Cardiovascular Drugs and Therapy (2018) 32:313–317
https://doi.org/10.1007/s10557-018-6808-8

EDITORIAL

Thiamine Therapy for Heart Failure: a Promise or Fiction?

Ajoe John Kattoor[1] · Akshay Goel[1] · Jawahar L. Mehta[1]

Published online: 18 July 2018

Introduction

Thiamine (vitamin B1) is an essential water-soluble vitamin required for cellular energy production. Thiamine pyrophosphate (TPP) is a coenzyme in the pentose phosphate pathway for transketolation of glucose-6-phosphate to ribose-5-phosphate. In the Kreb's cycle, TPP is needed for the functioning of the pyruvate dehydrogenase complex (which converts pyruvate to acetyl CoA) and alpha-ketoglutarate dehydrogenase (which converts alpha-ketoglutarate to succinate). These reactions are needed for aerobic metabolism and production of ATP. Thiamine also helps in the conduction of nerve impulses, independent of its coenzyme functions. It is important for maintenance of nerve membrane stability and modulates membrane ion channels for efficient nerve conduction [1].

Humans neither synthesize thiamine nor store it in large quantities [2]. Thus, oral intake is the primary determinant of thiamine stores in the body. As per the 1980 Committee on Dietary Allowance, Food, and Nutrition Board, the recommended daily allowance of thiamine for adults is about 1.2 mg daily for men and 1 mg daily for women [3]. Thiamine levels can be estimated in different ways. Direct measurement of serum thiamine is not a reliable indicator of total body thiamine stores as most of it is present inside the cells. The erythrocyte transketolase activity (ETKA) is an indirect measure of thiamine levels in the body and has high sensitivity as erythrocytes are the first cell line to be affected by low thiamine levels [4]. Another useful method is high-performance liquid chromatography (HPLC) to directly measure TPP concentration in erythrocytes.

Deficiency of thiamine is far more common in underdeveloped and developing countries due to high incidence of poor nutritional status. In developed countries, thiamine deficiency is seen in patients with chronic alcohol use, patients on total parenteral nutrition, and in patients who have undergone weight loss surgery. Clinical signs of marginal thiamine deficiency are non-specific, like anorexia, weight loss, fatigue, sleep disorders, and depression [5]. Severe thiamine deficiency in diet causes beriberi. Dry beriberi presents as a symmetric peripheral sensorimotor neuropathy. On the other hand, the major manifestations of wet beriberi are tachycardia, cardiomegaly, high-output heart failure, and pedal edema, in addition to neuropathy. Direct impairment of myocardial energy production has been proposed as a possible basis for the development of heart failure state seen in beriberi (because of loss of thiamine's beneficial role in metabolic reactions) [6]. Decreased activity of pyruvate dehydrogenase due to thiamine deficiency results in build-up of pyruvate, which is then shunted towards anaerobic conversion into lactate [7]. This accumulation of lactate causes a decrease in peripheral resistance, thereby increasing venous return to the heart (preload). This increase in preload coupled with myocardial dysfunction has been proposed to be a basis of congestive heart failure in thiamine deficiency [8].

Heart failure is a major cause of mortality and morbidity in the West. Around 6.5 million Americans have heart failure and nearly a million new cases are being identified annually [9]. Though thiamine supplementation is recommended in high-output heart failure state seen in severe thiamine deficiency, its utility in the heart failure patients at large is unclear. Heart failure being a prominent feature of thiamine deficiency, several investigators have evaluated the potential of thiamine therapy in heart failure patients. In this review, we aim to discuss the utility of thiamine therapy in patients with heart failure.

Thiamine Deficiency in Heart Failure

Multiple studies have shown that thiamine deficiency is more prevalent in heart failure patients than that in general population [10]. In a meta-analysis of nine observational studies, irrespective of the type of assay used for measuring thiamine

✉ Jawahar L. Mehta
MehtaJL@uams.edu

[1] Division of Cardiology, Central Arkansas Veterans Healthcare System and the University of Arkansas for Medical Sciences, Little Rock, AR 72212, USA

(ETKA or TPP-HPLC), the incidence of thiamine deficiency in patients with heart failure has been reported to be higher compared to that of control subjects without heart failure (OR 2.53 [95% CI 1.65–3.87]). The incidence of thiamine deficiency has ranged from 3 to 91% in various studies conducted in both inpatient and outpatient settings [10]. Some of the proposed mechanisms for thiamine deficiency in heart failure are (a) decreased thiamine intake and its poor absorption due to cardiac cachexia and splanchnic congestion, (b) increased urinary excretion related to use of diuretics, and (c) altered thiamine metabolism. The increased urinary excretion of thiamine in patients with heart failure who are on high-dose loop diuretics, such as furosemide, is thought to be the most important factor contributing to thiamine deficiency in these patients (Fig. 1) [11].

