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Small but Mighty: Selected Micronutrient Issues in Gastric Bypass Patients



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Obesity has reached epidemic proportions in the United States and as a result, gastric bypass surgery is in demand. Patients can achieve and maintain surgically-induced significant weight loss of 50%–75% of excess body weight. However, due to the malabsorption created by virtue of the bypassed surface area, more than calories are lost. Iron, vitamin B₁₂ and folate are commonly recognized nutrient deficiencies found post-surgery. As the experience of the clinicians and number of surgeries increase, other less well-known deficiencies are starting to emerge. This article focuses on four such nutrients—copper, thiamine, calcium and vitamin D, including signs and symptoms of deficiencies, when to expect them after gastric bypass surgery and how to treat them.

CASE STUDY

A 49-year-old woman was transferred to the University of Virginia Health System (UVAHS) from a local hospital where she had experienced hypotension on hemodialysis and subsequently was found to have left lower lobe pneumonia. She had also experienced dysphagia with both solids and liquids the week before her transfer. Her recent medical history

was significant for watery eyes, left facial droop, falls, and diplopia along with chronic weakness, all of which prompted her admission into a skilled nursing facility three months prior. Her difficulty in walking progressed to the point of being wheelchair dependent. Interestingly, she also experienced a 40 pound unintentional weight loss over the past six months.

Her past medical history includes end stage renal disease (dialysis dependent), chronic obstructive pulmonary disease (COPD) requiring oxygen, diabetes mellitus, and gastric bypass surgery (GBP) in 1990 which was complicated by subglottic stenosis requiring a tracheostomy for 14 months.

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At UVAHS, otolaryngology was consulted and found no evidence of a mass. A modified barium swallow demonstrated profound pharyngeal dysphagia; a bronchoscopy showed paralyzed vocal cords with a narrowed trachea and normal airways. The patient refused a tracheostomy, but was agreeable to a gastrostomy tube. However, given extensive mesh and adhesions in her abdomen, the bariatric surgeons elected not to place a gastrostomy tube and a nasojejun tube was placed instead.

Based on the lab values in Table 1, the patient was supplemented with 1.0 mg intravenous (IV) copper until discharge; 25,000 IU vitamin A for seven days, 50,000 IU vitamin D three times per week, and a daily renal multivitamin (Nephrovite). She was eventually discharged to a rehabilitation facility on enteral feeding and the Nephrovite. Initially, thiamine was not replaced because the value was within normal limits of the reference range. However, upon further evaluation of the literature and of her overt signs and symptoms of thiamine deficiency, thiamine supplement was strongly urged.

INTRODUCTION

According to the Center for Disease Control, 32.9% of adults in the United States are obese. In 1998, there was no state with more than 25% of its adult population defined as obese, compared to 22 states in 2006 (1). As the rate of obesity rises in the United States, the demand for bariatric surgery has also risen. The number of surgeries increased by 600% from 1993 to 2003 (2). In 2006, 170,000 people underwent bariatric surgery.

During the GBP procedure, a 15-30 mL pouch is directly attached to the jejunum in a Roux-en-Y configuration via a narrow anastomosis (3,4) (Figure 1). The length of the roux limb is variable, depending on the patient’s BMI. In addition to weight loss, patients often experience vitamin and mineral deficiencies due to: the small gastric pouch, bypass of the duodenum (a primary absorption site in the small intestine), nutrient-pancreatobiliary secretion mismatch, and non-compliance with supplements. Many articles have focused on the most common deficiencies after GBP surgery including vitamin B₁₂, iron, and folate. The incidence of vitamin B₁₂ deficiency ranges from 26%–70% while folate deficiency ranges from

Table 1
Baseline laboratory values

Vitamin	Level	Reference Range
D ₂ + D ₃	6.2 ng/mL	25–80 ng/mL
Vitamin A*	273 ug/L	360–1200 ug/L
Vitamin E	6.1 mg/L	5.5–17 mg/L
Ferritin	246 ng/mL	5–200 ng/mL
Copper	0.17 ug/mL	0.75–1.45 ug/mL
Thiamine	3.75 ng/mL	0.50–9.4 ng/mL
WBC	10.9 k/uL	4.0–11.0 k/uL
HGb	9.9 g/dL	12–19 g/dL
Hct	33.0%	35%–47%
MCV	100.9 fL	83–95 fL
MCH	30.0 pg	28–32 pg

*Negative acute phase reactant

9%–35%. Iron deficiency is most common in premenopausal women and may occur in 20%–49% of patients (3,5,6).

