



## Thiamine

### Introduction

Thiamine, also known as vitamin B1, is a water-soluble, B-complex vitamin necessary for metabolism of proteins, carbohydrates, and fats. Thiamine is involved as a cofactor in numerous enzymes, and is essential in every cell for ATP production via the Krebs cycle.

### Biochemistry and Pharmacokinetics

Thiamine functions as a coenzyme in more than 24 enzymes, most importantly pyruvate dehydrogenase (for energy production in the Krebs cycle), transketolase (for lipid and glucose metabolism, production of branched chain amino acids, and production and maintenance of myelin sheath), and 2-oxo-glutarate dehydrogenase (for synthesis of acetylcholine, GABA, and glutamate).<sup>1</sup> Thiamine is necessary in the functioning of the hexose monophosphate shunt, an anabolic pathway used proportionately more in adrenal cortex, leukocytes, erythrocytes, and mammary gland tissue. Thiamine is crucial in glucose energy-utilizing pathways, particularly in the central nervous system, which needs a continuous supply of glucose. Thiamine has also been shown to mimic acetylcholine in the brain,<sup>2</sup> which may explain its possible action in Alzheimer's disease and other dementias.<sup>3,4</sup>

The body stores approximately 25-30 mg of thiamine, mainly in skeletal muscle, heart, brain, liver, and kidneys – organs with high metabolic need. In a deficient state, body stores can be depleted in 2-3 weeks.<sup>5</sup> As early as one week after thiamine stores are depleted the blood-brain barrier is disrupted and local cerebral hypoperfusion results, leading to the classic signs of Wernicke's encephalopathy.<sup>6</sup>

### Deficiency States and Symptoms

Thiamine deficiency, manifesting as beriberi or Wernicke-Korsakoff psychosis, has been considered to be a problem only in non-developed countries where white rice is a staple of the diet or in advanced alcoholics. However, the work of Lonsdale<sup>7</sup> and others has shown thiamine deficiency occurs in a variety of situations, including a diet high in simple carbohydrates consisting mainly of processed food (sulfiters destroy thiamine),<sup>7</sup> complications of alcohol misuse,<sup>8</sup> total parenteral nutrition (TPN),<sup>9</sup> gastrointestinal surgery,<sup>10</sup> severe infection,<sup>11</sup> eating disorders,<sup>12</sup> hyperemesis gravidarum,<sup>13</sup> renal dialysis,<sup>14</sup> cancer (especially if the patient is being treated with chemotherapy),<sup>15</sup> long-term diuretic use,<sup>16</sup> and AIDS.<sup>17</sup> Lonsdale has also reported clinical evidence of increased thiamine need in major depressive disorder, inborn errors of metabolism, hyperactivity, and autonomic dysfunction.<sup>1</sup>

Symptoms of thiamine deficiency are diverse, vary with the degree of severity of the deficiency, and include depression, weakness, dizziness, insomnia, back pain, myalgia, muscular atrophy, palpitations, anorexia, nausea, vomiting, weight loss, hypotension, hypothermia, bradycardia at rest, tachycardia with sinus arrhythmia on exertion,<sup>18</sup> constipation, digestive disturbances, memory loss, peripheral neuropathy, pain sensitivity, dyspnea, and sonophobia.<sup>19</sup> Emotional instability, mood lability, uncooperative behavior, and fearfulness with agitation have also been seen in adolescents with documented thiamine deficiency.<sup>20</sup> Signs of severe thiamine deficiency seen in Wernicke's encephalopathy include ataxia, ophthalmoplegia, nystagmus, and delirium.<sup>8</sup>

Thiamine deficiency, diagnosed by plasma levels, red cell transketolase, or thiamine pyrophosphate percentage effect, has been documented in adolescents eating an average American diet,<sup>20</sup> in 38 percent of a group of non-alcoholic psychiatric patients,<sup>21</sup> 33-55 percent of geriatric populations,<sup>22</sup> and 30-80 percent of alcoholic populations.<sup>23,24</sup> Thiamine is also depleted in those exposed to formaldehyde, and by long-term use of the following prescription drugs: phenytoin, penicillins, cephalosporins, aminoglycosides, tetracycline derivatives, loop diuretics, fluoroquinolones, sulfonamide derivatives, and trimethoprim.<sup>25</sup>

