Managing Micronutrient Deficiencies in the Bariatric Surgical Patient

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Introduction

Bariatric surgery has been endorsed as an acceptable weight loss option for patients with severe (also called extreme, morbid or class III) obesity or those with moderate obesity who have comorbid conditions by several authoritative guidelines and conferences [1–6]. The exponential growth in procedures is due to several factors including improved surgical techniques, reduction in the postoperative mortality rate, significant improvement in obesity-related comorbid conditions [7], increased media attention, and profitability. The upsurge in surgical procedures also reflects the increasing prevalence of severe obesity in the United States. Approximately 6 % of adult Americans are considered severely obese (body mass index $\geq$40 kg/m^2) with prevalence figures reaching 18 % for non-Hispanic black women [8]. It is therefore likely that healthcare professionals from all disciplines will encounter patients who have undergone a bariatric surgical procedure. Similarly, primary care physicians and specialists will be expected to monitor and manage their patients on a long-term basis. Although physicians are trained to manage chronic diseases

commonly associated with severe obesity, such as type 2 diabetes, obstructive sleep apnea, hypertension, mixed hyperlipidemia, and arthritis among others, nutritional management following bariatric surgery is not routinely taught. The combined restrictive-malabsorptive surgical procedures—Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD), and biliopancreatic diversion with duodenal switch (BPDDS), place patients at high risk for development of both macro- and micronutrient deficiencies unless they are properly counseled and supplemented. Since most of the deficiencies can be identified early at a preclinical stage, early treatment will prevent or reduce symptoms and deficiency syndromes. This chapter will review the identification and management of the most common micronutrient deficiencies that may occur following restrictive-malabsorptive bariatric surgeries.

Bariatric Surgery-Related Micronutrient Deficiencies

By definition, micronutrients are essential nutrients that are required in only small quantities (mg or micrograms) such as minerals, trace elements, and vitamins. Deficiencies of micronutrients following bariatric surgery can arise from several mechanisms that include (1) preoperative deficiency, (2) reduced dietary intake, (3) malabsorption, and (4) inadequate supplementation. Bariatric surgery is unique in that the RYGB, LGS, BPD,

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and BPDDS procedures surgically alter the gastro-intestinal anatomy in known ways. By bypassing the stomach, duodenum, and varying portions of the jejunum and ileum, malabsorption of four vitamins (thiamine, folate, vitamin B_{12}, and vitamin D) and two minerals (calcium and iron) may occur. Although less common, deficiencies of other vitamins and minerals have also been described, including vitamin A and copper. In general, the greater the malabsorption, the higher the risk for developing nutritional deficiencies. The prevalence of these deficiencies varies widely in the literature due to differences in surgical technique, patient population, definition of deficiency, supplementation protocols, and length and completion of patient follow-up. For example, iron deficiency is reported to range from 20 to 49 % and vitamin B_{12} deficiency from 26 to 70 % [9–17]. In the following section, 'at-risk' micronutrients will be each reviewed considering pathophysiology, clinical presentation, screening tests, and treatment. Table 18.1 provides a summary of the assessment and treatment of micronutrient deficiencies. Other recent review articles address the general topic of nutritional and metabolic problems following bariatric surgery [18–24].

Micronutrient Deficiency

Thiamine

Thiamine (vitamin B_1) is a coenzyme for the essential enzymes transketolase, pyruvate dehydrogenase, and pyruvate carboxylase, in the early stages of the tricarboxylic acid cycle and in the pentose phosphate pathway [25]. Thiamine is mainly absorbed in the jejunum by both active and passive diffusion. Since the biological half-life of the vitamin is rather short (in the range of 9–18 days) and only a small percentage of a high dose is absorbed [26], patients are at risk of developing deficiency syndromes after bariatric surgery. Over the past 3 decades, numerous case reports of thiamine deficiency have been reported following both restrictive and restrictive-malabsorptive surgeries [27–44]. An acute deficiency of thiamine associated with rapidly

progressing clinical symptoms appears to most commonly result from a combination of restricted food intake and persistent intractable vomiting. Symptoms commonly occur 1–3 months postoperatively although may occur later. The clinical presentation varies but three conditions have been reported. Classical Wernicke's encephalopathy is the most common presentation and consists of double vision, nystagmus, ataxia, and a global confusion manifested by apathy, impaired awareness of the immediate situation, disorientation, inattention, and an inability to concentrate. Dry beriberi presents as bilateral, symmetric, lower extremity paresthesia, while wet beriberi manifests as high output congestive heart failure, edema, and metabolic acidosis.