The first study to analyze thiamine deficiency in humans on high-dose furosemide was conducted by Seligmann et al. [12] in 1991. They selected 23 hospitalized heart failure patients, who were being treated with high-dose furosemide (80–240 mg for a duration ranging from 3 to 14 months) and compared the incidence of thiamine deficiency with control group (non-heart failure patients, $n = 16$). Out of the 23 heart failure patients on furosemide, 21 had thiamine deficiency measured by ETKA, compared to 2 out of 16 in control group ($P < 0.001$). Urinary thiamine levels were inappropriately elevated in the furosemide-treated heart failure patients compared to those of the control group. Rieck et al. [13] also suggested that increased urinary flow is a likely cause of increased urinary thiamine excretion. In their study, six healthy adults were treated with varied doses of intravenous furosemide; urinary thiamine excretion increased in these patients with furosemide use and then returned to baseline after furosemide use was stopped. Importantly, urinary thiamine excretion was found to be proportional to urinary flow rate.

A counter argument to these proposed mechanisms is that heart failure itself is a risk factor for thiamine deficiency and the presence of thiamine deficiency with high furosemide doses merely indicates the severity of heart failure [10]. Zenuk et al. [14] studied this concept in 32 patients with heart failure who were on at least 40 mg/day of furosemide per day for 3 months. They found that patients who received > 80 mg/day had a significantly higher incidence of thiamine deficiency (24 of 25 patients) compared to those who were on a lower dose of furosemide (4 of 7 patients). Thus, thiamine deficiency may be more common when high doses of furosemide (> 80 mg per day) are used for long periods.

However, not all diuretics cause a decline in thiamine levels as seen with furosemide. Rocha et al. [15] selected 22 ambulatory patients with NYHA III/IV heart failure on high-dose loop diuretics. They observed that patients on spironolactone, in addition to loop diuretics, had significantly higher thiamine levels than those who were only on loop diuretics ($p < 0.001$). This led to the conclusion that factors in addition to increased urinary excretion may be playing a role in inducing thiamine deficiency in patients treated with loop diuretics.

There are no reliable human studies that specifically evaluated thiamine absorption and metabolism in heart failure patients. However, animal experiments have shown that thiamine depletion causes increased reactive oxygen species concentrations and increased cardiomyocyte apoptosis [16, 17].

In essence, the overall incidence of thiamine deficiency was consistently found to be high in heart failure patients when compared to that of non-heart failure controls, perhaps related to use of large doses of loop diuretics in the former. It may be postulated that thiamine deficiency may worsen heart failure state in these patients [11, 14]. However, the evidence for loop diuretics causing thiamine deficiency is limited due to the small sample size studies.

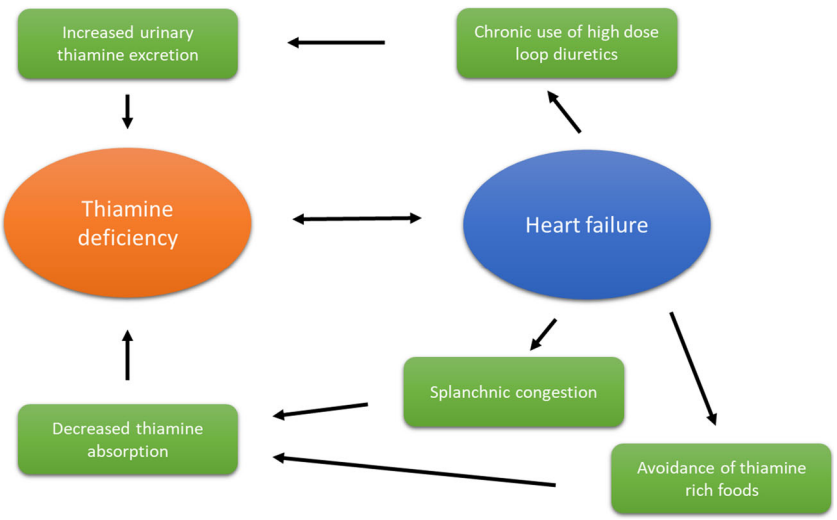

Fig. 1 Proposed mechanism of increased incidence of thiamine deficiency in heart failure

