Thiamin in Clinical Practice

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Abstract
Thiamin is a water-soluble vitamin also known as vitamin B1. Its biologically active form, thiamin pyrophosphate (TPP), is a cofactor in macronutrient metabolism. In addition to its coenzyme roles, TPP plays a role in nerve structure and function as well as brain metabolism. Signs and symptoms of thiamin deficiency (TD) include lactic acidosis, peripheral neuropathy, ataxia, and ocular changes (e.g., nystagmus). More advanced symptoms include confabulation and memory loss and/or psychosis, resulting in Wernicke’s encephalopathy and/or Wernicke’s Korsakoff syndrome, respectively. The nutrition support clinician should be aware of patients who may be at risk for TD. Risk factors include those patients with malnutrition due to 1 or more nutrition-related etiologies: decreased nutrient intake, increased nutrient losses, or impaired nutrient absorption. Clinical scenarios such as unexplained heart failure or lactic acidosis, renal failure with dialysis, alcoholism, starvation, hyperemesis gravidarum, or bariatric surgery may increase the risk for TD. Patients who are critically ill and require nutrition support may also be at risk for TD, especially those who are given intravenous dextrose void of thiamin repletion. Furthermore, understanding thiamin’s role as a potential therapeutic agent for diabetes, some inborn errors of metabolism, and neurodegenerative diseases warrants further research. This tutorial describes the absorption, digestion, and metabolism of thiamin. Issues pertaining to thiamin in clinical practice will be described, and evidence-based practice suggestions for the prevention and treatment of TD will be discussed. (JPEN J Parenter Enteral Nutr. 2015;39:503-520)

Keywords
adult; life cycle; nutrition; nutrition assessment; vitamins; research and diseases

Digestion and Absorption
Thiamin (vitamin B1) is a water-soluble vitamin found in many food products including meat (with pork being the best source of thiamin), legumes, sunflower seeds, vegetables, and whole or enriched grain products.1 In plants, thiamin exists in its free form. In animal products, >95% of thiamin is found in its phosphorylated and biologically active form, thiamin pyrophosphate (TPP) (also known as thiamin diphosphate [TDP]).2 Absorption of thiamin from food is thought to be high; however, thiamin is rapidly destroyed in an alkaline environment with a pH >8 or with high temperatures. Furthermore, several food and beverages contain anti-thiamin factors, impairing thiamin absorption.1,3 For example, raw fish contains thiaminases, which catalyze the cleavage of thiamin, destroying its activity. However, these thiaminases are heat labile such that cooking fish renders the thiaminases inactive. Other anti-thiamin factors, which inactivate thiamin by an oxyreductive process, include polyhydroxyphenols. These polyhydroxyphenols are heat stable and include tannic and caffeic acids found in coffee, tea, betel nuts, blueberries, black currents, Brussels sprouts, and red cabbage.3 The destructive process of these compounds can be facilitated by the presence of divalent cations, calcium and magnesium, and can be prevented by reducing compounds such as vitamin C.

Thiamin absorption is most efficient in the upper jejunum and to a lesser amount in the duodenum and ileum.3 A progressively decreased absorption of thiamin in the more distal bowel has been described.3 Other investigators have shown that luminal bacteria synthesize thiamin in the colon; however, to the extent to which this contributes to whole-body thiamin status is yet to be determined.5 The degree of intestinal adaptation for
thiamin uptake is unknown; however, further investigation is warranted, especially as it pertains to individuals with shortened bowel lengths (e.g., post–bariatric surgery patients or patients with short-bowel syndrome). In a prospective cohort study, improved intestinal absorption due to adaptation and increased intestinal surface area over time after Roux-en-Y gastric bypass surgery has been theorized for the decreased incidence of vitamin deficiencies at 2-year follow-up. More studies are needed to explore the impact of intestinal adaptation as a means to improve thiamin uptake and nutriture.

Free, nonphosphorylated thiamin is absorbed into the intestinal mucosal cells. Once inside the mucosal cell, thiamin is often found in its phosphorylated form. However, since thiamin absorption across the mucosal cell needs to be in its dephosphorylated form, intestinal phosphatases hydrolyze the phosphates prior to absorption. The small intestine has a dual system of thiamin absorption. At low concentrations (<2 μM), absorption of the thiamin is an active, carrier-mediated, saturable process dependent on a sodium-dependent ATPase. The active transport mechanism is on the serosal side of the cell. At high concentrations (>2.5-mg dose for a human), absorption is via passive diffusion. Other studies have demonstrated that thiamin can be absorbed by sodium-independent carrier-mediated transport. Two thiamin protein transporters, ThTr1 and ThTr2, from the SLC19 gene family, have been characterized. Both of these carriers have been isolated from the basolateral membrane of the intestine, where thiamin transport occurs by a thiamin/H+ antiport system. Defects in the SLC gene coding for ThTr1 have been shown to cause TD.

Enteral absorption of thiamin is dependent on overall nutrition status as well as alcohol intake. Malnutrition can reduce intestinal thiamin absorption by ~70%, decreasing serum levels from 30%-90% below the lower level established for normal subjects. Moreover, alcohol alone can decrease absorption by 50% in one-third of patients who are not malnourished. Ethanol interferes with the sodium-dependent active transport mechanism of thiamin from the mucosal cell across the basolateral membrane but not the brush-border membrane.

Thomson et al reported that the maximum amount of oral thiamin absorbed was 4.77 mg per dose, reaching a plateau when 20 mg was administered to malnourished, alcoholic patients. However, these investigators used a maximum dose of only 50 mg, and conclusions were based on urinary thiamin excretion. In contrast, a recent study using healthy adults demonstrated that high blood concentrations of thiamin are rapidly achieved with doses of oral thiamin hydrochloride up to 1,500 mg.

**Distribution**

Thiamin in the blood is typically in its free form, found as the thiamin monophosphate (TMP) form. Thiamin transport into the red blood cell (erythrocyte) and/or white blood cell (leukocyte) occurs via facilitated diffusion. The erythrocytes and leukocytes contain approximately 90% of the total thiamin in whole blood, predominately in the form of TPP. When concentrations of the vitamin are low, transport into other tissues requires a sodium-dependent active transport mechanism, similar to enteric absorption. However, high concentrations of thiamin are absorbed into tissues by passive diffusion. The concentration of total thiamin (free thiamin plus its phosphate esters in whole blood) is 5–12 μg/dL.

A specific binding protein for thiamin, thiamin-binding protein (TBP), has been identified in rat serum, which is believed to be a specific, hormonally regulated carrier protein that is essential for the distribution of thiamin to critical tissues. Although the specific roles of TBPs in humans remains unclear, there is now growing evidence in favor of the existence of TBPs with specific roles in the nervous system, possibly in the regulation of neurotransmitter release.

Free thiamin or TMP can cross the cell membranes and can be found in extracellular fluids, plasma, and cerebrospinal fluid. Thiamin is transported into mammalian cells by specific transporters and immediately phosphorylated to its diphosphate form by cytosolic pyrophosphokinase. Following absorption from the gastrointestinal tract, most of the free thiamin is transported by the portal blood to the liver and phosphorylated to its active form, TPP. Within the cell, TPP can be phosphorylated by TDP kinase, to form thiamin triphosphate, or it can be transformed to ademylated derivatives. However, the most obvious fate for cytosolic-free TPP is hydrolysis to TMP, which requires the action of thiamin phosphatase. TMP can be recycled to free thiamin or can be excreted.

Thiamin concentrations are generally greatest in the heart (0.28–0.79 mg/100 g), kidneys (0.24–0.58 mg/100 g), liver (0.20–0.76 mg/100 g), and brain (0.14–0.44 mg/100 g), with brain concentrations retained the longest. There is no appreciable storage of thiamin in any tissue; the half-life of thiamin in humans has been estimated to be 9.5–18.5 days. The average total thiamin storage in a healthy adult is approximately 0.11 mmol (30 mg), with 40% stored in the muscle tissues. The limited total pool of thiamin coupled by its short half-life and constant requirement for use in metabolic processes results in the need for consistent thiamin intake.

