Thiamine (whole blood, urine)

1 Name and description of analyte

1.1 Name of analyte

Thiamine (whole blood, urine).

1.2 Alternative names

Thiamin, vitamin B1, thiamine diphosphate (TDP), thiamine pyrophosphate (TPP).
3-[4-amino-2-methyl-pyrimidyl-5-methyl]-4-methyl-5-[β-hydroxyethyl]thiazole.

1.3 This heading is not used

1.4. Function(s) of analyte

Thiamine is a water-soluble vitamin involved in numerous functions, including the nervous system (axonal conduction), muscular functioning (electrolyte flow), carbohydrate metabolism and production of hydrochloric acid needed for digestion.

Thiamine commprises pyrimidine and thiazole rings. The alcohol side-chain is esterified with one (thiamine monophosphate; TMP), two (thiamine diphosphate; TDP, also called thiamine pyrophosphate; TPP) or three (thiamine triphosphate; TTP) phosphate groups. All forms of thiamine can be interconverted *in vivo*.

TDP is formed in the jejunal mucosa, liver, kidneys and leukocytes, and is the main (90%) circulating form of thiamine, being present mainly in erythrocytes (80% of total). Approximately half of thiamine stores are in skeletal muscle and the rest is in heart, kidneys, liver and nerve tissue.

TDP is an important magnesium-coordinated cofactor for essential reactions catalysed by decarboxylase subunits of dehydrogenase complexes for pyruvate, 2-oxoglutarate, and branched-chain oxo acids. It is also required for transketolations in the pentose phosphate pathway (necessary for the synthesis of fatty acids, steroids, nucleic acids, and the aromatic amino acid precursors to a range of neurotransmitters and other bioactive compounds essential to brain function).

Thiamine also has non-cofactor roles: TTP is found in nerve and muscle cells where it activates membrane ion channels, possibly by phosphorylating them. It also plays a neuro-modulatory role in the acetylcholine neurotransmitter system, and contributes to the structure and function of cellular membranes (including neurons and neuroglia).

Dietary sources of thiamine include cereals (especially whole grain), brown rice, vegetables (green, leafy, beets and potatoes), legumes (lentils, soybeans, nuts and seeds), oranges and tomatoes, milk and milk products, pasta, meat, fish, poultry, and eggs. Thiamine is often added to food (e.g. cereals) in developed countries. Raw fish and shellfish contain thiaminases, which convert TDP to an inactive form. Tea and coffee contain thiamine antagonists.

Thiamine is absorbed in the jejenum by two processes; active transport when thiamine concentrations in the small intestine are low

(<5 mg/24 h), and passively (mucosally) when small intestine concentrations are high. Excretion is via urine following dephosphorylation of TDP in the kidneys.

2 Sample requirements and precautions

2.1 Medium in which measured

1. TDP measurement in whole blood is the most appropriate test to assess thiamine status. Blood should be collected into a lithium-heparin (non-gel) or EDTA tube following an overnight (12–14 hours) fast .The sample should be protected from light and frozen immediately.

2. Thiamine can be measured in a 24 h urine sample (with low outputs in clinical deficiency states) or a 4 h urine sample before and after a test load of thiamine (with retention of a higher proportion seen in deficiency).

2.2 Precautions re sampling, handling etc.

Blood must not be collected into a glass vial.
If the patient is on oral supplementation or being parenterally fed, a fasting blood sample or sample collected 8 hours post-treatment is needed.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

Measurement of whole blood thiamine may occasionally be useful in patients with suspected alcoholic or nutritional cardiomyopathy, neuropathy or Wernicke-Korsakoff syndrome.

3.2 Limitations

Urinary excretion of thiamine reflects dietary intake, and is influenced by absorption and other factors. It is therefore not a reliable indicator of thiamine status.

4 Analytical considerations

4.1 Analytical methods

Early microbiological methods and the chemical conversion of thiamine to thiochrome detected fluorometrically are now outdated.
Thiamine is now measured by electrophoretic, ion-exchange, or HPLC methods to quantitate the free vitamin and its phosphate esters. HPLC methods for TDP utilise fluorometric or mass spectrometric detection (LC-MS/MS). TDP concentration is sometimes related to the amount of haemoglobin (Hb) in the sample for reporting (e.g. ng TDP/g Hb).

4.2 Reference method

None.

