Special Article

Pathophysiology, prevention, and treatment of beriberi after gastric surgery

Robert Beaumont Wilson

Beriberi is a nutritional complication of gastric surgery, caused by deficiency of vitamin B_1, or thiamine. Thiamine deficiency leads to impaired glucose metabolism, decreased delivery of oxygen by red blood cells, cardiac dysfunction, failure of neurotransmission, and neuronal death. This review describes the history and pathophysiology of beriberi as well as the relationship between beriberi and nutritional deficiencies after gastric surgery. A literature review of the history and pathophysiology of beriberi and the risk factors for thiamine deficiency, particularly after gastric resection or bariatric surgery, was performed. Recommendations for nutritional follow-up post gastric surgery are based on current national guidelines. Patients may have subclinical thiamine deficiency after upper gastrointestinal surgery, and thus beriberi may be precipitated by acute illness such as sepsis or poor dietary intake. This may occur very soon or many years after gastrectomy or bariatric surgery, even in apparently well-nourished patients. Prompt recognition and administration of supplemental thiamine can decrease morbidity and mortality in patients with beriberi. Dietary education post surgery and long-term follow-up to determine nutritional status, including vitamin and mineral assessment, is recommended for patients who undergo gastric surgery.

INTRODUCTION

Gastric resection for malignancy and bariatric surgery for morbid obesity are associated with deficiencies of both macro- and micronutrients, including thiamine (vitamin B_1).[1–15] Gastrectomy alters the dietary behavior of patients with regard to appetite, food selection, and satiety.[5] Achlorhydria, vagotomy, functional pancreatic exocrine insufficiency, and removal of the pylorus all contribute to disruption of the normal neuroendocrine regulation of food digestion and absorption. Postgastrectomy malabsorption, dumping, and diarrhea are particularly associated with total gastrectomy or Billroth II partial gastrectomy.[3,4] This is related, in part, to diversion of chyme from the duodenum to the jejunum. The rate of thiamine absorption is highest in the duodenum.[13] Up to 30% of patients who have had upper gastrointestinal resectional or bypass surgery may have subclinical thiamine deficiency, even when such patients appear well nourished.[12]

Thiamine is a cofactor necessary for normal glucose and substrate metabolism, which involves enzymes such as transketolase in erythrocytes and pyruvate dehydrogenase and α-ketoglutarate dehydrogenase in mitochondria (Figure 1[13]). Thiamine is required for the production of ribose, RNA, DNA, nicotinamide adenine dinucleotide (NAD), and adenosine triphosphate (ATP). It is particularly important in tissues that are highly metabolically active, including neurons, cardiac myocytes, and erythrocytes, all of which rely on glucose as a main energy substrate. Thiamine triphosphate is

Affiliation: *R.B. Wilson* is with the Upper Gastrointestinal Surgery Department, University of New South Wales, Liverpool Public Hospital, Liverpool, Sydney, New South Wales, Australia, and the Sydney Institute for Obesity Surgery, Ashfield, Sydney, New South Wales, Australia.

Correspondence: *R.B. Wilson*, Department of Upper Gastrointestinal Surgery, Liverpool Public Hospital, Elizabeth Street, Liverpool, Sydney, 2170 NSW, Australia. Email: robert.wilson@unsw.edu.au.

Key words: bariatric, beriberi, gastrectomy, lactate, polyneuropathy, thiamine deficiency, vitamin B_1.

doi: 10.1093/nutrit/nuaa004

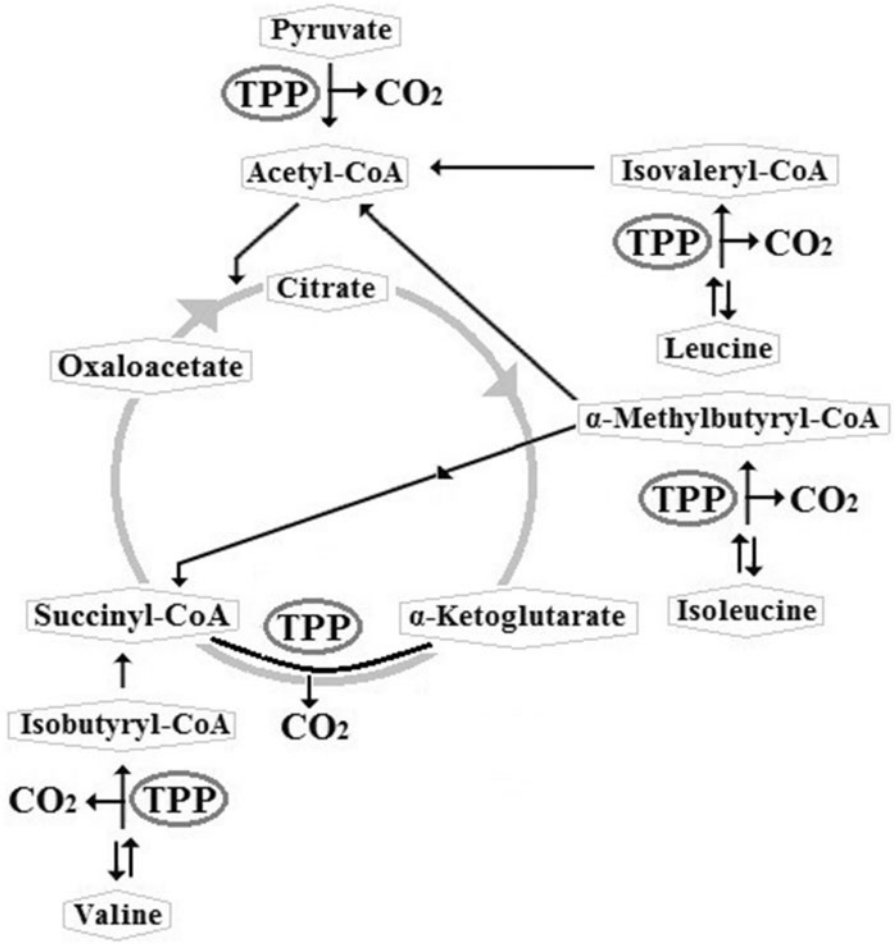

Figure 1 **Thiamine pyrophosphate and the Krebs cycle.** Thiamine pyrophosphate (TPP) is required to feed pyruvate, α-ketoglutarate, and branched-chain amino acids into the Krebs cycle for production of adenosine triphosphate (ATP).[13]

required for normal function of neurotransmission, high-conductance chloride channels, and neuromuscular acetylcholine receptors. Thus, thiamine deficiency is the basis for Wernicke encephalopathy, Korsakoff psychosis, mixed sensory and motor neuropathy (dry beriberi), hypotension, cyanosis, edema, arrhythmias, and cardiac failure (wet beriberi) seen in thiamine deficiency.

Thiamine, a water-soluble vitamin, cannot be stored in appreciable amounts. Thiamine requirements are increased by surgery, fasting, strenuous activity, fever, sepsis, pregnancy, breast feeding, adolescent growth, and anorexia. Koike et al[12] described thiamine-deficient polyneuropathy after gastrectomy in Japanese patients in 2012, distinguished it from alcoholic neuropathy in 2003,[14] and suggested it to be identical to beriberi neuropathy in 2004.[15] Increased requirement for thiamine or decreased consumption of thiamine following gastrectomy can result in acute or fulminant beriberi, with aging patients being more susceptible. Beriberi may occur many years after gastrectomy and may not be recognized by treating physicians, resulting in delayed treatment. Early recognition and treatment of beriberi, as well as prompt exclusion of other differential diagnoses, is crucial.

GASTRIC SURGERY AND NUTRITIONAL DISORDERS

Gastric surgery is associated with numerous nutritional disorders, including pernicious anemia,[1] iron deficiency anemia, bone mineral disease,[2] postvagotomy syndrome, early and late dumping syndromes, hyperinsulinemic hypoglycemia, malnutrition, malabsorption, and functional pancreatic exocrine insufficiency.[3,4] Deficiencies of fat-soluble vitamins (A, D, E, K) and water-soluble vitamins (B group, C) can be related to inadequate intakes, aversion to particular foods,[5] diarrhea, small intestinal bacterial overgrowth, or malabsorption. Malabsorption of iron, copper, zinc, magnesium, or calcium can be caused by postgastrectomy achlorhydria, decreased solubility of dietary salts or trace elements, or inadequate contact of minerals with the absorptive surface of the duodenum after bypass surgery.[6,7] Peripheral neuropathy after gastric

surgery can result from deficiency in vitamin B_1 (thiamine), vitamin B_2 (riboflavin), vitamin B_6 (pyridoxine), vitamin B_{12} (cobalamin), folate, zinc, copper, or vitamin E (α-tocopherol). Deficiencies of multiple B group vitamins may coexist after gastric surgery and can contribute to nutritional polyneuropathy, which manifests with numbness, paresthesia, neuritic pain, sensory loss, gait disturbance, muscle weakness, muscle wasting, or loss of reflexes.[1,8–14]

HISTORY OF BERIBERI

Thiamine deficiency causes edema, breathlessness, muscle weakness, and a sheep-like pattern of gait, known as *beriberi*. One of the earliest written descriptions of beriberi appears in the ancient Chinese medical treatise, the *Huangdi Neijing (Yellow Emperor's Inner Canon),* compiled between the fifth and third centuries BCE. The entymology of the term *beriberi* is obscure. It is said to be derived from the Singhalese word *Bharyee*, meaning "weak movement," the Hindustani word *beri* for sheep, or the Arabic words *buhr*, meaning "asthma," and *bahri*, meaning "sailor" ("Sailor's asthma"). Beriberi is known in Japan as *Kak'ke*, derived from 2 Chinese words, *kiaku*, meaning "legs," and *ke*, meaning "disease." The earliest Western reference to beriberi was made by Dr Jacobus Brontius, the Dutch East India Company physician in Batavia in 1627. Brontius reported that the high-stepping gait, shaking knees, tremor, loss of sensation, and partial paralysis of (thiamine-deficient) neuropathy was referred to as *biri-biri* by the native population, which meant "sheep." The exact cause of biri-biri, however, was not known until after 1889. Christian Eijkman, a Dutch military doctor, had been sent to Batavia in 1886 to find the cause of beriberi in the Dutch troops. He serendipitously discovered that chickens fed the leftovers of the polished white rice from the officer's table in the military hospital developed stargazing (opisthotonos), staggering, and polyneuropathy. A new cook had disapproved of the "civilian" chickens being fed the "military grade" processed white rice and resumed feeding them the local unmilled red rice. Once the chickens were fed the whole rice diet, they promptly recovered.[12–28]