**Metabolism**

Thiamin plays essential coenzyme and non-coenzyme roles in the body, specifically in energy transformation, synthesis of pentoses and nicotinamide adenine dinucleotide phosphate (NADPH), and membrane and nerve conduction. In energy transformation, thiamin is a cofactor for several enzymes involved in decarboxylation reactions (removal of carboxyl groups or carbon dioxide) and dehydrogenation reactions (removal of hydroxyl groups; Figure 1). TPP serves as a cofactor for several enzymes playing a role in oxidative and non-oxidative carbohydrate metabolism. In oxidative metabolism, TPP is required for the mitochondrial multienzyme complex pyruvate dehydrogenase (PDH), responsible for the conversion of...
Figure 1. Enzymes in which thiamin serves as a cofactor in carbohydrate metabolism. Acetyl CoA, acetyl coenzyme A; NAD+, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; NADP+, oxidized nicotinamide adenine dinucleotide-phosphate; NADPH, reduced nicotinamide adenine dinucleotide-phosphate; TPP, thiamin pyrophosphate.

(1) Pyruvate dehydrogenase complex. (2) α-Ketoglutarate dehydrogenase (α-KGDH) complex. (3) Transketolase. In thiamin deficiency, pyruvate will convert to lactate and α-ketoglutarate will convert to glutamate (depicted as heavy-weighted arrows). Data from Gropper et al.3

Pyruvate to acetyl coenzyme A (ACoA). Three enzymes make up the PDH complex: a TPP-dependent pyruvate decarboxylase, a lipoic acid–dependent dihydrolipoyl transacetylase, and an FAD (riboflavin)–dependent dihydrolipoyl dehydrogenase. The action of PDH requires the roles of 4 vitamins, including thiamin (vitamin B₁), riboflavin (vitamin B₂), niacin (vitamin B₃), and pantothenic acid (vitamin B₅). Magnesium and adenosine triphosphate (ATP) are also required. Therefore, one possible sign of TD may be lactic acidosis due to the inability of pyruvate to enter the mitochondria and undergo aerobic metabolism where ACoA initiates its oxidation through the Krebs cycle.

Within oxidative metabolism, TPP is also needed as a cofactor for the mitochondrial enzyme α-ketoglutarate dehydrogenase (α-KGDH), responsible for converting α-ketoglutarate (α-KG) to succinyl coenzyme A within the Krebs cycle. The action of this enzyme also requires niacin (as NAD) and pantothenic acid (as coenzyme A). Therefore, an accumulation of α-KG may also be a diagnostic indicator of TD. However, the Krebs cycle may continue despite impaired α-KGDH activity by bypassing the step through glutamate and γ-aminobutyric acid (GABA) metabolism, which can constitute 10% of the Krebs cycle’s activity.

Muscle and extrahepatic tissues possess branched-chain aminotransferases both in the cytoplasm and in the mitochondria. These transaminases are needed for the transamination of the branched-chain amino acids (BCAAs): valine, isoleucine, and leucine. Following transamination, the α-keto acids of the BCAAs may remain within the muscle for further oxidation or may be transported by albumin in the blood to other tissues, mainly the liver. Decarboxylation of the α-keto acids is an irreversible reaction and carried out by the enzyme complex branched-chain α-keto acid dehydrogenase (BCKAD). This enzyme complex is similar to the PDH complex and requires the roles of several nutrients including thiamin, niacin, magnesium, and pantothenic acid. A genetic defect diminishing the BCKAD enzyme complex activity, known as branched-chain ketoaciduria or maple syrup urine disease (MSUD), causes both the BCAAs and their respective α-keto acids to accumulate in the blood and other body fluids.

In non-oxidative carbohydrate metabolism, TPP is a coenzyme for the transketolase reaction, found within the pentose phosphate pathway (also known as the hexose monophosphate shunt). This pathway is where sugars of varying length are
interconverted and is essential for the generation of pentoses (5-carbon-length sugars) for nucleic acid synthesis and NADPH for the synthesis of fatty acids, maintenance of myelin sheaths, nerve membrane function, and transmission. Furthermore, NADPH is required to reduce glutathione in order to maintain the normal structure of red blood cells and maintain hemoglobin in the ferrous state.

In addition to its coenzyme roles, TPP plays a role in nerve structure and function as well as brain metabolism.2,3,17,19

**Brain Metabolism**

Thiamin has been identified in mammalian brain, in synapticomembranes, and in cholinergic nerves.2 In nerve function, protective effects of thiamin have been described. Thiamin protects retinal neurons against glutamate toxicity23 and promotes the survival of hippocampal neurons in high-cell-density cultures.24 Thiamin’s role in nerve transmission may be 2-fold: thiamin may act as an excitatory neurotransmitter when produced by neurons and/or some of its phosphate esters facilitates neurotransmission, probably by potentiation of the release of the neurotransmitters acetylcholine,25,26 dopamine,27 and norepinephrine.26

Brain pathophysiology related to TD may be due to thiamin’s non-coenzyme roles within nerve structure and function or impaired coenzyme roles needed for PDH and α-KGDH.17,19 It remains unclear whether thiamin’s coenzyme role in transketolase is important in brain metabolism.7 Other investigators have reported that transketolase, present in myelinated neurons, is responsible for maintaining myelin sheaths.28 The aberrations in nerve function observed in TD may therefore be due to a lack of energy, a decreased amount of acetylcholine, and/or a reduction in nerve impulse transmission.19,29,36

The major consequence of TD is focal cerebral vulnerability.17,19,30 Neuropathologic evaluation of brain tissue from patients with Wernicke’s encephalopathy (WE) show a clear pattern of selective damage to the subcortical areas of the brain that includes the thalamus and mammillary bodies, the midbrain inferior colliculus, and brainstem structures including the vestibular nuclei and olivary complex.29 The exact cause of the regionally and cellular distinctive pattern of neurodegeneration remains unclear.19

In TD, decreased thiamin-dependent α-KGDH activity from cellular carbohydrate metabolism can increase the potential for α–KG to cross the blood-brain barrier (BBB).3 Once inside the brain, or from brain oxidative metabolism itself, decreased activities of α-KGDH will increase the likelihood that α-KG will convert to glutamate through reductive amination, using the vitamin B6-dependent enzyme, glutamate synthase.5,19 Glutamate acts as an excitatory neurotransmitter.2,3,19,25 Glutamate may be further metabolized to GABA through the action of the vitamin B6-dependent enzyme, glutamate decarboxylase.3 GABA is an inhibitory neurotransmitter and is believed to be the neurotransmitter to exert an inhibitory effect on other cells of the central nervous system.2,3,19 TD may promote an increased conversion of α-KG to glutamate and GABA, causing increased neural inhibition.19 Glutamate can also be converted to glutamine through the enzymatic activity of glutamine synthase, which is highly active in neural tissues.2 Glutamine, formed whenever excessive ammonia is present in the brain, is involved in the glutamate-glutamine cycle within the astrocyte.

Decreased activities of brain α-KGDH have been reported among patients with TD19,29,31 Moreover, decreased activities of α-KGDH may result in compromised brain energy metabolism and in lactate accumulation in the brain, both of which can contribute to the decrease energy status in affected areas of the brain, resulting in irreversible neuronal cell death.30–32

Increased production of brain levels of reactive oxygen species has been reported in TD patients.33–38 Furthermore, oxidative stress is related to the pathology in human WE.19 Markers of oxidative stress include increased neuronal peroxidase activity;23 up-regulation of proinflammatory cytokines including tumor necrosis factor–α, interleukin-18 (IL-18), and IL-619,34; increased expression of heme oxygenase (HO-1) and intercellular adhesion molecule 1 (ICAM-1)35; as well as microglial activation.36 TD has been shown to selectively induce neuronal expression of the chemokine monocyte chemoattractant protein-1 (MCP-1) in the submedial thalamus nucleus prior to microglial activation and neurodegeneration.36 Interestingly, both reductions in α-KGDH activity and microglia activation have been described in Alzheimer’s disease,34–38 ischemic brain injury,38 and Wernicke’s Korsakoff syndrome (WKS).32

