Determining the Role of Thiamine Deficiency in Systolic Heart Failure: A Meta-Analysis and Systematic Review

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ABSTRACT

Background: Approximately 5.7 million Americans carry the diagnosis of systolic heart failure (HF), a major health care burden. HF is a known manifestation of thiamine deficiency (TD). HF patients are at unique risk for developing TD, which may contribute to further altered cardiac function and symptoms.
Methods and Results: We performed a systematic review of the literature and a meta-analysis to evaluate the prevalence of TD in HF patients, risk factors for and mechanisms of development of TD in HF population, and outcomes of thiamine supplementation in HF patients. We found 54 studies that met our selection criteria, 9 of which were suitable for meta-analysis. TD is more common in HF patients than control subjects (odds ratio 2.53, 95% confidence interval 1.65−3.87). Diuretic use, changes in dietary habits, and altered thiamine absorption and metabolism were identified as possible mechanisms of TD in HF patients. Small observational studies and randomized control trials suggest that thiamine supplementation in HF population may improve ejection fraction and reduce symptoms.
Conclusions: Thiamine deficiency is more prevalent in the HF population, and its supplementation may be beneficial. The therapeutic role of thiamine in HF warrants further study. (*J Cardiac Fail 2015;21:1000−1007*)
Key Words: Thiamine deficiency, heart failure, meta-analysis.

More than 5.7 million Americans carry the diagnosis of heart failure (HF), with a yearly incidence of 870,000 patients. This is a significant burden on the health care system with more than 1 million hospitalizations and 2 million outpatient visits each year. Despite advances in HF management with improved longevity, this condition continues to cause poor quality of life (QOL), frequent hospitalizations, and mortality of up to 50%.[1] Thiamine deficiency (TD) is a known cause of HF. Thiamine has both coenzymatic and noncoenzymatic roles. It is a precursor for thiamine pyrophosphate (TPP), which is a cofactor for >20 enzymes involved in bioenergetic processes from sugars and branched-chain fatty acids metabolism to ATP synthesis. It has also been shown to regulate multiple gene expression pathways and has effects on stress response, immunity, and nerve conduction.[2]

Thiamine is a water-soluble vitamin that is absorbed in the jejunum and renally excreted. The adult human body has a limited thiamine reserve of ~30 g, whose consumption depends mainly on the rate of carbohydrate metabolism. Approximately 50% of the total body content of thiamine resides in the cardiovascular system (Fig. 1). Thiamine uptake and excretion is a complex process that is abnormal in HF patients. Thiamine intake may be decreased in HF patients with early satiety due to splanchnic congestion and cardiac cachexia.[3] Some dietary thiamine sources may also be high in sodium content and thus are generally avoided by HF patients.[4] In addition, HF patients have increased thiamine requirements as a result of chronic diuretic use which may promote renal wasting.[5,6] Given the fact that HF is a prominent feature of thiamine deficiency (beriberi), there is value in studying the role of thiamine in the prevention and management of acute and chronic HF.

Although TD appears to be present in HF patients,[5,7,8] determining the true prevalence of TD in HF patients has been difficult owing to variations in disease definitions and

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Manuscript received August 13, 2015; revised manuscript received October 6, 2015; revised manuscript accepted October 14, 2015.
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See page 1006 for disclosure information.
1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2015.10.005