Effect of Thiamine Supplementation in Chronic Systolic Heart Failure

Based on the observations of thiamine deficiency, several small trials have been conducted to determine the effects of thiamine supplementation in patients with heart failure (Table 1). In almost all studies, patients with identifiable causes of thiamine deficiency like alcoholism, malnutrition, and catabolic state, as well as those on vitamin supplements, were excluded. In the study by Seligmann et al. [12], six heart failure patients were treated with intravenous thiamine for 7 days. Functional capacity improved by at least one NYHA class in all six patients. Also, the left ventricular ejection fraction increased from 24.0 ± 4.3% to 37.0 ± 2.4% in four of five patients studied by echocardiography, and was unchanged in the remaining patient. Though this was the first study to examine this concept, the intervention was without any placebo control.

Pfitzenmeyer et al. studied 35 hospitalized geriatric (age 76–95 years) heart failure patients who were age- and sex-matched with controls, i.e., 35 hospitalized geriatric patients without heart failure. There was no difference in the baseline thiamine status between the heart failure group and the non-heart failure group. Of note, only 20 of the heart failure patients were on furosemide, dose range 20–40 mg/day in this study. The heart failure patients were then divided into two groups and randomly allocated to either receive thiamine therapy or not receive thiamine. After 7 days, there was no significant difference in NYHA class or the clinical status between thiamine-treated heart failure patients and patients not treated with thiamine. The low dose of furosemide used, absence of significant thiamine deficiency in the study population at baseline, and absence of echocardiographic evaluation limit the generalizability of this study [5].

Recently, Jikrona et al. performed a cross-sectional prospective observational analysis on 32 male patients with stage II heart failure on prolonged diuretic therapy. Sixteen of these 32 patients received 300 mg/day of thiamine for 28 days. The authors reported a 13.5% increase in ejection fraction in thiamine recipients ($p = 0.021$) when compared to heart failure patients who did not get thiamine supplementation [18]. However, this study is marred by lack of defined inclusion criteria, unclear dose and duration of furosemide use among patients, and poor representation of echocardiographic data and results.

Shimon et al. randomized 30 hospitalized heart failure patients secondary to myocardial ischemia and administered intravenous thiamine for 7 days or placebo in a double-blind manner followed by 6 weeks of oral thiamine 200 mg/day in all patients [19]. Only patients who were on at least 80 mg or more of furosemide for minimum of 3 months were included in the study. The study showed an increase in left ventricular ejection fraction (28 ± 0.11% to 32 ± 0.09%, $p < 0.05$) in the thiamine group at the end of 7 days. However, it is unclear from the study whether this improvement in left ventricular ejection fraction was significant compared to that in the placebo group. In addition, 27 patients who completed the full intervention (including 6 weeks of oral thiamine) had a 22% increase in ejection fraction as compared to the baseline value ($p < 0.01$). Small sample size and high degree of variability in left ventricular ejection fraction and lack of a clear comparison to the placebo group are some of the limitations of this study.

Likewise, Schoenenberger et al. in a randomized double-blind placebo-controlled cross-over study in nine symptomatic patients with heart failure were able to demonstrate an increase in left ventricular ejection fraction from 29.5 to 32.8% ($p = 0.024$) after supplementation with oral thiamine 300 mg/day for 28 days [20]. There was also a non-significant improvement in walking time in six of nine patients. A washout period of 6 weeks was given between cross-over from thiamine to placebo or from placebo to thiamine. Free thiamine concentration was measured in the study using HPLC. Though, by using a cross-over study design, the investigators were able to account for inter-individual variabilities, it is unclear whether 6 weeks of washout period is enough to reinstate thiamine deficiency in placebo group who were previously treated with thiamine supplementation prior to cross-over. In addition, small sample size and short follow-up period are other limitations.