Nitric oxide (NO) has been implicated in playing a role in the selective vulnerability in thalamic structures resulting from TD.19,37–39 NO is an inorganic free radical gas that vascular endothelial cells are able to synthesize from L-arginine as a transcellular signal.40 The enzymes responsible for the synthesis of NO from L-arginine in mammalian tissues are known as NO synthases (NOS). Three different isoenzymes for NOS exist: neuronal NOS (nNOS), originally identified as constitutive in neuronal tissue (also known as type I NOS); endothelial NOS, originally identified as constitutive in vascular endothelial cells (also known as type III NOS); and inducible NOS (iNOS), originally identified as being inducible by cytokines in macrophages and hepatocytes (also known as type II NOS).41 Other investigators maintain that an additional NOS has been identified in mitochondria.42 The physiological settings in which these isoenzymes operate are different such that eNOS synthesizes NO in vascular endothelial cells in response to acetylcholine, nNOS synthesizes NO in neurons in response to glutamate, and iNOS synthesizes NO in macrophages following its induction by cytokines or inflammation.34 NO can be found in almost all the tissues of the body and can even coexist in the same tissue. NO is a well-known vasorelaxant agent, but it works as a neurotransmitter when produced by neurons and is also involved in defense functions when it is produced by immune and glial cells.42
In TD, increased expression and activity of iNOS, leading to increased nitrotyrosine immunoreactivity in vulnerable regions in the brain, have been described. Vascular factors contribute to oxidative damage to neurons, including increased eNOS expression, accounting for selective damage to the thalamic structures. NO can react with the superoxide radical (O2·−) to form peroxynitrite (ONOO−), which is toxic to neurons. Moreover, NO has the ability to disrupt the BBB and to exert an inhibitory effect on the activities of α-KGDH and cytochrome C oxidase in isolated mitochondria and neuronal preparations. Therefore, it is likely that NO and peroxynitrite-mediated mitochondrial dysfunction and damage play a role in the pathogenesis in TD-related neuronal cell loss.

In WE, cerebral edema is shown from antemortem brain tissue using magnetic resonance imaging (MRI) with signal hyperintensities in foci areas of damage reflecting increased water content. However, the reversibility of such MRI hyperintensities on computed tomography following thiamin administration suggests that cerebral edema may be an important underlying factor in many of the neurologic abnormalities occurring in thiamin-deficient patients. Although the causal mechanism of brain edema is unclear, disruption of the BBB may be to blame. Furthermore, since lactic acidosis is a major consequence of TD, astrocyte lactate production most likely leads to cytotoxic edema. Such astrocyte swelling also plays a role in glutamate-mediated excitotoxicity since previous studies have established that swelling of these cells results in the release of glutamate. Overstimulation of neurons by glutamate results in a rise in extracellular K+ that may also contribute to sustained deplorization, further contributing to swelling and excitotoxic-mediated damage.

Increased brain inflammation, as evidenced by increased proinflammatory cytokines, chemokines, interferons, and interferon-inducible proteins, as well as up-regulated inflammatory gene expression, is shown in TD. Of note, cerebral inflammation is now recognized as a key component of several neurologic diseases including stroke, multiple sclerosis, Alzheimer’s disease, and brain trauma. A thorough review by Hazell and Butterworth describes the major contributors to the brain pathophysiology associated with TD including oxidative stress, glutamate-mediated excitotoxicity, and inflammation. Further reading is encouraged for a more detailed explanation. Figure 2 summarizes the impact of TD on mitochondrial dysfunction and cell death from impaired oxidative metabolism, inflammation, and neuroexcitotoxicity.

**Excretion**

Free thiamin, TPP, and TMP in excess of tissue needs are excreted intact or catabolized for urinary excretion. Thiamin losses are significantly increased, up to 2 times baseline, by loop diuretics such as furosemide. Moreover, diuretic administration in rats showed that the single significant predictor,

**Figure 2.** Thiamin deficiency–induced neuroexcitotoxicity, reactive oxygen species, lipid peroxidation, and cell death. α-KGDH, α-ketoglutarate dehydrogenase; eNOS, epithelial nitric oxide synthase, NO, nitric oxide; ONOO−, peroxynitrate; PDH, pyruvate dehydrogenase.

**Daily Requirement**

The dietary reference intakes for thiamin for most age groups are listed as the recommended dietary allowance (RDA). According to the Institute of Medicine, “the RDA is the average daily dietary intake level; sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals in a group and is calculated from an Estimated Average Requirement (EAR).” The RDA for thiamin depends on age. Children 1–3 years, 4–8 years, 9–13 years, and 14–18 years, respectively, have a thiamin requirement of 0.5 mg/d, 0.6 mg/d, 0.9 mg/d, and 1–1.2 mg/d, respectively. The RDA for adult men, adult women, and women during pregnancy and lactation is 1.1, 1.2, and 1.4 mg/d, respectively. Adult thiamin recommendations of 0.5 mg per 1,000 kcals have also been cited.

**Toxicity**

According to the Institute of Medicine, there is no determined tolerable upper intake level for thiamin. Oral doses of large amounts (500 mg daily) for >1 month failed to elicit any adverse effects. Wrenn et al prospectively evaluated the safety of thiamin hydrochloride given as a 100-mg intravenous (IV) bolus in 989 consecutive patients (1,070 doses) and reported a total of 12 adverse reactions (1.1%). Minor reactions consisting of transient local irritation were seen in 11

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plasma thiamin, presumably by interfering with the absorption of the vitamin; thus, thiamin is included in multivitamin therapy designed for dialysis patients.58 In contrast, serum thiamin is increased among patients with acute hepatic injury.59

**Table 1. Laboratory Assessment of Thiamin Status.**

<table>
<thead>
<tr>
<th>Assessment Tool</th>
<th>Interpretation</th>
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<tr>
<td>Plasma or serum levels</td>
<td>Decreased</td>
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<tr>
<td>Erythrocyte transketolase activity (ETKA)</td>
<td>Decreased</td>
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<tr>
<td>Whole-blood (erythrocyte) thiamin levels</td>
<td>Decreased</td>
</tr>
<tr>
<td>Whole-blood (erythrocyte) thiamin pyrophosphate (TPP) levels</td>
<td>Decreased</td>
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<tr>
<td>TPP stimulation or TPP activity coefficient</td>
<td>Increased</td>
</tr>
<tr>
<td>Serum pyruvate, lactate, or α-ketoglutarate</td>
<td>Increased</td>
</tr>
<tr>
<td>Urinary thiamin levels</td>
<td>Decreased</td>
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patients (1.02%), and there was only 1 major reaction (0.093%) consisting of generalized pruritus.52 Therefore, patient-centered treatment should be individualized based on severity of TD and availability of repletion options. In a retrospective survey, Wrenn et al53 identified no cases of significant adverse reactions to thiamin in >300,000 treatments. Physiologic doses of thiamin given IV or intramuscularly (IM) have resulted in headaches, convulsions, cardiac arrhythmias, anaphylactic shock, and other signs and symptoms.1-3,21 Administration of IV therapy should be provided slowly over 30 minutes to minimize the risk of anaphylaxis.21,53,54

**Assessment**

Thiamin assessment prior to repletion may be used to confirm a suspected deficiency. However, since serious and potentially irreversible neurologic damage can occur with untreated TD, practitioners should treat the patient without laboratory confirmation of deficiency and monitor and evaluate resolution of signs and symptoms. Furthermore, in the acute care setting, reliable laboratory tests may not be available, may be too costly, and may be impractical because of a long turnaround time. Thiamin status can be determined by plasma or serum measurement or assessed in whole blood. Furthermore, the functional status of the vitamin can be evaluated by measuring the activity of TPP. Details of these measurements are described below. Table 1 summarizes these laboratory assessment options and the overall impact on thiamin status if TD is present.