Several recent reviews of neurologic complications following bariatric surgery have been published [45–50]. These authors describe a constellation of symptoms including mono- and polyneuropathy with weakness and/or paresthesias, burning feet syndrome, and hyporeflexia. Chang et al. [51] coined the acronym APGARS (Acute post-gastric reduction surgery neuropathy) to describe conditions with features of weakness, hyporeflexia, and vomiting. Since all symptoms did not improve with thiamine treatment, the authors suggest that additional nutritional deficiencies may be involved in the etiology of this syndrome.

Thiamine status is best assessed by determining erythrocyte transketolase activity. Magnetic resonance imaging (MRI) is useful in confirming the diagnosis of acute Wernicke's encephalopathy with a sensitivity of 53 % and specificity of 93 % [52]. With this test, increased T2 signal of paraventricular regions of the thalamus and increased T2 signal of periaqueductal regions of the midbrain are seen. However, treatment should not be delayed if a thiamine deficiency syndrome is suspected. Treatment with thiamine 100 mg IV every 8 h for 7–14 days followed by 50–100 mg po daily is recommended for these syndromes until the patient fully recovers. To avoid deficiency, patients should be routinely discharged from the hospital receiving a chewable multiple vitamin-mineral supplement that contains between 1.5 and 1.8 mg thiamine.

Table 18.1 Assessment and treatment of micronutrient deficiencies

Nutrient	Etiology	Deficiency conditions	Assessment/Monitoring	Treatment
Thiamine (vitamin B_1)	Precipitated after 1–3 months of intractable persistent vomiting	Wernicke's syndrome (double vision, nystagmus)	Diagnosis typically made by clinical presentation	Acute deficiency
		Acute polyneuropathy	Laboratory confirmation:	Thiamin 100 mg IV or IM × 7–14 days, then 10 mg/day orally until patient fully recovers
		Korsakoff encephalopathy (mental confusion)	Low basal erythrocyte transketolase activity (ETKA), enhanced response after TPP addition	Prophylaxis
		Dry beriberi (paresthesia)	Increased T2 signal on MRI of brain in thalamus and midbrain	1.5–1.8 mg po qd
		Wet beriberi (high output CHF)		
Iron	Diminished consumption of iron-rich foods (meats) due to intolerance	Iron deficiency is asymptomatic	Serum ferritin (reflects size of the storage of iron compartments (normal >12 μg/L)	All patients should take a multivitamin/ mineral supplement containing 28–40 mg iron/day
	Achlorhydria—acid needed to reduce ferric to ferrous state	Iron deficiency Anemia (IDA)—fatigue, poor exercise tolerance, pale conjunctiva, spoon nails		Iron supplementation with ferrous iron 40-65 mg orally TID (+vitamin C)
	Bypassed site for absorption	Pica (pagophagia)	Increased total iron-binding capacity (TIBC), reduced transferrin saturation, microcytosis, microcytic anemia	Parenteral iron with iron dextran, sucrose or gluconate, ferumoxytol
	Iron losses in menstruating women			
Vitamin B_{12}	Decreased acid and pepsin digestion of protein-bound B_{12} from foods	Asymptomatic until development of anemia	Serum vitamin B_{12}	Vitamin B_{12} 350–1,000 μg orally or sublingually or
	Achlorhydria—acid needed to convert pepsinogen to pepsin	With advanced deficiency, development of polyneuropathy, paresthesias, and permanent neural impairment	<200 pg/mL	Nasal spray (Nascobal) 500 μg q weekly or
	Inadequate release of intrinsic factor (IF)		Macrocytic anemia, hypersegmented polymorphonuclear leukocytes	Intramuscular injection
	Incomplete release of B_{12} from R binders		Elevated serum homocysteine and methylmalonic acid (MMA) levels	100 μg monthly
Calcium		Tetany	Low serum calcium	Prophylaxis
		Osteoporosis	Elevated parathyroid hormone (PTH) level	Calcium citrate 1,200–2,000 mg q daily

Table 18.1 (continued)

Nutrient	Etiology	Deficiency conditions	Assessment/Monitoring	Treatment
Calcium and Vitamin D	Reduced intake of calcium and vitamin D-containing foods	Asymptomatic until development of osteoporosis or	Increased alkaline phosphatase	All patients should take 1,200–2,000 mg calcium and ~3,000 IU vitamin D daily
	Malabsorption/ decreased absorption due to bypassed intestine and poor mixing of pancreatic and biliary secretions	Osteomalacia. May present as a bone fracture	Serum 25(OH)D level <30 ng/mL	If deficiency, 50,000 IU vitamin D orally three times weekly; repeat 25(OH)D and PTH in several months
	Dark skin pigmentation, poor sun exposure, and obesity		Increased parathyroid hormone (PTH)—secondary hyperparathyroidism	
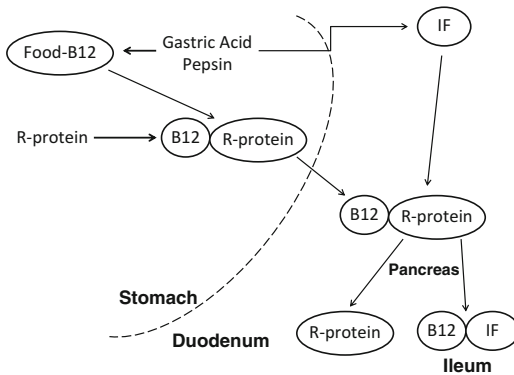
Fig. 18.1 Vitamin B_{12} absorption. See text for individual metabolic steps in absorptive process

