



REVIEW

Thiamine deficiency and cardiovascular disorders

E.S. Eshak ^{a,b,*1}, A.E. Arafa ^{c,1}



^a Department of Public Health and Preventive Medicine, Faculty of Medicine, Minia University, Minia, 61511, Egypt
^b Public Health, Department of Social Medicine, Osaka University, Graduate School of Medicine, Suita Shi, 565-0871, Osaka, Japan
^c Department of Public Health, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

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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.

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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

* Corresponding author. Public Health, Department of Social Medicine, Osaka University, Graduate School of Medicine, Suita Shi, 565-0871, Osaka, Japan. Fax: +81 6 6879 3919.

E-mail address: ehab@pbhel.med.osaka-u.ac.jp (E.S. Eshak).

¹ Both authors equally contributed to the study.

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].

Table 1 Prevalence of thiamine deficiency in populations with CVDs and its risk factors.

Study	Methods	Population	Findings	Study limitations
Carney et al. [72]	Cross-sectional	154 psychiatric patients	37.7% thiamine deficiency Thiamine-deficient patients were malnourished and alcoholics	No multivariate analysis
Carrodeguas et al. [22]	Cross-sectional	303 (BMI = 60 kg/m ²)	15% thiamine deficiency No neurological symptoms	Prepared for bariatric surgery
Flancbaum et al. [23]	Cross-sectional	379 (BMI = 51.8 kg/m ²)	29% thiamine deficiency African Americans and Hispanics had more thiamine deficiency	Prepared for bariatric surgery
Thornalley et al. [13]	Cross-sectional	26 T1D, 48 T2D, and 20 healthy	76% thiamine deficiency in T1D 75% thiamine deficiency in T2D	Small sample size
Waheed et al. [40]	Cross-sectional	40 T2D and 20 healthy	Low thiamine in patients with T2D Negative correlation with LDL, TGs, and cholesterol	
Zhang et al. [71]	Cross-sectional	1587 (50–70 years)	28.2% thiamine deficiency (subclinical) Thiamine deficiency associated with depressive symptoms	
Nix et al. [11]	Cross-sectional	120 T2D	98% thiamine deficiency in patients with microalbuminuria 100% thiamine deficiency in patients without microalbuminuria	No control group
Al-Daghri et al. [12]	Cross-sectional	77 T1D and 81 healthy	Lower thiamine in patients with T1D Negative correlation with HDL	No multivariate analysis
Nath et al. [24]	Cross-sectional	400 with morbid obesity	16.5% thiamine deficiency Inverse correlation between thiamine and BMI	Prepared for bariatric surgery

Preoperative assessment of obese patients selected for bariatric surgeries estimated thiamine deficiency by 15.5% in 303 patients whose mean body mass index (BMI) was 60 kg/m² [22] and by 29% in 379 patients whose mean BMI was 51.8 kg/m² [23]. A recent study of more than 400 patients with a minimum BMI of 35 kg/m² showed that 16.5% of patients reached the diagnosis of clinical thiamine deficiency, mostly with cardiac and neurological manifestations, and BMI showed a negative correlation with thiamine levels (Table 1) [24]. However, it should be noted

that the three studies assessed thiamine deficiency in patients recommended for bariatric surgeries. These patients usually have a high prevalence of T2D: 15.5% in patients with a BMI of 40–49.9 kg/m² and 20.5% in patients with a BMI higher than 50 kg/m² [25].

Thiamine deficiency has also been reported following bariatric surgeries. In addition to the prolonged vomiting and poor oral intake after the surgery, the altered gut ecology could lead to SIBO, which induces thiamine deficiency [26,27]. Lakhani et al. concluded that in patients

Table 2 Impact of thiamine supplementation on CVDs and risk factors.