4.3 Reference materials

Thiamine hydrochloride is available from the United States Pharmacopeia (USP), European Pharmacopeia (EP); thiamine mononitrate is available from the British Pharmacopeia (BP).

4.4 Interfering substances

Gross lipaemia causes assay interference.

4.5 Sources of error

See section 2.2.

5 Reference intervals and variance

5.1.1 Reference interval (adults)

This varies depending on method.
Whole blood: 275–675 ng TDP/g Hb or 50–220 nmol/L.
Marginal deficiency: 150–275 ng TDP/g Hb or 27–50 nmol/L.
Overt deficiency: <150 ng TDP/g Hb or <27 nmol/L.

5.1.2 Reference intervals (others)

Urinary thiamine: 100-200 μg 24 h.

5.1.3 Extent of variation

5.1.3.1 Interindividual CV:

TDP = 12%.

5.1.3.2 Intraindividual CV:

TDP = 4.8%.

5.1.3.3 Index of individuality:

TDP = 0.47.

5.1.3.4 CV of method:

Typically ~6% at 326 ng TDP/g Hb and ~4% at 1135 ng TDP/g Hb.

5.1.3.5 Critical difference:

TDP = 15.8%.

5.1.3.6 Sources of variation

Nothing in addition to normal analytical and biological variation.

6 Clinical uses of measurement and interpretation of results

6.1 Indications and interpretation

TDP measurement may be requested when patients have behavioural changes, eye signs, gait disturbances, delirium and encephalopathy; or in patients with questionable nutritional status, especially those who appear at risk and who also are being given insulin for acute hyperglycemia.
Testing may also be requested in those with a condition that puts them at risk of deficiency, including individuals with a limited or inadequate diet, with signs of malnutrition, being given parenteral nutrition, and those who have had gastric bypass surgery. Individuals with alcohol

dependence or with chronic diseases associated with malabsorption such as coeliac disease are also at risk of thiamine deficiency.

One or more B vitamins may be tested to detect deficiencies in those with characteristic symptoms. However, this is rarely required for clinical purposes, as treatment with vitamin B complex is safe and cheap and physical signs of deficiency are rapidly reversed.

6.2 Confounding factors

Vitamin supplementation and non-fasting specimens may result in elevated TDP concentrations.

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

It appears that no conditions are directly attributable to thiamine excess and thiamine administration is generally safe except in rare cases of anaphylaxis with intravenous thiamine.

Toxic effects (ataxia) have been described in adults with chronic intakes of >50 mg/kg body weight or >3 g/24 h.

7.1.2 Investigation

Measurement of TDP in whole blood.

7.2 Low values

7.2.1 Causes

Signs and symptoms of mild-to-moderate deficiency are non-specific and include irritability, malaise, weight loss, indigestion, confusion, sleep disturbances, and paraesthesiae.

Body stores are limited to an average 30 mg (30 X the daily requirement) and so marginal deficiency can develop fairly quickly (in ten days) and more severe deficiency within 21 days if intake is restricted.

Deficiency used to be widespread in areas where rice formed the major part of the diet (eating rice without the husk containing thiamine). However, it is now more typically seen in alcoholics due to reduced absorption.

Approximately 80% of chronic alcoholics are thiamine deficient due to poor nutrition and inhibition of thiamine absorption by alcohol. Diets high in carbohydrate require more thiamine for their utilisation than diets high in fat and subclinical deficiency may be unmasked by refeeding with a carbohydrate-rich diet.

Deficiency is more common in those with:

- low intake e.g. malnutrition, the elderly, anorexia nervosa, prolonged hyperemesis gravidarum
- gluten sensitivity, which can diminish thiamine absorption (the processes used to minimise gluten content in food also result in removal of thiamine).
- malabsorption e.g. chronic diarrhoea, gastrointestinal disease, bariatric surgery, and and cytotoxic treatment

- increased requirements e.g. pregnancy, fever, breast feeding, rapid adolescent growth, parenteral nutrition (see below)
- increased loss e.g. haemodialysis, renal dialysis, long-term diuretic therapy.
- thiamine-responsive inherited metabolic disorders including: megaloblastic anaemia of unknown mechanism, lactic acidosis caused by low or defective pyruvate decarboxylase, branched-chain oxoaciduria, and subacute necrotising encephalomyelopathy.

