Paper Accepted*

Review Article / Прегледни рад

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Vitamin B1, eye and brain

Витамин Б1, око и мозак

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Received: September 29, 2021
Revised: January 24, 2022
Accepted: February 3, 2022
Online First: February 10, 2022
DOI: https://doi.org/10.2298/SARH210929019B

*Accepted papers are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author’s last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. *Srp Arh Celok Lek*. Online First, February 2017.

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SUMMARY
Vitamin B1 (aneurin, thiamine) is a water-soluble vitamin necessary for the normal function of the nervous system, visual system and heart and is part of important enzymes in the body. Thiamine enables the normal use of glucose, other carbohydrates and proteins, and enables the supply of energy to the organism. The main sources of thiamine are exogenous and small amounts are synthesized by microorganisms of the human intestinal microbiome. Vitamin B1 cannot accumulate in the body, so signs of deficiency are quickly manifested. Hypovitaminosis B1 is seen in chronic ethanol abuse, persistent vomiting (as in some pregnant women) or after bariatric surgical procedures, but in a mild form it is present in the general population. Normal daily needs for vitamin B1 depend on calorie intake, and 0.4 mg should be ingested for every 1000 kcal. Keywords: vitamin B1; eye, brain

INTRODUCTION
Although importance of vitamins for visual function is well known, the importance of all of them is not yet elucidated [1]. Vitamin B1 (aneurin, thiamine) is a water-soluble vitamin that is crucial for glucose metabolism and is necessary for normal growth and development of the organism. Thiamine is essential for functioning of both central (CNS) and peripheral (PNS) nervous systems, visual, digestive and cardiovascular systems [2].

The main sources of thiamine are exogenous, with food, and small amounts are synthesized by microorganisms of the human intestinal microbiome [3]. Most thiamine is found naturally in pork and other meats, germ grains, liver, eggs, fish, beans, peas, nuts and whole grains. The recommended daily intake (RDA) is 0.4 mg per 1000 kcal. Significant amounts of vitamin B1 are lost during heat treatment of food. The polyphenols in coffee and tea can inactivate thiamine. The recommended daily intake of thiamine is 2 mg [2].
Vitamin B1 cannot accumulate in the body, so signs of deficiency are quickly manifested [2]. Thiamine stores in the body are only about 30 mg, with a half-life of 10-18 days [4]. Hypovitaminosis B1 is seen in chronic ethyl abuse, persistent vomiting (as in some pregnant women) or after bariatric surgical procedures, but in a mild form it is present in the general population [5].

**PHYSIOLOGY**

Vitamin B1 is necessary for the normal function of the nervous system, visual system and heart and is part of important enzymes in the body. Thiamine enables the normal use of glucose, other carbohydrates and proteins, and enables the supply of energy to the organism. Thiamine-dependent enzymes use thiamine diphosphate (ThDP) as a coenzyme. These enzymes are also called ThDP-dependent enzymes. Other thiamine derivatives are thiamine triphosphate and thiamine adenylate which participate in homeostasis that is the non-enzymatic activity of vitamin B1 [6].

**DEFICIENCY**

Historically, hypovitaminosis B1 - beriberi was first described in Japan, several centuries ago, and in the 19th century, Wernicke's encephalopathy and Korsakov's syndrome [3]. Hypovitaminosis B1 is even today more common than previously thought, primarily due to the discrepancy between high intake of pure calories and low intake of vitamins, with the situation being exacerbated by the fact that this vitamin deficiency is a major imitator [7]. The modern way of eating with "fast" food favors the development of the withdrawal period of vitamin B1. The aggravating factor is the lack of pathognomonic signs and reliable laboratory diagnostics. A study conducted by Williams in the United States in 1943 showed a significant prevalence of vitamin B1 deficiency in the general population [8].
The most commonly affected systems in thiamine deficiency are the heart, blood vessels, NS, eyes, and gastrointestinal system [9]. Periventricular gray matter neurons are particularly sensitive to thiamine deficiency [10]. Damage to the nuclei of the vestibular and abducens nerves may precede B1 encephalopathy with mild ophthalmoparesis and bilateral vestibular damage. Aneurin deficiency leads to pseudohypoxia at the cellular level, and later to dysautonomy in various tissues [7]. In deficiency states, lactates, pyruvate and other substances increase. Thiamine deficiency disrupts the function of nitric oxide (NO) which is an important transmitter, especially in the vascular system. Vitamin B1 deficiency has been found to correlate with degeneration of ganglion cells of the brain and spinal cord and reduced retinal ganglion cell layer thickness in animal models [11].