Vitamin B_{12}

Vitamin B_{12} (cobalamin) is a cofactor in the biosynthesis of succinyl-coenzyme A and methionine and is important for the functioning of hemopoetic and neural cells [25]. Vitamin B_{12} absorption requires a complex sequence of orchestrated metabolic steps within the gastrointestinal tract (Fig. 18.1). In the stomach, food-bound B_{12} is first dissociated from animal proteins by acid and peptic hydrolysis to liberate free vitamin B_{12}. Once released, the vitamin is avidly bound to R proteins, which are glycoproteins secreted by the salivary glands and the gastric mucosa. In the intestine, pancreatic proteases then degrade R proteins and permit vitamin B_{12} to associate with intrinsic factor (IF), a glycoprotein that the parietal cells of the stomach secrete after being stimulated by food. The resulting IF-vitamin B_{12} complex is then bound to specific receptors in the distal ileum, where absorption occurs [26].

The restrictive-malabsorptive procedures disrupt several of these key steps. Vitamin B_{12} deficiency may occur due to decreased acid and pepsin digestion of protein-bound cobalamins from food, incomplete release of vitamin B_{12} from R proteins, and decreased availability of IF to form IF-vitamin B_{12} complexes. Because the parietal cells which secrete acid and IF, and chief cells which secrete pepsinogen, are located primarily in the fundus and body of the stomach, the LGS and RYGB procedures essentially excludes food from the normal gastric digestive process. Acid secretion has been demonstrated to be virtually absent in the small pouch constructed from the gastric cardia [53, 54]. Consequently, cobalamins are not liberated from protein and are not available for intestinal absorption. In all three restrictive-malabsorptive procedures, pancreatic secretions are diverted distally to mix with nutrients in a shortened common channel, thus affecting the vitamin's binding to IF and subsequent attachment to ileal IF-vitamin B_{12} receptors.

Although B_{12} deficiency is predictable, onset of signs and symptoms are typically delayed for months to years due to prolonged hepatic storage of the vitamin. When they do occur, clinical effects of deficiency are similar to those of pernicious anemia—hematological and neurological. Hypersegmented polymorphonuclear leukocytes and macrocytic erythrocytes can be seen on peripheral blood smear along with a macrocytic anemia. Neurological manifestations include sensory disturbances in the lower extremities (tingling and numbness); motor disturbances including abnormalities in gait; and cognitive changes ranging from loss of concentration to memory loss and disorientation [26].

Vitamin B_{12} status is most commonly and easily assessed by serum or plasma vitamin levels. The concentration of B_{12} in the serum or plasma reflects both the B_{12} intake and stores. The lower limit is considered to be approximately 120–180 pmol/L (170–250 pg/mL). However, a more sensitive biochemical indicator of deficiency is elevation of serum homocysteine and methylmalonic acid (MMA), levels which rise when the supply of B_{12} is low and virtually confirms the diagnosis.

All patients who undergo restrictive-malabsorptive procedures should receive prophylactic vitamin B_{12} supplementation to prevent deficiency. In contrast to the disruption of food-bound B_{12} absorption, crystalline vitamin B_{12} (the form found in vitamin supplements) can be absorbed in the surgical patient since approximately 1 % of orally administered crystalline cobalamin is absorbed by passive diffusion [55, 56]. An oral dose of at least 200 times the recommended dietary allowance (RDA) was shown to normalize mild vitamin B_{12} deficiency in older people assessed by reduction in plasma MMA concentration [57]. Oral treatment has also been effective in patients with pernicious anemia [58]. As a practical matter, patients should receive at least 500 μg B_{12} daily as a dietary supplement delivered orally as a tablet or liquid or sublingually; as a once weekly nasal spray 500 μg cyanocobalamin gel (Nascobal®), or by intramuscular injection (100 μg monthly to 3,000 μg every 6 months). The route of delivery is based on patient preference and monitoring of vitamin B_{12} status.