**Plasma or Serum Measurement**

Thiamin can be measured in the blood (plasma, serum); however, <10% of blood thiamin is contained in the plasma, and assessment of thiamin in the serum or plasma suffers from low specificity and sensitivity.16 In addition, certain disease states can influence serum or plasma levels of the vitamin. Serum thiamin is transiently decreased in critically ill patients with sepsis,55,56 after coronary artery bypass graft surgery,57 and after trauma.56 Renal replacement therapies can also significantly decrease plasma thiamin, presumably by interfering with absorption of the vitamin; thus, thiamin is included in transketolase enzyme.60 The erythrocyte transketolase test requires a sample of hemolyzed blood to be incubated with excess ribose 5-phosphate (or xylulose 5-phosphate), in the presence of excess added TPP (matched with a control that has no added TPP). After the incubation period, the amount of substrate remaining and the amount of product formed are quantified. These concentrations are measured by using high-performance liquid chromatography (HPLC) and an ultraviolet absorbance detector. In cases of TD, the enzyme increases activity with the addition of thiamin to the incubation medium.1 The extent of deficiency in thiamin is expressed in percentage stimulation over the control value. An increase in ETKA of >25% indicates that patients are at high risk of TD, increases between 16% and 25% indicates that patients are at moderate risk of TD, and activity coefficients ≤15% suggest adequate thiamin status.3,16 Transketolase concentrations of <120 nmol/L have also been used to indicate deficiency, while concentrations of 120–150 nmol/L suggest marginal thiamin status.3

The ETKA assay is a functional test rather than a direct measurement of thiamin status and therefore may be influenced by factors other than TD.16,60 These include loss of reactivatable apoenzyme during chronic deficiency in vivo,51,62 altered binding of apoenzyme and coenzyme because of the presence of isoenzymes of transketolase,63 and reduced synthesis of apoenzyme in patients with diabetes mellitus, polynu- teritis,64 and malnourished alcoholics with cirrhosis.16 In contrast, patients with pernicious anemia have been shown to present with significantly elevated ETKA values.64 Other factors that have reduced the usefulness of the transketolase assays have been the relatively poor interassay precision of the assay, difficulty with standardization, and sample storage instability because of rapid inactivation of the transketolase enzyme.61 These factors contribute to the lack of agreement over the upper limit of the reference range for the activation assay, with values ranging from 15.5% to 40%.65,66

**TPP Measurement**

Studies by Warnock et al67 and Baines and Davies68 have suggested that direct measurement of erythrocyte TPP concentrations is a more sensitive index of thiamin status than the indirect measurement of ETKA. Moreover, the use of HPLC for the direct determination of TPP has clear advantages in terms of sensitivity, specificity, precision, and robustness.16 According to these researchers, whole-blood testing is superior to serum or plasma assessment of the vitamin because
approximately 90% of the total thiamin content of whole blood is found as the biologically active form, TPP. The expected concentration of TPP in whole blood is 70–180 nmol/L. The HPLC assay has an acceptable between-batch precision, and because of the availability of pure TPP, the assay is easy to standardize. More importantly, these investigators found that samples stored at −70°C were stable for TPP for at least 7 months and TPP was stable in whole blood for 48 hours at room temperature.

Talwar et al found that erythrocyte TPP concentrations measured by HPLC compared well with the ETKA assay when assessing patients with suspected TD. Clinical assessments showed that the 2 methods agreed in 58 of the 63 patients in patients on hemodialysis for chronic renal failure. These researchers also reported that the TPP assay had the advantage over the ETKA assay for detecting tissue thiamin accumulation. Moreover, these investigators reported that because TPP is present predominately in erythrocytes, TPP concentrations showed good agreement when corrected for hemoglobin. Therefore, whole-blood analysis is appropriate if also accompanied by hemoglobin estimation to correct for any cell volume variability.

Other Assessment Tools for Thiamin

Measurement of thiamin status can also be determined by urinary thiamin excretion. Urinary thiamin excretion decreases with decreased thiamin status and also correlates with dietary intakes. Urinary thiamin excretion <40 µg or <27 µg/g creatinine suggests TD. Accumulation of pyruvate and/or lactate in the blood has been used to assess thiamin status; however, these measurements are limited by a lack of specificity and technical difficulty. In addition, increased serum lactic acid concentrations in critically ill patients may be confused with lactic acid production from sepsis or inadequate perfusion, and therefore, TD should be suspected in cases of metabolic acidosis driven by hyperlactemia.

Computed axial tomography or MRI can be done to search for central nervous system morphology for patients with suspected WE. A recent study of MRI of the brain in patients with WE showed hyperintensities in typical (thalamus, mammillary bodies, tectal plate, and periaqueductal area) and atypical areas (cerebellum, cranial nerve nuclei, and cerebral cortex). These authors suggest that MRI is the most important and effective tool in the diagnostic assessment of WE.

Deficiency: Signs and Symptoms

Low concentrations of the vitamin do not always result in clinical manifestations. Moreover, there is not a specific threshold of serum or red blood cell thiamin that indicates when an individual will develop symptoms of TD. Therefore, the clinician should be skilled at detecting physical signs and symptoms of TD, often affecting various organ systems, including the heart, gastrointestinal tract, and peripheral and central nervous systems. Dry beriberi, devoid of edema, is identified by neurologic symptomology. These include brisk tendon reflexes, peripheral neuropathy, and/or polyneuritis with or without parasthesias, muscle weakness and/or pain of upper and lower extremities, gait ataxia, and/or convulsions. High-output cardiac or wet beriberi: Heart failure with high cardiac output, edema in the lower extremities, tachycardia or bradycardia, lactic acidosis, dyspnea, heart hypertrophy and dilatation (particularly of the right ventricle), respiratory distress, systemic venous hypertension, and/or bounding arterial pulsations. Gastroenterologic: Slow gastric emptying, nausea, vomiting, jejunal dilatation or megacolon, and/or constipation. Neuropsychiatric (eg, Wernicke’s encephalopathy): polyneuropathy and ataxia, ocular changes (ophthalmoplegia and nystagmus), mental confusion (confabulation), short-term memory loss; if psychosis and/or hallucinations are present, the condition is often referred to as Korsakoff psychosis and/or Wernicke-Korsakoff syndrome.

Table 2. Signs and Symptoms of Thiamin Deficiency.

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<th>Stage</th>
<th>Symptoms</th>
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<tr>
<td>Early symptoms</td>
<td>Neurologic or dry beriberi (devoid of edema): Brisk tendon reflexes, peripheral neuropathy and/or polyneuritis with or without parasthesias, muscle weakness and/or pain of upper and lower extremities, gait ataxia, and/or convulsions</td>
</tr>
<tr>
<td>Advanced symptoms</td>
<td>High-output cardiac or wet beriberi: Heart failure with high cardiac output, edema in the lower extremities, tachycardia or bradycardia, lactic acidosis, dyspnea, heart hypertrophy and dilatation (particularly of the right ventricle), respiratory distress, systemic venous hypertension, and/or bounding arterial pulsations</td>
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Table 2 summarizes the signs and symptoms of TD.
At-Risk Patient Populations

The nutrition support clinician should be aware of patients who may be at risk for TD. Risk factors of TD include those patients with malnutrition due to 1 or more nutrition-related etiologies: decreased nutrient intake, increased nutrient losses, or impaired nutrient absorption. TD should be suspected in different clinical scenarios such as severe sepsis, burns, unexplained heart failure or lactic acidosis, neurologic disorder in patients with previous history of alcoholism, starvation, chronic long-term parenteral feeding, hyperemesis gravidarum, or bariatric surgery.56 TD may be part of a constellation of polyvitamin deficiencies; thus, nutrition interventions must consider the metabolic derangements peculiar to multiple underlying disease processes and associated complications.

The highest prevalence of WE has been documented among patients with alcoholism.12,13,21,32,75-78 Other clinical settings with a high prevalence of WE include malignant disease, gastrointestinal disease and surgery, and vomiting due to hyperemesis gravidarum.76 Other causes of WE include fasting, starvation, malnutrition, and the use of unbalanced diets. The nutrition support clinician should be aware of the characteristics to identify adult malnutrition79 and recognize the signs and symptoms of TD (see Table 2).

Vulnerable, at-risk populations should be identified by a thorough history and physical examination.79-81 Identification of TD should include a thorough nutrition assessment, nutrition-focused physical assessment, and, if available, biochemical evaluation.81 Therapy for patients with suspected TD should occur without waiting for laboratory confirmation of deficiency. The goal of therapy should be to replete thiamin status, reverse symptoms of deficiency, and prevent irreversible neurologic damage. Treatment suggestions for the at-risk populations will be further discussed below.