Other researchers, including Gerrit Grijns, Richard Pearson Strong, and Richard Fletcher subsequently proposed that beriberi was a disease of deficiency related to white rice consumption rather than an infectious disease or a response to a neurotoxin in the rice endosperm. In the 1880s, Dr Kanehiro Takaki also independently observed that white rice consumption was associated with beriberi. He demonstrated that replacing the predominantly white rice diet of sailors in the Japanese Navy with a high-protein Western diet of meat, milk, vegetables, and barley prevented beriberi. However, he erroneously concluded that the Japanese low-protein diet was to blame. In 1912, Frederick Gowland Hopkins proposed that minute amounts of essential "accessory food factors" were required, together with macronutrients, for normal growth and survival of rats.[29] Casimir Funk first used the term *vitamine* ("vital amine") in 1911 for the antineuritic substance in unmilled rice. The antineuritic factor was eventually isolated and crystallized from rice polishings and named *aneurine* by Dutch chemists Barend Jansen and Willem Donath in 1926 in the Dutch East Indies. The chemical structure of thiamine was elucidated in 1934, and thiamine was synthesized in the laboratory by Robert Runnels Williams's group in 1935. Different forms of beriberi include neuropsychiatric or Wernicke encephalopathy–Korsakoff syndrome (Wernicke-Korsakoff syndrome), wet beriberi, dry beriberi, gastrointestinal beriberi, fulminant or *Shoshin* beriberi, and subtypes of infantile beriberi.[12–34]

POLYNEUROPATHY INDUCED BY THIAMINE DEFICIENCY

Polyneuropathy due to thiamine deficiency has been described 2 months to 39 years after gastrectomy.[12] The clinical syndrome is quite distinct from alcoholic neuropathy[13] but is identical to beriberi.[14] It includes neuropathic symptoms, clinical progression, cranial nerve palsy, urinary retention, anorexia, dysphagia, severe constipation, ileus, orthostatic hypotension, cardiac arrhythmia and coexistence of heart failure and Wernicke encephalopathy. A symmetric polyneuropathy with more marked involvement of the lower limbs than the upper limbs is typical. Nerve conduction studies typically show markedly decreased amplitude of compound motor action potentials and sensory nerve action potentials, especially in the lower limbs.[12] Sural nerve biopsies show axonal degeneration, loss of myelinated fiber density, and subperineural edema with minimal demyelination.[12,15–17]

In their series of 17 gastrectomy patients with postsurgical thiamine-deficiency polyneuropathy, Koike et al[12] reported the initial symptoms to be limb weakness or burning paresthesia in the feet. Symptoms progressed over an interval of 3 days to 8 years. Most patients (9 of 17) progressed to loss of ambulation within 1 month of the start of symptoms.[12] The pattern of rapidly progressive ascending motor loss can be similar to, and initially mistaken for, Guillain-Barré syndrome in some patients.[18] Most patients presented many years after total or subtotal gastrectomy, many with acute symptoms despite apparent normal dietary intake.

Table 1 **Dietary sources of thiamine, expressed as milligrams of thiamine per 100 g of food**[32,122]

Type of food	Thiamine content (mg/100 g)
Cereals	
Rice bran (crude)	2.75
Whole wheat flour	0.55
Brown rice	0.33
Wheat crackers	0.28
White rice (unfortified)	0.08
Fish	
Bream (steamed)	0.06
Salmon (canned)	0.04
Meat	
Pork chop	0.50
Chicken (steamed)	0.06
Beef sirloin	0.05
Vegetables	
Black beans (raw)	0.90
Cabbage (raw)	0.12
Eggplant	0.04
Lentils	0.10
Onion (boiled)	0.02
Peas green (raw)	0.27
Potato (baked)	0.07
Pumpkin	0.04
Sweet corn (on cob)	0.13
Tomato (raw)	0.04
Nuts and seeds	
Cashew nuts (raw)	0.42
Chia seeds (dried)	0.62
Hazelnuts	0.64
Flaxseed	1.64
Hemp seed (hulled)	1.27
Sesame seed	0.79
Sunflower seeds (dried)	1.48
Yeast preparations	
Vegemite, Marmite	11.0
Brewer's yeast	4.0
Milk	
Cow's milk (3.25% fat)	0.044
Cow's milk (2% fat)	0.039
Cow's milk (1% fat)	0.02
Fruit	
Tamarind (raw)	0.43
Orange juice (frozen concentrate, undiluted)	0.28
Orange (raw)	0.10
Cantaloupe (raw)	0.04
Banana (raw)	0.03
Strawberries (raw)	0.02
Apple (raw with skin)	0.02

PHYSIOLOGY OF THIAMINE

Thiamine (vitamin B_1) is a water-soluble vitamin that, unlike the fat-soluble vitamins, cannot be readily stored in the body. It is an aminopyrimidine attached to a thiazole ring by a methylene linkage. Thiamine is an essential nutrient that is manufactured by plants, yeasts, and prokaryotes, but not eukaryotic animals.[19,20] Animals, including humans, rely mainly on dietary thiamine sources such as pork, fish, whole grain cereals, yeast, nuts, green vegetables, and legumes. The thiamine content of dairy products and fruit is minimal (Table 1[3]). Thiamine is degraded by ultraviolet light as well as by preservation, storage, drying, thawing, gamma irradiation, and pasteurization or prolonged cooking (temperature $> 120°C$) of foods. It is removed by milling of grains or by alkaline limewater treatment of maize. Milling or polishing removes the kernel of whole grains, particularly the scutellum and the germ, which are much richer in thiamine than the remaining white starchy endosperm. The Recommended Dietary Intake of thiamine for adults is 1.1 to 1.4 mg. Because there is no reported toxicity from administration of excess thiamine, there is no upper level of intake. The Recommended Dietary Intake of thiamine is influenced by muscle mass, physical activity, body weight, age, sex, pregnancy, and lactation. The Recommended Dietary Intake is set by assuming a coefficient of variation of 10% for the Estimated Average Requirement[12,19–28,30–33] (Table 2[12,19–30,32,33]).

ABSORPTION OF THIAMINE

The rate of thiamine absorption is highest in the duodenum and proximal jejunum, which is why patients undergoing Roux-en-Y gastric bypass, Billroth II partial gastrectomy, or total gastrectomy are particularly at risk of developing thiamine deficiency.[12,13,21–26] Most thiamine is ingested as thiamine pyrophosphate (TPP) and then converted to free thiamine by brush border ectophosphatases. Small intestinal absorption of free thiamine at high luminal concentrations occurs via passive diffusion, or through active transport by carrier-mediated transporters, ie, thiamine transporter 1 and thiamine transporter 2. Active intestinal transport of thiamine becomes vital when dietary intake is inadequate or marginal.[34,35] Colonic microbiota manufacture thiamine in 2 forms—free thiamine and TPP—and provide a nondietary source of thiamine in animals. Colonocytes absorb the bacterial-derived free thiamine via active transport and the TPP by a high-affinity TPP transporter not found in the small intestine.[36] Once absorbed, intracellular free thiamine is converted to TPP by thiamine pyrophosphokinase 1 via a process that drives cellular uptake. Thiamine is then delivered to the liver by the mesenteric portal venous system. Raising free thiamine levels in the bloodstream does not necessarily lead to a substantial increase in thiamine transport across the blood-brain barrier, as thiamine is not lipophilic and requires a slow, carrier-mediated transporter. Allithiamine (thiamine allyl disulfide) is a lipid-soluble form of thiamine found in allium vegetables, including leeks, garlic, chives, and onions. It readily diffuses across cell membranes and has better bioavailability than water-soluble thiamine. After the

Table 2 **Estimated Average Requirement (EAR) and Recommended Dietary Intake (RDI) for thiamine**[12,19–30,32,33]

Population	Thiamine EAR (mg)	Thiamine RDI (mg)
Children (9–13 y)	0.7	0.9
Children (14–18 y)		
Male	1.0	1.2
Female	0.9	1.1
Adults		
Male	1.0	1.2
Female	0.9	1.1
Lactating or pregnant women	1.2	1.4
Postoperative bariatric surgery patients		
Good health, no vomiting		12–50 mg orally, twice daily, in vitamin B complex/MV form
Vomiting, poor oral intake, paresthesia		500 mg IV or IM, twice daily
Neurological signs/WE/WKS		500 mg IV, 3 times daily

Abbreviations: IV, intravenous; IM, intramuscular; MV, multivitamin; WE, Wernicke encephalopathy; WKS, Wernicke-Korsakoff syndrome.

discovery of allithiamine, 2 synthetic lipophilic disulfide versions of thiamine (fursultiamine and sulbutiamine) and a water-soluble, more bioavailable *S*-acyl thiamine derivative (benfotiamine) were developed, mainly in Japan, for the treatment of beriberi.[37,38]

MEASUREMENT OF THIAMINE LEVELS

Thiamine pyrophosphate is the magnesium-dependent, active cofactor for the enzymes pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, branched-chain α-ketoacid dehydrogenase, and transketolase. These enzymes are vital for normal cellular metabolism (Figure 1). Other intracellular phosphorylated forms of thiamine include thiamine monophosphate, thiamine triphosphate, and adenosine thiamine triphosphate. Thiamine pyrophosphate is dephosphorylated to thiamine monophosphate by thiamine pyrophosphatase. Thiamine monophosphate can be converted back to free thiamine by thiamine monophosphatase.[39] In the past, thiamine levels were determined by serum thiamine concentrations, erythrocyte TPP levels, or the TPP effect. The TPP effect measures the activity of erythrocyte transketolase when extra thiamine is added in vitro and is reported as a percentage increase in activity over baseline. (normal activity, 0%–15%; marginal deficiency, 15% to 24%; and severe deficiency, $>$ 25%). The TPP effect represents the functional intracellular level of thiamine: the higher the TPP effect, the greater the thiamine deficiency. Serum thiamine is not a reliable indicator of overall thiamine levels in the body, as only 0.8% of thiamine in the body is found in the blood.[34] Today, TPP is more commonly measured directly in whole blood using high-performance liquid chromatography, with the normal clinical reference range being 74 to 222 nmol/L. Not all patients with beriberi will have abnormally low levels of TPP in whole blood ($<$ 70 nmol/L).[39]