Table 1 Results of thiamine supplementation in patients with chronic systolic heart failure

Study	Study design	Sample size	Intervention	Outcome
Seligmann et al. 1991	Observational	6	IV thiamine 100 mg b.i.d	Improved LVEF, NYHA, urine output
Pfitzenmeyer et al. 1995	Observational	35	Oral thiamine 200 mg daily—7 days	No change in EF
Shimon et al. 1995	RCT	45	IV thiamine/placebo for 7 days + oral 200 mg daily for 28 days	Improved LVEF and diuresis
Schoenenberger et al. 2011	RCT	18	Thiamine 300 mg daily for 28 days	Improved EF
Mousavi et al. 2017	RCT	52	Thiamine 300 mg daily for 1 month	Improved peripheral edema, no change in EF.
Jikrona et al. 2017	Observational	32	Thiamine 300 mg daily for 28 days	Statistically significant increase in EF.

IV intravenous, *LVEF* left ventricular ejection fraction, *EF* ejection fraction, *RCT* randomized controlled trial

A meta-analysis of the above-mentioned randomized, double-blind placebo-controlled trials [19, 20] showed a small increase in left ventricular ejection fraction (3.28%, 95% CI 0.64–5.93%, $I^2 = 0\%$) with thiamine therapy in heart failure patients compared to placebo [21]. Given the small sample size and inherent limitations within the individual studies, the results of this meta-analysis should be interpreted cautiously.

In a more recent study, Mousavi et al. randomized 52 patients with heart failure (left ventricular ejection fraction < 40%) who were already on optimal medical therapy to receive 300 mg/day of thiamine or a matching placebo for a period of 1 month [22]. No significant difference was observed in either systolic or diastolic echocardiographic parameters, or dyspnea between these patient groups. However, patients in the thiamine group showed significant improvement in peripheral edema (34.6 vs 3.8%, $p = 0.005$). It is to be noted that the proportion of patients who were on furosemide in this study was low (10 out of 52) and the dose of furosemide was not reported. Further, spironolactone was prescribed to most (22 out of 26) patients in the thiamine group which may have caused a decrease in the incidence of thiamine deficiency in this cohort. Unlike furosemide, spironolactone use has been shown to be associated with a small increase in blood thiamine level in patients who are on loop diuretics [15]. Further, thiamine levels were not obtained at any point in this study.

The reasons for the variations in the results from multiple studies may be due to a wide range of incidence of thiamine deficiency in heart failure patients, small sample size, and geographical and environmental factors.