## Clinical Indications

### *Alcoholism*

Thiamine deficiency in alcoholism stems from a variety of causes. In addition to low intake, absorption is inhibited and hepatic activation of thiamine coenzymes is decreased.<sup>26</sup> Psychosis resulting from chronic alcohol use is believed to be primarily a result of thiamine deficiency, and appears to be on the rise worldwide.<sup>2</sup>

Wernicke's encephalopathy, the condition leading to sensory, motor, and cognitive deficits and the long-term consequence of Korsakoff's psychosis in alcoholics, occurs primarily as a consequence of thiamine deficiency.<sup>27</sup> Treatment of Wernicke's encephalopathy necessitates

intravenous thiamine for at least 3-10 days followed by a high potency B-vitamin complex for as long as improvement continues.<sup>8</sup>

### *HIV/AIDS*

Moderate to severe thiamine deficiency has been observed in up to 23 percent of HIV-positive or AIDS-diagnosed non-alcoholic individuals.<sup>17</sup> In prospective epidemiological studies, thiamine intakes above 7.5 mg (the RDA is 1.5 mg) were associated with increased survival. The highest levels of vitamin B1 and vitamin C intake were associated with significantly decreased progression from HIV to AIDS.<sup>28</sup> Thiamine-deficiency encephalopathy has been seen in HIV/AIDS patients with no alcohol abuse history.<sup>11</sup>

### *Congestive Heart Failure (CHF)*

The etiology of heart failure is complex, but evidence for the role of micronutrients, particularly thiamine, is clear.<sup>29</sup> Thiamine deficiency leads to impaired oxidative metabolism. Subsequently, pyruvate and lactate levels increase, leading to vasodilation and possible metabolic acidosis, retention of water and sodium leading to edema, and biventricular heart failure known as "wet beriberi." Reversal occurs with thiamine repletion. Iatrogenic contributions may include the use of cardiac medications (specifically furosemide and digoxin) that decrease thiamine uptake in myocytes. Low whole blood levels of thiamine are evident in CHF patients who have been treated with loop diuretics.<sup>30</sup>

Thiamine supplementation in patients with CHF has been shown to significantly improve left ventricular ejection fraction and raise blood pressure 10 mm Hg, an indication of reversal of the pathological vasodilation seen in cardiac beriberi.<sup>31</sup>

### *Pregnancy, Hyperemesis Gravidarum, and Gestational Diabetes*

Thiamine deficiency is common in pregnancy; in one study, 25-30 percent of pregnant women had low red-cell transketolase levels

compared to controls.<sup>32</sup> Pregnant women with hyperemesis gravidarum have a greater risk of thiamine deficiency, and may need to be supplemented with high doses of thiamine.<sup>13</sup>

Women with gestational diabetes are even more likely to become thiamine deficient; 50 percent of study populations have been shown to have low transketolase levels.<sup>33</sup> In one study, 19 percent of gestational diabetics on standard prenatal thiamine supplementation were thiamine deficient.<sup>35</sup> A significant correlation exists between maternal thiamine deficiency and macrosomia (abnormally high body weight) in infants; however, an even stronger correlation was seen in macrosomic neonates from gestational diabetic mothers when the infants were born thiamine deficient.<sup>34</sup>

### **Mood and Cognitive Performance**

A controlled, one-year trial with 127 young adults given 15 mg thiamine, along with other B vitamins at dosages 10 times the RDA,<sup>4</sup> found the most significant association to be enhanced cognitive function and improved thiamine status in females.

Another controlled trial of thiamine and mood investigated 80 elderly females on 10 mg thiamine daily for 10 weeks.<sup>35</sup> Compared to baseline assessment and placebo, those on thiamine experienced significant increases in appetite, body weight, energy intake, general well-being, reduced daytime sleep, improved sleep patterns, decreased fatigue, and increased activity levels.