RISK FACTORS FOR THIAMINE DEFICIENCY

Thiamine deficiency may result from inadequate dietary intake, administration of total parenteral nutrition without adequate vitamin replacement, impaired intestinal absorption, small intestinal bacterial overgrowth,[40,41] genetic metabolic diseases,[42] increased losses of thiamine or increased physiological requirements, or consumption of antithiamine factors, antacids, sulfites, or sodium bicarbonate food preservatives.[32] The maximum body store of thiamine is 30 mg, which is rapidly depleted within 2 weeks of beginning a thiamine-deficient diet. Risk factors for decreased thiamine intake include protracted vomiting, bariatric or gastrointestinal surgery, malnutrition, hyperemesis gravidarum, anorexia, and alcoholism.[34]

Examples of foods that can lead to inadequate thiamine intake upon prolonged consumption include sago, cassava flour, unfortified white bread, or highly refined cereals such as polished white rice. The consumption of a diet composed mainly of refined carbohydrates or one that includes high alcohol intake also reduces body thiamine stores. To attain maximal erythrocyte transketolase activity, at least 0.6 mg of thiamine per 1000 kcal of carbohydrate is required. Most humans will develop symptoms of thiamine deficiency when intake is below 0.2 mg of thiamine per 1000 kcal. Whole wheat flour contains 0.55 mg of thiamine per 100 g, brown rice 0.33 mg per 100 g, and highly milled white rice only 0.08 mg per 100 g. Adding baking powder (sodium bicarbonate) to wholemeal flour when baking bread reduces the thiamine content. Washing white rice in water prior to cooking reduces the thiamine content by half. Thiamine is heat labile, chlorine sensitive, and water soluble, so discarding the rice water after cooking or using chlorinated water for cooking or washing rice contributes to thiamine loss from the diet.[32] Parboiling of rice was originally developed in India but is not practiced in Southeast Asia or Japan, where milled white rice is preferred. Rice parboiling distributes the

thiamine content from the bran and aluerone layer to the endosperm prior to milling. This is why beriberi is rare in India, where parboiled rice is the primary form of rice consumed.

After 1878, mechanical roller milling of wheat and polishing of rice became widespread. Consumption of mass-produced, polished white rice as the staple diet in East Asian countries led to epidemics of beriberi (polyneuritis endemica) in the 1800s and 1900s.[21,33] Polished rice and milled wheat were also popular because removal of the oil-rich bran layer from rice or the wheat bran from wheat grains prolonged storage times, minimized rancidity, and reduced the susceptibility to weevils. Mandatory fortification of wheat flour with the thiamine mononitrate vitamer was introduced in Australia in 1991. Since then, Wernicke-Korsakoff syndrome has become very uncommon in Australia. The thiamine mononitrate vitamer is used because it is nonhygroscopic and more stable than thiamine hydrochloride.[43] Mandatory fortification of bread with iodine and folate was commenced in Australia in 2009. Folate deficiency may indirectly contribute to thiamine deficiency, as folate is required for the regeneration of reduced nicotinamide adenine dinucleotide (NADH) by dihydrofolate reductase. NADH is necessary for the regeneration of TPP.[44] Vitamin C may protect against the development of symptoms of thiamine deficiency.[32]

ANTITHIAMINE FACTORS AND BERIBERI

Antithiamine factors include thiaminases, mycotoxins, thiamine antagonists, and hemin. These factors can precipitate a thiamine deficiency crisis in susceptible individuals. Ingestion of foods containing antithiamine factors (particularly thiaminase I) is associated with mass mortality in fish and birds, cerebrocortical necrosis in ruminants, equine encephalomyelitis (blind staggers) in horses, and acute beriberi in humans. Thiaminases, which are structurally similar to hemin, split thiamine at the methylene linkage.[45] Type I thiaminases are found in raw or fermented fish (paa dek),[46] crustaceans, mussels, and shellfish; rhizomes of Christmas fern (*Polystichum acrostichoides*) and bracken fern (*Pteridium aquilinum*); Australian nardoo sporocarps (*Marsilea drummondii*)[47] and rock fern (*Cheilanthes sieberi*); and some anaerobic intestinal bacteria (*Clostridium sporogenes*, *Clostridium botulinum*, *Paenibacillus thiaminolyticus*). The type I thiaminases in fish, shellfish, and crustaceans are thought to be produced by the intestinal and visceral bacteria of these animals, rather than by the primary host's tissues. Similarly, the source of thiaminase I ingested by herbivores is thought to be bacteria in fern rhizomes. Both elevated thiaminase I activity and associated *Bacillus thiaminolyticus* have been found in the feces of patients with beriberi.[48] Type II thiaminases are produced by *Bacillus subtilis*, *Aneurinibacillus aneurinilyticus*, *Candida* spp, *Helicobacter pylori*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Sulfolobus solfataricus*.[49–51] The disulfide and *S*-acyl synthetic derivatives of thiamine are less susceptible than the parent thiamine to degradation by thiaminases.[52]

Thiamine antagonists are found in tea and betel nuts (tannic acid), coffee (chlorogenic acid, caffeic acid), bracken fern (caffeic acid), and pigmented polyphenol-containing foods such as red cabbage, blueberries, red currants, and red beets. These cause oxidation of the thiazole ring of thiamine, forming nonabsorbable thiamine disulfide.[32] For example, consumption of 1 g of dry tea leaves boiled in 100 mL of water for 5 minutes caused thiamine loss of 0.21 mg per hour.[53] Vitamin C and cysteine can protect thiamine from degradation caused by organic acids and polyphenols.[54] Outbreaks of beriberi in the wet season in some countries may be related to low availability of food, importation of poor-quality rice or milled white rice, seasonal variations in plant tannin levels, or the mycotoxin citreoviridin, produced by rice mold.[55–57]

FOOD ADDITIVES AND THIAMINE

Thiamine is unstable under alkaline conditions produced by food additives such as preservatives and antacids (eg, sodium bicarbonate), which cause disruption of the thiamine methylene bridge. Sulfite-type food preservatives include sulfur dioxide, sodium sulfite, sodium and potassium bisulfite, and sodium and potassium metabisulfite. These are used extensively in the production and preservation of foods and beverages, including dried fruit, ready-to-eat salad vegetables, frozen fried potatoes, wine, beer, soft drinks, packaged fruit juices, shellfish, and pickled and pureed foods. Sulfites possess antioxidant and antimicrobial activities, which inhibit the enzymatic and nonenzymatic (browning) spoiling of food. This preserves the color, freshness, flavor, and crispness of food but substantially reduces the available thiamine. For example, respective thiamine loss from cabbage blanched with sulfite-treated water versus untreated water was 45% vs 15%.[32] The use of sulfiting agents in foods recognized as important sources of thiamine is prohibited by the US Food and Drug Administration[58] (Figure 2[32,58]).

INCREASED LOSSES CAUSED BY THIAMINE–DRUG INTERACTIONS

Increased losses of ingested thiamine can be caused by drug-related polyuria or diarrhea, drug interactions, or

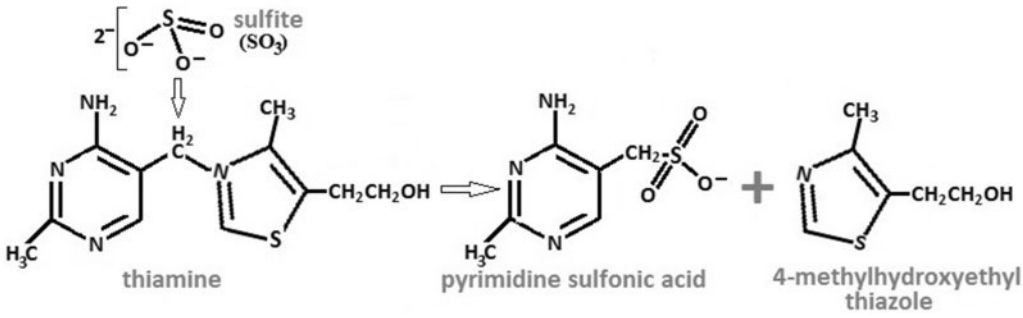

Figure 2 **Sulfite disruption of the methylene bridge of thiamine**.[32,58]

chronic excessive alcohol consumption. Thiamine is a polar, water-soluble vitamin and is not protein bound, which allows it to be easily dialyzed or filtered in the glomerulus. Increased urine flow, loop diuretics, or dialysis can all cause thiamine deficiency. Thiamine deficiency is associated with drugs such as omeprazole, phenytoin, 5-fluorouracil, metformin, alcohol, antibiotics, furosemide, and thiazide diuretics.[34] Because of its azole analogue molecular structure, omeprazole may cause inactivation of pyruvate decarboxylase and human erythrocyte transketolase, resulting in antagonism of thiamine.[59] Omeprazole may inhibit gastric proton pumps by competing with thiamine for binding to hydrogen/potassium adenosine triphosphatase.[42,59] Proton pump inhibitor drugs[60] or Roux-en-Y gastric bypass surgery may also worsen subclinical thiamine deficiency by promoting small intestinal bacterial overgrowth, which alters luminal thiamine levels.[41] Hypomagnesemia induced by proton pump inhibitors can contribute to functional thiamine deficiency, as magnesium is a required cofactor for the formation of TPP and acetyl coenzyme A.[60] 5-Fluorouracil decreases hepatic thiamine levels and thiamine-dependent transketolase activity. This is associated with an increase in the TPP effect in vitro and in whole blood.[61] 5-Fluorouracil is catabolized to fluoroacetate, which blocks the Krebs cycle and ATP production, leading to neurotoxicity, ammonia formation, and encephalopathy.[62–64] Metformin, a substrate and inhibitor of the human thiamine transporter 2, reduces both intestinal absorption of thiamine and levels of thiamine in tissues and liver.[65–67] Alcohol decreases carrier-mediated thiamine transport in the brush border and basolateral membrane of enterocytes in the jejunum (thiamine transporter 1) and potentially decreases thiamine production by intestinal flora in the lumen.[68]

Small intestinal bacterial overgrowth can be treated specifically with certain oral antibiotics such as rifaximin, neomycin, and metronidazole, which can improve postoperative thiamine deficiency in Roux-en-y gastric bypass patients.[40,41,69] The use of broad-spectrum antibiotics (penicillins, cephalosporins, aminoglycosides, tetracyclines, fluoroquinolones, sulfonamides, trimethoprim), however, can potentially cause thiamine deficit in some patients by reducing counts of normal intestinal bacteria that produce thiamine (eg, *Escherichia coli*, bifidobacteria, *Lactobacillus* spp) and by promoting the growth of pathogenic flora such as *Clostridium* spp, which produce thiaminases.[34,70] Metronidazole, a thiazole, has been shown to be a substrate for thiaminase I. Formation of thiamine antimetabolites from metronidazole, which can occur particularly with high cumulative doses or prolonged use of metronidazole, can inhibit thiamine pyrophosphokinase, leading to irreversible, painful, peripheral neuropathy.[54]

Patients with congestive heart failure who receive chronic therapy with furosemide or thiazide diuretics can also develop thiamine deficiency. The prevalence of thiamine deficiency in this patient population varies from 21% to 98%. Supplementation with thiamine has been shown to improve left ventricular ejection fraction by 22%, New York Heart Association Functional Classification, and TPP effect (from 11.7% to 5.4%) in these patients.[71] Mechanisms for exacerbation of heart failure by diuretics include increased thiamine loss in urine, furosemide-related inhibition of cardiac myocyte thiamine uptake, furosemide-induced anorexia, furosemide inhibition of intestinal absorption or cellular uptake of thiamine, and hypomagnesemia.[34] Unrecognized thiamine deficiency in heart failure patients treated with long-term diuretic therapy may result in *Shoshin* beriberi[72] (Table 3[32,34,41,54,59,61,68,71]).