Conclusion

It is known that thiamine supplementation significantly improves heart failure state caused by severe thiamine deficiency, but it is not clear if thiamine supplementation will be useful in patients with heart failure at large. The preliminary studies presented here suggest that it may be prudent to screen all patients with heart failure for thiamine deficiency. Those who exhibit low thiamine levels may be given thiamine supplementation. High oral doses often result in high blood concentrations [23]. Thiamine is a relatively safe drug and no major side effects have been reported at high doses in the range of 300–900-mg daily dose. With low cost and relatively few side effects, it is likely that thiamine supplementation may be useful in some patients, especially those on high doses of loop diuretics. Notably, majority of the studies on thiamine supplementation conducted until to date are old, and were conducted before the establishment of contemporary therapies. Further, these studies were of small sample size and short duration. There is lack of good-quality data on improvement in functional status of the patients after thiamine supplementation; this is especially important as symptoms of thiamine deficiency are often non-specific. High-quality large sample size, long duration, and randomized control studies are essential to suggest or refute the routine use of thiamine. Based on the available evidence, it is not unreasonable to evaluate heart failure patients for thiamine deficiency, or even empirically provide thiamine supplementation to heart failure patients on high doses of furosemide.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Bâ A. Metabolic and structural role of thiamine in nervous tissues. Cell Mol Neurobiol. 2008;28(7):923–31.
2. Young RC, Blass JP. Iatrogenic nutritional deficiencies. Annu Rev Nutr. 1982;2:201–27.
3. Anderson S, Vickery C, Nicol A. Adult thiamine requirements and the continuing need to fortify processed cereals. Lancet. 1986;328(8498):85–9.
4. DiNicolantonio JJ, Liu J, O'Keefe JH. Thiamine and cardiovascular disease: a literature review. Prog Cardiovasc Dis. 2018;
5. Pfitzenmeyer P, Guilland JC, d'Athis P, Petit-Marnier C, Gaudet M. Thiamine status of elderly patients with cardiac failure including the effects of supplementation. Int J Vitam Nutr Res. 1994;64(2):113–8.
6. Oliveira FA, Guatimosim S, Castro CH, Galan DT, Lauton-Santos S, Ribeiro AM, et al. Abolition of reperfusion-induced arrhythmias in hearts from thiamine-deficient rats. Am J Phys Heart Circ Phys. 2007;293(1):H401.
7. Dabar G, Harmouche C, Habr B, Riachi M, Jaber B. Shoshin beriberi in critically-ill patients: case series. Nutr J. 2015;14(1):51.
8. Lei Y, Zheng M, Huang W, Zhang J, Lu Y. Wet beriberi with multiple organ failure remarkably reversed by thiamine administration: a case report and literature review. Medicine (Baltimore). 2018;97(9):e0010.
9. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e603.
10. Jain A, Mehta R, Al-Ani M, Hill JA, Winchester DE. Determining the role of thiamine deficiency in systolic heart failure: a meta-analysis and systematic review. J Card Fail. 2015;21(12):1000–7.
11. Katta N, Balla S, Alpert MA. Does long-term furosemide therapy cause thiamine deficiency in patients with heart failure? A focused review. Am J Med. 2016;129(7):753.e11.
12. Seligmann H, Halkin H, Rauchfleisch S, Kaufmann N, Tal R, Motro M, et al. Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: a pilot study. Am J Med. 1991;91(2):151–5.
13. Rieck J, Halkin H, Almog S, Seligman H, Lubetsky A, Olchovsky D, et al. Urinary loss of thiamine is increased by low doses of furosemide in healthy volunteers. J Lab Clin Med. 1999;134(3):238–43.
14. Zenuk C, Healey J, Donnelly J, Vaillancourt R, Almalki Y, Smith S. Thiamine deficiency in congestive heart failure patients receiving long term furosemide therapy. Can J Clin Pharmacol. 2003;10(4):184–8.
15. Rocha RM, Silva GV, de Albuquerque DC, Tura BR, Albanesi Filho FM. Influence of spironolactone therapy on thiamine blood levels in patients with heart failure. Arq Bras Cardiol. 2008;90(5):324–8.

16. Roman-Campos D, Campos AC, Gioda CR, Campos PP, Medeiros M, Cruz JS. Cardiac structural changes and electrical remodeling in a thiamine-deficiency model in rats. Life Sci. 2009;84(23–24):817–24.
17. Gioda CR, de Oliveira Barreto T, Primola-Gomes TN, de Lima DC, Campos PP, Capettini L d S, et al. Cardiac oxidative stress is involved in heart failure induced by thiamine deprivation in rats. Am J Phys Heart Circ Phys. 2010;298(6):H2045.
18. Jikrona R, Suharjono S, Ahmad A. Thiamine supplement therapy improves ejection fraction value in stage ii heart failure patients. Folia Medica Indonesiana. 2017;53(2):139–43.
19. Shimon H, Almog S, Vered Z, Seligmann H, Shefi M, Peleg E, et al. Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. Am J Med. 1995;98(5):485–90.
20. Schoenenberger A, Schoenenberger-Berzins R, der Maur C, Suter P, Vergopoulos A, Erne P. Thiamine supplementation in symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled, cross-over pilot study. Clin Res Cardiol. 2012;101(3):159–64.
21. Dinicolantonio JJ, Lavie CJ, Niazi AK, O'Keefe JH, Hu T. 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(4):495–9.
22. Mousavi M, Namazi S, Avadi M, Amirahmadi M, Salehifar D. Thiamine supplementation in patients with chronic heart failure receiving optimum medical treatment. J Cardiol Curr Res. 2017;9(2):00316.
23. Smithline HA, Donnino M, Greenblatt DJ. Pharmacokinetics of high-dose oral thiamine hydrochloride in healthy subjects. BMC Clin Pharmacol. 2012;12(1):4.