Recent case studies, abstracts, and reviews have alerted health care professionals to other, less well-
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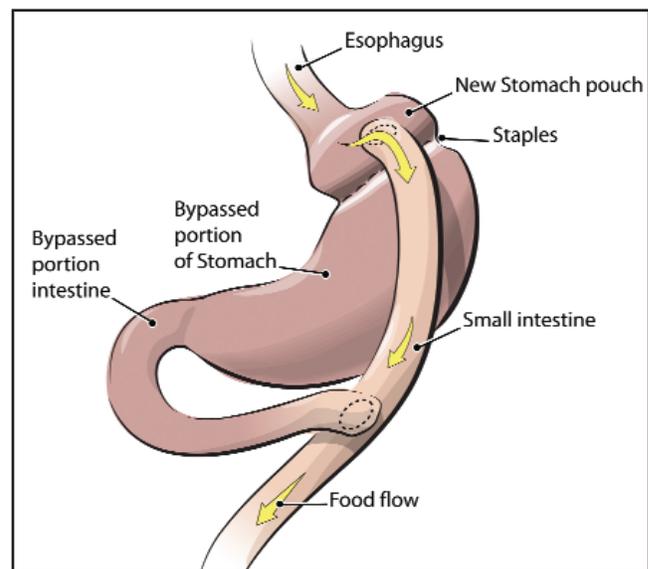


Figure 1. Roux-en-Y Gastric Bypass (Illustration courtesy of Intuitive Surgical, Inc., 2008)

*(continued from page 38)***Table 2**
Dietary Reference Intakes (DRIs) for healthy adults

<i>Vitamin/Mineral</i>	<i>DRI</i>
Thiamine	1.1–1.2 mg/d
Copper	900 mcg
Calcium	1,000–1,200 mg
Vitamin D	800–1,000* IU

*Based on recent research (not DRI)

know nutrient deficiencies after GBP surgery. This article highlights four such nutrients: copper, thiamine, calcium and vitamin D.

COPPER

Copper is a trace metal that is absorbed in the stomach and proximal duodenum, both of which are isolated following GBP surgery. Copper is an important element of enzyme systems involved in hematopoiesis, catecholamine synthesis, vascular and skeletal tissues as well as a key component in the structure and function of the nervous system. The dietary reference intake is 900 mcg per day for healthy adults (7) (Table 2). It is not stored in significant quantities and is excreted in bile. Copper deficiency is rare and symptoms often mimic B₁₂ deficiency, making diagnosis difficult. Symptoms of deficiency include neutropenia, microcytic, hypochromic anemia, severe ataxia, peripheral neuropathy and myeloneuropathy (4,8–10).

Case Studies

- Kumar described 13 patients with symptoms of copper deficiency. All had severe sensory ataxia, lower limb spasticity and acral paresthesias (9). Patients at risk for deficiency include those with malnutrition, excess zinc intake, parenteral feeding with insufficient copper, enteral feeding into the proximal and mid-jejunum for an extended period, and gastrointestinal surgery (10). There have been several reports in the literature describing copper deficiency after a gastrectomy (4).
- Tan, et al described a 74-year old male with a history of peptic ulcer disease who underwent a partial gastrectomy in the 1970's followed by a Roux-en-Y

esophagojejunostomy and jejunostomy feeding tube (10). He received enteral nutrition over the next 25 years providing 2.96 mg copper. He presented with a one-year history of progressive lower extremity numbness, gait disturbance, ataxia, word-finding difficulty and paresthesias in his hands and arms. The symptoms did not improve with vitamin B₁₂ injections. A severely depressed serum copper level was detected and the patient was treated with 2.5 mg of oral elemental copper plus a vitamin and mineral supplement providing another 4 mg of copper. Copper levels slowly increased and the patient had no further progression of symptoms.