INCREASED REQUIREMENTS FOR THIAMINE

Thiamine requirements increase in rapidly dividing or metabolically active cells or during the mobilization of energy substrates. This occurs during infancy, adolescent growth, pregnancy, lactation, hyperthyroidism, fever, sepsis, strenuous exercise, major surgery, refeeding syndrome, or rapid growth of cancers.[12–27,39,55,73] Fever

Table 3 **Effects of drugs and antithiamine agents on thiamine**[32,34,41,54,59,61,68,71]

Drug family/antithiamine agent	Drug	Effect on thiamine
Alcohol	Ethanol	Decreased intestinal thiamine transport
Antibiotic	Metronidazole	Production of thiamine antimetabolites
Antibiotics	β-lactams, aminoglycosides, trimethoprim, quinolones	Decreased production of thiamine by intestinal microbiota
Chemotherapy	5-fluorouracil	Decreased production of hepatic thiamine, decreased TKT activity
Polyphenols (coffee, tea)	Caffeic acid, tannic acid	Oxidation of thiazole ring
Diuretics	Furosemide, thiazides	Increased renal excretion, decreased intestinal absorption
Flavonoids	Quercetin, rutin	Oxidation to thiamine disulfide
Food preservatives	Sulfites	Disruption of thiamine methylene bridge
Oral hypoglycemics (biguanide)	Metformin	THTR2 inhibitor, prevents active transport of thiamine
Proton pump inhibitors	Omeprazole	Inactivation of PDH, erythrocyte transketolase, and H/K ATPase

Abbreviations: H/K ATPase, hydrogen/potassium adenosine triphosphatase; PDH, pyruvate dehydrogenase; TKT, transketolase; THTR2, thiamine transporter 2.

can critically increase the requirement for thiamine, as a rise in core body temperature of 1°C will increase the basal metabolic rate by 10%.[74] Consumption of a high-fat or a high-carbohydrate diet results in increased metabolic consumption of thiamine.[44] This is particularly relevant in individuals with preexisting thiamine deficiency, such as refugees, prisoners of war, persons with alcoholism, oncology patients, and postoperative bariatric surgery or gastrectomy patients. Administering oral, enteral, or parenteral nutrition to these patients without concomitant thiamine supplementation can result in fulminant beriberi or acute refeeding syndrome.[32,75–79]

THIAMINE PYROPHOSPHATE AND ACETYL COENZYME A

Thiamine is a vital cofactor for the production of energy in cells. Both NADH and flavin adenine dinucleotide are produced in cells during cytosolic glycolysis and in mitochondria via the Krebs cycle. These are strong reducing agents that are oxidized in mitochondria to generate ATP. NADH transport from the cytosol to the mitochondria is mediated by the malate–aspartate and glycerol phosphate shuttles.[80] During strenuous, intense exercise, there is limited oxygen in muscles for the oxidation of pyruvate and NADH. NAD^+ is regenerated from NADH via the reduction of pyruvate to lactate (anaerobic glycolysis). The lactate then diffuses out of the muscle and is transported to the liver, where it is converted back to pyruvate by lactate dehydrogenase and glucose by gluconeogenesis (Cori cycle). Oxidative phosphorylation is more efficient than anaerobic glycolysis, producing a net yield of 34 molecules of ATP per molecule of glucose compared with a net yield of 2 molecules of ATP from 1 molecule of glucose.[80,81] However, the production of lactate from glucose occurs 10 to 100 times faster than the complete oxidation of glucose via mitochondrial respiration. Therefore, over a given time period, the net amount of ATP generated may be comparable when either fermentation or oxidative phosphorylation of glucose is utilized. The fermentation of glucose to lactate, even in the presence of adequate oxygen, is used by cancer cells for proliferation, a process known as the Warburg effect.[82]

The active form of thiamine is TPP, also known as thiamine diphosphate. The synthesis of TPP from thiamine requires magnesium, ATP, and thiamine pyrophosphokinase. Hypomagnesemia may exacerbate thiamine deficiency, particularly in patients with beriberi or refeeding syndrome. For example, concomitant administration of intravenous magnesium sulfate and thiamine in alcoholic patients significantly improved erythrocyte transketolase activity compared with intravenous thiamine alone.[83] Thiamine pyrophosphate, NAD, pantothenic acid (vitamin B_5), and magnesium are required for the oxidative decarboxylation of pyruvate by pyruvate dehydrogenase to produce active acetate and acetyl coenzyme A. Pyruvate dehydrogenase links cytosolic glycolysis to mitochondrial aerobic metabolism during oxidative phosphorylation and ATP production. Pyruvate cannot be utilized in the Krebs cycle in thiamine deficiency and is converted to lactate by lactate dehydrogenase. Lactic acidosis, depletion of cellular ATP, and venous hyperoxia ensues. This may manifest in abdominal pain, nausea, and vomiting, known as gastrointestinal beriberi.[84] Similarly, TPP is a cofactor in the oxidative decarboxylation of α-keto acids, during which α-ketoglutarate dehydrogenase catalyzes the conversion of α-ketoglutaric acid to succinyl-coenzyme A. In addition, TPP is a cofactor for the branched-chain α-ketoacid dehydrogenase, acting on the 2 ketocarboxylates produced from the branched-chain amino acids L-leucine, L-isoleucine, and L-valine.

The production of mitochondrial ATP by oxidative phosphorylation in the Krebs cycle is necessary for maintenance of transmembrane electrochemical gradients, sodium–potassium pumps, myosin–actin interactions, and cellular metabolism. The inability to feed pyruvate, keto acids, or amino acids into the Krebs cycle in thiamine deficiency leads to failure of

energy-dependent cells, particularly neurons, myocytes, and myocardial cells[85] (Figure 1). The neurotransmitter acetylcholine is produced from choline and acetyl coenzyme A. Impaired synthesis of acetylcholine and γ-amino butyric acid (GABA) in thiamine deficiency can also cause neuronal dysfunction, manifested by numbness, paresthesia, and muscle cramps.[86] Thiamine pyrophosphate is also thought to be a cofactor for 2-hydroxyacyl-coenzyme A lyase, required for the production of neural myelin and cerebroside from 2-hydroxy carboxyl substrates.[87]

THIAMINE AND TRANSKETOLASE

Red blood cells lack mitochondria and cannot store glycogen. They are entirely dependent on facilitated diffusion of glucose and anaerobic glycolysis for their energy needs. Erythrocyte metabolism of glucose occurs through the hexokinase glycolysis pathway, the hexose monophosphate shunt or pentose phosphate pathway, and the Rappaport–Luebering glycolytic shunt. Thiamine pyrophosphate is a coenzyme for the transketolase reaction, which has an essential function in the pentose phosphate pathway. The oxidative branch of the pentose phosphate pathway converts 1 molecule of glucose 6-phosphate to ribulose 5-phosphate and produces 2 molecules of nicotinamide adenine dinucleotide phosphate (NADPH). Because mammalian erythrocytes lose their mitochondria during the third phase of erythropoiesis, they have no other way of producing NADPH apart from the pentose phosphate pathway. NADPH is required for the reduction of glutathione, which preserves the erythrocyte cytoskeleton and cell membrane structure and maintains hemoglobin in the ferrous state. This is necessary for successful delivery of oxygen by erythrocytes to the body. Under conditions of erythrocyte oxidative stress, up to 90% of glucose is utilized via the pentose phosphate pathway, which increases erythrocyte requirements for TPP.[88] When erythrocyte transketolase is inactivated in thiamine deficiency, failure of delivery of oxygen may exacerbate lactic acidosis and tissue hypoxia, contributing to fulminant organ failure, *Shoshin* beriberi, or Wernicke-Korsakoff syndrome.

BERIBERI AND THE PENTOSE PHOSPHATE PATHWAY

NADPH produced from the TPP/transketolase–dependent oxidative branch of the pentose phosphate pathway is used for the synthesis of fatty acids and cholesterol as well as for the production of ribose for synthesis of nucleic acids and nucleotides. The pentose phosphate pathway also provides a large reserve of NADPH in synaptosomes to prevent oxidative stress and to remove hydrogen peroxide produced by the action of monoamine oxidase on neurotransmitters released at neuronal synapses.[89] The reversible nonoxidative branch of the pentose phosphate pathway produces glycolytic intermediates such as fructose 6-phosphate and glyceraldehyde 3-phosphate, which can be converted into pentose phosphates for DNA synthesis or directed back to glucose 6-phosphate for NADPH production.[90] Neurons are more susceptible to mitochondrial dysfunction and oxidative stress than astrocytes. This is possibly due to neuronal dependence on the pentose phosphate pathway–based use of glucose and neuronal inability to sustain prolonged glycolysis. Neurons are also dependent on reduced glutathione, produced by astrocytes, for redox homeostasis and removal of reactive oxygen species.