Folate

Folate deficiency occurs with lower frequency than vitamin B_{12} deficiency; however, it should be considered when evaluating a patient who develops anemia. Folate is a cofactor in the biosynthesis of methionine, thymidine, and purine nucleotides, and for the synthesis of the coenzyme tetrahydrofolate [25]. Folate is absorbed primarily from the proximal third of the small intestine after food folate polyglutamates are hydrolyzed to monoglutamates by intestinal brush border conjugases. Folate deficiency presents with many features similar to vitamin B_{12} deficiency, including hypersegmentation of the neutrophils, increased mean cell volume (MCV), and macrocytic anemia. Inadequate folate intake first leads to a decrease in serum folate concentration, then a decrease in erythrocyte folate concentration, a rise in homocysteine concentration, followed by clinical hematological changes as mentioned above [26]. A serum folate concentration of less than 7 nmol/L (3 ng/mL) indicates negative folate balance. All patients undergoing a restrictive-malabsorptive bariatric operation should receive supplemental doses of folate to prevent deficiency. Supplements of folic acid are nearly 100 % bioavailable. Typically, the amount of folate present in a general (400 μg) or prenatal multivitamin supplement (800–1,000 μg) is adequate to prevent deficiency.

Iron

Patients who undergo restrictive-malabsorptive procedures are at particular risk for developing iron deficiency and iron deficiency anemia (IDA) due to reduced iron absorption, decreased iron intake, and for menstruating women, increased iron losses. Surgical bypass of the duodenum and proximal jejunum decreases total iron uptake because the majority of iron absorption occurs across the apical and basolateral membrane of duodenal enterocytes [59]. Furthermore, acid secretion is nearly absent in the small gastric pouch [53, 54] or remnant gastric sleeve due to the paucity of parietal cells. Hypoacidity exacerbates

iron deficiency because both heme (found only in animal products) and nonheme (found in cereals and green leafy vegetables) iron depend upon the acidic environment of the stomach for efficient absorption [60]. Specifically, nonheme iron requires an acidic pH to reduce it from the ferric (Fe^{3+}) to the ferrous (Fe^{2+}) state, before it can be transported across the brush border membrane by divalent metal ion transporter 1 (DMT 1) in the alkaline duodenum. Although heme iron is more soluble and readily absorbed than nonheme iron, it must be released from its protein structure by the acid and proteases present in gastric juice before absorption can occur [61]. If iron is required by the body, it will cross the basolateral membrane through iron export protein ferroportin and enter the circulation in which is binds to plasma transferrin [62]. Iron absorption from the diet or from supplementation has been shown to decrease significantly after 6 months following RYGB to 33 % and 40 % of their initial values, respectively [63].

In addition to decreased iron absorption, bariatric surgical patients typically consume less heme iron due to an intolerance of meat products (which is full of hemoglobin and myoglobin) [64]. Women with menorrhagia are particularly prone to develop iron deficiency and IDA due to excessive menstrual blood loss. Menstrual iron losses range from 1.5 to 2.1 mg/day, bringing the RDA for females between 19 and 50 years old to 18 mg/day compared to 8 mg/day for males [65]. Due to the combination of these factors, IDA occurs postoperatively in 33–50 % of patients, with a higher incidence in menstruating women [66–68].

Iron deficiency may also be exacerbated in these patients as a result of a nutrient–nutrient inhibitory absorptive interaction between iron and calcium, another mineral that is routinely supplemented during the postoperative period. Most [69–74] but not all [75, 76] studies show that nonheme- and heme-iron absorption is inhibited up to 50–60 % when consumed in the presence of calcium supplements or with dairy products. Calcium at doses of 300–600 mg has a direct dose-related inhibiting effect on iron absorption. This has been seen with calcium carbonate, calcium citrate, and calcium phosphate. Studies by Hallberg et al. [70, 72] suggest that the inhibitory effect is situated within the intestinal mucosal cells. These observations are particularly important for bariatric surgical patients who are routinely prescribed calcium supplements and advised to consume dairy foods high in calcium, such as milk, cheese, and yogurt. In these patients, it appears prudent to recommend that iron and calcium supplementation be separated by several hours to avoid inhibitory interaction.

Early functional symptoms of iron deficiency include fatigue, poor exercise tolerance, and decreased work performance [77]. Signs on physical examination include pale conjunctiva and spoon nails. Serum ferritin is the most sensitive indicator of iron status (normal values usually fall in the range of 20–300 μg/L) and is recommended for diagnosing early iron deficiency [78]. The concentration of serum ferritin reflects the size of the storage iron compartment, with each μg/L representing 8–10 mg of storage iron [60]. However, caution is needed in interpreting ferritin concentration levels in the presence of acute and chronic inflammation since ferritin is also an acute phase reactant. Thus, serum ferritin concentrations may fall within normal range in individuals who have diminished iron stores. The concentration of liver-derived peptide hepcidin reflects body iron requirements and may be useful in the future as a biomarker for monitoring iron status [62]. Hepcidin regulates iron homeostasis by regulating ferroportin-mediated release of iron from enterocytes and macrophages. After the iron storage pool is depleted, there is an increase in total iron-binding capacity (TIBC), decreased serum transferrin saturation (serum iron concentration divided by TIBC × 100), followed by microcytosis (reduced mean corpuscular volume or MCV), hypochromia (reduced mean corpuscular hemoglobin concentration or MCHC), and anemia.