**Beriberi**

Vitamin B1 deficiency causes beriberi with: weight loss, emotional disorders, changes in perception, weakness of the extremities, irregular heartbeat and tissue edema. Heart failure can be fatal. No sign of beriberi is pathognomonic, and the clinical picture is very variable [7]. There is a division into dry beriberi (neurological) where polyneuropathy predominates and wet beriberi (cardiological) where cardiomyopathy with peripheral edema predominates, although they are often associated [9]. Disorders of the gastrointestinal system are also present.

Beri-beri was first described in Japan in people who used glazed rice. Thus, food contained high levels of calories with a lack of other essential nutrients called high-calorie malnutrition [12]. Today, high-calorie malnutrition is not uncommon in the West in obese people, where thiamine deficiency is present in as many as 15-29% of people with mild and nonspecific symptoms [13]. Beriberi can be divided into alcohol-induced and non-alcoholic. At risk are people who use diuretics, e.g., furosemide that enhance vitamin B1 secretion [4].

As a rule, patients with beriberi are pale. Slightly elevated body temperature is due to
dysautonomy. At the beginning of the disease, palpitations can occur in exertion or stress, while later they might also occur at rest [7]. Edema may be only mild pretibial with sensitivity to palpation. The heart is enlarged, especially the right. Diastolic pressure is below 60mm/Hg, and sometimes even drops to zero, especially in children.

Oxygen saturation becomes low in arterial and high in venous blood, which indicates the role of thiamine in oxygen transport. In the initial stages, the vagal tone is increased, and in the advanced stages, the sympathetic tone. Thus, bradycardia can sometimes be found, and sometimes tachycardia. Changes in the electrocardiogram (ECG) are seen only in the later stages.

The neurological findings are dominated by signs of damage to peripheral nerves, autonomic, sensory and motor [9]. Initially the loss of superficial sensibility for touch can be found due to damage to long fibers ("socks" and "gloves" type) and the vibrational sensibility also suffer. When the process spreads to shorter fibers, the abdomen is also affected, with a vague border of loss. Paresthesias also occur. Later, the fibers for pain are also affected. Loss of sensibility is in most cases symmetrical, but the dominant extremities are usually affected first.

Nystagmus and decreased visual acuity may be observed in the eyes, followed by narrowing of the visual field. Eventually, optic neuritis may develop with papillary edema and then temporal pallor, similar to multiple sclerosis [3, 14]. Blurred vision and blindness are possible with severe neuropathy.

Patients experience stomach pain and constipation, and in more severe forms anorexia, thirst, nausea and vomiting [15]. There is a disorder in the secretion of saliva, gastric and intestinal juices, usually a decrease, due to dysautonomy. Lymphocytosis, neutropenia and eosinophilia can be seen in the blood count. Erythrocyte sedimentation rate is also often elevated. In advanced cases, normoblasts are seen in the peripheral blood.
Wernicke/Korsakoff syndrome

Wernicke's encephalopathy and Korsakoff's dementia/psychosis are often interrelated phenomena caused by vitamin B1 deficiency. Both disorders require urgent treatment, but the diagnosis is often made late or not at all. Autopsy shows pathological findings characteristic of these diseases significantly more common than is the prevalence in both the general population and the ethyl abuse individuals [16]. Korsakoff's psychosis is a severe acute dementia with the impossibility of remembering new information, that is, anterograde amnesia and confabulations and is difficult to treat [9].

Wernicke's encephalopathy manifests itself as global confusion, oculomotor disorder (nystagmus, ophthalmoplegia) and gait ataxia, which is a classic triad that is seen in only 16-20% of cases, so the diagnosis is often wrong [16]. It is especially difficult to diagnose Wernicke's encephalopathy during a drunken state, other causes of confusion, the use of benzodiazepines, sepsis, hypoxia, hepatic encephalopathy, delirium tremens and head injuries. Untreated Wernicke's encephalopathy is fatal in about 20% of cases [17].

Wernicke's encephalopathy and/or Korsakov's dementia most often occur in chronic alcoholics, followed by a decreasing incidence in cancer, gastrointestinal surgery, Hyperemesis gravidarum, starvation, fasting, gastrointestinal diseases, AIDS, resorption disorders, dialysis and kidney disease, parenteral nutrition, vomiting, psychiatric diseases with eating disorders and schizophrenia, infections, intoxication, thyroid disorders, iatrogenic, poor nutrition, hypoxic encephalopathy, diarrhea, magnesium deficiency, some congenital conditions and other [16].

