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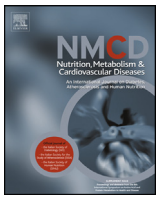

REVIEW

Thiamine deficiency and cardiovascular disorders

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Thiamine supplementation

Abstract *Background and aim:* Thiamine, also known as vitamin B1, functions as a cofactor in the metabolism of carbohydrates and amino acids. Thiamine deficiency has been suggested to be associated with many cardiovascular diseases (CVDs) and risk factors including type 1 and type 2 diabetes (T1D and T2D, respectively), obesity, chronic vascular inflammation, dyslipidemia, heart failure (HF), myocardial infarction (MI) and conduction defects, and depression. The aim of this review was to explore the evidence of thiamine deficiency among subjects with CVDs or risk factors, illustrate the theories explaining the thiamine-CVDs associations, and describe the effect of thiamine supplementation.
Methods: Human and animal studies were collected from various scientific databases following the PRISMA guidelines without limitation regarding the publication year. Studies investigating the prevalence of thiamine deficiency among patients with CVDs and the effect of thiamine supplementation on their conditions were summarized.
Results and conclusions: Thiamine deficiency could have a role in the development of CVDs. Future studies should focus on the impact of thiamine supplementation on reversing CVDs and risk factors associated with its deficiency.

Introduction

Thiamine, also referred to as vitamin B1 or aneurin, is an essential micronutrient that takes four forms in the human body according to its phosphorylation status: unphosphorylated, mono-, di-, and triphosphate. Thiamine is involved in many oxidation–reduction reactions involved in the metabolism of glucose and branched-chain amino acids. In the Krebs cycle, thiamine is essential for the oxidative decarboxylation, which occurs within the mitochondria, for adenosine triphosphate (ATP) production. It is also important for the pentose shunt pathway, which supplies reduced nicotinamide adenine dinucleotide phosphate (NADPH) for reducing the oxidized glutathione and provides pentose phosphate for nucleotide synthesis [1].

Thiamine is absorbed by both passive and active uptake in the jejunum and ileum and then transferred to the liver to enter the red blood cells (RBCs) by facilitative transport. Excess thiamine that is not bound to protein is excreted through the distal nephrons, and the rate of thiamine loss is closely related to the amount of renal clearance [2,3].

Although thiamine can be obtained from various food sources such as cereals, beef and pork, seeds and nuts, and

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yeast, some common food groups are deficient in thiamine, such as polished rice, milled wheat flour, milk, vegetables, and fruits [4]. High temperature and pH have a denaturing effect on thiamine; therefore, cooking, baking, pasteurization, and preserving foods can degrade thiamine [3]. In addition, the half-life of thiamine in the body is between 1 and 3 weeks [4]. These factors together could explain the relatively short period needed for thiamine deficiency and the appearance of clinical symptoms after consuming a thiamine-deficient diet, which is approximately 3 weeks and 3 months, respectively [4].

Thiamine loss is strictly associated with urinary clearance. Therefore, diuretics have been identified as the main cause of thiamine deficiency in patients with cardiovascular diseases (CVDs) [5]. Because thiamine is crucial for glucose metabolism, ingestion of a high-calorie diet containing simple carbohydrates will increase thiamine requirements, thereby resulting in thiamine deficiency [6]. In addition, chronic alcoholism is one of the primary causes of thiamine deficiency in clinical practice. Alcohol abuse affects thiamine cellular transport and its intracellular phosphorylation [7]. Moreover, increased thiamine requirements due to fever, excessive exercise, pregnancy and lactation, stress, and trauma may also lead to thiamine deficiency [4].

Thiamine levels can be measured directly in the serum or urine or indirectly by measuring the activity of the transketolase enzyme. However, because of the short half-life of thiamine in the blood, the direct way evaluates the recent thiamine intake rather than the actual thiamine status [2].

For decades, thiamine deficiency was portrayed in the context of beriberi attributed to eating polished rice. However, this perception has changed, and the interest in thiamine deficiency as a risk factor for many systemic disorders has been increasing [8]. On the other hand, CVDs account for the major causes of morbidities and mortalities in developed and underdeveloped countries and are greatly associated with nutritional imbalances [9].

Increasing evidence, directly or indirectly, links thiamine deficiency with many CVDs and risk factors. This review aims at providing a summarized report on thiamine deficiency in patients with various CVDs. The suggested theories explaining this linkage and the effect of thiamine supplementation are also provided.

Methodology

Articles, book chapters, and books were collected from scientific databases (PubMed, Web of Science, Scopus, Embase, CINAHL, MEDLINE, and the Cochrane Library) using the search terms ("Thiamine," "Thiamin," "vitamin B1," "vitamin deficiency," "Beriberi," and "thiamine supplementation") and ("cardiovascular diseases," "cardiovascular disorders," "cardiovascular risk factors," "diabetes," "obesity," "inflammation," "dyslipidemia," "endothelial dysfunction," "acute myocardial infarction," "depression," "cerebrovascular diseases," "heart failure," and "stroke"). Literature in only English was considered. There was no limit regarding publication year. Human studies were selected and animal models were cited whenever the information examines a question that cannot be studied in humans or suggests a question that can then be studied in humans.

Cardiovascular disorders and risk factors

Diabetes mellitus

Diabetes mellitus (DM) increases the risk of cardiovascular morbidity and mortality by causing several abnormalities in the metabolism of glucose, lipid, and lipoprotein; increased platelet aggregation; endothelial dysfunction; and increased risk of cardiac arrhythmia [10].

A study of 120 adults with type 2 diabetes (T2D), among whom 46 had microalbuminuria, showed that thiamine deficiency was highly prevalent in 98% and 100% of patients with and without microalbuminuria, respectively [11]. Another study showed that patients with type 1 diabetes (T1D) had significantly lower blood levels of thiamine than healthy controls, and thiamine showed an inverse correlation with glucose levels [12]. Thronalley and colleagues stated that low plasma thiamine concentration was noted in 76% of patients with T1D and in 75% of patients with T2D (Table 1) [13].

Although the link between DM and thiamine deficiency is not clearly explained, the reciprocal association between insulin and thiamine could partially solve the clue. Although insulin deficiency reduced the intestinal uptake of thiamine in rats [14], thiamine deficiency led to remarkable dysfunction in insulin synthesis and secretion in rats and human cell lines [15]. In addition, the dysfunction of the proximal tubule, where reuptake of thiamine occurs, is one of the early markers of diabetic nephropathy, and thiamine deficiency might be attributed to the increased renal clearance caused by DM [13]. Furthermore, the autonomic neuropathy in DM affects the intestinal motility, which promotes small intestinal bacterial overgrowth (SIBO), thus preventing thiamine absorption [16].

A clinical trial on 40 patients with T2D and microalbuminuria who were instructed for a daily dose of 300 mg of thiamine for 3 months showed regressions in urinary albumin excretion (UAE) [17]. Another study of 100 patients with T2D using the same dose for the same period reached the same conclusion [18]. In drug-naïve patients with T2D, a daily dose of 150 mg of thiamine for 1 month resulted in a significant decrease in plasma fasting glucose concentration (Table 2) [19].

Although the evidence of thiamine deficiency in patients with T1D and T2D seems reliable, further research on the efficacy of thiamine supplementation in patients with DM for long durations and using different doses is needed.

Obesity

Obesity is closely associated with a high risk of many comorbidities including T2D and CVDs as well as increased disease-specific and all-cause mortalities [20,21].

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