### **Drug-Nutrient Interactions**

Thiamine can be depleted by long-term use of the following prescription drugs: phenytoin, penicillins, cephalosporins, aminoglycosides, tetracycline derivatives, loop diuretics, fluoroquinolones, sulfonamide derivatives, and trimethoprim.<sup>25</sup>

### **Side Effects and Toxicity**

Thiamine toxicity from oral dosage is not presently known.<sup>7</sup>

### **Dosage**

Dosages of thiamine are condition-specific. To treat Wernicke's encephalopathy, parenteral thiamine is necessary.<sup>8</sup> Oral doses of 50 mg thiamine daily have been used in alcoholics without encephalopathy to raise RBC transketolase levels.<sup>36</sup> Research by Cheraskin and Ringsdorf of "recommended optimal nutrient levels" found individuals taking 9 mg thiamine daily had fewer symptoms associated with illness and chronic degenerative disease than their peers.<sup>37,38</sup> The authors also suggest a wider range of supplemental intake (5-15 mg daily) may be necessary for those on diets high in refined carbohydrates. Lonsdale<sup>7</sup> has published case studies indicating 150 mg thiamine in divided daily doses may be needed to treat individuals with thiamine deficiency symptoms resulting from increased individual requirements.

### **References**

1. Thomson AD, Pratt OE. Interaction of nutrients and alcohol: absorption, transport, utilization and metabolism. Watson RR, Watzl B, eds. *Nutrition and Alcohol*. Boca Raton, FL: CRC Press;1992:75-99.
2. Meador K, Nichols ME, Franke P, et al. Evidence for a central cholinergic effect of high dose thiamine. *Ann Neurol* 1993;34:724-726.
3. Meador K, Loring D, Nichols M, et al. Preliminary findings of high-dose thiamine in dementia of Alzheimer's type. *J Geriatr Psychiatry Neurol* 1993;6:222-229.
4. Benton D, Fordy J, Haller J. The impact of long-term vitamin supplementation on cognitive functioning. *Psychopharmacol* 1995;117:298-305.
5. Velez RJ, Myers B, Guber MS. Severe acute metabolic acidosis (acute beriberi): an avoidable complication of total parenteral nutrition. *JPEN J Parenter Enteral Nutr* 1985;9:216-219.
6. Heye N, Terstegge K, Sirtl C, et al. Wernicke's encephalopathy – causes to consider. *Intensive Care Med* 1994;20:282-286.
7. Lonsdale D. *The Nutritionist's Guide to the Clinical Use of Vitamin B-1*. Tacoma, WA: Life Sciences Press: 44-77.
8. Cook C, Hallwood PM, Thomson AD. B vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. *Alcohol Alcohol* 1998;33:317-336.