An unusual and fascinating symptom that is particularly associated with IDA is ice eating, or pagophagia, one of the most commonly reported forms of pica. Pica has been previously reported to occur with IDA of pregnancy [79, 80], gastrointestinal blood loss [81], and sickle cell disease [82].

Our group previously reported the first five cases of pagophagia associated with RYGB surgery [83, 84]. All patients were women between 34 and 45 years old with menorrhagia. Onset of pica symptoms ranged from 1 to 23 months post-surgery. Three of the patients described symptoms suggestive of pica when they were children and one during a previous pregnancy.

In order to prevent iron deficiency, all patients undergoing restrictive-malabsorptive surgeries should be prescribed a daily multivitamin–mineral supplement containing elemental iron. Supplementation with one prenatal vitamin and mineral tablet, which typically contains 28–40 mg elemental iron, is often sufficient. High-risk individuals, for example, those who have preoperative iron deficiency or excessive blood loss or those who develop iron deficiency or any degree of anemia, require additional supplementation with an iron salt preparation. Only ferrous iron formulations should be used such as ferrous sulfate, gluconate, or fumarate, since they are more readily absorbed [85]. However, it is important to note that a tablet of the sulfate salt contains twice the amount of elemental iron (65 mg) as a tablet of the other two salts. Therefore, twice as many ferrous gluconate or ferrous fumarate tablets are required to provide the amount of elemental iron in ferrous sulfate tablets [86]. Typical dosing of iron therapy is 150–200 mg/day po given in 2–3 divided doses for several months or until the serum ferritin reaches 50 µg/L. Patients who are responsive to treatment should develop reticulocytosis followed by an increase in hemoglobin. Co-administration with ascorbic acid (vitamin C), the best known reducing agent, is recommended to increase iron absorption [87]. In the presence of ascorbic acid, ferrous iron forms a soluble iron-ascorbic acid complex. Patients who were anemic may require long-term daily supplementation in addition to their other nutritional supplements. In patients with profound iron deficits and severe anemia unresponsive to oral iron supplementation, intravenous administration of iron dextran (InFed), ferric gluconate (Ferrlecit), ferric sucrose (Venofer), or ferumoxytol (Feraheme) will be required.

Calcium and Vitamin D

Calcium and vitamin D are considered together since deficiency of both nutrients may result in metabolic bone disease and their metabolism is interrelated. A negative calcium balance may result from limited intake of calcium- and vitamin D-containing dairy products, reduced fractional intestinal absorption due to surgical bypass of the absorptive sites, and vitamin D deficiency. The latter factor is important since calcium is absorbed by an active transport process dependent on the action of 1,25-dihydroxyvitamin D $(1,25(OH)_2D)$ which binds with high affinity to the vitamin D receptor (VDR) to enhance calcium absorption primarily in the duodenum and jejunum [88] although most of the absorption occurs in the lower segment of the small intestine, the ileum [89]. Calcium is also absorbed by passive diffusion across the intestinal mucosa which becomes important at high calcium intakes such as supplemental calcium [90]. In a prospective study of women who underwent RYGB, fractional radiolabeled calcium absorption in milk was reduced 33 % 6 months after surgery [91].

Vitamin D deficiency may occur for the same reasons listed above for calcium deficiency, that is, reduced intake of vitamin D fortified dairy products and malabsorption of vitamin D due to mismixing of pancreatic and biliary secretions in the distal small intestine. Since vitamin D is fat soluble, it must be incorporated into the intestinal micelle along with bile salts for absorption. However, the major source of vitamin D for most people comes from casual exposure to sunlight. Unlike any other vitamin, vitamin D_3, or cholecalciferol is photosynthesized by the skin by UVB irradiation, converting 7-dehydrocholesterol (provitamin D) to previtamin D_3 in the plasma membrane of skin keratinocytes. Once formed in the skin, previtamin D_3 is rapidly converted to vitamin D_3 [90]. In the liver, vitamin D undergoes hydroxylation at the 25-carbon position to form 25-hydroxy vitamin D (25(OH)D) and subsequently transported to the kidney for additional hydroxylation at the 1-carbon position to form $1,25(OH)_2D$, the biological active form of the

vitamin. Several factors will impede the initial photosynthetic process including living at northern latitudes, wearing sunscreen lotion, limited sun exposure, dark skin pigmentation [92], aging, and obesity itself [93–96]. Melanin skin pigmentation is an effective natural sunscreen that greatly reduces UVB-mediated cutaneous synthesis of vitamin D_3. Thus dark-skinned individuals need longer UVB exposure to generate the same 25(OH)D stores compared with fair-skinned individuals. Several studies have demonstrated an inverse correlation between vitamin D concentrations and BMI or body fat percentage, suggesting decreased bioavailability of skin-derived vitamin D in obese individuals [97]. Thus, severely obese individuals are predisposed to vitamin D insufficiency or deficiency prior to undergoing bariatric surgery.