Lactate produced by astrocyte glycolysis and lactate dehydrogenase 1 is shuttled to neurons (the astrocyte–neuron lactate shuttle) to provide the substrate for production of oxidative mitochondrial energy. Neurons take up this lactate via monocarboxylate transporter 2 and convert it back to pyruvate with lactate dehydrogenase 5, which spares neuronal glucose to be directed into the pentose phosphate pathway.[88,89,91] Rapidly dividing cells, including hematological and epithelial cancers, require purines from the nonoxidative branch of the pentose phosphate pathway for RNA and DNA synthesis.[92] Non-oxidative glucose is also utilized via the pentose phosphate pathway to produce nucleotides for synaptic remodeling and neuronal plasticity during brain and nerve development or repair.[88]

While TPP is essential for utilization of normal energy substrates, thiamine triphosphate is required for neurotransmission and normal function of high-conductance chloride channels and neuromuscular acetylcholine receptors in excitable tissues. Thiamine deficiency thus causes neuronal loss, neuromuscular dysfunction, and oxidative stress, which can lead to muscle weakness, areflexia, and progressive sensorimotor neuropathy (dry beriberi), along with confusion, nystagmus, ataxia, and ophthalmoplegia (Wernicke encephalopathy). Failure of rapid thiamine administration in Wernicke encephalopathy leads to irreversible damage to the thalamus, mammillary bodies, basal forebrain, and cerebellum, characterized by anterograde and retrograde amnesia, confabulation, cognitive impairment, and memory deficits (Korsakoff psychosis). Cardiovascular manifestations of thiamine deficiency include high-output cardiac failure, peripheral vasodilation, arteriovenous shunting of blood, activation of the renin-angiotensin-aldosterone system, dyspnea, edema, and dysrhythmias (wet beriberi).[12,26] The fulminant *Shoshin* form of wet beriberi is characterized by a low cardiac ejection fraction, peripheral vasoconstriction,

cold periphery, severe lactic acidosis, profound hypotension, Torsades des Pointes, cyanosis, biventricular heart failure, refractory cardiovascular collapse, and death within hours if not treated immediately with parenteral thiamine.[93]

NEUROPATHY AND STATIN DRUGS

Severe sensorimotor polyneuropathy has also been described in patients who receive long-term treatment for hypercholesterolemia with statin drugs, including lovastatin, simvastatin, pravastatin, and atorvastatin.[94–97] This should be considered in patients who present with an acute illness suggesting dry beriberi but do not respond quickly to thiamine rescue.[18] Guillain-Barré syndrome can occur soon after initiation of statin therapy, though rarely within 24 hours. Potential mechanisms include inhibition of hydroxylmethylglutaryl-coenzyme A reductase or mitochondrial dysfunction caused by decreased concentration or transport of ubiquinone. Ubiquinone, or coenzyme Q10, is a key redox molecule in the mitochondrial respiratory chain required for neuronal function. Other drugs that can cause the typical demyelination in Guillain-Barré syndrome include allopurinol, arsenic, amitriptyline, and cisplatin.[94–97] Thiamine deficiency may exacerbate heavy metal toxicity, as both arsenic trioxide and mercury can inhibit the pyruvate dehydrogenase complex, leading to irreversible axonal neuropathy.[98]

POSTGASTRECTOMY BERIBERI

Up to 30% of patients will have evidence of thiamine deficiency after surgery involving the upper gastrointestinal tract, including partial gastrectomy, total gastrectomy, and Roux-en-Y gastric bypass.[12,25] Thiamine deficiency in these patients may be multifactorial, involving behavioral, dietary, neurohormonal, absorptive, and anatomical changes that occur after surgery. Gastric surgery alters the dietary behavior of patients with regard to appetite, food selection, and satiety.[5] Acquired aversion to fat-containing foods such as meat and dairy products is common. Pylorus resection, vagotomy, achlorhydria, functional pancreatic exocrine insufficiency, and postcibal asynchrony all contribute to disruption of the normal neuroendocrine regulation of food digestion and absorption. Malabsorption, dumping, and diarrhea post gastrectomy are particularly associated with total gastrectomy or Billroth II partial gastrectomy.[3,4] This is related to defunctioned small intestinal segments, diversion of chyme from the duodenum to the jejunum, and impaired release of cholecystokinin-pancreozymin and secretin following Roux-en-Y reconstructions.[3,4] For example, in a series of postoperative Roux-en-Y gastric bypass patients, 27 of 151 (18%) had thiamine deficiency at a mean of 5 years (range, 0.16–9 years) of follow-up.[41] Of these 27 patients, 14 showed evidence of neuropsychiatric (Wernicke-Korsakoff syndrome) beriberi, 18 wet beriberi, 3 dry beriberi, and 11 gastrointestinal beriberi. Different subtypes of beriberi coexisted.[41] Some Roux-en-Y gastric bypass patients with symptoms of thiamine deficiency do not respond to oral thiamine supplementation. This can be caused by small intestinal bacterial overgrowth, which can be diagnosed by glucose-hydrogen breath testing and treated by rotating oral antibiotics with thiamine replacement.[40]

WORSENING OF THIAMINE DEFICIENCY

Because thiamine is not stored in appreciable amounts, patients with subclinical thiamine deficiency after gastric surgery may develop acute symptoms of thiamine deficiency during times of physical stress. Refeeding syndrome related to thiamine deficiency may occur immediately after surgery, particularly if the patient experienced substantial preoperative weight loss or received neoadjuvant chemotherapy or radiotherapy. Such patients also require simultaneous administration of magnesium, potassium, and phosphate.[75–78,99] Beriberi may occur in the subsequent weeks to months after surgery if the patient has persistent vomiting, poor nutrition, or poor compliance with vitamin intake, or it may manifest many years later, when other risk factors may contribute. This is why daily thiamine replacement after gastric surgery with a good-quality oral multivitamin supplement has been advocated by national bariatric and gastrointestinal surgical societies and is recommended in multiple nutritional guidelines.[12,27,99–105]

Thiamine requirements increase with surgery, aging, sepsis, fever, anorexia, physical exertion, and broad-spectrum antibiotic treatment.[12,34,74] Worsening of subclinical thiamine deficiency can also occur with aging. This may explain the lag time of development of neuropathic symptoms after gastrectomy in some older patients.[12,27] The required ratio of thiamine to caloric intake may be higher in older persons than in younger individuals, particularly those who are physically active.[32] Weight loss and anorexia can be caused directly by thiamine deficiency, which inhibits hypothalamic adenosine monophosphate–activated protein kinase and upregulates brown fat uncoupling protein 1. This reduces food intake by up to 75%, increases resting energy expenditure by 9-fold, and reduces body weight by 17% to 24% in murine models.[100] Thiamine supplementation with oral benfotiamine rapidly restores lean body mass, but with slower return of fat mass.[100] The initial apathy, weight loss, and anorexia of thiamine deficiency

may contribute to a fulminant presentation of beriberi.[47]

EARLY RECOGNITION OF BERIBERI

The early recognition and rapid administration of parenteral thiamine in suspected beriberi is crucial to prevent progression from Wernicke encephalopathy to Wernicke-Korsakoff syndrome and to minimize permanent neurological damage. Only 16% to 54% of patients with Wernicke encephalopathy present with all 3 features of the classic triad (ataxia, altered mental state, nystagmus/ophthalmoplegia). Patients may initially present with nonspecific symptoms such as lethargy, somnolence, depression, irritability, fatigue, headaches, or restlessness. Peripheral neuropathy may manifest with burning feet, paresthesia, muscle tenderness, or calf cramps. Other symptoms may include anorexia, vomiting, dysphagia, abdominal pain, and constipation (gastrointestinal beriberi).[106,107] Thiamine replacement therapy in individuals at risk should not be delayed while waiting for the results of blood TPP assays to become available.[99] Guidelines for treatment of patients with acute beriberi presentations include 500 mg of intravenous thiamine, 3 times daily for 3 to 5 days, followed by intravenous thiamine, 250 mg/d for 3 to 5 days or until the symptoms disappear, and then further treatment with oral thiamine, 100 mg/d. Because multiple vitamin deficiencies coexist in acute beriberi, other B group vitamins should also be administered (50 mg vitamin B_6 IV, 4 mg riboflavin IV, 150 mg niacin IV; 3 times daily) along with vitamin C (500 mg/d IV), for 3 days, followed by oral supplementation.[99] The rationale for using thrice-daily dosing of intravenous thiamine in acute presentations is based on the short half-life of intravenous thiamine (96 minutes) and the slow, carrier mediated process of thiamine transport across the blood–brain barrier. A single intravenous dose of thiamine is less likely to achieve sufficient brain tissue levels, and the bioavailability of oral thiamine hydrochloride is only 3.7% to 5.3%.[99]

Subclinical thiamine deficiency can develop after both malabsorptive (Roux-en-Y gastric bypass, biliopancreatic diversion) and restrictive (laparoscopic adjustable gastric band, laparoscopic sleeve gastrectomy) types of bariatric surgery. It can be prevented by ensuring that 100% to 200% of the Recommended Dietary Intake of thiamine is included in the routine daily multivitamin supplement. Among individuals who undergo bariatric surgery and subsequently present with Wernicke encephalopathy, noncompliance with oral vitamin supplementation is common (10.3%). Noncompliance may be exacerbated by the impaired cognition, the apathy, or the progressive encephalopathy associated with chronic or acute thiamine deficiency.[106] The incidence of thiamine deficiency is increased after surgical complications, prolonged vomiting, or inadequate food intake. This can be related to a poorly adjusted laparoscopic adjustable gastric band, marginal ulcer or gastrojejunal anastomotic stricture, gastric volvulus, intra-abdominal abscess, hiatal hernia, or sleeve stenosis after laparoscopic sleeve gastrectomy.[103,108–114] Such patients require rapid intervention, including administration of high-dose empirical thiamine (500 mg IV, 3 times daily) and the use of alternative routes of nutrition and hydration (eg, total parenteral nutrition, nasojejunal tube, gastrostomy feeding tube). This is important from both a clinical and a medicolegal perspective.[111]