Marginal thiamine deficiency

Mild forms of thiamine deficiency are common because depoes are scarce (liver, muscle) and can occur as early as 2-3 weeks after thiamine-deficient nutrition [9]. Alcohol, tea and
coffee lower thiamine levels as well as higher amounts of carbohydrates. Also at risk are people with increased thiamine needs such as pregnant and lactating women, people exposed to heavy physical exertion, people with cancer, liver, infections and hyperthyroidism, patients undergoing surgical procedures, as well as thiamine resorption disorders (excess alcohol intake, gastrointestinal diseases, vomiting, diarrhea).

Thiamine deficiency can manifest as anorexia, malaise, burning in the extremities distally, irritability and depression, while later, after 2-3 months, insomnia, cough, emotional lability, panic attacks, pain in the joints, muscles or extremities may occur. It also increased need for sugar, gastro-esophageal reflux, abdominal pain with constipation and diarrhea, daily headaches or migraines, edema of the nasal mucosa, dyspnea, polyneuropathy with numbness, paresthesias, cold extremities, palpitations, also chest pain, intolerance to ambient temperature as well as recurrent nausea and vomiting [9, 7].

Chronic vitamin B1 deficiency significantly contributes to the development of neurodegenerative diseases [2]. Thiamine is associated with Alzheimer’s disease, Parkinson's disease (PD), Huntington's disease (HP) and Wernicke-Korsakoff syndrome. Thiamine administration not only has a neuroprotective effect but also has a beneficial effect even in advanced neurodegenerative diseases.

Thiamine deficiency in children should be suspected in a whole range of non-specific symptoms such as: emotions, behavior and attention disorders, learning disabilities, redness of the cheeks, pale eyes, blood pressure disorders, muscle reflex disorders, dermatographism and others [7].

**Benfotiamine**

Benfotiamine is a synthetic vitamin B1 that is liposoluble and passes many times better into the brain and peripheral nerves, which makes it suitable in the treatment of nervous
diseases [18]. Comparative studies have shown that lipophilic thiamine derivatives are significantly better resorbed than hydrophilic thiamine [19]. Benfotiamine is a liposoluble precursor of thiamine that can be converted to thiamine in tissues and then metabolized to thiamine monophosphate and thiamine diphosphate [20].

The effects of benfotiamine are mild inhibition of cholinesterase, reduction of amyloid plaque production and hyperphosphorylated tau [21,22]. It also accelerates the recovery of peripheral nerves after various injuries. In an animal model, administration of benfotiamine improved spatial memory in a dose-dependent manner and reduced in Alzheimer’s disease (AD) model both amyloid beta plaques and hyperphosphorylated tau levels, with other forms of thiamine not being effective. Long-term use of benfotiamine in a small study in patients with AD improved cognitive status [23].

Benfotiamine has been used successfully in diabetic polyneuropathy [24]. The greatest effect was achieved after 3 and 6 weeks of administration with large doses of benfotiamine of 320 mg per day, but smaller doses were also effective (150 mg per day). The feeling of pain is reduced and the vibrational sensitivity is improved. Usually, 150 mg twice a day or 300 mg twice a day of benfotiamine are given with food. In some cases of Korsakov's psychosis, long-term administration of benfotiamine is required with gradual reduction of doses to maintenance doses with excellent results. Benfotiamine can be given up to 600 mg daily.

**Sulbutiamine**

Another synthetic derivate of vitamin B1, with beneficial effects in treatment of Alzheimer’s disease. Sulbutiamine enhances cholinergic and glutamanergic transmission, mainly by hippocampus and prefrontal cortex. Sulbutiamine has proven neuroprotective effect on retinal ganglion cells [25]. This is a highly lipid soluble synthetic analogue of vitamin B1, clinically used for asthenia treatment. When tested on retinal ganglion cells in vitro, it showed
effects of preventing trophic factor induced apoptotic cell death. Sulbutiamine is lipophilic and easily crosses brain blood barrier. Numerous studies showed that this agent stimulates reticular activating system, potentiates cholinergic activity in hippocampus and glutamatergic activity in the prefrontal cortex [26,27].