Clinical deficiency of calcium or vitamin D due to bariatric surgery cannot be detected on a routine chemistry panel, although an elevated alkaline phosphatase level and low calcium or phosphorus level may be seen. Symptoms of vitamin D deficiency are commonly nonspecific such fatigue or easy tiring, muscular weakness predominantly of the proximal limb muscles, and chronic musculoskeletal pain [98]. Unless specifically monitored, the first indication of deficiency is likely to be a vertebral or wrist fracture secondary to development of osteoporosis or osteomalacia. Physiologically, chronic calcium deficiency causes the circulating ionized calcium concentration to decline, which triggers an increase in parathyroid hormone (PTH) synthesis and release. In turn, PTH acts on three organs to restore the circulating calcium concentration to normal. At the kidney, PTH promotes the reabsorption of calcium in the distal tubule. PTH affects the intestine indirectly by stimulating the production of $1,25(OH)_2D$. PTH also induces bone resorption, thereby releasing calcium into the blood [88]. Chronic vitamin D deficiency can result in secondary hyperparathyroidism, increased bone turnover, enhanced bone loss, and increased risk of fragility fracture [99]. Secondary hyperparathyroidism is diagnosed by an elevated PTH level in the setting of low or normal serum calcium [92]. Therefore, detection of subclinical calcium and/or vitamin D deficiency requires

measurement of several nutrients, hormone levels, and biochemical markers of bone turnover that are not routinely assessed.

Serum 25(OH) vitamin D is the best indicator for determining adequacy of vitamin D intake since it represents the combination of cutaneous production of vitamin D and the oral ingestion of both vitamin D_2 (ergocalciferol or plant-based vitamin D) and vitamin D_3. 25(OH)D is not only the transport form of the vitamin D but a direct measure of stores [100]. In the current literature, severe vitamin D deficiency is identified as a 25(OH)D level of less than 5–8 ng/mL (12.5–20 nmol/mL) and mild deficiency or insufficiency as a serum level less than 20 ng/mL (50 nmol/mL) [101]. However, there is debate about the exact cutoff values defining 'deficiency' and 'insufficiency' since these are static rather than functional definitions. When elevated PTH levels (secondary hyperparathyroidism) are used as a functional indicator of vitamin D deficiency, circulating levels of 25(OH)D of at least 30 ng/mL appear optimal [102, 103]. Biochemical monitoring of bone turnover includes measurement of bone formation markers—serum osteocalcin and bone-specific alkaline phosphatase, and the bone resorption marker—serum and urine peptide-bound N-telopeptide crosslinks of type 1 collagen (NTX) [104]. Assessment of bone mineral density (BMD) and bone mineral content (BMC) by dual energy X-ray absorptiometry (DXA) remains the gold standard for the diagnosis of osteoporosis [105].

Abnormalities in vitamin D and bone metabolism among patients undergoing restrictive-malabsorptive bariatric operations have been reported in numerous case series, case reports, and recent reviews [106–118]. Although the studies are primarily observational, contain few patients, and uncontrolled for diet and vitamin mineral supplementation, most studies document the occurrence of hypovitaminosis D and elevated PTH over the first 1–3 postoperative years, with a prevalence ranging from 30 [98] to 80 % [119]. Many of the studies also show a corresponding elevation in alkaline phosphatase levels and biochemical markers of bone turnover. There are multiple factors involved in post-surgical bone mass loss that includes nutritional

deficiencies, rapid weight loss, and possibly changes in adipokines and gut-derived appetite regulatory hormones [118]. In a prospective study of 73 patients who underwent either a restrictive or restrictive-malabsorptive bariatric surgical procedure, both urinary NTX and osteocalcin increased significantly by 3 months after surgery and remained significantly elevated through 18 months [120]. Median serum PTH levels at 9 and 12 months were higher in patients who underwent a restrictive-malabsorptive procedure compared to those who underwent LAGB. PTH levels were associated with increased serum $1,25(OH)_2D$.