- Kumar, et al reported two case studies involving copper deficiency in which both patients experienced progressive lower limb paresthesias and gait difficulty due to severe sensory ataxia (8). One patient had undergone GBP surgery 24 years prior and the other had undergone a Billroth II, partial gastrectomy and vagotomy 15 years prior. Both received vitamin B₁₂ injections with no improvement in symptoms. After copper deficiency was detected, 2 mg IV cupric sulfate was administered for five days and paresthesias improved, but gait disturbances persisted. One patient was unable to sustain normal copper levels and symptoms worsened when IV copper was changed to oral copper.
- The following year Kumar, et al published another case study involving copper deficiency in a 64-year old twelve-years status-post gastric bypass (4). The patient had experienced a nine month history of hand and leg paresthesia as well as gait disturbances. A low serum copper level was identified as 0.11 mcg/mL (normal 0.75–1.45 mcg/mL). Therapy for this patient was not discussed.
- Deppe, et al identified five Roux-en-Y GBP patients at his institution (12 months to 3.5 years post-surgery) with low serum copper levels presenting with neurological complaints (11). All showed improvement with IV followed by oral copper replacement. Actual amounts of supplementation were not disclosed. In 2007, Deppe measured serum copper levels and ceruloplasmin levels during 1,220 patient encounters and found only three patients to be hypocupremic (12). Each patient was at least two-years post-surgery.

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Table 3
Assessment, Monitoring and Supplementation of Copper, Thiamine, Calcium and Vitamin D in Gastric Bypass Patients

<i>Vitamin/Mineral</i>	<i>Signs/Symptoms of deficiency</i>	<i>Supplementation for deficiency</i>	<i>When deficiency might occur</i>
Copper	<ul style="list-style-type: none"> • Neutropenia • Anemia • Ataxia • Peripheral neuropathy • Myeloneuropathy 	2.5 mg elemental po + therapeutic vitamin/mineral supplement or 2 mg IV x 5 days	Suspect (usually >2 yrs post op) when no improvement in symptoms after giving B ₁₂
Thiamine	<ul style="list-style-type: none"> • Peripheral neuropathy • Wernicke's encephalopathy 	50–200 mg IM/IV x 3-14 days followed by 10–100 mg po until symptoms resolve followed by maintenance dose of 1.2 mg/d found in a therapeutic vitamin/mineral supplement	4–12 weeks post op in the presence of persistent nausea/vomiting or rapid weight loss
Calcium and Vitamin D	<ul style="list-style-type: none"> • Elevated PTH • Alkaline phosphatase • Decreased 25-OHD 	1,200–1,500 mg calcium* + 400–800 IU Vitamin D	Screen pre-op and 6–12 months annually Post menopausal Long roux limb African Americans at increased risk

*Calcium citrate in divided doses may be better absorbed

Currently, copper levels are not routinely checked after GBP surgery and supplementation is not standardized (Table 3).

THIAMINE

Thiamine is an essential coenzyme in carbohydrate metabolism. Because of its constant demand and limited storage thiamine is required daily (13). Absorption occurs primarily in the jejunum and proximal ileum. The DRI for men is 1.2 mg/d and 1.1 mg/d for women (7) (Table 2). Thiamine deficiency, or beriberi, occurs as either neurologic beriberi (dry beriberi) or cardiac beriberi (wet beriberi). Neurologic beriberi is the type most often found in bariatric patients (13). Clinical symptoms may include Wernicke's encephalopathy which is characterized by ophthalmoplegia, ataxia, and mental status changes including confusion, apathy, inattentiveness and agitation. Another prominent symptom observed is peripheral neuropathy, both sensory and motor, involving primarily the lower extrem-

ities (13–15). The neuropathy is often mistaken for Guillain-Barre syndrome (16,17). According to Worden, patients with excessive weight loss of greater than 7 kg per month coupled with persistent nausea and vomiting should be monitored for thiamine deficiency (15). Nausea and vomiting are common after surgery and the cause may be due to dysfunctional eating habits such as overeating, eating too fast or not chewing well (3). However, anastomotic strictures (usually occurring four-to-six weeks post-op), or dumping syndrome may be the culprit. The incidence of anastomotic stricture ranges from 0.5% to 4.9% and post-operative bowel obstruction occurs in 0.4% to 5.5% of patients (18). In the setting of poor oral thiamine intake, thiamine stores may be utilized in ≤18–20 days, especially in the presence of persistent vomiting (16,19). Both encephalopathy and peripheral neuropathy may develop despite oral supplementation with thiamine if emesis precludes effective ingestion and absorption. Functional recovery usually takes three-to-six months of therapy, but neurological recov-

ery may be incomplete. Thiamine deficiency can be confirmed by checking erythrocyte transketolase studies. However, this test is often expensive and not readily available, therefore, the clinical cluster of symptoms which respond to administration of parenteral thiamine may prove diagnostic. There are no standard guidelines available for monitoring thiamine status after gastric bypass surgery.