Study	Methods	Population	Findings	Study limitations
Smidt et al. [76]	RCT (6 weeks)	80 elderly females (thiamine vs. placebo)	10 mg/day thiamine improved sleep time and patterns, appetite, and activity and decreased fatigue	
Seligmann et al. [66]	Non-RCT (1 week)	23 CHF and 16 healthy	Baseline 91.3% thiamine deficiency 200 mg/day thiamine improved LVEF in 80%	Patients were on diuretics
Shimon et al. [67]	RCT (1 week)	30 CHF (thiamine vs. placebo)	4% improvement in LVEF on 200 mg/day	Patients were on diuretics
Benton et al. [77]	RCT (2 months)	120 females (thiamine vs. placebo)	50 mg/day improved mood	Subjects were well nourished
Rabbani et al. [17]	RCT (3 months)	40 T2D (thiamine vs. placebo)	No improvement in the memory 300 mg/day thiamine reduced UAE No glycemic control	
Al-Attas et al. [42]	Non-RCT (6 months)	60 T2D and 26 healthy	100 mg/day thiamine reduced creatinine Reduction of LDL and HDL cholesterol	
González-Ortiz et al. [19]	RCT (1 month)	24 T2D (thiamine vs. placebo)	150 mg/day thiamine reduced glucose Reduction of leptin	Small sample size
Alam et al. [18]	RCT (3 months)	100 T2D and 50 healthy	300 mg/day thiamine reduced UAE No glycemic control	
Schoenenberger et al. [68]	RCT (4 weeks)	9 CHF (thiamine vs. placebo)	3.3% improvement in LVEF on 300 mg/day	Patients were on diuretics

with SIBO, oral thiamine could not correct thiamine deficiency, whereas antimicrobial agents restored thiamine levels [27].

Thiamine deficiency in obese people could be explained by the fact that obesity is associated with a diet that is low in thiamine-rich cereals and high in simple sugars; this type of diet not only lacks thiamine but also needs additional thiamine for the metabolism of sugars [4,28].

In a small clinical trial, a daily dose of 150 mg of thiamine for 1 month resulted in significant decreases in leptin concentration, a marker of obesity [19]. Among the findings of other clinical trials that assessed the effect of intentional weight loss on thiamine intake and thiamine levels, one trial reported that overweight women on weight loss who consume a high-cereal diet had increased thiamine intake and thiamine levels compared with overweight women on weight loss who consume a high-vegetable diet [29]. In another trial in patients with T2D, biochemical thiamine deficiency was evident in patients on hypocaloric, adequate-thiamine diets, whereas patients on hypocaloric, high-thiamine diet had attained normal thiamine levels by the end of the study [30]. Although we have to interpret the results of the latter trial carefully because of the possible role of altered thiamine renal clearance and thiamine absorption in patients with T2D, both studies concluded that the metabolic changes and efforts associated with weight loss should be compensated with extra thiamine intake.

The metabolism of sugars in high-sugar intake in obese subjects consumes most of their serum thiamine levels, and intentional weight loss using hypocaloric diets was associated with thiamine deficiency; moreover, surgical management of obesity impairs thiamine absorption owing to the high risk of SIBO. It seems that extra thiamine intake is needed for patients with any level of obesity.

Endothelial dysfunction, chronic vascular inflammation, and dyslipidemia

Endothelial dysfunction is an early stage of atherosclerosis and the development of CVDs [31]. Chronic vascular inflammation as a response to lipid peroxidation, injury, or infection increases the risk of developing dyslipidemia manifested with elevated low-density lipoprotein (LDL)-cholesterol and triglyceride (TG) and decreased high-density lipoprotein (HDL)-cholesterol levels. Chronic vascular inflammation is the main cause of all stages of atherosclerosis and considered as a prominent risk factor for many CVDs [32].

In an earlier study, loss of arteriovascular resistance was noted in patients with clinical thiamine deficiency [33]. Thiamine had a protective effect against glucose- and insulin-mediated proliferation of human infragenicular arterial smooth muscle cells that are known to play a pivotal role in the development of the atherosclerotic plaque [34]. In addition, thiamine counteracts the damaging effect of high glucose concentrations on the endothelium by reducing intracellular protein glycation [35].

In previous reports, intravenous thiamine administration resulted in an improvement of cardiac functions [33] and hemodynamic features [36] and a decrease in systemic vascular resistance [37]. Arora et al. assessed the effect of 100 mg of intravenous thiamine on the endothelium-dependent vasodilatation of 30 subjects with hyperglycemia, 10 being healthy, 10 with impaired glucose tolerance, and 10 with T2D. The results showed that the endothelium-dependent vasodilatation improved in the three groups. The authors recommended routine administration of thiamine to improve endothelial functions and slow down the progression of atherosclerosis [38]. In addition, a randomized, cross-over, blinded clinical trial proved that a short-term therapy (a 3-day therapy) with thiamine restored the endothelial function in 20 volunteered healthy smokers with smoking-induced endothelial dysfunction [39].