Refeeding syndrome

Clinical evidence of thiamine deficiency may become apparent on refeeding, owing to the high thiamine requirement imposed by increased energy intake in the form of glucose. Those at risk of refeeding syndrome should be supplemented with 200–300 mg/day thiamine for the first tendays (NICE guidelines).

Beriberi

Prolonged deficiency is termed beriberi and is more common in South East Asian countries owing to the consumption of milled rice. Beriberi means "I can't" in Singhalese and is classically divided into wet and dry forms, which relate to the amount of fluid accumulation in the body.

Dry beriberi

Involves the central nervous system and symptoms can include the following; poor appetite, fatigue, peripheral neuropathy consisting of bilateral symmetric lower-extremity paraesthesiae, absent knee jerk and other deep tendon reflexes, and progressive weakness and atrophy. Cerebral involvement occurs, producing the picture of the Wernicke-Korsakoff syndrome.

Wernicke-Korsakoff syndrome is most classically seen in individuals with chronic alcoholism. Wernicke encephalopathy is characterised by a triad of confusion, ataxia and ocular abnormalities (nystagmus and seventh nerve palsy). Severe Wernicke encephalopathy is a medical emergency that can progress to coma and death, or lead to an irreversible amnestic dementia and a confabulatory state known as Korsakoff syndrome. Rapid treatment of Wernicke encephalopathy with thiamine can prevent Korsakoff syndrome.

Wernicke encephalopathy and Korsakoff psychosis were originally described as two separate conditions, but now appear to be the acute and chronic manifestations of a single condition. In 80%, the encephalopathy fails to resolve completely and psychosis develops. Once established, this responds less readily to thiamine. Susceptibility may be greater in individuals with a genetic variant of transketolase that binds thiamine less avidly.

Wet beriberi

Deficiency impairs pyruvate dehydrogenase with accumulation of lactate and pyruvate, producing peripheral vasodilatation and eventually oedema. Wet beriberi presents with cardiovascular disturbances including tachycardia, weakness, congestive heart failure, and shortness of breath. Initially there is a high-output state with a bounding pulse and

raised venous pressure, but eventually heart failure with low cardiac output supervenes.

Infantile beriberi

This variant occurs in breastfed babies of thiamine-deficient mothers and may present with dyspnoea, tachycardia and cyanosis, and later diarrhoea and vomiting. The infant becomes anorexic, develops oedema and has a degree of aphonia. Infantile beriberi has a high rate of fatality.

7.2.2 Investigation

There is no rapid and reliable test for thiamine deficiency. The safest confirmatory test is a trial of thiamine supplementation, since delay may be harmful in deficient patients and if the patient responds to treatment, it is safe to assume that a measure of thiamine deficiency was responsible for their condition. The response to parenteral thiamine (minimum 100 mg/day) is usually rapid and in wet beriberi occurs within hours, but in dry beriberi can be slower. Reversal of neuropathy is unpredictable and may take up to 12 months to resolve. Infantile beriberi is treated by giving thiamine to the mother, which is passed on to the infant via the breast milk.

7.3 Notes

None.

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions

None reported.

9 Systematic reviews and guidelines

9.1 Systematic reviews

1. Isenberg-Grzeda E, Rahane S, DeRosa AP *et al.* Wernicke-Korsakoff syndrome in patients with cancer: a systematic review. Lancet 2016; 7:e142-8. *The authors conclude that oncologists should be aware of the risk factors for cancer-related Wernicke-Korsakoff syndrome, especially in the absence of alcohol misuse disorders.*

2. ter Borg S, Verlaan S, Hemsworth J *et al*. Micronutrient intakes and potential inadequacies of community-dwelling older adults: a systematic review. Brit J Nutr 2015;113:1195-206. *The authors included 37 articles in their systematic review. They analysed twenty nutrients and determined that thiamine is one of six that is a public health concern in older adults.*

3. Jain A, Mehta R, Al-Ani M *et al.* Determining the role of thiamine deficiency in systolic heart failure: a meta-analysis and systematic review. J Card Fail 2015; 21:1000-7. *The authors determine that thiamine deficiency is more prevalent in the heart failure population and its supplementation may be beneficial.*

4. DiNicolantonio JJ, Lavie CJ, Niazi AK *et al.* Effects of thiamine on cardiac function in patients with systolic heart failure: Systematic review and metaanalysis of randomized, double-blind, placebo-controlled trials.