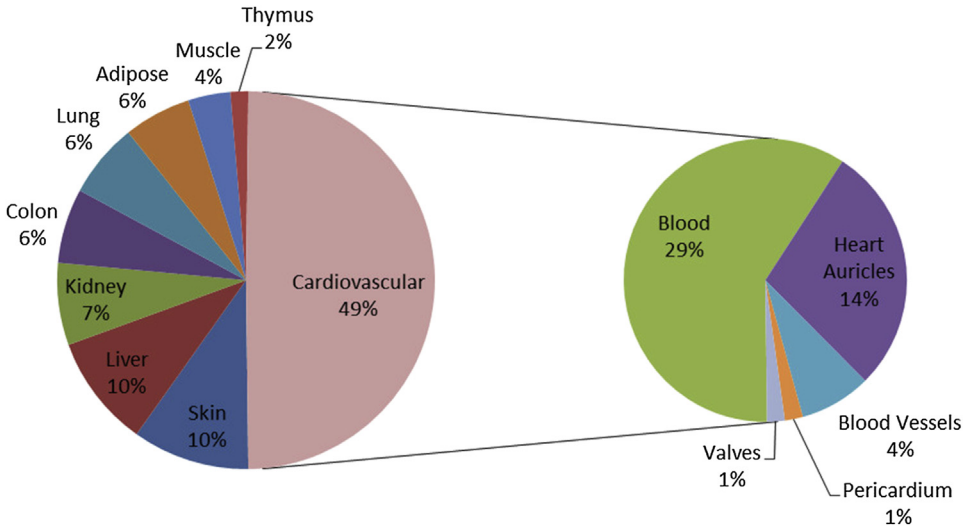

Fig. 1. Proportional distribution of total body thiamine in major organs. About one-half of thiamine is in the cardiovascular system, of which a significant percentage resides in the myocardium.

testing methods. We conducted a systematic review of the literature to (1) determine the prevalence of TD in HF patients, (2) determine the risk factors for TD that may be present in HF patients, (3) determine the risk of TD in HF patients compared with non-HF patients, and (4) summarize the evidence for thiamine supplementation in HF patients.

Methods

Search Strategy

We used Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for quality of reporting from observational studies.[9] Inclusion criteria were established before the search. We conducted a literature search with the use of Pubmed and ClinicalTrials.gov with the terms "thiamine," "heart," and "failure." A total of 228 studies were identified for abstract review (Fig. 2). We excluded studies with nonhuman animal models, case reports, combined interventions (eg, multiple micronutrients), duplicate publications, or nonrelevant topics (alcoholic cardiomyopathy, beriberi, etc). All studies were in the context of systolic heart failure. We reviewed the full text of all remaining studies, and reviewed the references from these studies to identify any additional articles. For the meta-analysis, we further excluded studies without control subjects, studies on the wrong topic, and studies that used neither erythrocyte thiamine transketolase activity (ETKA) nor thiamine pyrophosphate high-pressure liquid chromatography (TPP-HPLC) testing.

Defining TD

Studies included in our review frequently used variable disease definitions and testing methods for the diagnosis of TD. In general, most studies avoided using clinical criteria for the diagnosis of TD because symptoms of TD, such as fatigue, low energy, and poor appetite, lack specificity and are difficult to distinguish from similar symptoms in HF itself. Instead, most studies used 1 of 3 laboratory tests to evaluate the bodies' thiamine status: urine thiamine levels, ETKA assay, or TPP-HPLC. The latter 2 tests rely on the wide distribution of thiamine stores in the human body to correlate thiamine deficiency in blood thiamine stores with thiamine deficiency in total body stores.[10] We excluded studies that used only urine excretion for the diagnosis of TD, because this is no longer considered to be an accurate test for the evaluation of TD.[7,11]

Almost 80% of thiamine exists in the human body as thiamine diphosphate (TDP), also known as thiamine pyrophosphate (TPP), and this is the active form of thiamine responsible for most biologic functions. ETKA indirectly infers thiamine status by measuring the activity of the enzyme transketolase, which requires thiamine as a cofactor. TPP effect is the percentage increase in ETKA activity after the addition of TPP. The advantage of the ETKA test is easy clinical interpretation of TD from a direct measurement of biologic dysfunction. However, old age, liver disease, renal disease, and altered binding-side affinity of transketolase isoenzymes can affect test results regardless of thiamine availability. Additionally, poor interassay precision, difficulty in standardization, and instability during storage can also cause inaccurate ETKA results.[12] Overall, ETKA remains a viable method of diagnosing TD. TD had been traditionally defined as ETKA value $<15\%$ or $<30\%$, depending on the reference.

The 3rd testing method is TPP-HPLC, which directly measures serum concentration of TPP with high sensitivity, precision, and reliability.[13] The usual cutoff for normal value in the reviewed trials was either predetermined by the study protocol or set at 2 standard deviations below the population average.[14]

Data Review and Statistical Analysis

Two authors (A.J. and R.M.) independently completed data extraction from all studies with the use of standardized forms. Inconsistencies were resolved through discussion until consensus was reached. We performed a pooled meta-analysis of all included studies as well as a separate meta-analysis by test method (ETKA vs TPP-HPLC). The Mantel-Haenszel random effects method was used for calculating pooled odds ratios and the Cochran Q-test with the I^2 statistic for testing heterogeneity. We conducted all statistical analysis with the use of the R statistical software package version 2.15.3 (open source). Meta-analysis results were also confirmed with the use of Medcalc for Windows, version 15.8 (Medcalc Software, Ostend, Belgium) as well as with Comprehensive meta-analysis software version 3. Egger