Original Article

Brief Overview About Anemia And Copper Deficiency In Bariatric Surgery

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Abstract

Background: Anemia is considered a public health problem that affects a third of the population and contributes to increased morbidity and mortality, decreased work productivity, and impaired neurological development. Anemia is known as a condition in which either the number of red blood cells or their oxygen-carrying capacity is lower than normal and insufficient to meet body physiological needs. After bariatric surgery, iron deficiency develops as a consequence of the alterations in the gastrointestinal anatomical architecture and the associated changes in the physiology of the gastrointestinal tract. Several factors involved in the development of iron deficiency after bariatric surgery such as reduced iron intake, reduced secretion of hydrochloric acid and a reduction in the surface area for absorption. Unlike certain heavy metals such as iron or lead, which receive a great deal of attention during formal medical education, copper's role in the human body often goes neglected except during brief discussions of Wilson's disease. Bariatric surgery has arisen as a tremendously helpful modality for improving weight loss and other comorbidities, such as type 2 diabetes. The number of bariatric and metabolic surgeries has been on the rise, up to 216,000 procedures in 2016 (a marked 10% increase from 2015). A large number of patients undergoing bariatric surgery are deficient in copper, and Roux-en-Y gastric bypass can further aggravate it. Delays in diagnosis and treatment of copper deficiency can leave patients with residual neurological disability. This has led to recommendation from the British Obesity and Metabolic Surgery Society that copper levels should be monitored annually after gastric bypass.

Keywords: Anemia, Copper Deficiency, bariatric surgery

INTRODUCTION

Anemia is considered a public health problem that affects a third of the population and contributes to increased morbidity and mortality, decreased work productivity, and impaired neurological development. Anemia is known as a condition in which either the number of red blood cells or their oxygen-carrying capacity is lower than normal and insufficient to meet body physiological needs. Anemia is most commonly diagnosed by a low Hb concentration or a low hematocrit, anemia can also be diagnosed using RBC count, mean corpuscular volume, blood reticulocyte count, blood film analysis, or Hb electrophoresis ***(1).***
The role of Hb is to carry oxygen to the tissues which explains the most common symptoms of anemia like fatigue, shortness of breath, palpitations, and pallor. Severe anemia (defined by WHO as Hb <70 g/L which may result in high-output heart failure and death**.** Anemia is one of the most common consequences of micronutrient deficiency post-bariatric surgery. It develops due to a change in food habits or impaired affect the absorption of micronutrients such as iron, zinc, selenium, folate, B12 and copper. To avoid any adverse consequences of vitamins and trace elements deficiency, proper monitoring and tests are recommended at any stage, from pre- to post-surgery (periodical check-up), followed by specific and individual nutritional supplementation treatments and a proper healthy diet ***(2).***

Iron deficiency anemia
After bariatric surgery, iron deficiency develops as a consequence of the alterations in the gastrointestinal anatomical architecture and the associated changes in the physiology of the gastrointestinal tract. Several factors involved in the development of iron deficiency after bariatric surgery such as reduced iron intake, reduced secretion of hydrochloric acid and a reduction in the surface area for absorption. Iron is known to be important for many cellular functions including DNA synthesis, ATP generation, and cellular proliferation. A class of small non-coding RNA known as microRNA (miRNA) has also been

involved in the control of iron metabolism. Recently, miRNA have been demonstrated to post-transcriptionally regulate the expression of genes associated with iron and iron storage (ferritin), the variable miRNA factors that contribute to change in miRNA expression, biogenesis, and processing will enhance variable changes in iron demand and/or iron availability to control cellular iron homeostasis ***(3)***.