**Diagnosis of vitamin B1 deficiency**

The diagnosis of vitamin B1 deficiency requires, above all, a high degree of suspicion of these disorders in all increased risk conditions because the clinical picture is highly variable [28]. A detailed anamnesis regarding the consumption of food, alcohol, vomiting, digestion, etc. is also necessary, as well as a careful clinical examination. Vitamin B1 testing is based on measuring concentrations: thiamine pyrophosphate or transketolase (thiamine-dependent enzyme) activity in erythrocytes [5].

Well-documented cases of Wernicke's encephalopathy with normal or even elevated thiamine levels have also been described [28]. This is probably due to the discrepancy of levels in serum and tissues, as is the case with vitamin B12 and magnesium [7, 9, 29]. Normal serum thiamine values are 70-180 nmol/L, and deficits indicate values less than 70 nmol/L.

**THERAPY**

Normal daily needs for vitamin B1 depend on calorie intake: 0.4 mg should be ingested for every 1000 kcal [9]. This would mean e.g. that an adult man who ingests 3200 kcal per day should take 1.3 mg of thiamine per day, and a woman who ingests 2300 kcal to take 0.9 mg of thiamine. Slightly different is the recommendation of the National Research Council from the United States, which states the required intake of 0.5 mg / 1000 kcal, with the proviso that the daily intake should not be less than 1.0 mg regardless of calorie intake.

National Research Council states that due to the additional caloric needs of the fetus,
pregnant women [30, 31] should take an additional 0.4 mg per day of thiamine at the appropriate daily intake, and during lactation, the infant needs another 0.5 mg per day for their own needs. Infants should take 0.17 mg of thiamine daily. The recommendation of the World Health Organization (WHO) is 0.3 mg/L or 0.4 mg/1000. Children and adolescents have the same needs as adults, ie 0.4 mg / 1000 and 0.5 mg/1000 kcal [31].

**THERAPEUTIC APPLICATION**

Thiamine has been used in patients with: anxiety disorders, chronic fatigue, sleep disorders, anorexia, nausea, indigestion, chest and abdominal pain, depression, aggression, headaches, etc. Some studies have shown a beneficial effect of vitamin B1 in people with neurodegenerative diseases [6]. The benefit of thiamine therapy in Wernicke-Korsakov syndrome, beriberi and other deficiencies is unequivocal. Prompt thiamine replacement is necessary to prevent irreversible changes [16]. Due to urgency, vitamin B1 is usually applied empirically, especially since the level of B1 in the blood is not a reliable measure of deficiency. Benfotiamine is also used.

There are no generally accepted guides to the use of thiamine. There are schemes with the administration of thiamine for prophylactic purposes in persons at risk with 100 mg intramuscularly three times a day for 3-5 days or 250 mg intramuscularly for 3-5 days, as well as many other schemes [16]. In the case of diagnosed Wernicke and/or Korsakoff syndrome, thiamine is administered intravenously in doses of 100-500 mg for at least 5 days, and then in smaller doses, e.g. 250 mg intramuscularly until improvement occurs. Prolonged oral administration is usually required to achieve better effects. Giving doses of ≥500 mg intravenously daily is safe [31]. According to recommendations, in mild deficits, 100 mg should be given orally daily.

In children with vitamin B1 deficiency and heart failure, convulsions or coma, 25–50 mg
of thiamine is given very slowly intravenously, then daily 10 mg intramuscularly for one week and then 3-5 mg daily orally for at least 6 weeks [9].

SAFETY

Excess thiamine is excreted by the kidneys [9]. Isolated cases of adverse reactions have been reported with intravenous administration in doses of 5-100 mg, and very rarely an allergic reaction may occur with extremely high oral doses of 5-10 g [32]. Also, it has been proven that long term use of thiamine supplements (along with other B group vitamins and vitamin A) is associated with reduced prevalence of nuclear and cortical cataract [33, 34]. In this study a supplement user was defined as a subject who consumed vitamin supplements for at least 4 days per week, with variable dosage from 0.8 to 1 mg/day.

CONCLUSION

Thiamine, or Vitamin B1, is an essential nutrient with many health benefits, especially protecting the brain and heart [33, 34, 35]. Time will tell whether vitamin supplementation, especially thiamine, has an impact on winning the covid pandemic [36]. This is an opportunity for medical workers and ordinary people, to be reminded of its importance, natural sources and possible supplementation.

ACKNOWLEDGMENT

This article is partially financed by the Ministry of Science, Republic of Serbia, Project No 175033 and 175022

Conflict of interest: None declared.
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