Thiamin

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Importance of thiamin for health

Thiamin is an essential micronutrient for humans and animal life. Since the human body cannot produce thiamin, its supply depends almost completely on dietary intake (1, 2). Given the short half-life of this vitamin, body stores are limited and require a regular supply to maintain tissue thiamin levels. Thiamin diphosphate (TDP), also called thiamin pyrophosphate (TPP), is the coenzymatic form of vitamin B1 and constitutes about 80% of total body thiamine. It is a key factor in carbohydrate and branched-chain amino acid, and lipid metabolism (1, 3). Its synthesis from free thiamin requires magnesium, adenosine triphosphate (ATP), and the enzyme thiamin pyrophosphokinase (TPK) (4).

Thiamin absorption in the human body occurs after de-phosphorylation to free thiamin, in the intestinal lumen through a pH- and Na^+-dependent carrier mediated system, while thiamin transporters *THTR1* and *THTR2* support the uptake in the intestinal epithelium cells (5). Free thiamin is then transported to the cells, where phosphorylation to TDP occurs by thiamine pyrophosphokinase-1 (TPK-1). There is no known intracellular role for TMP (6).

Whole grains, meat, and fish are good food source of vitamin B1, while dairy products and most fruits are low in thiamin. Some studies have shown increased thiamin adsorption with low intake, but data on thiamin bioavailability from foods are sparse. Food processing such as heating, pasteurization, or cooking in water can noticeably reduce thiamin levels in the foods. White rice -without thiamin enrichment- only contains 1/10 of the thiamin available in unenriched brown rice (4).

Risks of deficiency:

Inadequate intake can lead to thiamin deficiency; however, lower absorption or higher excretion than normal, or consumption of anti-thiamin factors in food can also cause thiamin insufficiency. Other thiamin affecting conditions include alcohol dependence, HIV/AIDS status, or the use of some medication (4).

Increased thiamin requirements are commonly due to strenuous exertion, fever, pregnancy, breastfeeding, and adolescent growth, which increases the risk of deficiency in settings of marginal thiamin intake (3, 4).

Thiamin is a key factor for enzymes involved in glucose metabolism; thus, conditions of increased glucose demands such as Malaria, or providing carbohydrates to severely starved individuals can lead to a higher demand for thiamin in glycolysis and the citric acid cycle that precipitates thiamin deficiency (4, 7).

Beriberi is the main thiamin deficiency syndrome, caused by severe thiamin deficiency, and can be sub-divided into categories as outlined in Table 1.

Risks of excess:

Excess thiamin is excreted in the urine. No upper intake levels have been established given to the lack of reports of adverse effects due to excess thiamin intake. The short half-life of thiamin may contribute to the lack of toxicity, and the Food and Nutrition Board notes that high thiamin intake levels could have adverse effects (4, 7).

Table 1: Beriberi sub-categories (1, 4, 7)

Deficiency	Effect
Dry beriberi	Neuropathy, "burning feet syndrome" exaggerated reflexes diminished sensation and weakness of arms and legs muscle pain and tenderness
Wet beriberi	Neurologic symptoms Rapid heartbeat, edema, difficulty breathing, congestive heart failure
Cerebral beriberi	Wernicke's encephalopathy, Korsakoff's psychosis
Gastrointestinal beriberi	Decreased activity of thiamin-dependent enzymes cause accumulation of pyruvate and lactate: nausea, vomiting, abdominal pain

Wernicke's encephalopathy is a result of wet berberi and its diagnosis is based on a "triad" of signs including abnormal eye movements, stance and gait ataxia, and cognitive impairments. Without treatment, irreversible neurologic damage can lead to further clinical manifestations, known as *Korsakoff's psychosis*, which involves a confused, apathetic state and a profound memory disorder, with severe amnesia and loss of recent and working memory. Thiamin deficiency which affects the central nervous system is also known as *Wernicke-Korsakoff syndrome* (WKS), when an individual presents with the amnesic state along with eye-movement and gait disorders (7).

Human biomarkers for measuring thiamin intake and status

Thiamin status is either assessed by analysing the thiamin metabolites in the human sample or by measuring the degree of TDP-saturation of a thiamin-dependent enzyme (erythrocyte transketolase (ETK) assay) (1, 3).

Urinary thiamin

Vitamin B1 is mainly excreted in urine as free thiamin and TMP, but some TDP and several other metabolites are present in smaller quantities. Urinary thiamin metabolites are related to plasma thiamin concentrations, showing values >100µg/day with intakes of more than 0.3-0.4mg/1000kcal, and <25µg/day under thiamin deficient conditions (1).

Table 2: Thiamin biomarkers for recent intake and status modified from (1)

Biomarker	Analysis type	Sample	Benefits	Intricacies
ETK activity	Indirect measurement	Washed RBC	Assay of biological activity	Not readily available
Thiamin	Direct analysis	Plasma	Reflects recent intake	Does not reflect status
TMP	Direct analysis	Plasma	Reflects recent intake	Does not reflect status
TDP	Direct analysis	WB, RBC	Analysis of biological active form; reflects status	Proper handling of specimen required

ETK: erythrocyte transketolase; RBC: red blood cells; TDP: thiamin diphosphate; TMP: thiamin monophosphate; WB: whole blood

ETK activity

This assay has been commonly used in the past and was regarded as the best functional test of thiamin status (3). Erythrocytes are lysed and ETK activity is measured before and after stimulation by the addition of TDP. However, this technique has been shown to be sensitive towards various interferences such as enzyme inhibition by alcohol or acetaldehyde, certain drugs, or high background absorbance from haemoglobin (8). Results obtained may be therefore subjected to uncertain variabilities.

Methods: ETK activity is measured in washed erythrocytes, see references (9, 10)

TDP analysis

More recently, TDP analysis in whole blood (WB) or erythrocytes has emerged as a useful biomarker of thiamin status as it reflects body stores and offers a superior evaluation of thiamin status than total thiamin. It should be noted that the direct analysis of TDP does not reflect thiamin metabolic function (1). TDP can be measured in erythrocytes, but WB is preferred due to minimal required sample handling, and results obtained for TDP in WB are highly correlated to TDP in erythrocytes. However, WB samples for thiamin analysis need to be frozen to ensure lysis of the cells. When analysing TDP, procedures should be carried out under dim light due to the light sensitivity of thiamin vitamers (1). TDP and other thiamin vitamers can be measured simultaneously using chromatographic methods, mainly HPLC-FLD, and more recently, LC-MS.

Methods

- Direct measurement of TDP and other thiamin vitamers by LC-FLD, see reference (11)
- Direct measurement of TDP and other thiamin vitamers by LC-MS, see reference (12)

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Technical assistance

For questions on methods of thiamin assessment or for technical assistance, please contact the OpeN-Global team at https://open-global.kcl.ac.uk/contact/ or write to:

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Useful links

US National Academies Press IOM Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline, 2000: http://nationalacademies.org/hmd/reports/2000/dietary-reference-intakes-for-thiamin-riboflavin-niacin-vitamin-b6-folate-vitamin-b12-pantothenic-acid-biotin-and-choline.aspx

Linus Pauling Institute Micronutrient Information Center (Oregon State University): https://lpi.oregonstate.edu/mic/vitamins/thiamin

NIH Health Information on thiamin: https://ods.od.nih.gov/factsheets/Thiamin-HealthProfessional/

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