium) deficiencies may also coexist and should be ruled out and corrected as necessary, especially with diarrhea and malabsorption.[67-69] Copper is essential for transferrin formation, and because copper deficiency inhibits liver iron mobilization, hypocupremia may result in microcytic hypochromic anemia.[70] Furthermore, the divalent metals copper, iron, and zinc compete for absorption in the duodenum and proximal jejunum, and excess intake of one of these metals may inhibit the absorption of the others. It remains unknown, however, if this competition for absorption occurs in the alimentary limb and common channel of DS patients.

Conclusion

DS is associated with severe malabsorption, malnutrition, and nutrient deficiencies. Copper deficiency is a complication of DS, and its clinical manifestations may not appear until months to years after surgery. Intravenous copper supplementation should be used for copper repletion when diarrhea is present. When diarrhea is absent, oral elemental copper 4 mg (as copper gluconate) 3 times daily maintains normal serum copper concentrations. Early and periodic monitoring of copper status is necessary following DS surgery to detect and treat any copper deficiency before severe or irreversible neurologic damage occurs. Chronic copper supplementation is likely necessary to maintain normal copper status in DS patients.

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