Case Studies

- Nakamura reported two case studies involving GBP patients three months post surgery that had experienced nausea, vomiting, anorexia, and a rapid 90 pound weight loss (17). Both patients experienced numbness and weakness of the hands and lower extremities; one exhibited altered mental status and ocular abnormalities (Wernicke's). Both improved with IV thiamine. One patient never had a thiamine level obtained and the author questions the usefulness of the lab since levels are often normalized with a single dose of thiamine (17). Sola, et al agrees that the diagnosis of thiamine deficiency remains essentially clinical (14).
- Chaves, et al reported five cases of Wernicke's encephalopathy during a nine-month period in the first year of a newly opened bariatric center (20). Four patients had a Roux-en-y GBP and the fifth patient, with a BMI of 92.6, received an intragastric balloon as a preliminary step before undergoing a gastric bypass. All patients were prescribed a daily multivitamin containing 1.5 mg of thiamine, beginning on the 30th post-op day when the diet was advanced beyond liquids. Vomiting started in these patients within one to three weeks and all exhibited ataxia, paresthesias and peripheral neuropathy between two and three months. Only one patient displayed Wernicke Korsakoff's cognitive symptoms. All patients were treated with 100 mg/d injectable thiamine for one-to-two weeks. All complications resolved with thiamine treatment, although total recovery time ranged from one to 12 months. Serum values were not obtained. The author emphasized the importance of supplementing at the earliest suspicion of thiamine deficiency as evidenced by persistent vomiting or rapid weight loss. Additionally, Nakamura and Salas-Alvado discussed gastric bypass patients who developed thiamine deficiency in the setting of both rapid weight loss and repeated vomiting, occurring anywhere from three months post-surgery up to one year (17, 21).
- Angstadt presented a case study involving a 42-year old GBP patient who lost 34 kg three months after surgery (13). The patient reported persistent nausea, vomiting and poor oral intake for six weeks prior to readmission into the hospital. She also experienced paresthesias along her thighs which progressed to difficulty with walking and standing. She was neurologically intact. There was no improvement in symptoms after receiving a B₁₂ injection or potassium supplementation. She then received 50 mg IV thiamine every 12 hours. Thiamine levels were severely low at 45 (normal 80–280). She was transferred to a rehabilitation center where IV thiamine continued and after three weeks, muscle weakness resolved. She was discharged at four weeks with a normal thiamine level on oral thiamine with only mild residual weakness.
- Loh, et al recommended administering 50–100mg IV or IM thiamine at six weeks post-surgery as a preventative measure in patients with protracted vomiting (22). Similarly, many practitioners treat deficiencies with 50–100 mg IV or IM thiamine for seven to 14 days and then convert to an oral dose of 10 mg per day until full resolution of symptoms followed by a maintenance dose of at least 1.2 mg per day (14,23,24). Malinsowki recommends treating a deficiency with 50–200 mg parenteral thiamine until symptoms resolve and then converting to 10–100 mg oral thiamine (5). The typical amount in a multivitamin is 1.5 mg per day. In one bariatric center, patients are prescribed a daily multivitamin containing 20 mg thiamine (19) (Table 3).

CALCIUM AND VITAMIN D

Osteoporosis, osteomalacia and secondary hyperparathyroidism are characteristics of metabolic bone disease (25). Secondary hyperparathyroidism often precedes the others and is a result of calcium and/or vitamin D deficiency. When calcium levels are low, parathyroid hormone (PTH) is elevated causing an increased conversion of inactive 25-OHD to the active 1,25-dihydroxy vitamin D (calcitriol) which increases calcium reabsorption from the bone as well as from the