It is important to prospectively monitor patients preoperatively and postoperatively since many obese patients present to surgical centers with underlying vitamin and mineral deficiencies, including D deficiency and some with secondary hyperparathyroidism [121–125]. Several cases of severe secondary hyperparathyroidism with osteomalacia have been reported to occur from 9 to 17 years post-surgery [112, 126]. However, since weight reduction itself is associated with reduced BMD and BMC [127, 128], it is important to distinguish between the weight loss and malabsorptive effects of bariatric surgery. Pugnale et al. [129] showed that BMD of the cortical bone decreased significantly among 31 women who underwent a restrictive banding procedure without evidence of secondary hyperparathyroidism. In a 1-year prospective study among 23 obese men and women who underwent RYGB, there was a significant decrease in BMD at the femoral neck and total hip by 9.2 % and 8 %, respectively, associated with a significant increase in urinary NTX and serum osteocalcin [130]. Similarly, Guney et al. demonstrated that weight reduction causes bone loss among both diet treated patients and those who underwent a restrictive vertical banded gastroplasty without a significant change in PTH levels [131]. In another study, six obese control patients were compared to four patients who underwent an RYGB and nine patients who received gastric banding [111]. The RYGB operation resulted in significant net loss of bone mass in comparison to the banding and obese control group. In the study by El-Kadre et al. [109], 10 % of patient had elevated PTH levels preoperatively, whereas the prevalence was 22 % and 25 % in the series by Johnson et al. [114] and Hamoui et al. [110], respectively.

Inclusion of calcium- and vitamin D-containing dairy products in the postoperative diet is important. One serving of milk contains approximately 300 mg calcium. However, many patients will avoid or limit dairy foods due to lactose intolerance or lack of an acquired taste. Choosing lactaid milk or adding lactase to dairy products will address the former problem. To avoid deficiency and supplement the diet, all patients should receive calcium supplements of at least 1,200–2,000 mg/day in divided doses, depending on the adequacy of dietary calcium. Postmenopausal, lactating or pregnant women may require higher ranges due to increased needs. Calcium citrate + vitamin D is the preferred preparation because it is more soluble than calcium carbonate in the absence of gastric acid production [132]. The optimal dose for vitamin D is more controversial since some studies have shown continued deficiency despite high dose supplementation [116, 120, 121]. General guidelines recommend 3,000–5,000 IU per day. Since multivitamin–mineral tablet typically contains 400 IU and calcium + Vitamin D tablets typically contain 500 IU, many patients will require additional vitamin D.

If vitamin D deficiency is detected, measurement of PTH should be obtained to provide a functional assessment. Treatment may involve recommending higher supplemental doses of calcium and vitamin D and reassessing in about 3 months. In patients with severe vitamin D deficiency, initial repletion of stores should be treated with vitamin D 50,000 IU 1–3 times weekly for 8 weeks, then checking 25(OH)D levels [111]. Monitoring of the alkaline phosphatase level and serum and urinary calcium should also be performed.

Other Deficiencies

Micronutrient deficiencies of vitamin A and copper have been reported following bariatric surgery, although less often that the aforementioned nutrients. They will briefly be reviewed.

Vitamin A

Vitamin A, whether ingested as preformed vitamin A (retinyl esters) or as provitamin A carotenoids, requires processing in the intestine to release the nutrients in an absorbable form [25]. Since vitamin A is a fat-soluble vitamin, any condition that interferes with emulsification is likely to reduce intestinal absorption of retinol. Thus vitamin A dietary compounds are more likely to be malabsorbed with the BPD and BPDDS procedures which limit the exposure of food with biliopancreatic digestive secretions within a shortened common channel. Subsequently, deficiency of vitamin A has been more frequently reported among patients who have undergone a BPD or BPDSS procedure compared to RYGB [16], although deficiency has been reported following RYGB as well [133–135]. Slater et al. [136] observed an incidence of vitamin A deficiency of 52 % at 1 year which increased to 69 % by year 4. Similarly elevated incidence rates of vitamin A deficiency were seen by Dolan et al. [137] at 12–18 months after BPD or BPDDS. In a retrospective chart review among 122 patients who underwent RYGB, 35 % and 18 % of patients were vitamin A deficient at 6 weeks and 1 year, respectively [135]. Several cases of symptomatic vitamin A deficiency have been reported following bariatric surgery, occurring 18 and 24 months postoperatively [138, 139]. Patients presented with night blindness (nyctalopia) while one developed diffuse conjunctival xerosis with a Bitot's spot, and diffuse punctuate keratitis of both corneas. In another study of 64 RYGB patients who completed a postoperative survey, reported ocular symptoms potentially related to vitamin A deficiency included xerosis (38 %), night vision changes (68 %), and eye pain/foreign body sensation (23 %) [133].