9. Kitamura K, Yamaguchi T, Tanaka H, et al. TPN-induced fulminant beriberi: a report on our experience and a review of the literature. *Surg Today* 1996;26:769-776.
10. Seehra H, MacDermott N, Lascelles RG, Taylor TV. Wernicke's encephalopathy after vertical banded gastroplasty for morbid obesity. *BMJ* 1996;312:434.
11. Lindboe CF, Loberg EM. Wernicke's encephalopathy in non-alcoholics. An autopsy study. *J Neurol Sci* 1989;90:125-129.
12. Winston AP, Jamieson CP, Madira W, et al. Prevalence of thiamin deficiency in anorexia nervosa. *Int J Eat Disord* 2000;28:451-454.
13. Togay-Isikay C, Yigit A, Mutluer N. Wernicke's encephalopathy due to hyperemesis gravidarum: an under-recognised condition. *Aust N Z J Obstet Gynaecol* 2001;41:453-456.
14. Reuler JB, Girard DE, Cooney TG. Wernicke's encephalopathy. *N Engl J Med* 1985;312:1035-1039.
15. Bleggi-Torres LF, de Medeiros BC, Ogasawara VS, et al. Iatrogenic Wernicke's encephalopathy in allogeneic bone marrow transplantation: a study of eight cases. *Bone Marrow Transplant* 1997;20:391-395.
16. Wilcox CS. Do diuretics cause thiamine deficiency? *J Lab Clin Med* 1999;134:192-193.
17. Butterworth RF, Gaudreau C, Vincelette J, et al. Thiamine deficiency and Wernicke's encephalopathy in AIDS. *Metab Brain Dis* 1991;6:207-212.
18. Williams RD, Mason HL, Power MH, et al. Induced thiamine deficiency in man; relation of depletion of thiamine to development of biochemical defect and of polyneuropathy. *Arch Int Med* 1943;71:2176-2177.
19. Werbach MR. *Nutritional Influences on Illness, 2nd Ed.* Tarzana, CA: Third Line Press; 1993:676-677.
20. Lonsdale D, Schamberger RJ. Red cell transketolase as indicator of nutritional deficiency. *Am J Clin Nutr* 1980;33:205-211.
21. Schwartz RA, Gross M, Lonsdale D, Schamberger RJ. Transketolase activity in psychiatric patients. *J Clin Psychiatry* 1979;40:427-429.
22. Chen MF, Chen LT, Gold M, Boyce HW Jr. Plasma and erythrocyte thiamin concentration in geriatric outpatients. *J Am Coll Nutr* 1996;15:231-236.
23. Baines M. Detection and incidence of B and C vitamin deficiency in alcohol-related illness. *Ann Clin Biochem* 1978;15:307-312.
24. Thomson AD, Jeyasingham M, Pratt O, Shaw GK. Nutrition and alcoholic encephalopathies. *Acta Med Scand Suppl* 1987;717:55-65.
25. Pelton R, LaValle JB, Hawkins E, Krinsky DL, eds. *Drug-Induced Nutrient Depletion Handbook.* Hudson, OH: Lexi-Comp; 1999:258.
26. Leevy CM. Thiamin deficiency and alcoholism. *Ann NY Acad Sci* 1982;378:316-326.
27. Lishman WA. Cerebral disorder in alcoholism. *Brain* 1981;104:1-20.
28. Tang AM, Graham NM, Kirby AJ, et al. Dietary micronutrient intake and risk of progression to acquired immunodeficiency syndrome (AIDS) in human immunodeficiency virus type-1 (HIV-1)-infected homosexual men. *Am J Epidemiol* 1993;138:937-951.
29. Witte KK, Clark AL, Cleland JG. Chronic heart failure and micronutrients. *J Am Coll Cardiol* 2001;37:1765-1774.
30. Brady JA, Rock CL, Horneffer MR. Thiamine status, diuretic medications and the management of congestive heart failure. *J Am Diet Assoc* 1995;95:541-544.
31. Seligmann H, Halkin H, Raucfleisch S, et al. Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: a pilot study. *Am J Med* 1991;91:151-155.
32. Heller S, Salkeld RM, Korner WF. Vitamin B1 status in pregnancy. *Am J Clin Nutr* 1974;27:1221-1224.
33. Bakker SJ, ter Maaten JC, Gans RO. Thiamine supplementation to prevent induction of low birth weight by conventional therapy for gestational diabetes mellitus. *Med Hypotheses* 2000;55:88-90.
34. Baker H, Hockstein S, DeAngelis B, Holland BK. Thiamin status of gravidas treated for gestational diabetes mellitus compared to their neonates at parturition. *Int J Vit Nutr Res* 2000;70:317-320.
35. Smidt LJ, Cremin FM, Clifford AJ. Influence of thiamin supplementation on the health and general well-being of an elderly Irish population with marginal thiamin deficiency. *J Gerontol* 1991;46:M180.
36. Baines M, Bligh JG, Madden JS. Tissue thiamine levels of hospitalized alcoholics before and after oral or parenteral vitamins. *Alcohol Alcohol* 1988;23:49-52.
37. Cheraskin E, Ringsdorf WM, Medford FH, Hicks BS. The "ideal" daily vitamin B1 intake. *J Oral Med* 1978;33:77-79.
38. Cheraskin E, Ringsdorf WM. How much carbohydrate should we eat? *Am Lab* 1974;6:31-35.