intestine. If PTH remains elevated for an extended period of time, vitamin D deficiency and secondary hyperparathyroidism can lead to metabolic bone disease (26). The DRI for calcium is 1,000 mg for adults and 1,200 mg for those over 50 years old (7). The DRI for vitamin D was established in 1997, suggesting adults consume 200–400 IU daily (7). However, the 2005 Dietary Guidelines for Americans recommend that high-risk groups such as older adults, people with dark skin, and those exposed to insufficient sunlight should consume 1,000 IU vitamin D (27). Recent research also suggests that recommended daily intakes for adults should be increased to at least 800 IU of vitamin D (28) (Table 2). As GBP patients age, it has been postulated that metabolic bone disease will become an important issue. After gastric bypass, loss of bone mineral content is accelerated and becomes more pronounced over time leading to osteoporosis and osteomalacia (29). Alterations in lab values, including depressed serum calcium and 25-OHD, along with elevations in PTH and alkaline phosphatase, have been observed and may be the only early signs of metabolic bone disease (25). The reasons for this are multifactorial and may include malabsorption of calcium and vitamin D, bypassing the primary site of calcium absorption in the duodenum and jejunum, poor mixing of bile salts, and lactose intolerance. Holick suggests that 25-OHD levels >30 ng/mL indicate sufficient vitamin D since PTH levels stabilize at this level; in addition, calcium transport increases by 45% to 65% when 25-OHD levels are increased from 20 to 32 ng/mL (28). Currently, a 25-OHD level of <20 ng/mL is commonly used to define deficiency. Many physicians may not be familiar with this complication given that, to date, most complications after bariatric surgery are reported in the surgical literature yet the majority of patients receive long-term follow-up with their primary care physicians (29).

Case Studies

- Coates, et al compared obese patients awaiting surgery to 25 men and women who were at least six months post-surgery and found a significant increase in bone resorption associated with loss of bone mineral content in the surgery group (30). All patients were prescribed 1,200 mg calcium and 400–800 IU

Vitamin D daily. There was no significant difference in PTH, 25-OHD or urinary calcium between the two groups, however, the average time from surgery to evaluation was 10.8 months. A subset of 15 patients was followed at baseline, three months, and nine months after GBP surgery and found that bone resorption may increase as early as three months.

- In a study by Goode, et al no difference was found in bone mass between premenopausal GBP patients who were three years post-surgery and a matched control group (31). Postmenopausal women, however, showed evidence of secondary hyperparathyroidism, enhanced bone loss and resorption. Those with low bone mass were supplemented with 600 mg calcium, 5 mcg (200 IU) vitamin D, plus a multivitamin for six months and compared to matched controls who received no supplements. No difference was found in PTH or bone resorption. The authors suggested that greater vitamin and mineral supplementation might be beneficial.
 - De Prisco reported four patients who developed osteomalacia and osteoporosis nine to 12 years after GBP surgery (29). Three of the four patients experienced fatigue, arthralgia and myalgia for months to years before they were correctly diagnosed. All had hypocalcemia, low or undetectable levels of 25-OHD, secondary PTH, and increased alkaline phosphatase levels. One patient had not taken any calcium or vitamin D supplements and the three remaining patients consumed a wide range of supplements including 500–3,000 mg calcium and 100–400 IU vitamin D. The authors recommended monitoring serum levels of calcium, alkaline phosphatase, PTH and 25-OHD periodically.
 - In a longitudinal study, 243 GBP patients had vitamin D, calcium and PTH levels measured between three-to-five years post surgery (26). Those patients with a long roux limb (>100 cm) had significantly lower vitamin D levels and higher PTH levels than those with a short roux limb (<100 cm). There was no difference in serum calcium levels. Thirty-six patients had low vitamin D levels, and of those, 88.9% had elevated PTH. The average vitamin D level was 21.7 ng/mL (lab normal value >8.9 ng/mL). When >30 ng/mL was used as a cutoff for
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Table 4
Summary Guidelines

Copper

- Monitor for neutropenia, anemia, and myeloneuropathy
- Check serum levels when above symptoms not responsive to B₁₂ supplementation
 - Otherwise, check levels annually
- Therapeutic vitamin/mineral supplement q day

Thiamine

- Treat when deficiency suspected:
 - Unintentional weight loss
 - Persistent n/v
- 50–200 mg IV/IM ×2 weeks
- 10–100 mg po supplementation until symptoms resolve
- Maintenance therapeutic vitamin/mineral supplement