Patients With Alcoholism

In 1881, Carl Wernicke was the first to report 3 patients presenting with a disorder characterized by ataxia, ophthalmoplegia, and mental changes. This disorder was given the name Wernicke’s encephalopathy (WE).76 It was discovered that WE was caused by TD. Later, the neuropsychiatric disorder WKS was identified, characterized by ophthalmoplegia, gait ataxia, and confusion/memory loss and psychosis.12,13,21,32,73-78

As stated, alcohol abuse is the most common cause of WE and WKS.12,13,21 The prevalence of WE in chronic alcoholics has been reported to be approximately 35%, compared with approximately 1.5% in the population as a whole.75 However, other investigators have reported the prevalence of WE among chronic alcoholics to be as high as 80%.12 Malnutrition is common due to replacement of nutrient-dense foods with alcohol intake. In addition, liver cirrhosis, a consequence of alcoholism, results in impaired hepatic thiamin storage.18,59

When an individual is suspected of alcohol abuse, most hospitals follow the Clinical Institute Withdrawal for Alcohol (CIWA) protocol, a validated assessment tool to guide benzodiazepine dosing in alcohol withdrawal.82 Thiamin-repletion protocols both in the emergency department and in the inpatient setting are generally applied.18 The traditional dosing regimen used in the United States is 100 mg IV thiamin for 3–5 days.18 Historically, the 100 mg thiamin dose was chosen arbitrarily in the 1950s based on an estimate of what would constitute a “high dose.” However, postmortem studies have reported that at-risk patients for TD are underrecognized, WE is severely underdiagnosed, and thiamin repletion protocols are often inadequate.83 With more recent pharmacokinetic data,7 and the fact that the half-life of thiamin is <2 hours,18 the practitioner should keep in mind that at-risk patients may require higher thiamin doses 2–4 times daily to achieve clinical benefit. Several case reports have been published of patients who had persistent neurologic symptoms with standard doses of thiamin administration; however, recovery ensued after very large thiamin doses (500–1000 mg) for an extended period of time (up to 2 months).10,84

According to The Royal College of Physicians from the United Kingdom, the usual dose of thiamin required to prevent or treat WE in most alcoholic patients is believed to be >500 mg once or twice daily, given parenterally for 3–5 days.21,75,77 However, this estimate is based on data from uncontrolled trials and from clinical practice.21 These authors conclude that oral thiamin is poorly absorbed and is ineffective in both the prophylaxis and treatment of WE in patients with alcoholism.

For the treatment of suspected or confirmed WE, the European Federation of Neurological Societies (EFNS) guidelines recommend 200 mg thiamin be given IV 3 times daily, before any carbohydrate.78 These authors also recommend sampling total thiamin in blood measured immediately before its administration. An MRI to support the diagnosis of acute WE in both alcoholics and nonalcoholics is recommended, and an autopsy should be used to confirm the diagnosis of WE postmortem.

Ambrose et al85 conducted a randomized double-blind multidosage study examining the therapeutic benefits of thiamin in an alcoholic-dependent sample without clinically apparent WE and found that an intramuscular dose of ≥200 mg of thiamin may be required to show improvement in this group compared with a dose of ≤100 mg. However, according to the EFNS, thiamin should be given by the IV instead of IM route.78 Therefore, there is debate on the best thiamin repletion protocol for the alcoholic patient. However, there is agreement across studies that high, frequent doses of thiamin either via the IV or IM routes are more effective than oral supplementation.

Post–Bariatric Surgery Patients

Postoperative bariatric surgery patients are at increased risk for TD for many reasons, including restriction of nutrient intake and noncompliance with vitamin and mineral supplementation.54,81 Furthermore, combination restrictive/maalbsorptive bariatric surgeries, such as the Roux-en-Y gastric bypass, puts
patients at risk for TD because of the bypassing of the duodenum and jejunum, preferred absorption sites of the vitamin. Moreover, malabsorptive surgeries such as the duodenal switch results in a high prevalence of TD. Lakhani et al reported that 49% of 80 post–gastric bypass patients had TPP levels less than the lower limit of the reference range with concomitantly high folate levels, which was due to SBBO, also known as small intestinal bacterial overgrowth.

Several reviews and studies on “bariatric beriberi” and neurologic complications following bariatric surgery have been published. In a nonrandomized controlled study, Thaisetthawatkul et al evaluated the frequency of peripheral neuropathy in post–bariatric surgery patients compared with age- and gender-matched controls of obese patients undergoing cholecystectomy. Of the 435 patients who had bariatric surgery, 71 (16%) developed peripheral neuropathy. Patients undergoing bariatric surgery experienced significantly greater peripheral neuropathy compared with patients undergoing cholecystectomy (P < .001).

Risk factors associated with peripheral neuropathy included rate and absolute amount of weight loss, prolonged gastrointestinal symptoms, not attending a nutrition clinic after surgery, and reduced serum albumin and transferrin.

Several systematic reviews regarding the risk of WE among patients after bariatric surgery have been published. In a recent review, Kumar has suggested that WE due to TD is an early complication of bariatric surgery compared with late complications such as myelopathy or myeloneuropathy due to vitamin B12 or copper deficiency. In a recent systematic review of 255 published cases of either post–bariatric surgery beriberi or WKS, women and patients of increased age presented with greater risk. These authors reported that most patients developed symptoms of a dry beriberi with peripheral neuritis, ataxia, and paraplegia, indicating an advanced stage of disease approximately 4–12 weeks postoperatively.

Clinical practice guidelines (CPGs) for the assessment and care of bariatric surgery patients have been previously described. An update of 2008 nutrition guidelines from the American Society of Metabolic and Bariatric Surgery is currently under review (unpublished data). Mechanick et al recommended screening for thiamin and/or supplementing with thiamin in post–bariatric surgery patients who present with the following risk factors: rapid weight loss, protracted vomiting, parenteral nutrition (PN), excessive alcohol use, neuropathy, encephalopathy, or heart failure. However, other investigators urge that bariatric surgery patients should benefit from careful nutrition follow-up with routine monitoring of micronutrients at 6 weeks and at 3, 6, and 12 months postoperatively and then annually after surgery as well as multivitamin supplementation for life. According to a recent systematic review, immediate substitution of thiamin in clinical suspicion or prolonged PN is necessary to minimize the risk of severe consequences among at-risk bariatric surgery patients. Therefore, multidisciplinary knowledge on the development of TD, including the symptomatology, and emergency treatment, are essential.

**Oral Thiamin Supplementation**

Patients who are seen on an outpatient basis or who do not have IV access may be treated with oral thiamin supplementation. Previous CPGs suggested that early symptoms of neuropathy may be resolved by providing the patient with oral thiamin doses of 20–30 mg/d until symptoms disappear. Other authors recommend 100 mg oral thiamin two to three times per day until symptoms resolve. However, oral thiamin therapy may be inadequate to treat symptomatic patients, and data are lacking in bariatric surgery patients where thiamin absorption may be impaired because of altered gastrointestinal structure and function. In recalcitrant or recurrent cases of TD without one of the classic risk factors, the addition of antibiotics for suspected SBBO should be considered.

**IV Thiamin Supplementation**

IV therapy should be considered as an inpatient approach. For patients presenting with mild deficiency symptomology and who have access to IV therapy, Mechanick et al recommended that patients receive 100 mg IV thiamin for 7–14 days. These guidelines are somewhat modified from previous nutrition practice guidelines recommending parenteral treatment in patients after bariatric surgery with hyperemesis of 100 mg/d for first 7 days followed by daily oral doses of 50 mg/d until complete recovery.

For bariatric surgery patients with suspected or established severe TD (eg, Wernicke’s syndrome), there has been discrepancy between the 2 CPGs. Aills et al suggested that patients with WE or WKS generally require ≥100 mg thiamin administered IV for several days or longer, followed by IM thiamin or high oral doses until symptoms have resolved or significantly improved. Other investigators have suggested that bariatric surgery patients presenting with WE should receive a minimum of 250 mg daily given parenterally or IM for at least 3–5 days. In contrast, Mechanick et al recommended 500 mg/d of parenteral thiamin for 3–5 days followed by 250 mg/d for 3–5 days or until resolutions of symptoms and then to consider treatment with 100 mg/d orally, usually indefinitely or until risk factors have been resolved. These guidelines are similar to those recommended by the Royal College of Physicians for the treatment of WE among alcoholic patients. Therefore, research is needed to better understand whether guidelines for alcoholic patients are sufficient for the bariatric surgery patient with WE.