In a cross-sectional study of patients with DM with macroalbuminuria and microalbuminuria, plasma thiamine levels showed a negative correlation with TG and LDL levels and a positive correlation with HDL levels (Table 1) [40]. In the healthy elderly, plasma thiamine concentrations showed an inverse correlation with total cholesterol concentrations [41]. These functions may delay vascular inflammation and atherosclerosis.

Further, a significant decrease in total cholesterol and LDL concentrations was noted in 60 patients with T2D instructed for 100 mg/day of thiamine supplement for 6 months (Table 2) [42].

There is fair evidence that chronic vascular inflammation and consequent dyslipidemia are inversely associated with thiamine levels, and thiamine intake could hinder the inflammatory sequelae.

Myocardial infarction and conduction defects

Ischemic heart disease including myocardial infarction (MI) is the leading cause of death worldwide [9]. In an animal study, bradycardia, elevated ST-segment, and T-wave changes have been reported in electrocardiograms of thiamine-deficient rats; these changes did not persist after thiamine administration [43]. After isoproterenol-induced MI in rats, the cardiac thiamine stores were reduced greatly indicating the deterioration of their cardiac oxidative energy metabolism during acute myocardial ischemia [44].

In another study of experimentally induced MI in dogs, 150 mg/kg thiamine administration through a central line after 15 and 45 min of the ligation of left anterior descending artery resulted in improved electrocardiogram reading, increased stroke volume, reduced heart rate, vascular resistance, and myocardial oxygen consumption [45]. On exposing the cultured neonatal rat cardiomyocytes to severe hypoxia, thiamine demonstrated a cytoprotective effect against hypoxia-induced apoptosis [46]. Unfortunately, the evidence in humans is restricted to a few case reports on fatal cardiac beriberi, and these reports showed acute MI, myonecrosis, and electrocardiogram changes consistent with MI [47].

Moreover, conduction deficits could be attributed to thiamine deficiency. Induced thiamine deficiency led to a significant decline in the heart rate of rats [48]. Furthermore, thiamine administration led to improvement in bradycardia in a patient with encephalopathy [49].

Many studies have discussed Shoshin beriberi, a fulminant form of cardiac beriberi. One case report described the remarkable improvement of an 87-year-old man with cardiogenic shock and ST-segment elevation on thiamine 100 mg administered intravenously [50]. Another patient with acute coronary syndrome with cardiogenic shock but with ST-segment depression showed improvement after a single dose of 100-mg thiamine administered intravenously [51]. A study of 29 infants with pulmonary hypertension showed resolution of metabolic complications and improvement of pulmonary hypertension after 100 mg/kg intravenous administration of thiamine [52].

Further human research is needed to assess the prevalence of thiamine deficiency in patients with MI and whether thiamine intake could have preventive roles in MI and conduction defects or could improve cardiac energy metabolism and minimize necrosis in MI cases.

Cerebrovascular diseases

In the early 1880s, Carl Wernicke described a medical emergency in three subjects with acute superior hemorrhagic polioencephalitis, the Wernicke encephalopathy. Later, in the 1940s, Wernicke encephalopathy was attributed to thiamine deficiency [53].

A reasonable number of case studies have suggested a potential role of thiamine deficiency in hemorrhagic and ischemic cerebrovascular events. For example, in one of the case studies, a 48-year-old hypertensive obese male with coronary artery disease was diagnosed with intraventricular hemorrhage and neurological deficits, and these conditions improved after thiamine administration [54]. In another report, manifestations of ischemic stroke were improved with thiamine supplementation in a 20-year-old girl with thiamine-responsive megaloblastic anemia syndrome [55]. Costantini et al. succeeded in improving the poststroke fatigue in three patients with stroke by administering a high dose of thiamine [56]. The exact biological mechanisms that associate thiamine with brain health are still not fully understood; however, in a thiamine-deficient rat model, it has been shown that thiamine improved brain endothelial function [57]. However, it is worth pointing out that the interventional studies included a few patients, and the mechanisms explaining how thiamine could improve the cerebrovascular manifestations are still unknown.

Heart failure

Heart failure (HF) is associated with high morbidities and mortalities, and its management represents a major challenge for patients and healthcare systems [58].