For example, in a systematic review of patients who developed Wernicke encephalopathy after bariatric surgery, 49% (40 of 84) had persistent cognitive impairment despite thiamine repletion treatment. Types of bariatric surgery included gastric bypass in 43 of 84 (51%), various restrictive procedures in 37 of 84 (44%), and biliopancreatic diversion in 4 of 84 (5%). The time from surgery to Wernicke encephalopathy presentation was less than 6 months in 79 of 84 cases (range, 3 weeks to 18 months). The median age was 32 years (range, 14–55 years), and 68 of 84 (82%) were women. The primary risk factor for Wernicke encephalopathy in this review was protracted vomiting in 76 of 84 patients (90%). In the remaining 8 patients (10%) without vomiting, risk factors included rapid weight loss, loss of appetite, eating avoidance, or noncompliance with vitamin supplementation. In 15 of 84 patients (18%), intravenous dextrose had been administered without prior thiamine repletion. Peripheral neuropathy occurred in 64 of 84 patients (76%) and was more frequent in the lower limbs than in the upper limbs (61 of 84 vs 30 of 84 patients).[101] A 2018 review of 118 patients who developed Wernicke encephalopathy after bariatric surgery (Roux-en-Y gastric bypass, 52%; laparoscopic sleeve gastrectomy, 21%; gastroplasty, 9%; laparoscopic adjustable gastric band, 5%; biliopancreatic diversion, 3%) found that the dose of parenteral thiamine rescue therapy was inadequate ($<$ 500 mg/d) in 44 of 57 patients (77%). Clinical progression of initial symptoms of Wernicke encephalopathy to chronic Korsakoff syndrome occurred in 31.6% of patients and was associated with delayed diagnosis or inadequate thiamine replacement.[106]

Micronutrient deficiencies also occur preoperatively in patients undergoing bariatric surgery. This consistent finding from academic bariatric units in different countries is related to poor-quality, high-calorie diets with low micronutrient intake.[112] In a Dutch study conducted in 200 morbidly obese patients prior to

Box 1 **Summary of thiamine for prevention and treatment of beriberi after gastric surgery**

Thiamine (vitamin B_1) is a water-soluble vitamin that, unlike fat-soluble vitamins (vitamins A, D, E, K), cannot be stored in the body.
Thiamine is essential for the function and survival of excitable cells (neurons, skeletal/cardiac/smooth muscle cells) and cells that rely exclusively on glucose (erythrocytes).
The Recommended Dietary Intake (RDI) of oral thiamine for men and women is 1.2 mg and 1.1 mg, respectively, and the daily Estimated Average Requirement (EAR) is 1.0 mg and 0.9 mg, respectively.[32]
Thiamine deficiency results in sensorimotor peripheral neuropathy; Wernicke encephalopathy; Korsakoff psychosis (dry beriberi); and cardiac failure, edema, and arrhythmia (wet beriberi).
Bariatric surgery results in changes in food choices, disruption in absorption of thiamine, and decreased thiamine intake.
The incidence of peripheral neuropathy related to deficiency of B-complex vitamins (B_1, B_2, B_6, B_{12}) after bariatric surgery (including Roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy, and biliopancreatic diversion) is 0.7%.[109]
Risk factors for thiamine deficiency include poor oral intake, dysphagia, nausea, anorexia, prolonged vomiting, female gender, sepsis, aging, consumption of highly processed carbohydrates, alcohol consumption, and use of antithiamine agents.[32]
Postoperative bariatric surgery patients should receive thiamine supplementation as part of routine multivitamin therapy (12–50 mg orally, twice daily).[99]
Postoperative bariatric surgery or gastrectomy patients with prolonged vomiting or neurological symptoms suggestive of beriberi should receive immediate high-dose parenteral thiamine (500 mg IV, 3 times daily) as well as other B-complex vitamins (50 mg of vitamin B_6 IV, 4 mg of riboflavin IV, and 150 mg of niacin IV, all 3 times daily) and vitamin C (500 mg IV daily) for 3 days.[99,121]
Preoperative micronutrient deficiency (including vitamin D, thiamine, magnesium, and vitamin C) in morbidly obese patients is common. Bariatric surgery patients should receive preoperative supplementation with a good-quality multivitamin to prevent postoperative complications, including beriberi and scurvy.[99]
Thiamine mononitrate is a more stable form of thiamine than thiamine hydrochoride in sterile solutions, compressed tablets, multivitamin capsules, and dry-filled capsules.[105]
Postoperative thiamine testing in symptomatic or high-risk groups should be performed at least once during the first 6 months after bariatric surgery and then every 3 to 6 months until symptoms resolve.[99]
Long-term nutritional follow-up of both gastric and bariatric surgery patients is recommended.

laparoscopic sleeve gastrectomy, respective levels of vitamin D, iron, folic acid, thiamine, and vitamin B_{12} were abnormally low in 81%, 38%, 24%, 5.5%, and 11.5% of patients.[113] Twelve months after laparoscopic sleeve gastrectomy, which resulted in an average of 70% excess weight loss, pre-existing micronutrient deficiencies persisted (vitamin D in 36%, iron in 18.5%, folic acid in 12.4%, thiamine in 9%, vitamin B_{12} in 11.5%) or were found de novo (vitamin D in 15%, iron in 7.5%, folic acid in 6%, thiamine in 8%, vitamin B_{12} in 7%) in a significant proportion of patients. This was *despite* postoperative vitamin supplementation.[113] In a German study of 43 patients prior to laparoscopic sleeve gastrectomy, 84% had vitamin D levels below 50 nmol/L, 33% had vitamin C levels below 28 μmol/L, 100% had β-carotene levels below 9 μmol/L, and 5% had retinol levels below 7 μmol/L.[114] The incidence of preoperative hypomagnesemia varies between studies (0%–19%).[114–116] Magnesium deficiency may exacerbate subclinical thiamine deficiency and contribute to an acute presentation.[83,117]

In a 2005 US study of thiamine levels in 303 patients prior to Roux-en-Y gastric bypass or laparoscopic adjustable gastric banding, 47 (15.5%) were thiamine deficient. This is an important finding, as perioperative diets are very low in carbohydrates, low in meat, and often based on dairy or fruit products, which may exacerbate a preexisting thiamine deficiency (Table 1). Female patients were found to have lower mean preoperative thiamine levels (71.1 nmol/L) than male patients (94.9 nmol/L).[118] Micronutrient screening (including that for thiamine) is recommended for all patients prior to weight loss surgery, with administration of early preoperative vitamin and mineral replacement based on laboratory assessment, in order to prevent postoperative complications such as beriberi and scurvy.[99,109] Thiamine levels after bariatric surgery should also be determined in patients at high risk of thiamine deficiency, ie, women; African Americans; patients not attending nutritional clinic follow-up; diabetic patients treated with biguanides, diuretics, or statins; and patients with comorbidities such as cardiac failure/furosemide treatment, small intestinal bacterial overgrowth, or recurrent gastrointestinal symptoms.[99,119–122]

CONCLUSION

Beriberi is a nutritional complication of gastric surgery with devastating clinical consequences. Thiamine is absorbed in the duodenum and proximal jejunum, which therefore places patients who undergo total gastrectomy, Billroth II gastrectomy, or Roux-en-Y diversion at particular risk. Beriberi has also been described after restrictive procedures such as laparoscopic sleeve gastrectomy, gastroplasty, and laparoscopic adjustable

gastric banding. Patients often have subclinical thiamine deficiency after upper gastrointestinal surgery. Thiamine deficiency leads to impaired glucose metabolism, decreased delivery of oxygen by red blood cells, cardiac dysfunction, axonopathy, failure of neurotransmission, and neuronal death. Beriberi may also be precipitated by acute illness such as sepsis or poor dietary intake. This may occur very soon or many years after gastric surgery, even in apparently well-nourished patients. Other contributing factors include anorexia, vomiting or food avoidance, malabsorption, drug interactions, increased thiamine requirements, thiamine losses, ingestion of antithiamine agents, and consumption of alcohol or highly processed carbohydrates. The diagnosis of beriberi relies on treating physicians and dietitians being aware of not only the association between gastric surgery and thiamine deficiency but also the variable clinical presentations of beriberi. Long-term follow-up of nutritional status in gastrectomy and bariatric surgical patients, including vitamin and mineral assessment, is recommended (Box 1).

Acknowledgments

Author contributions. R.B.W. conceived, researched, and drafted the manuscript. The submitted article represents the original work of the author.

Funding/support. No external funds supported this work.

Declaration of interest. The author has no relevant interests to declare.