The EFNS guidelines for the diagnosis, therapy, and prevention of WE included specific recommendations for bariatric surgery patients: follow-up of thiamin status for at least 6 months and parenteral thiamin supplementation of 200 mg 3 times daily, before any carbohydrate alone is given, among patients presenting with 2 of the following 4 signs: (1) dietary deficiencies, (2) eye signs, (3) cerebellar dysfunction, and (4) either an altered mental state or mild memory impairment.
**IM Thiamin Supplementation**

Use of the IM route for thiamin repletion should be limited to patients without IV access in emergent situations. Moreover, it may be impractical to treat patients IM as most hospitals do not use the IM route for repletion but rather either oral or parenteral routes. In the bariatric surgery patient presenting with WE, Bal et al. recommended 250 mg of thiamin given IM for 3–5 days. These recommendations were previously written for the patient with alcoholism. To date, no studies have examined the therapeutic benefits of IM thiamin in bariatric surgery patients. Hence, further research is needed to confirm whether the treatment regimen recommended for alcoholic patients should apply to the post–bariatric surgery patient.

**Nutrient-Nutrient Interactions**

Magnesium is an essential cofactor for TPP metabolism; therefore, serum magnesium concentrations must be normalized and monitored when treating patients with TD. Simultaneous therapeutic doses of other B vitamins including vitamin B6 and vitamin B12 at doses of 100 mg and 1000 mg, respectively, may also be of benefit to the bariatric surgery patient. The Royal College of Physician’s management of WE recommends that per 250-mg thiamin dose (eg, 1 ampule), there should be the addition of 4 mg riboflavin (vitamin B2), 50 mg pyridoxine (vitamin B6), 160 mg nicotinamide (vitamin B3), 500 mg vitamin C, 10–30 mEq magnesium, 60–180 mEq potassium, and 10–40 mmol/l phosphate daily. Therapy should be initiated urgently, as late interventions may put the patient at risk for long-term damage and irreversible sequelae.

**Patients With Cardiac Failure**

The prevalence of TD in heart failure patients ranges from 21% to 98%. In a prospective study, Zenek et al. examined 32 patients receiving either 40 mg/d or ≥80 mg/d of furosemide diuretic therapy. Biochemical evidence of severe TD was found in 98% (24 of 25) of patients receiving at least 80 mg/d of furosemide and in 57% (4 of 7) patients taking 40 mg furosemide daily. Other investigators have found a statistically higher prevalence of TD in patients with congestive heart failure (CHF) taking diuretics compared with controls (33% vs 12%, P = .007). In these patients, TD was related to urine thiamin losses (P = .03), nonuse of thiamin-containing supplements (P = .06), and preserved renal function (P = .05).

Patients with CHF may be at increased risk for TD as a result of diuretic-induced urine thiamin excretion, disease severity, malnutrition, and advanced age. Moreover, high output cardiac or wet beriberi manifests as CHF. Therefore, the clinician should rule out TD among heart failure patients.

DiNicolantonio et al. conducted a systematic review of the literature and meta-analysis of randomized, double-blind, placebo-controlled trials to examine the effects of thiamin on cardiac function in patients with systolic heart failure. These investigators combined the results from 2 randomized, placebo-controlled studies (n = 38) to conclude that thiamin supplementation compared with placebo significantly improved the net change in left ventricular ejection fraction (LVEF). These 2 studies are described below.

Shimon et al. examined the effect of thiamin repletion on thiamin status, functional capacity, and LVEF in patients with moderate to severe CHF who had received furosemide in doses of 80 mg/d or more for at least 3 months. Thirty patients were randomized to 1 week of inpatient therapy with either 200 mg/d IV thiamin or placebo (n = 15 each). Following discharge, all 30 patients received 200 mg/d oral thiamin on an outpatient basis for 6 weeks. Thiamin status was determined by the erythrocyte thiamin-pyrophosphate effect (TPPE). LVEF was determined by echocardiography. In patients receiving IV thiamin, TPPE decreased (11.7% ± 6.5% to 5.4% ± 3.2%; P < .01) and LVEF increased (0.28 ± 0.11 to 0.32 ± 0.09; P < .05).

In a randomized, double-blind, placebo-controlled, crossover pilot study, Schoenenberger et al. examined the effects of thiamin supplementation in 9 patients with symptomatic chronic heart failure. Patients (mean age, 56.7 ± 9.2 years; range, 44.9–75.4 years) receiving diuretic treatment for symptomatic chronic heart failure and an LVEF <40% were randomly assigned to receive oral thiamin (300 mg/d) or placebo for 28 days. After a washout of 6 weeks, the patients crossed over to a second treatment period. The primary outcome was a change in LVEF. Baseline LVEF was similar for both treatment groups (29.5% in the thiamin group and 29.5% in the placebo group, P = .911). After 28 days of thiamin treatment, the LVEF increased to 32.8%, which was significantly (P = 0.024) different from the LVEF in the placebo group (28.8%).

Several other investigators have reported benefits from thiamin supplementation (50–100 mg once or twice daily) among patients with heart insufficiency/failure with improvement in function. However, a recent review of the literature suggested that the impact of thiamin supplementation in patients with CHF is inconclusive. This author also concluded that published studies are limited by their small sample size, indirect methods of assessing thiamin concentration, methodological inconsistencies, use of impractical means of thiamin supplementation, and lack a robust technique for the assessment of cardiac function. Therefore, a higher level of evidence from large prospective studies and randomized controlled trials is needed to understand the clinical benefit of thiamin supplementation in patients with cardiac insufficiency and/or failure.

**Patients on Nutrition Support**

Enteral nutrition (EN) products in the United States provide adequate thiamin to meet or exceed the RDA as long as adequate energy intakes are achieved. Standard adult EN formulas contain 1.6–4 mg thiamin per 1,500–2,000 kcals. Theoretically, patients who are permissively underfed such as obese patients or patients not receiving goal calories due to various reasons may...
not receive adequate thiamin. Moreover, small-bowel feeding via jejunostomy vs gastrostomy feeds may impair intake of the vitamin because of the bypassing of the preferred absorption site. Nishiwaki et al\textsuperscript{111} has described a similar situation in a patient presenting with copper deficiency.

Clinical TD can occur in patients receiving PN void of thiamin supplementation. A case report of acute TD occurring as a complication of vitamin-free PN has been described.\textsuperscript{112} A case series of thiamin-deficiency–induced lactic acidosis from patients receiving PN void of thiamin has been reported.\textsuperscript{113} In these patients, thiamin replenishment at IV doses of 100 mg every 12 hours resolved lactic acidosis and improved the clinical condition in 50% of patients. A retrospective case review showed that PN-induced fulminant beriberi became evident 4–40 days after the initiation of PN and was more likely to develop in patients with malignancies, ulcerative colitis, and short-bowel syndrome as well as in those receiving chemotherapy.\textsuperscript{114} In these patients, the severity of metabolic acidosis was extremely high and refractory to bicarbonate administration, but it responded quickly to 100 mg IV thiamin. Moreover, many cases of severe lactic acidosis related to TD have been reported by the Centers for Disease Control and Prevention due to nationwide shortages of IV multivitamins used in PN formulas within U.S. hospitals and home healthcare agencies.\textsuperscript{20} The nutrition support clinician should be aware of the potential for IV micronutrient shortages and the potential clinical impact on patient outcomes.

Considerable breakdown of thiamin may occur in the presence of bisulfite-containing amino acid parenteral solutions; thus, subclinical TD may develop with the use of these solutions, even with appropriate thiamin supplementation.\textsuperscript{115} A study aimed to evaluate the nutrition adequacy of 3 mg thiamin in home, long-term (up to 164 months) PN was conducted in patients with short-bowel syndrome, radiation enteritis, or draining gastrostomies that precluded all intestinal absorption;\textsuperscript{116} these authors concluded that 3 mg of thiamin hydrochloride added to PN solutions is adequate to maintain normal thiamin status, even in patients with compromised intestinal thiamin absorption and in the presence of bisulfite-containing amino acid solutions.