Copper Deficiency

Unlike certain heavy metals such as iron or lead, which receive a great deal of attention during formal medical education, copper's role in the human body often goes neglected except during brief discussions of Wilson's disease. Still, knowledge of copper metabolism and deficiency has clinical utility. For example, patients with microcytic hypochromic anemia refractory to iron replacement therapy may actually have hypocupremia ***(4).***

Deficiency of this trace element can also cause myelopathy that presents as subacute combined degeneration of the spinal cord, which is usually attributed to inadequate vitamin B12. These neurologic manifestations of copper deficiency are less likely to improve with increased duration of symptoms**.** Thus, the longer the clinician overlooks copper deficiency, the worse her patient's prognosis becomes. Copper deficiency, a recognized cause of anemia, neutropenia, myelopathy, and peripheral neuropathy, undoubtedly deserves physician attention ***(5).***

Biochemistry and Physiology

Copper, a transition metal, can physiologically exist in either a reduced (Cu1+) or oxidized (Cu2+) state. This ability to freely ferry electrons allows copper to participate in redox reactions. Approximately one dozen enzymes, mostly oxidoreductases and monooxygenases, exist that require copper for catalytic activity. These cupro-enzymes have reduced activity in a copper-deficient state. Numerous other copper-binding proteins exist in the body Impaired function of these copper-utilizing enzymes and proteins can produce several features of copper deficiency, such as hypopigmentation, coagulopathy, and weakness ***(6).***

After iron and zinc, copper is the third most prolific trace element in the human body. It is an essential dietary micronutrient; the Recommended Dietary Allowance for adult men and women is 0.9 mg/day, although an argument has been made for higher intake (i.e., 2.3 mg/day)**.** In a typical Western diet, copper is usually found in vegetables, legumes, grains, and animal products (e.g., beef, fish, poultry)**.** Attaining adequate levels of copper through a regular diet is thought to be feasible; the median intake of copper from food is approximately 1.0 to 1.6 mg/day for adult men and women**.** Thus, in healthy people in most parts of the world, acquired hypocupremia due to malnutrition is relatively infrequent**.** Dietary copper absorption occurs in the stomach and proximal duodenum ***(7)***

The stomach promotes uptake via enhanced copper solubility; by creating an acidic environment, copper readily dissociates from copper- containing dietary macromolecules. Mechanisms underlying intestinal absorption include saturable-mediated transport at lower levels of dietary copper and nonsaturable-nonmediated (i.e., paracellular) transport at high levels. At the intestinal apical surface, membrane-bound copper transport protein (Ctr1) actively transports copper into the enterocytes **(8).** At the basolateral surface, Menkes protein (ATP7A) shuttles copper into the hepatic portal circulation; mutation in this protein underlies Menkes syndrome, leading to impaired copper absorption and symptoms of severe deficiency ***(9).***

Albumin and transcuprein in the portal blood bind copper and deliver it to the liver parenchymal cells for uptake**.** Hepatocytes incorporate copper into superoxide dismutase, cytochrome c oxidase, and the carrier protein ceruloplasmin, while excess copper binds to metallothionein to form a nontoxic complex. Ceruloplasmin transports copper from the liver to systemic tissues. It then binds to peripheral cell surface receptors and releases copper into the cell, which integrates into the numerous proteins listed above ***(10).***

Beyond copper transport, ceruloplasmin also facilitates iron metabolism via copper-dependent ferroxidase activity ***(11).***

Ferric iron then can bind to transferrin for systemic transport. Hephaestin, another copper-dependent ferroxidase, is expressed in the duodenal mucosa and facilitates ferric iron transport across the basolateral surface for transferrin loading**.** Copper homeostasis is maintained, and copper toxicity is avoided via biliary excretion**.** Wilson P-type ATPase (ATP7B) mediates copper efflux from the hepatocyte into the biliary tract; mutation in this protein underlies Wilson's disease, leading to excessive copper deposition and subsequent free radical formation in the liver, brain, and other tissues ***(12).***