In a systematic review of nine observational studies determining the prevalence of thiamine deficiency among patients with HF, the prevalence in ambulatory settings ranged from 3% to 27% and 5%–91% in the hospital setting. Compared with non-HF controls, the overall prevalence of thiamine deficiency was significantly higher (odds ratio [OR] 2.5, 95% confidence interval [CI]: 1.7–3.9). The included studies avoided using clinical criteria for diagnosis and adopted laboratory tests instead [59].

The potential mechanisms explaining the reasons underlying thiamine deficiency in patients with HF are diuretic use, advanced age, and altered metabolism. Because thiamine is a water-soluble vitamin, the use of diuretics, which are usually prescribed to patients with HF, contributes to thiamine loss in the urine [5,60]. Further, HF has been referred to as the disease of the elderly. Elderly people, regardless of their cardiac function, have a high prevalence of thiamine deficiency [61,62], and those with HF have strikingly higher thiamine deficiency rates [63].

In addition, because most of the absorbed thiamine is phosphorylated for ATP production, abundance of ATP is required for myocardial contractility, and the depletion of ATP stores leads to HF, thiamine deficiency can deprive the myocardium of ATP, thus resulting in HF [64,65].

Seligmann et al. assessed the impact of intravenous administration of thiamine 200 mg/day for 1 week on six patients with HF and who are receiving diuretics, and they found that the left ventricular ejection fraction (LVEF) has improved in four patients from 24% to 37% [66]. Another trial on a larger sample, wherein 30 patients were administered 200 mg/day intravenous thiamine for 1 week, followed by 6 weeks of daily doses of 200-mg thiamine, resulted in a significant improvement in LVEF from 27% to 33% [67]. Schoenenberger et al. demonstrated improvement in LVEF from 29.5% to 32.8% following 300-mg/day thiamine supplementation for 4 weeks in nine patients with HF (Table 2) [68]. In a systematic review and meta-analysis of randomized, double-blinded, placebo-controlled trials that included two clinical trials, the LVEF in patients with congestive HF improved with thiamine supplementation by 3.28% (95% CI: 0.64%–5.93%) [69].

Several reports that have examined only a few participants also suggested benefits of using thiamine in patients with HF. The doses used varied widely and the improvement in cardiac functions did not correlate with the differences in doses across studies. On the basis of the available studies, we believe that thiamine is needed for patients with HF to compensate the extra loss; however, the evidence on thiamine supplementation in those patients with the aim of improving their cardiac functions is still inconclusive.

Depression

Depression is a leading risk factor for CVDs, and it also delays recovery after major CVD events [70]. In a cross-sectional study of 1587 Chinese people aged 50–70 years, low concentrations of thiamine were associated with high prevalence of depressive symptoms [71].

Another study of 74 malnourished patients who were newly admitted to a psychiatric unit revealed that thiamine deficiency was associated with clinical signs of depression (Table 1) [72].

To date, it is not clear whether depression is a risk factor for thiamine deficiency or whether insufficient thiamine levels and metabolism could lead to depression. On the one hand, thiamine is an essential coenzyme in the synthesis of many neurotransmitters such as glutamate, aspartate, acetylcholine, and serotonin. The malfunctions in the mechanisms of these neurotransmitters lead to the development of depression [73]. On the other hand, thiamine deficiency induces oxidative stress [74], and this in turn is linked to decreased hippocampal volume and damage of neurons in patients with depression [75].

Although the impact of thiamine supplementation on depressive symptoms has not been assessed yet, a daily dose of 10 mg thiamine for 6 weeks led to a feeling of well-being in 80 elderly people [76]. Additionally, thiamine dose of 50 mg/day for 2 months improved the energetic status and the clear-headedness of 120 young women (Table 2) [77].

Considering available evidence, we cannot consolidate an association between depression and thiamine levels. Future case-control studies that compare thiamine levels in patients with and without depression are needed. In addition, randomized controlled trials assessing the efficacy of thiamine supplementation in patients with depression are also required.

Conclusion

Thiamine deficiency is not just a common finding in patients with CVDs, but it might also have a role in the development and prognosis of these disorders. Screening for thiamine deficiency could be considered in patients with CVDs. We believe that thiamine supplementation is needed for patients with CVDs or its risk factors to improve the poor thiamine status regardless of the potential beneficial effects of thiamine supplements on the symptoms or the pathogenesis of the condition itself. Further research should focus on the adequate dose and period needed for thiamine supplementation to reverse or ameliorate the negative consequences of thiamine deficiency on CVDs and its risk factors.

Conflict of interest

None.

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