

# Thiamin<sup>1,2</sup>

## Nutrient

Thiamin, or vitamin B-1, is an essential water-soluble vitamin critical for carbohydrate and amino acid catabolism and gluconeogenesis. Specifically, thiamin pyrophosphate (TPP) is a cofactor for 2 enzymes in oxidative pathways after glycolysis: the pyruvate dehydrogenase complex, used to convert pyruvate to acetyl-CoA, and the  $\alpha$ -ketoglutarate dehydrogenase complex, used to convert  $\alpha$ -ketoglutarate to succinyl-CoA.

TPP is also a cofactor for the branched-chain  $\alpha$ -ketoacid dehydrogenase complex used to convert leucine, isoleucine, and valine into acetyl-CoA and succinyl-CoA, which are then similarly fed into the ATP-generating Krebs cycle.

In addition to serving as a cofactor for these 3 enzymes, TPP is a cofactor for the biochemical reactions driven by transketolase in the anabolic pentose phosphate pathway. NAD(P)H, one product of this pathway, is required for fatty acid (FA) and steroid hormone synthesis and reduction of glutathione (an endogenous antioxidant). Ribose 5-phosphate, a substrate for nucleotide and nucleic acid synthesis, is also generated by this thiamin-dependent pathway.

#### Deficiencies

Because thiamin is not directly monitored by the NHANES, the prevalence of thiamin deficiency in the United States is not known, but it is likely that it often goes unrecognized in our modern era of vitamin-fortified food products-especially in patients without alcohol use disorders. Over 20 y ago, autopsy studies demonstrated a prevalence of thiamin deficiency of 0.4-2.8% in Western society, and only a small portion of these cases were diagnosed before death (1, 2). Although alcohol abuse is a well-known cause of thiamin deficiency, it is not the only cause. Twenty-three percent of chronic cases and 39% of acute cases were found in nonalcoholics, and none of these were identified clinically before death (2). Because thiamin must be obtained from the diet, is water soluble, and is not stored in large amounts in the body, people who are thiamin deficient (e.g., from calorie-restricted diets, prolonged nausea and vomiting, or parenteral nutrition), those with malabsorption (e.g., patients after roux-en-Y gastric bypass surgery), those with excessive thiamin metabolism (e.g., from high carbohydrate diets, major illness, or surgery), or those with excessive losses (e.g., from loop diuretic use, hemodialysis or peritoneal dialysis, or diabetes) can deplete their thiamin reserves within a few weeks. The prevalence of thiamin deficiency previously has been reported to be between 15.5% and 29% in people with obesity who are seeking bariatric surgery, but it is not clear whether this rate would be comparable in all people with obesity, or simply in those who have recently been on calorie-restricted weight-loss diets (3).

Because of its critical role in oxidative ATP synthesis, thiamin is essential for the proper function of most tissues and organs. Thiamin deficiency can therefore have myriad clinical effects. Major organs, including the brain and heart, account for ~60% of basal energy expenditure; therefore, thiamin deficiency affects nervous and cardiovascular systems most dramatically, and may rapidly lead to death if not corrected. The main deficiency syndromes defined in humans include the following:

- Wernicke's encephalopathy—a neuropsychiatric condition characterized primarily by confusion and delirium, ataxia, and ocular findings, such as visual disturbances, nystagmus (rapid involuntary beating eye movements), or weakness of the oculomotor muscles. Korsakoff syndrome refers to the chronic permanent neurologic sequelae of thiamin deficiency on the brain (including profound memory loss with confabulation, or unconscious fabrication of information).
- Dry beriberi—primarily characterized by peripheral neurologic manifestations, such as paresthesia, weakness, or paralysis.
- Wet beriberi—exemplified by cardiac effects, including decompensated systolic heart failure with associated pulmonary and peripheral edema, tachycardia, a widened pulse pressure and/or hypotension, and/or cardiogenic shock (sometimes referred to as Shoshin beriberi).
- Gastrointestinal beriberi—a newly described syndrome (4) that includes nausea and vomiting, abdominal pain, and lactic acidosis.