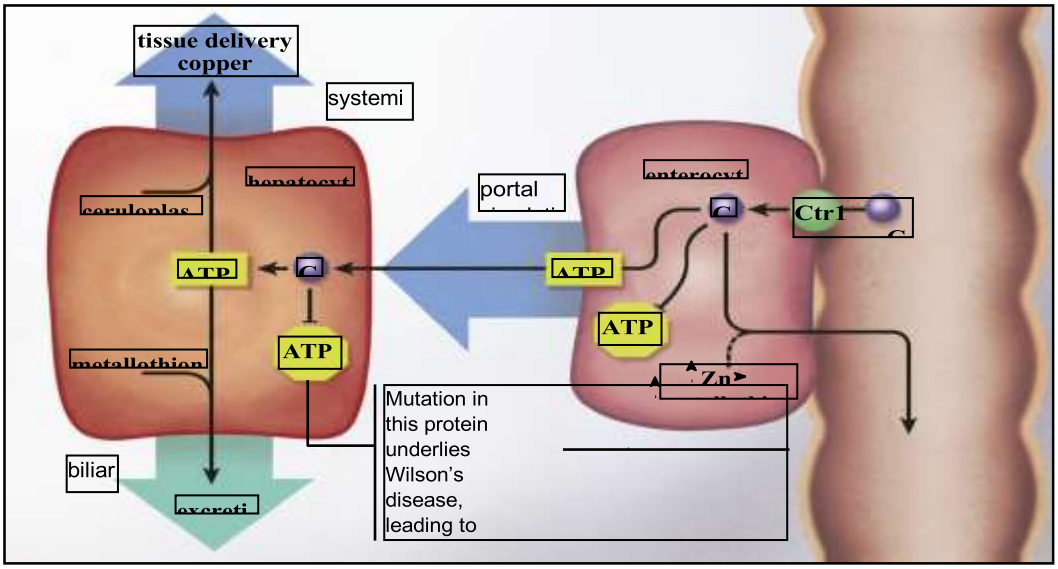

Fig. (1): Summary of Copper physiology Graphic by Wake Forest Baptist Medical Center, Creative Communication ***(12).***

Pathogenesis of copper defeciency

Copper deficiency limits copper-dependent enzymatic activity and leads to clinical features such as hair and skin hypopigmentation, osteoporosis, anemia, neutropenia, sensory ataxia, myelopathy, and peripheral neuropathy**.** The manifestations of copper-deficient state in the blood (i.e., anemia, neutropenia) and nervous system (i.e., myelopathy) arise not due to impairment of singular enzymatic processes but rather multifactorial interplay. Copper deficiency anemia (often microcytic, but normocytic and macrocytic varieties exist) results from the aforementioned interaction between copper-dependent ferroxidases and iron ***(13).***

Decreased activity of ceruloplasmin leads to impaired iron absorption from the small bowel and diminished conversion of ferrous to ferric iron. These changes cause disruption of systemic transport by transferrin and inadequate incorporation of iron into protoporphyrin**.** Poor heme synthesis, in conjunction with erythrocyte membrane fragility due to decreased copper-zinc superoxide dismutase activity, leads to mitochondrial iron accumulation and ringed sideroblast formation ***(13).***
Clear mechanisms underlying copper deficiency neutropenia have been elusive, although numerous plausible explanations have been put forward ***(14).***

These include loss of myeloid progenitor cells in the bone marrow, destruction of mature neutrophils due to increased clearance from the circulation, impaired egress of neutrophils from the marrow, and dysfunctional granulocytic maturation within the marrow**.** Hypocupremia-induced myelopathy produces a clinical and radiologic picture identical to subacute combined degeneration, leading to speculation that both disease processes may share a final common pathway ***(15).***
It is currently unknown whether methionine synthase, an enzyme whose dysfunction causes subacute combined degeneration of the spinal cord, depends on copper for its catalytic activity. Thus, its involvement in copper deficiency myelopathy remains unclear**.** An alternative proposed mechanism for the neurological features of copper deficiency involves cytochrome c oxidase dysfunction**.** Copper deficiency in humans produces a cytochrome enzyme with aberrant structure and kinetics. Impaired activity of any number of copper-dependent enzymes with critical roles in the nervous system (e.g., dopamine β-monooxygenase) can contribute to this disease process ***(16).***