Of note, parenteral thiamin is generally in the form of thiamin hydrochloride.\textsuperscript{110} In 1985, the American Medical Association/Nutrition Advisory Group recommended an increase in the daily dose of parenteral thiamin to 6 mg/d for adults and children older than 11 years of age who receive PN. Adult parenteral multivitamin products manufactured in the United States provide 6 mg thiamin in each dose, while European products provide 3.1–3.5 mg. The recommended dose for parenteral thiamin is greater than the oral/enteral dose because urinary excretion of thiamin is increased with parenteral administration.\textsuperscript{101} However, oftentimes, the patient requiring nutrition support will require additional thiamin to prevent TD, especially if 1 or more risk factors for TD are present.

**Refeeding Syndrome**

Refeeding syndrome (RS) can be defined as the potentially fatal shifts in fluid and electrolytes that may occur in malnourished patients receiving nutrition support (whether enterally or parenterally).\textsuperscript{116-119} RS occurs in 4% of cases in patients receiving PN.\textsuperscript{117} A prospective series looking at patients receiving nutrition support in institutions with nutrition support teams found an incidence of 1%–5%.\textsuperscript{117} During refeeding, glucose (or dextrose)-induced insulin secretion causes abrupt reverse of lipolysis and a switch from catabolism to anabolism.\textsuperscript{116-119} Hormonal and metabolic changes cause shifts from catabolism to anabolism and may cause serious clinical complications.

The hallmark biochemical feature of RS is hypophosphatemia as extracellular phosphorus shifts into the intracellular compartment to support energy production in the form of ATP.\textsuperscript{116-119} However, the syndrome is complex and may also feature changes in macronutrient metabolism as well as abnormal sodium and fluid balance, hypokalemia and hypomagnesemia.\textsuperscript{120} Low thiamin levels and TD are also hallmark manifestations of RS.\textsuperscript{116-119} Since the oxidation of glucose is a thiamin-dependent process, caution needs to be taken with the administration of dextrose or intake of carbohydrates void of thiamin supplementation.\textsuperscript{3} Therefore, simultaneous administration of thiamin along with magnesium, potassium, and phosphorus are required for patients at risk for RS.\textsuperscript{118,119}

In 2006, the guidelines from the National Institute for Health and Clinical Excellence for the recognition and treatment of RS were published in the United Kingdom\textsuperscript{121} and are summarized in Table 3. Treatment of RS includes a judicious, slow initiation of caloric intake\textsuperscript{118} as well as correction of electrolyte and fluid imbalances simultaneously with feeding.\textsuperscript{119} This includes 200–300 mg daily oral thiamin (eg, high-potency vitamin B, 1–2 tablets, 3 times daily) or a full dose of IV thiamin and a multivitamin or trace element supplement once daily.\textsuperscript{118}

Differential diagnosis for RS exists. A recent case report of 2 patients with malnutrition and leukemia who developed acute TD has been published.\textsuperscript{122} These authors concluded that despite sharing many laboratory similarities, RS and acute TD should be viewed as separate entities in which the electrolyte abnormalities reported in cases of RS with TD and refractory lactic acidosis may be due to renal tubular losses instead of a shifting from extracellular to intracellular compartments. Other case reports of severe, acute TD have been published.\textsuperscript{123} These authors reported sudden symptoms of dry beriberi with typical neurologic symptoms, metabolic acidosis, hyperglycemia, and hyponatremia as well as improvement in these symptoms upon thiamin administration.

**Critical Illness**

TD should be suspected in different clinical scenarios such as severe sepsis, burns, trauma,\textsuperscript{55,56} and after coronary artery bypass surgery.\textsuperscript{57} Furthermore, patients with chronic lymphocytic...
leukemia are prone to develop primary TD possibly promoted by the increased leukocyte span, which may increase thiamin consumption. Donnino et al. determined the prevalence of absolute TD in 30 critically ill patients with sepsis and examined the association between thiamin levels and lactic acidosis. Absolute TD was defined as ≤9 nmol/L. In the study group, 3 (10%) of 30 patients had absolute TD upon presentation, and an additional 3 patients (6/30, 20%) developed TD within 72 hours. Absolute TD was displayed by 7.7% (2/26) of the vasopressor-dependent group. For the group overall, there was no correlation between thiamin and lactic acidosis. However, in patients without liver dysfunction, thiamin was significantly negatively correlated with lactic acidosis (r = −0.50; P = .02). The relationship between thiamin and lactic acidosis held after multivariable regression analysis controlling for age, sex, and comorbid disease (P < .02). Different studies have shown that critical illness in adults and children is characterized by absolute or relative thiamin depletion, which is associated with an almost 50% increase in mortality. The critically ill patient presents with unique challenges in metabolism, which may increase the metabolic demand for thiamin.

Increased lactic acidosis from TD may be misdiagnosed as characteristics of sepsis or inadequate perfusion. For example, Shoshin beriberi mimicking central line sepsis has been reported regarding a child with short-bowel syndrome receiving PN. This patient was treated unsuccessfully with antibiotics and supportive measures but was treated successfully with administration of thiamin and folate. Moreover, supplemental thiamin provided to patients with burns showed that thiamin supplementation increased serum thiamin and that this increase was associated with a decrease in pyruvate and lactate levels. Therefore, supplemental thiamin should be provided to patients who present with high lactate levels and at risk for TD. Administration of 100 mg IV thiamin to 400 mg IV thiamin, twice daily, has been suggested for patients who present with high lactate levels and who are at risk for TD.

Symptoms and signs associated with TD lack sensitivity and specificity in critically ill patients. Consequently, depletion is frequently unrecognized and underdiagnosed by clinicians. Potentially deleterious consequences of thiamin depletion should be avoided by early and appropriate supplementation. However, more experimental studies are needed to determine safe and effective thiamin supplementation levels and duration among patients with critical illness.

### Patients With Renal Failure

Renal failure exists when the kidneys cannot adequately excrete nitrogenous and metabolic wastes, either acutely due to dehydration or critical illness or chronically over years of declining renal function. In the renal failure patient, there is variability in clinical presentation, ranging from anuria to adequate urine output. The duration of reduced glomerular filtration may be short or long term, requiring the need for prolonged renal replacement therapy. Because of these differences, the Acute Dialysis Quality Initiative Group recommended a change in terminology from acute renal failure to acute kidney injury (AKI). The major causes of AKI include sepsis, trauma, hypotension, IV contrast dye, medications, and preexisting chronic kidney disease (CKD). Despite improvements in dialysis therapy and the delivery of nutrition support, the mortality of AKI can be as high as 50%–60%.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative CPGs for CKD, including the evaluation, classification, and stratification, have been published. CKD has been classified into 5 categories (I–V) based on measured glomerular filtration rate. The most common causes of CKD include diabetes mellitus, hypertension, and glomerular disease. In the United States, there is a rising incidence and prevalence of kidney failure, with poor patient outcomes and high healthcare costs. According to the U.S. Renal Data System, an annual mortality rate in excess of 20% is expected for dialysis patients.

Adult renal failure and critical illness represent by far the largest group undergoing artificial nutrition. However, adult renal failure, especially in the intensive care unit (ICU), seldom occurs as isolated organ failure but rather is a component of multiple organ failure. Nutrition interventions for renal...
failure patients must consider the metabolic derangements peculiar to renal failure, the underlying disease process, and associated complications. Furthermore, because relevant derangements in nutrient balance occur with highly efficient renal replacement therapies, such as continuous venous hemofiltration, or prolonged intermittent modalities such as sustained low-efficiency dialysis, the nutrition support clinician must consider appropriate prevention or treatment strategies for TD.

Patients with chronic renal failure are at increased risk for TD because of increased renal losses, increased tissue retention, and poor nutrient intake. Infection, surgery, and a glucose-rich infusion may especially increase the need for thiamin. In addition, patients with acute and chronic renal failure are often malnourished, especially those receiving continuous renal replacement therapy (CRRT). Indeed, CRRT is likely to affect nutrition via 2 main mechanisms: (1) losses of nutrients through the filtration and dialysis processes and (2) supply of substrates and other components with the replacement fluids.