Ochsner J 2013; 13:495-9. *The authors conclude that compared to placebo, thiamine supplementation resulted in improvement in net change in left ventricular ejection fraction.*
5. Day E, Bentham PW, Callaghan R *et al.* Thiamine for prevention and treatment of Wernicke-Korsakoff syndrome in people who abuse alcohol. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No. CD004033. *Concludes that the use of thiamine in the treatment of acute Wernicke-Korsakoff syndrome allows rapid resolution of ataxia and opthalmoplegia and slow but significant improvement in the severity of nystagmus. The global confusional state also appears to improve rapidly within hours of thiamine treatment. Impairment of memory and learning responds more slowly and often incompletely, suggesting a different mechanism of effect. Available evidence from RCTs is insufficient to guide clinicians in the dose, frequency, route or duration of thiamine treatment for prophylaxis against or treatment of established Wernicke-Korsakoff syndrome due to alcohol abuse.*
6. Rodríguez JL, Qizilbash N, López-Arrieta JM. Thiamine for Alzheimer's disease. Cochrane Database of Systematic Reviews 2001, Issue 2. Art. No. CD001498. *The authors conclude that there is no reliable evidence on which to base a decision to use thiamine to treat patients with Alzheimer's disease.*

9.2 Guidelines

1. O'Kane M, Barth J, Batterham RL *et al.* Guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery. British Obesity & Metabolic Surgery Society 2014. Available at: http://www.bomss.org.uk/wp-content/uploads/2014/09/BOMSS-guidelines-Final-version1Oct14.pdf
2. Alcohol-use disorders: diagnosis and management. NICE Quality Standard 11, August 2011.
3. Galvin R, Bråthen G, Ivashynka A *et al.* European Federation of Neurological Societies guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur J Neurol 2010; 17:1408-18.
4. Alcohol-use disorders: diagnosis and management of physical complications. NICE Clinical Guideline 100, June 2010 updated April 2017.
5. Nutrition Support for Adults: oral nutrition support, enteral tube feeding and parenteral nutrition. NICE Clinical Guideline 32, February 2006 updated August 2017.
6. Thiamine deficiency and its prevention and control in major emergencies. WHO/NHD/99.13. 1999. *The authors conclude that frank thiamine deficiency is rare today, however, subclinical thiamine deficiency can manifest as frank beriberi under some circumstances. They summarise the options for intervention to prevent or control thiamine deficiency.*

9.3 Recommendations

1. https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-b/ (accessed 1 March 2018). *Information regarding the recommended daily intake of vitamins and minerals.*
2. https://bnf.nice.org.uk/drug/thiamine.html (accessed 1 March 2018). *Indications for thiamine supplementation and important safety information.*

10 Links

10.1 Related analytes

1. Red cell transketolase requires two cofactors, thiamine and magnesium, and although measuring transketolase activity is relatively specific for detection of thiamine deficiency, a normal activity should not discourage treatment if deficiency is suspected. Other factors can also decrease transketolase activity and since it is an indirect assessment of thiamine status it is now considered an inadequate method. The method also has poor precision and concerns regarding specimen stability.
Transketolase activity is usually measured by the determination of the rate of disappearance of D-ribose 5-phosphate with the orcinol reagent (orcinol and ferric chloride in concentrated hydrochloric acid), or by the amount of fructose 6-phosphate formed. A functional enzymatic assay of transketolase activity measured before and after the addition of TTP is a more reliable way to measure thiamine nutritional status. A stimulation exceeding 20%–25% after the addition of TTP indicates severe thiamine deficiency.

2. Measurement of urinary metabolites, notably thiamine acetic acid, have also been used as a measure of thiamine deficiency.

3. Plasma pyruvate and lactate: reduced activity of transketolase and the pyruvate dehydrogenase complex, results in increased pyruvate in the blood, which, in turn, is not converted to acetyl-coA and is unable to enter the tricaroxylic acid (Krebs) cycle (for aerobic oxidative metabolism). Thus, there is a buildup of pyruvate, which is metabolized anaerobically to lactate. Neither test is specific to thiamine deficiency.

10.2 Related tests

Thiamine is usually ordered as part of a vitamin B panel.
Thyroid-stimulating hormone should be measured to rule out thyrotoxicosis-induced high-output heart failure.

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