Clinical Features

The primary challenge in identifying copper deficiency is the nonspecific set of signs and symptoms that characterize it. Copper deficiency anemia can easily be attributed to iron deficiency, and copper deficiency myelopathy is often mistaken for vitamin B12 deficiency**.** Furthermore, hematologic and neurologic abnormalities frequently occur together. Thus, awareness of the constellation of risk factors and features of copper deficiency is required. Hematologically, copper deficiency most often produces anemia, ranging from microcytic to macrocytic, and neutropenia**.** Cases of thrombocytopenia and pancytopenia, although rare, have also been documented Because copper deficiency mimics iron deficiency or megaloblastic anemia but remains refractory to replacement of those nutrients, bone marrow surveys are frequently conducted ***(17).***
The bone marrow of copper-deficient patients demonstrates ringed sideroblasts, vacuolated myeloid and erythroid precursors, hemosiderin deposition in plasma cells, and overall left-shifted granulopoiesis and erythropoiesis ***(15).***
Neurologically, copper deficiency most often produces myelopathy or myeloneuropathy**.**This presents as sensory ataxia with lower extremity spasticity, impaired proprioception, and loss of vibratory sensation ***(18)***

Diagnosis

The normal range of serum copper levels is 0.75 – 1.45 µg/Ml**.** Measuring serum copper alone is generally sufficient to make a diagnosis of hypocupremia, but marginal copper deficiency may not be detected**.** If tests confirm copper deficiency, subsequent evaluation of serum zinc levels (normal range 0.66-1.10 µg/mL) to assess zinc-induced hypocupremia ***(19).***

Treatment

Oral replacement is preferred, with routine administration of 2 mg/day until symptoms and serum copper levels normalize. For intravenous replacement, 2 – 4 mg/day for 6 days is recommended for severe deficiency, and 3 – 8 mg/day is recommended for mild to moderate deficiency until symptoms improve. After copper replacement therapy, neurologic deficits often do not improve, but hematologic derangements promptly normalize within 1 – 3 months ***(7).***

Roux-en-Y gastric bypass (RYGB) surgery for morbid obesity is becoming increasingly common in the United States; most procedures bypass the duodenum and between 100–200 cm of proximal jejunum – the sites of most copper absorption in humans. RYGB patients are routinely prescribed multivitamin-mineral preparations, iron, calcium and vitamin B12, but copper is not routinely supplemented as a specific nutrient and little information on copper depletion after RYGB is available. ***(19).***

Gastric surgery (gastrectomy, gastric-bypass) and zinc supplementation have previously been identified as causes of copper deficiency. The intended gastric restrictive-small bowel malabsorptive effects of RYGB contribute to weight loss, but may also profoundly affect patient's nutritional status, depending on the level of nutrient intake and supplementation It is reported that between 12 to 33%% of patients following RYGB develop vitamin B12 deficiency and up to 52% of patients may be iron deficient Low blood levels of fat-soluble vitamins, zinc, and folate are also commonly noted unless specifically supplemented While copper deficiency may be a relatively rare occurrence, albeit one which is likely under reported in RYGB, the number of individuals undergoing this surgical procedures annually is increasing dramatically, creating a large population at risk for copper deficiency. ***(19).***

Bariatric surgery is considered a safe procedure for weight reduction compared with other traditional therapies, especially when performed by experienced surgeons. However, patients after surgery are liable to nutritional deficiencies including copper, iron, and many vitamins. The selection of appropriate nutrient salts and the change in dosage forms of the supplementations can improve nutrient replacement and improve bioavailability. **(20)**

In a recent study done by **Fathy A et al. (20)** Copper deficiency after bariatric surgery was associated with iron deficiency anemia. Thus, copper supplement in addition to iron supplement after bariatric surgery is necessary to avoid the occurrence of anemia

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