REFERENCES

1. McCombe PA, McLeod JG. The peripheral neuropathy of vitamin B_{12} deficiency. *J Neurol Sci*. 1984;66:117–126.
2. Baek KH, Jeon HM, Lee SS, et al. Short-term changes in bone and mineral metabolism following gastrectomy in gastric cancer patients. *Bone*. 2008;42:61–67.
3. Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. *Curr Gastroenterol Rep*. 2007;9:116–122. doi:10.1007/s11894-007-0005-4
4. Friess H, Tempia-Caliera A, Cammerer G, et al. Indication for pancreatic enzyme substitution following gastric resection. *Pancreatology*. 2001;1(suppl):41–48.
5. Tovey FI, Hobsley M. Post-gastrectomy patients need to be followed up for 20-30 years. *World J Gastroenterol*. 2000;6:45–48.
6. Schinke T, Schilling AF, Baranowsky A, et al. Impaired gastric acidification negatively affects calcium homeostasis and bone mass. *Nat Med*. 2009;15:674–681.
7. Tatara MR, Krupski W, Śliwa E, et al. Fundectomy-evoked osteopenia in pigs is mediated by the gastric-hypothalamic-pituitary axis. *Exp Biol Med (Maywood)*. 2007;232:1449–1457.
8. Botez MI, Peyronnard J-M, Bachevalier J, et al. Polyneuropathy and folate deficiency. *Arch Neurol*. 1978;35:581–584.
9. Tan JC, Burns DL, Jones HR. Severe ataxia, myelopathy, and peripheral neuropathy with acquired copper deficiency in a patient with history of gastrectomy. *JPEN J Parenter Enteral Nutr*. 2006;30:446–450.
10. Imataki O, Ohnishi H, Kitanaka A, et al. Pancytopenia complicated with peripheral neuropathy due to copper deficiency: clinical diagnostic review. *Intern Med*. 2008;47:2063–2065.
11. Rino Y, Suzuki Y, Kuroiwa Y, et al. Vitamin E malabsorption and neurological consequences after gastrectomy for gastric cancer. *Hepatogastroenterology*. 2007;54:1858–1861.
12. Koike H, Misu K, Hattori N, et al. Postgastrectomy polyneuropathy with thiamine deficiency. *J Neurol Neurosurg Psychiatry*. 2001;71:357–362.
13. Spinazzi M, Angelini C, Patrini C. Subacute sensory ataxia and optic neuropathy with thiamine deficiency. *Nat Rev Neurol*. 2010;6:288–293.
14. Koike H, Iijima M, Sugiura M, et al. Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. *Ann Neurol*. 2003;54:19–29.
15. Koike H, Iijima M, Mori K, et al. Postgastrectomy polyneuropathy with thiamine deficiency is identical to beriberi neuropathy. *Nutrition*. 2004;20:961–966.
16. Sobue G, Li M, Terao S, et al. Axonal pathology in Japanese Guillain-Barré syndrome: a study of 15 autopsied cases. *Neurology*. 1997;48:1694–1700.
17. Ohnishi A, Tsuji S, Igisu H, et al. Beriberi neuropathy. Morphometric study of sural nerve. *J Neurol Sci*. 1980;45:177–190.
18. Koike H, Ito S, Morozumi S, et al. Rapidly developing weakness mimicking Guillain-Barré syndrome in beriberi neuropathy: two case reports. *Nutrition*. 2008;24:776–780.
19. Bazurto JV, Farley KR, Downs DM. An unexpected route to an essential cofactor: *Escherichia coli* relies on threonine for thiamine biosynthesis. *mBio*. 2016;7: e01840–15.
20. Roje S. Vitamin B biosynthesis in plants. *Phytochemistry*. 2007;68:1904–1921.
21. Baeltz B. Ueber das Verhältniss der multiplen peripherischen Neuritis zur Beriberi (Panneuritis endemica) [in German]. *Z Klin Med*. 1882;4:616–617.
22. Funk C. On the chemical nature of the substance which cures polyneuritis in birds induced by a diet of polished rice. *J Physiol*. 1911;43:395–400.
23. Rindi G, Ferrari G. Thiamine transport by human intestine in vitro. *Experimentia*. 1977;33:211–213.
24. Laforenza U, Patrini C, Alvisi C, et al. Thiamine uptake in human intestinal biopsy specimens, including observations from a patient with acute thiamine deficiency. *Am J Clin Nutr*. 1997;66:320–326.
25. Shimomura T, Mori E, Hirono N, et al. Development of Wernicke-Korsakoff syndrome after long intervals following gastrectomy. *Arch Neurol*. 1998;55:1242–1245.
26. Xanthakos SA. Nutritional deficiencies in obesity and after bariatric surgery. *Pediatr Clin North Am*. 2009;56:1105–1121.
27. Markkanen T. Metabolic disturbance after gastro-oesophageal resection. *Int J Vitam Nutr Res*. 1973;43:549–554.
28. Butterworth RF. Thiamine deficiency and brain disorders. *Nutr Res Rev*. 2003;16:277–283.
29. Gowland Hopkins F. Feeding experiments illustrating the importance of accessory factors in normal dietaries. *J Physiol*. 1912;44:425–460.
30. O'Keeffe ST, Tormey WP, Glasgow R, et al. Thiamine deficiency in hospitalized elderly patients. *Gerontology*. 1994;40:18–24.
31. The Annotator. Beriberi from the historical and human aspect. *Am Med*. 1914;789–793.
32. World Health Organization, United Nations High Commissioner for Refugees. Thiamine deficiency and its prevention and control in major emergencies. http://apps.who.int/iris/bitstream/handle/10665/66139/WHO_NHD_99.13.pdf. Published 1999. Accessed May 15, 2016.
33. Arnold D. British India and the "Beriberi Problem", 1798–1942. *Med Hist*. 2010;54:295–314.
34. DiNicolantonio JJ, Niazi AK, Lavie CJ, et al. Thiamine supplementation for the treatment of heart failure: a review of the literature. *Congest Heart Fail*. 2013;19:214–222.
35. Bettendorff L, Wins P. Thiamin diphosphate in biological chemistry: new aspects of thiamin metabolism, especially triphosphate derivatives acting other than as cofactors. *FEBS J*. 2009;276:2917–2925.
36. Nabokina SM, Ramos MB, Valle JE, et al. Regulation of basal promoter activity of the human thiamine pyrophosphate transporter *SLC44A4* in human intestinal epithelial cells. *Am J Physiol Cell Physiol*. 2015;308:C750–C757.
37. Oyenihi AB, Ayeleso AO, Mukwevho E, et al. Antioxidant strategies in the management of diabetic neuropathy. *BioMed Res Int*. 2015;2015:1–15.
38. Volvert M-L, Seyen S, Piette M, et al. Benfotiamine, a synthetic S-acyl thiamine derivative, has different mechanisms of action and a different pharmacological profile than lipid-soluble thiamine disulfide derivatives. *BMC Pharmacol*. 2008;8:10.
39. Zastre JA, Sweet RL, Hanberry BS, et al. Linking vitamin B1 with cancer cell metabolism. *Cancer Metab*. 2013;1:16.
40. Lakhani SV, Shah HN, Alexander K, et al. Small intestinal bacterial overgrowth and thiamine deficiency after Roux-en-Y gastric bypass surgery in obese patients. *Nutr Res*. 2008;28:293–298.
41. Shah HN, Bal BS, Finelli FC, et al. Constipation in patients with thiamine deficiency after Roux-en-Y gastric bypass surgery. *Digestion*. 2013;88:119–124.
42. Brown G. Defects of thiamine transport and metabolism. *J Inherit Metab Dis*. 2014;37:577–585.
43. Truswell AS. Australian experience with the Wernicke-Korsakoff syndrome. *Addiction*. 2000;95:829–832.