Vitamin D

- Check 25 OH vit D at baseline
- Check 25 OH vit D and PTH @ 3 months and annually
- Keep 25 OH vit D >30 ng/mL
- DEXA scan at baseline and annually
- Replace w/ 50,000 IU vitamin D q week ×8 weeks followed by 50,000 IU ×2–4 weeks to keep 25 OHD >30 ng/mL

Calcium

- Calcium citrate 1,200–1,500 mg daily
 - Consume in divided doses (no >500 mg at a time)
 - Take separately from therapeutic vitamin/mineral supplement

vitamin D levels, only 7.3% of the patients fell within the normal range. In patients with normal vitamin D levels, 58% had elevated PTH. The authors suggested selective malabsorption of calcium as a cause or possibly poor absorption of calcium carbonate in a low acid environment. Calcium citrate may be a better choice of supplementation in this population. A linear decrease in vitamin D levels and increase in PTH was seen the longer the patients were followed. Alkaline phosphatase levels were elevated in 40.3% of patients which also correlated with PTH levels. As a result of these data, the authors changed their practice to include preoperative and annual screening of vitamin D and PTH levels. In addition, patients are

now routinely supplemented with 1,200 mg of calcium and 800 IU of vitamin D.

- Similarly, Youseff, et al studied 193 GB patients at three, six, 12, and 24 months after surgery (32). Those with a long roux limb (>150 cm) correlated with an increased risk of hyperparathyroidism. Vitamin D deficiency occurred in 18% of patients, but only 30% of those with high PTH levels also had low vitamin D levels. The authors suggested that low vitamin D levels are not the main cause of metabolic bone disease. Elevated PTH levels occurred in 53% of patients with only 2% developing hypocalcemia. The average time between surgery and secondary hyperparathyroidism was 9.1 months. Both African-Americans and women over 45 years of age were independent risk factors for developing secondary hyperparathyroidism. The authors concluded that calcium metabolism should be evaluated preoperatively with aggressive supplementation of calcium citrate and vitamin D as necessary.

Recommendations for supplementation of calcium and vitamin D in the literature range from 600 to 1,500 mg and 400 to 800 IU respectively (25,27,31,33). Malinowski recommends 1,200–1,500 elemental calcium in divided doses as calcium citrate plus vitamin D as the preferred preparation (or as much as it takes to keep the serum PTH level <100 pg/mL) (5) (Table 3). Both vitamin D₂ and D₃ are used in over-the-counter supplements but only vitamin D₂ is available by prescription (28). Vitamin D₂ is only 30% as effective as vitamin D₃ in maintaining serum 25-OHD levels. Holick suggests using 1,000 IU vitamin D₃ or 3,000 IU vitamin D₂ for supplementation (28). A cost-effective alternative consists of 50,000 IU vitamin D₂ once a week for eight weeks, repeating every two-to-four weeks if 25-OHD remains <30 ng/mL (Table 3). A short time after that publication, Holick tested whether vitamin D₂ was less effective than vitamin D₃ in maintaining 25-OHD levels (34). Sixty-eight adults were randomized to receive placebo, 1,000 IU vitamin D₃, 1,000 IU vitamin D₂, or 500 IU vitamin D₂ plus 500 IU vitamin D₃ for 11 weeks. At the onset of the study, 60% of the participants were vitamin D deficient. In all of the supplemented groups, the levels of 25-OHD increased to the

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same extent suggesting that vitamin D₂ is as effective as vitamin D₃ in maintaining 25-OHD levels above 20 ng/mL. However, none of the groups were able to increase 25-OHD levels above 30 ng/mL.

CONCLUSION

Unfortunately, there is no consensus for vitamin and mineral supplementation after gastric bypass surgery. Since GBP surgery is both a restrictive and malabsorptive procedure, some vitamin and mineral deficiencies are to be expected by virtue of the surgical procedure itself. Vitamin B₁₂ and iron are most often recognized as a potential deficiency after surgery, but more data are accumulating that copper, thiamine, calcium and vitamin D also bear monitoring. As both obesity and the need for GBP surgeries rise, frequent assessment and treatment plans for nutrient deficiencies need to be established. Perhaps the GBP population should be included in the “at risk” group for needing additional vitamin D. The information also needs to be disseminated to not only bariatric centers but primary care physicians who often are the long term care providers for these patients. ■

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