## **Diet Recommendations**

The RDA for thiamin was last updated in 1998 (Table 1) (5); RDAs are established to meet the needs of 97-98% of healthy people in a given group, so these recommendations may be inadequate for some people. When an individual's energy intake increases, thiamin-dependent enzymes are more active, and requirements for the vitamin increase. Consequently, the RDA is higher for men than for women, and is highest for pregnant and lactating women. An Adequate Intake (AI) is used for infants. The Institute of Medicine established a thiamin AI for infants  $\leq 6$  mo of age by assessing the mean thiamin intake of infants who consume only human milk from well-nourished mothers (5). Infants aged 7-12 mo usually consume solid foods in addition to human milk; therefore, the AI for this group was extrapolated from the adult RDA (5). Several methods are used to assess thiamin status, including measurement of urinary thiamin, thiamin concentration measurement in whole blood or serum via

TABLE 1 Dietary Reference Intake for thiamin<sup>1</sup>

Group	RDA or Al, <sup>2</sup> mg/d	UL <sup>3</sup>
Infants, mo		
0-6	0.2 <sup>2</sup>	ND
7-12	0.3 <sup>2</sup>	ND
Children, y		
1-3	0.5	ND
4-8	0.6	ND
Male subjects, y		
9-13	0.9	ND
14-18	1.2	ND
≥19	1.2	ND
Female subjects, y		
9-13	0.9	ND
14-18	1.0	ND
≥19	1.1	ND
Pregnancy	1.4	ND
Lactation	1.4	ND

<sup>1</sup> Al, Adequate Intake; ND, not determinable; UL, Tolerable Upper Intake Level. <sup>2</sup> An RDA has not been established for infants; the Al in this case is the mean intake for healthy breastfed infants rather than the intake believed to cover the needs of all individuals in the group (5).

<sup>3</sup> The maximum amount of daily thiamin intake from food and supplements that is likely to pose no danger of adverse effects. Because of a lack of reported data on adverse effects from thiamin, ULs could not be established. However, caution may be reasonable in consuming amounts above recommended intake, given the lack of data.

high performance liquid chromatography (HPLC), and the gold standard: measurement of erythrocyte transketolase activity.

#### **Food Sources**

Thiamin is found in fortified processed flours and ready-to-eat cereals, lean pork, beef, wheat germ and whole grains, yeast, organ meats (especially liver), eggs, fish, legumes, and nuts. One cup (237 mL) beans or oats contains  $\sim$ 1.8 or  $\sim$ 1.2 mg thiamin, respectively. However, fats and oils, polished rice, or other processed carbohydrates (other than fortified processed flours) are not good sources, nor are dairy products or many fruits and vegetables. Importantly, cooking and other heat processing dramatically reduce the thiamin content of foods. Similarly, coffee and tea contain certain polyphenolic compounds that can inactivate the vitamin, and raw fish and shellfish contain thiaminases that degrade and inactivate the vitamin.

#### **Clinical Uses**

Thiamin supplements are obviously used to treat the thiamin deficiency syndromes described above. There are also several rare genetic diseases that affect the metabolism of glucose and BCAAs that respond to high-dose thiamin supplementation. Perhaps the best-known disease is a variant of branched-chain ketoaciduria, more commonly known as maple syrup urine disease. The rare subset of patients with mutations in the E2 subunit of the branched-chain  $\alpha$ -ketoacid dehydrogenase complex can be successfully treated with high doses (10–1000 mg/d) of supplemental thiamin, and may consume BCAAs more liberally than may patients with traditional maple syrup urine disease. Other rare thiamin-responsive genetic diseases include biotin-thiamin-responsive basal ganglia disease, thiamin-responsive congenital lactic acidosis, and thiamin-responsive megaloblastic anemia syndrome.

## **Toxicity**

Thiamin is water-soluble, and excess is promptly excreted in the urine. The Institute of Medicine has not established a Tolerable Upper Intake Level because no adverse events have been reported after consuming thiamin from food or supplements to date (5).

#### Research

Research in the past decade has focused on thiamin deficiency and dysfunctional glucose metabolism in patients with both type 1 and type 2 diabetes; high-dose thiamin has been shown in some studies to improve the vascular complications of the disease, such as nephropathy, neuropathy, and retinopathy (6). In addition, thiamin deficiency may be associated with Alzheimer disease (7), although the therapeutic potential of supplemental thiamin in this disorder is less clear. Finally, recent critical care research shows that "metabolic resuscitation," including thiamin supplementation, may be a useful adjunctive treatment in septic shock with lactic acidosis and multiorgan dysfunction (8, 9).

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