44. Nguyen-Khoa D. Beriberi (thiamine deficiency). In: Khardori R, ed. *Medscape Reference*. New York, NY: Medscape Reference; 2014. https://emedicine.medscape.com/article/116930-overview. Accessed June 9, 2016.
45. De Vries J, ed. *Food Safety and Toxicity*. Boca Raton, FL: CRC Press; 1997.
46. Soukaloun D, Lee SJ, Chamberlain K, et al. Erythrocyte transketolase activity, markers of cardiac dysfunction and the diagnosis of infantile beriberi. *PLoS Negl Trop Dis.* 2011;5:e971.
47. Earl JW, McCleary BV. Mystery of the poisoned expedition. *Nature*. 1994;368:683–684.
48. Matsukawa D, Chang S, Misawa H, et al. Studies on the thiamine deficiency due to bacterial thiaminase I. Investigations on intestinal contents. *J Vitaminol (Kyoto)*. 1954;1:43–48.
49. Begum A, Drebes J, Perbandt M, et al. Purification, crystallization and preliminary X-ray diffraction analysis of the thiaminase type II from *Staphylococcus aureus*. *Acta Crystallogr Sect F Struct Biol Cryst Commun.* 2011;67:51–53.
50. Ringe H, Schuelke M, Weber S, et al. Infant botulism: is there an association with thiamine deficiency? *Pediatrics*. 2014;134:e1436–e1440.
51. Kraft CE, Gordon ERL, Angert ER. A rapid method for assaying thiaminase I activity in diverse biological samples. *PLoS One*.2014;9:e92688.
52. Murata K. Actions of two types of thiaminase on thiamin and its analogues. *Ann NY Acad Sci*. 1982;378:146–156.
53. Vimokesant S, Kunjara S, Rungruangsak K, et al. Beriberi caused by antithiamine factors in food and its prevention. *Ann NY Acad Sci*. 1982;378:123–136.
54. Bender DA. *Nutritional Biochemistry of the Vitamins. 1st ed*. Cambridge, UK: Cambridge University Press; 2003.
55. Thurnham DI, Cathcart AE, Livingstone M. A retrospective investigation of thiamin and energy intakes following an outbreak of beriberi in the Gambia. *Nutrients*. 2011;3:135–151.
56. Carvajal-Moreno M. Mycotoxins that affect the human cardiovascular system. *J Biomol Res Ther*. 2015;4:2.
57. Rosa CAR, Keller KM, Oliveira AA, et al. Production of citreoviridin by *Penicillium citreonigrum* strains associated with rice consumption and beriberi cases in the Maranhão State, Brazil. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. 2010;27:241–248.
58. Sulfiting agents: affirmation of GRAS status. *Fed Regis*. 1988;53:51065–51084.
59. Nixon PF, Diefenbach RJ, Duggleby RG. Inhibition of transketolase and pyruvate decarboxylase by omeprazole. *Biochem Pharmacol*. 1992;44:177–179.
60. Toh J, Ong E, Wilson R. Hypomagnesaemia associated with long-term use of proton pump inhibitors. *Gastroenterol Rep*. 2015;3:243–253.
61. Basu TK, Aksoy M, Dickerson JW. Effects of 5-fluorouracil on the thiamin status of adult female rats. *Chemotherapy*. 1979;25:70–76.
62. Arellano M, Malet-Martino M, Martino R, et al. The anti-cancer drug 5-fluorouracil is metabolized by the isolated perfused rat liver and in rats into highly toxic fluoroacetate. *Br J Cancer*. 1998;77:79–86.
63. Cho KP, Lee JS, Seong JS, et al. Two cases of Wernickés encephalopathy that developed during total parenteral nutrition in colon cancer patients treated with 5-fluorouracil-based chemotherapy. *Korean J Gastroenterol*. 2014;64:158–163.
64. Koenig H, Patel A. Biochemical basis for fluorouracil neurotoxicity. The role of Krebs cycle inhibition by fluoroacetate. *Arch Neurol*. 1970;23:155–160.
65. Chen L, Shu Y, Liang X, et al. OCT1 is a high-capacity thiamine transporter that regulates hepatic steatosis and is a target of metformin. *Proc Natl Acad Sci USA*. 2014;111:9983–9988.
66. Liang X, Chien HC, Yee SW, et al. Metformin is a substrate and inhibitor of the human thiamine transporter, THTR-2 (SLC19A3). *Mol Pharm*. 2015;12:4301–4310.
67. Schümann K. Interactions between drugs and vitamins at advanced age. *Int J Vitam Nutr Res*. 1999;69:173–178. doi:10.1024/0300-9831.69.3.173
68. Subramanya SB, Subramanian VS, Said HM. Chronic alcohol consumption and intestinal thiamin absorption: effects on physiological and molecular parameters of the uptake process. *Am J Physiol Gastrointest Liver Physiol*. 2010;299:G23–G31.
69. Salem A, Roland BC. Small intestinal bacterial overgrowth (SIBO). *J Gastroint Dig Syst*. 2014;4:225.
70. Pelton R, LaValle JB, Hawkins E, Krinsky DL, eds. *Drug-Induced Nutrient Depletion Handbook*. Hudson, OH: Wolters Kluwer Clinical Drug Information (Lexicomp);1999:258.
71. Shimon H, Almog S, Vered Z, et al. Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. *Am J Med*. 1995;98:485–490.
72. Misumida N, Umeda H, Iwase M. Shoshin beriberi induced by long-term administration of diuretics: a case report. *Case Rep Cardiol*. 2014;2014:878915.
73. Seligmann H, Levi R, Konijn A, et al. Thiamine deficiency in patients with B-chronic lymphocytic leukaemia: a pilot study. *Postgrad Med J*. 2001;77:582–585.
74. Khounnorath S, Chamberlain K, Taylor AM, et al. Clinically unapparent infantile thiamin deficiency in Vientiane, Laos. *PLoS Negl Trop Dis.* 2011;5:e969.
75. Chiappetta S, Stein J. Refeeding syndrome: an important complication following obesity surgery. *Obes Facts*. 2016;9:12–16.
76. Raziel A. Thiamine deficiency after bariatric surgery may lead to Wernicke encephalopathy. *Isr Med Assoc J*. 2012;14:692–694.
77. Silk Z, Jones L, Heath D. Refeeding syndrome: an important complication after bariatric surgery. *Surg Obes Relat Dis*. 2011;7:e21–e23.
78. Boateng AA, Sriram K, Meguid MM, et al. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. *Nutrition*. 2010;26:156–167.
79. Marinella MA. Refeeding syndrome: implications for the inpatient rehabilitation unit. *Am J Phys Med Rehabil*. 2004;83:65–68.
80. Shestov AA, Liu X, Ser Z, et al. Quantitative determinants of aerobic glycolysis identify flux through the enzyme GAPDH as a limiting step. *eLife*. 2014;3:e03342.
81. Fink MP. Bench-to-bedside review: cytopathic hypoxia. *Crit Care*. 2002;6:491–499.
82. Liberti MV, Locasale JW. The Warburg effect: how does it benefit cancer cells? *Trends Biochem Sci*. 2016;41:211–218.
83. Peake RWA, Godber IM, Maguire D. The effect of magnesium administration on erythrocyte transketolase activity in alcoholic patients treated with thiamine. *Scott Med J*. 2013;58:139–142.
84. Duca J, Lum CJ, Lo AM. Elevated lactate secondary to gastrointestinal beriberi. *J Gen Intern Med*. 2016;31:133–136.
85. Spencer PS, Palmer VS. Interrelationships of undernutrition and neurotoxicity: food for thought and research attention. *Neurotoxicology*. 2012;33:605–616.
86. Voss U, Sand E, Olde B, et al. Enteric neuropathy can be induced by high fat diet *in vivo* and palmitic acid exposure *in vitro*. *PLoS One*. 2013;8:e81413.
87. Casteels M, Sniekers M, Fraccascia P, et al. The role of 2-hydroxyacyl-CoA lyase, a thiamin pyrophosphate-dependent enzyme, in the peroxisomal metabolism of 3-methyl-branched fatty acids and 2-hydroxy straight-chain fatty acids. *Biochem Soc Trans*. 2007;35(pt 5):876–880.
88. Stincone A, Prigione A, Cramer T, et al. The return of metabolism: biochemistry and physiology of the pentose phosphate pathway [published online September 22, 2014]. *Biol Rev Camb Philos Soc*. doi:10.1111/brv.12140.
89. Hothersall JS, Greenbaum AL, McLean P. The functional significance of the pentose phosphate pathway in synaptosomes: protection against peroxidative damage by catecholamines and oxidants. *J Neurochem*. 1982;39:1325–1332.
90. Patra KC, Hay N. The pentose phosphate pathway and cancer. *Trends Biochem Sci*. 2014;39:347–354.
91. Brekke EMF, Walls AB, Schousboe A, et al. Quantitative importance of the pentose phosphate pathway determined by incorporation of ^{13}C from [2-^{13}C]- and [3-^{13}C]-glucose into TCA cycle intermediates and neurotransmitter amino acids in functionally intact neurons. *J Cereb Blood Flow Metab*. 2012;32:1788–1799.
92. Saha A, Connelly S, Jiang J, et al. Akt phosphorylation and regulation of transketolase is a nodal point for amino acid control of purine synthesis. *Mol Cell*. 2014;55:264–276.
93. Dabar G, Harmouche C, Habr B, et al. *Shoshin* beriberi in critically-ill patients: case series. *Nutr J*. 2015;14:51.
94. Chong PH, Boskovich A, Stevkovic N, et al. Statin-associated peripheral neuropathy: review of the literature. *Pharmacotherapy*. 2004;24:1194–1203.
95. Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs*. 2008;8:373–418.
96. Rajabally YA, Varakantam V, Abbott RJ. Disorder resembling Guillain-Barré syndrome on initiation of statin therapy. *Muscle Nerve*. 2004;30:663–666.
97. Gaist D, Jeppesen U, Andersen M, et al. Statins and risk of polyneuropathy: a case-control study. *Neurology*. 2002;58:1333–1337.
98. Kühn M, Sammartin K, Nabergoj M, et al. Severe acute axonal neuropathy following treatment with arsenic trioxide for acute promyelocytic leukemia: a case report. *Mediterr J Hematol Infect Dis*. 2016;8:e2016023.
99. Parrott J, Frank L, Rabena R, et al. American Society for Metabolic and Bariatric Surgery integrated health nutritional guidelines for the surgical weight loss patient 2016 update: micronutrients. *Surg Obes Relat Dis*. 2017;13:727–741.
100. Liu M, Alimov A, Wang H, et al. Thiamine deficiency induces anorexia by inhibiting hypothalamic AMPK. *Neuroscience*. 2014;267:102–113.
101. Aasheim ET. Wernicke encephalopathy after bariatric surgery: a systematic review. *Ann Surg*. 2008;248:714–720.
102. Goodman JC. Neurological complications of bariatric surgery. *Curr Neurol Neurosci Rep*. 2015;15:79.
103. Dagan SS, Goldenshluger A, Globus I, et al. Nutritional recommendations for adult bariatric surgery patients: clinical practice. *Adv Nutr*. 2017;8:382–394.
104. 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: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Obesity (Silver Spring)*. 2013;21(suppl 1):S1–S27.
105. Macek TJ, Feller BA, Hanus EJ. Pharmaceutical studies with thiamine mononitrate. *J Am Pharm Assoc Am Pharm Assoc*. 1950;39:365–369.
106. Oudman E, Wijnia JW, van Dam M, et al. Preventing Wernicke encephalopathy after bariatric surgery. *Obes Surg*. 2018;28:2060–2068.
107. Kröll D, Laimer M, Borbély YM, et al. Wernicke encephalopathy: a future problem even after sleeve gastrectomy? A systematic literature review. *Obes Surg*. 2016;26:205–212.
108. Aron-Wisnewsky J, Verger EO, Bounaix C, et al. Nutritional and protein deficiencies in the short term following both gastric bypass and gastric banding. *PLoS One*. 2016;11:e0149588.

109. Punchai S, Hanipah ZN, Meister KM, et al. Neurologic manifestations of vitamin B deficiency after bariatric surgery. *Obes Surg*. 2017;27:2079–2082.
110. Tang L, Alsulaim HA, Canner JK, et al. Prevalence and predictors of postoperative thiamine deficiency after vertical sleeve gastrectomy. *Surg Obes Relat Dis*. 2018;14:943–950.
111. DeMaria E, Trigilio-Black C. Alarming increase in malpractice claims related to Wernicke's encephalopathy post bariatric surgery: an alert to monitor for thiamine deficiency. *Bariatric Times*. 2018;15:8–9. https://bariatrictimes.com/malpractice-wernickes-encephalopathy-thiamine-deficiency/. Accessed August 23, 2019.
112. Roust LR, DiBaise JK. Nutrient deficiencies prior to bariatric surgery. *Curr Opin Clin Nutr Metab Care*. 2017;20:138–144.
113. van Rutte PW, Aarts EO, Smulders JF, et al. Nutrient deficiencies before and after sleeve gastrectomy. *Obes Surg*. 2014;24:1639–1646.
114. Wolf E, Utech M, Stehle P, et al. Preoperative micronutrient status in morbidly obese patients before undergoing bariatric surgery: results of a cross-sectional study. *Surg Obes Relat Dis*. 2015;11:1157–1163.
115. Boerlage TC, van Hees CL, Huitema AD, et al. Proton pump inhibitor prophylaxis after gastric bypass does not cause hypomagnesemia. *Obes Surg*. 2016;26:688–690.
116. de Lima KV, Costa MJ, Gonçalves Mda C, et al. Micronutrient deficiencies in the pre-bariatric surgery [article in English, Portuguese]. *Arq Bras Cir Dig*. 2013;26(suppl 1):63–66.
117. Sánchez-Larsen Á, Segura T, García-Muñozguren S, et al. Cerebral vasospasm and Wernicke encephalopathy secondary to adult cyclic vomiting syndrome: the role of magnesium. *BMC Neurol*. 2016;16:135.
118. Carrodeguas L, Kaidar-Person O, Szomstein S, et al. Preoperative thiamine deficiency in obese population undergoing laparoscopic bariatric surgery. *Surg Obes Relat Dis*. 2005;1:517–522; discussion 522.
119. Godo S, Yoshida Y, Fujita M, et al. The dramatic recovery of a patient with biguanide-associated severe lactic acidosis following thiamine supplementation. *Intern Med*. 2017;56:455–459.
120. Neale R, Reynolds TM, Saweirs W. Statin precipitated lactic acidosis? *J Clin Pathol*. 2004;57:989–990.
121. Ammouri W, Harmouche H, Alaoui M, et al. Gayet–Wernicke encephalopathy in non alcoholic patients: a serious complication. *J Rare Dis Res Treat*. 2016;1:59–63. https://www.rarediseasesjournal.com/articles/gayet-wernicke-encephalopathy-in-non-alcoholic-patients-a-serious-complication-rarediseases-1-1037.php. Accessed September 24, 2019.
122. Haytowitz DB, Ahuja JKC, Thomas R, et al. Composition of Foods Raw, Processed, Prepared. USDA National Nutrient Database for Standard Reference, Release 27. Beltsville, MD: US Department of Agriculture, Nutrient Data Laboratory; 2015. https://data.nal.usda.gov/dataset/composition-foods-raw-processed-prepared-usda-national-nutrient-database-standard-reference-release-27. Accessed July 8, 2019.