Preformed vitamin A is found in foods from animal sources, including dairy products, fish, and meat (especially liver). By far the most important provitamin A carotenoid is beta-carotene. Good sources of carotenoids include spinach, sweet potato, carrots, and cantaloupe. Routine screening for vitamin A is recommended for the BPD and BPDDS malabsorptive procedures. To prevent deficiency, a daily dose of at least 10,000 IU is recommended. For patients who undergo RYGB, a prenatal multiple vitamin-mineral supplement containing at least 5,000 IU vitamin A should be provided on a daily basis

Copper

Copper deficiency has emerged as a cause of an array of neurological symptoms that may occur among patients who have undergone bariatric surgery. Reported symptoms include unsteady gait, extremity numbness, paresthesias, or paralysis occurring as long as 10 years following the procedure [140–142]. Other accompanying presentations may include anemia, neutropenia, and pancytopenia. Copper is absorbed primarily in the small intestine with a small amount absorbed in the stomach through a saturable, active transport process [25]. Iron and zinc have been shown to interfere with copper absorption, a particularly important fact since bariatric surgical patients are often asked to take multiple mineral supplements. Copper is required for the formation and maintenance of myelin and in iron metabolism. Most of the copper in blood is bound to ceruloplasmin which is the most reliable index of copper status. The incidence of copper deficiency is uncertain since the micronutrient is not commonly measured.

Copper administration of 2 mg/day should be included as part of routine multivitamin–mineral supplementation. Routine copper screening is not recommended for bariatric surgery patients. However, patients presenting with signs and symptoms of myelopathy or myeloneuropathy should have serum copper and ceruloplasmin values measured. In severe deficiency, treatment can be initiated with IV copper (2–4 mg/day) for 6 days, followed by oral administration [23].

Prophylactic Management and Monitoring for Nutritional Deficiencies

Nutritional management of the bariatric surgical patient must include prophylactic administration of vitamins and minerals to avoid deficiencies.

Table 18.2 Vitamin and mineral supplementation products (selected 'at-risk' micronutrients)

Nutrient	DRI[a]	Flintstones complete chewable	Centrum adults	One-A-Day women's prenatal	Bariatric advantage	Bari Life
Serving size		1 Tablet	1 Tablet	1 Tablet	2 Tablets	3 Tablets
Vitamin A	900	3,000	3,500	4,000	7,500	5,000
Vitamin D (IU)	800	600	400	400	1,000	3,000
Thiamine (mg)	1.2	1.5	1.5	1.7	6.0	3.0
Folate (µg)	400	400	400	800	800	200
Vitamin B_{12} (µg)	2.4	6	6	8	100	500
Calcium (mg)	1,200	100	200	300	200	1,000
Iron (mg)	18	18	18	28	–	22.5
Copper (mg)	0.9	2.0	2.0	2.0	2.0	1.0

Products included in the table are intended to provide examples of commercially available products. Patients and providers should review the specific supplement facts label for the product chosen for clinical use

[a]Dietary Reference Intake, highest value per individual micronutrient for male or female adult ≥18 years old

As a practical manner, all patients should be discharged from the hospital receiving a chewable multiple vitamin-mineral supplement. After the first postoperative month, patients can be switched to a prescribed or over-the-counter supplement. Examples of products with nutrient content are shown in Table 18.2. Since the calcium, vitamin D, and vitamin B_{12} contents of the supplements are inadequate to meet postsurgical needs, all patients should receive additional calcium citrate 1,200–2,000 mg daily depending on dairy calcium along with at least 500 µg vitamin B_{12}.

Monitoring of nutritional status should begin preoperatively. Table 18.3 displays a list of routine laboratory and micronutrient tests and procedures. Once detected, deficiencies should be treated and monitored carefully. Patients at particularly high risk, such as women with menorrhagia, will likely require additional supplementation of selected nutrients.

Conclusion

The restrictive-malabsorptive bariatric surgeries are associated with an increased risk of developing several micronutrient deficiencies. With judicious monitoring and adequate supplementation, these deficiencies are largely avoidable and treatable. However, the long-term sequela of calcium and vitamin D malabsorption and development of

Table 18.3 Postoperative checklist for nutritional supplementation and monitoring for bariatric surgery

Early postoperative care
Multivitamin–mineral tablet
Calcium citrate, 1,200–2,000 mg/day
Vitamin D, at least 3,000 IU/day
Vitamin B_{12} 500–1,000 µg/day orally or sublingually
Maintain adequate hydration (usually >1.5 L/d)
Monitoring (preoperatively and at follow up ~3, 6, and 12 months, then annually)
CBC, chemistry profile
Vitamin B_{12} (if deficient, supplement and assess q 3–6 months)
Folic acid
Iron studies (iron, TIBC, transferrin saturation, ferritin)
25(OH)D and iPTH
Bone density (DXA) at 2 years
Vitamin A (for BPD and BPDDS procedures)
Copper, zinc, and selenium evaluation with specific findings
Thiamine evaluation with specific findings

Adapted from Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic & Bariatric Surgery. Obesity 2013;21:S1-S27

metabolic bone disease remains a major concern. It is recommended that patients be screened preoperatively and at periodic intervals postoperatively. Identification of micronutrient deficiencies should be aggressively treated.

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