Micronutrient requirements have been poorly investigated in adult renal failure patients. Renal replacement therapies can significantly decrease plasma thiamin, presumably by interfering with absorption of the vitamin; thus, thiamin is included in multivitamin therapy designed for dialysis patients. To test this hypothesis, Berger et al. studied 11 ICU patients aged 65 ± 10 years with acute renal failure receiving 19 sessions of CRRT in a prospective randomized crossover trial. These investigators reported that the 24-hour balances were negative for thiamin (−4.12 mg, or 1.5 times the recommended intakes). Therefore, patients receiving dialysis may require additional thiamin to prevent TD. In ICU patients with adult renal failure, the enhanced requirements for water-soluble vitamins induced by extracorporeal therapy should be met by supplementing multivitamin products. The typical dietary intake of 0.5–1.5 mg/d can be supplemented with a daily oral dose of 1–5 mg of thiamin hydrochloride. However, hemodialysis patients receiving an oral B-complex multivitamin containing 5 mg thiamin failed to prevent TD.

TD and unexplained encephalopathy in hemodialysis and peritoneal dialysis patients have been reported. Furthermore, neurologic complications associated with hemodialysis includes WE and uremic polyneuropathy. To determine whether unexplained encephalopathy in regular dialysis patients was associated with TD, Hung et al. conducted a prospective study that enrolled 30 consecutive dialysis patients with altered mental status during a 1-year period. Ten patients were identified with 1 or more of the following clinical manifestations: confusion, chorea, acute visual loss, rapidly progressive dementia, myoclonus, convulsions, and coma. All 10 patients had TD confirmed by a marked response to thiamin supplementation. In 9 of the 10 patients, a serum thiamin concentration of at least 0.5 nmol/L was confirmed after treatment. In the 3 surviving patients after a 6-month follow-up, the overall mortality rate in this study was 30%. Causes of death were ventilator-associated pneumonia, sudden cardiac death, and circulatory failure, apparently because TD was not treated promptly. These authors concluded that in dialysis patients, unexplained encephalopathy is mainly attributed to TD, which can be successfully treated with prompt thiamin replacement. However, this condition can be fatal if unrecognized and untreated.

Table 4 is a summary of evidence-based treatment strategies for TD in different clinical scenarios. It is clear that a lack of consistency with thiamin repletion protocols exist. Although more high-quality studies are needed, it is clear that the benefits of timely thiamin repletion outweigh the risks of detrimental clinical consequences associated with untreated TD.

Thiamin in Clinical Practice: Other Applications

Thiamin supplementation may be beneficial in patients with inborn errors of metabolism such as thiamin-responsive MSUD (branched-chain ketoaciduria) and thiamin-responsive PDH deficiency. Thiamin may also improve outcomes among patients with thiamin-responsive megaloblastic anemia syndrome. Early detection and recognition of the cause(s) of anemia in patients with diabetes, such as thiamin-responsive megaloblastic anemia, could help to prevent other clinical manifestations as well as the complications of diabetes. Since evidence for altered thiamin metabolism in diabetes has also been reported, thiamin supplementation among patients with diabetes may beneficial. However, experimental studies on the molecular mechanisms of TD in diabetes are needed before CPGs can be established.

It is clear that TD results in an impairment of oxidative metabolism. The consequences of TD include an orchestra of events including increased oxidative stress, excitotoxicity, and inflammation, resulting in cerebral vulnerability. Moreover, cerebral inflammation is now recognized as a key component of several neurologic diseases including stroke, multiple sclerosis, and Alzheimer’s disease, along with other conditions such as brain trauma. Thus, TD represents an excellent model for studying the interrelationships between these events and the pathophysiology of neurodegenerative diseases. Preliminary studies have shown that thiamin and some of its synthetic precursors with higher bioavailability have beneficial effects in several models of neurodegenerative diseases such as Alzheimer’s disease, Parkinson disease, amyotrophic lateral sclerosis, and other diseases. The understanding of the
molecular mechanisms and clinical benefits of thiamin in the prevention and/or treatment of neurodegenerative diseases deserves further investigation.

**Conclusion**

Thiamin plays both coenzyme and non-coenzyme roles within the body. TD results in impaired oxidative and energy metabolism. Serious and potentially irreversible neurologic damage or death can occur with untreated TD. The nutrition and metabolic support professional should be aware of the roles that thiamin plays in the body, consequences of TD, and treatment strategies for at-risk patients. Thiamin supplementation may also benefit patients with inflammatory and neurodegenerative diseases such as diabetes, Alzheimer’s disease, Parkinson disease, and amyotrophic lateral sclerosis. More research is needed to understand thiamin’s role in clinical practice to provide the clinician with high-level evidence-based practice recommendations.

**Further Reading**


### Glossary

**Bariatric surgery**: Also known as weight loss surgery and/or metabolic surgery. Restrictive surgeries include the adjustable gastric band and sleeve gastrectomy. Restrictive-malabsorptive surgery includes the Roux-en-Y gastric bypass. Malabsorptive surgeries include the bilio-pancreatic diversion with and without the duodenal switch.

**Decarboxylation reactions**: Removal of carboxyl groups (-OOC) or carbon dioxide (CO₂) in metabolic processes.

**Dehydrogenation reactions**: Removal of hydroxyl (-OH) groups in metabolic processes.

**Dry or neurologic beriberi**: Condition of thiamin deficiency that is devoid of edema and consists of several neurologic impairments including brisk tendon reflexes, peripheral neuropathy, and/or polyneuropathy with or without parasthesias typically affecting the lower extremities and, in subsequent stages, affecting the upper extremities; muscle weakness and/or pain of upper and lower extremities, gait ataxia, and/or convulsions.

**Hyperemesis gravidarum**: Complication of pregnancy characterized by intractable nausea, vomiting, and dehydration.

**Loop diuretics**: Type of diuretic that acts at the ascending loop of Henle in the kidneys to inhibit sodium and chloride resorption while increasing fluid and potassium losses. Examples are bumetanide, ethacrynic acid (Edecrin), furosemide (Lasix), and torsemide (Demadex).
Nystagmus: Fast, uncontrollable eye movements due to the effects of thiamin deficiency in the parts of the brain that affect eye movement. Movements may be side to side (horizontal nystagmus), up and down (vertical nystagmus), or rotary (rotary or torsional nystagmus).

Ophthalmoplegia: Paralysis or weakness of the eye muscles, affecting 1 or more of the 6 muscles that hold the eye in place and control its movement, generally caused by disruption of the messages that are sent from the brain to the eyes. People affected by ophthalmoplegia may have double vision or blurred vision, the inability to move both eyes in every direction, and/or drooping eyelids.

Polyhydroxypentols: Other anti-thiamin factors that inactivate thiamin by an oxidative process. These polyhydroxypentols are heat stable and include tannic and caffeic acids found in coffee, tea, betel nuts, blueberries, black currents, Brussels sprouts, and red cabbage.

Refeeding syndrome: Complications of fluid and electrolyte balance from hormonal and metabolic shifts, from the catabolic to the anabolic state, when carbohydrates (eg, dextrose in parenteral nutrition) are given with inadequate nutrients needed as cofactors for energy metabolism, including magnesium, potassium, phosphorus, niacin, riboflavin, and thiamin.

Thiaminases: Thiaminases are anti-thiamin enzymes found in raw fish, which catalyze the cleavage of thiamin, destroying its activity. However, these thiaminases are heat labile such that cooking fish renders the thiaminases inactive.

Thiamin pyrophosphate (TPP) (also known as thiamin diphtate): Biologically active form of thiamin playing coenzyme and non-coenzyme roles in the body.

Wernicke's encephalopathy: Condition of advanced thiamin deficiency in which the patient may present with polyneuropathy and ataxia, ocular changes (ophthalmoplegia and nystagmus), mental confusion (confabulation), and/or short-term memory loss. If psychosis and/or hallucinations are present, the condition is often referred to as Korsakoff psychosis and/or Wernicke-Korsakoff syndrome.

Wet or cardiac beriberi: Condition of thiamin deficiency with edema present, especially in the lower extremities. Other symptoms include tachycardia or bradycardia, lactic acidosis, dyspnea, heart hypertrophy and dilatation (particularly of the right ventricle), respiratory distress, systemic venous hypertension, bounding arterial pulsations, and heart failure with high cardiac output. Shōshin beriberi is an acute, fulminating form. Shōshin is a Japanese word meaning acute cardiac catastrophe.

References


80. Thomson AD, Marshall EJ, Guerrini I. Biomarkers for detecting thiamine-deficiency—improving confidence and taking a comprehensive history are also important. *Alcohol Alcohol*. 2010;45:213.


