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Characteristics of Thiamin and Its Relevance to the Management of Heart Failure

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Heart failure (HF) is a major public health problem in the United States that puts a significant burden on both patients and the healthcare system. The prevalence of malnutrition in HF patients is well-known and correlates with a dramatic decline in quality of life and disease progression, and is associated with high morbidity and mortality rates. The implication of HF on micronutrient status is underrecognized in the quest to offer "best practice" medical, device, and surgical interventions to this population. The micronutrient thiamin is of particular interest in the management of HF for several reasons: (*a*) HF is a disease of the elderly whose micronutrient status is in need of attention; (*b*) HF patients tend to have inadequate nutrient intake, which has been associated with thiamin deficiency; (*c*) thiamin deficiency (wet beriberi) impairs cardiac performance and can mimic the signs and symptoms of HF thereby potentially exacerbating the underlying disease; (*d*) use of loop diuretics to manage fluid and sodium imbalances associated with HF may cause the hyperexcretion of thiamin, thereby increasing the risk of deficiency; and (*e*) the prevention of thiamin deficiency should be a routine component in the overall management of this disease. (*Nutr Clin Pract.* 2008;23:487-493)

Keywords: thiamin; thiamin deficiency; heart failure; malnutrition; avitaminosis; diuretics

Approximately 5 million people in the United States suffer from heart failure (HF), and more than 550,000 people are diagnosed with this condition each year.[1,2] The aging population and the prolongation of life secondary to modern therapeutic innovations in cardiology and cardiothoracic surgery for HF patients have led to a significant increase in the reported incidence of HF, which is approaching 10 in 1000 people older than 65 years of age.[1,2] In the United States, HF results in 12–15 million office visits and 6.5 million hospital days each year.[2,3]

Despite therapeutic advancements in the medical management of HF with the use of angiotensin-converting enzyme (ACE) inhibitors, β-blockers, nonglycoside inotropic agents, and loop diuretics (ie, furosemide, bumetanide, etc.), as well as new surgical techniques designed to improve the structure and function of the heart, the disability and mortality rates associated with this disease are staggering.[4] The costs in terms of resources and expenses associated with the management of HF are also significant. In U.S. healthcare, HF is the most commonly used Medicare diagnosis-related group (DRG), and more Medicare dollars are spent annually for diagnosis and treatment of HF than for any other DRG with estimated total direct and indirect costs of almost $28 billion.[1,2]

As the disease progresses, HF patients lose the ability to carry out activities of daily living. A task force for the American College of Cardiology/American Heart Association recently made the following statement, "The implementation of therapies demonstrated to slow the progression of HF is imperative." We, as nutrition support clinicians, need to do everything within our power to improve the nutrition status, quality of life (QOL), and clinical outcomes of HF patients.

The development of cardiac cachexia and protein-calorie malnutrition in patients with HF puts them at risk for multiple nutrient deficiencies. A recent study concluded that the use of a multimicronutrient supplement, containing 200 mg thiamin/day improved QOL and left ventricular ejection fraction (LVEF) in elderly HF patients.[5] However, the specific role thiamin may have played in these outcomes is difficult to determine. Thiamin is of particular interest in the management of HF for several reasons: (*a*) HF is a disease of the elderly whose micronutrient status is in need of attention; (*b*) HF patients tend to have inadequate nutrient intake, which has been associated with thiamin deficiency; (*c*) thiamin deficiency (wet beriberi) impairs cardiac performance and can mimic the signs and symptoms of

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HF thereby potentially exacerbating the underlying disease[6-10]; (*d*) use of loop diuretics to manage fluid and sodium imbalances associated with HF may cause the hyperexcretion of thiamin, thereby increasing the risk of deficiency; and (*e*) the prevention of thiamin deficiency should be a routine component in the overall management of this disease. The purpose of this review is to increase awareness in the nutrition community regarding several characteristics of thiamin and to discuss the relevance of its deficiency to HF patients.

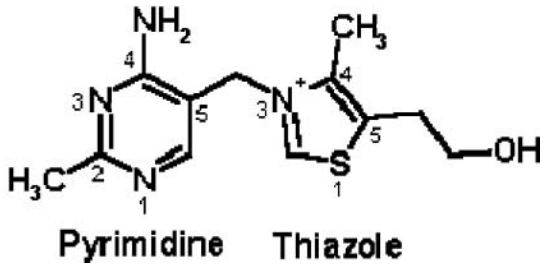

Figure 1. Chemical structure of thiamin.

Characteristics of Thiamin

History

Once referred to as the anti-beriberi factor and called "vitamine" for its "vital amine" properties, thiamin was first isolated in 1926 by 2 Dutch chemists, Dr B. C. P. Jansen and Dr W. Donath.[11] Initially, they named it aneurin after *a*nti*neur*itic vitam*in*.[11] Long before thiamin was given its current name, correctly identified, isolated, and synthesized in a clinical laboratory by Dr R. R. Williams, the disorder associated with thiamin deficiency was rampant in many parts of the world, especially in Asia. This disorder appeared after the introduction of polished rice into the diets of Asians. In the late 1800s, Dr K. Takaki first documented that beriberi seemed to be a nutrient deficiency after they were able to decrease the incidence of beriberi from 40% to 0% in 6 years by giving Japanese sailors a high-protein, low-carbohydrate diet consisting of vegetables, barley, fish, and meat at the expense of rice in daily rations. Dr Gerril Grijns had a different theory. He postulated that polished rice was lacking a specific, "substance of importance," in central nervous system metabolism.[11] His colleague, Dr Christian Eijkman, another Dutch physician, showed that a polyneuropathy could be induced in chicks eating polished rice and cured when the polishings were refed to them.

Chemical Properties

Thiamin, also referred to as thiamine and B_1, is a water-soluble and colorless vitamin with a characteristic odor and slightly bitter taste.[10-12] The chemical description for thiamin is 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium. The chemical structure of thiamin (Figure 1) consists of a pyrimidine ring connected to a thiazole ring by a 1-carbon link. The nitrogen atom within the thiazole ring serves many functions as an important electron sink in thiamin pyrophosphate (TPP)-catalyzed reactions.[11,12]

Thiamin exists in 3 forms: thiamin monophosphate (TMP), thiamin triphosphate (TTP), and thiamin pyrophosphate (TPP). Thiamin pyrophosphate is also known as thiamin diphosphosphate (TDP), which is the biologically active form of thiamin.[8,10] Thiamin pyrophosphate is an intracellular compound, which is why it provides the best expression of thiamin status.[10] Thiamin rarely exists in free form but, as such, travels in the serum. Thiamin is heat-stable and oxygen-stable in its dry form but is unstable in alkaline solution and decomposition is accelerated by light and increased temperature.[12]

Biochemical Functions

Thiamin in its various forms functions as a coenzyme for macronutrient oxidation and the production of adenosine triphosphate.[13] Thiamin pyrophosphate works in conjunction with magnesium to facilitate several oxidative decarboxylation reactions. Thiamin pyrophosphate is a catalyst in the reactions of pyruvate to acetyl CoA and α-ketoglutarate to succinyl CoA in the Krebs cycle. The pentose phosphate pathway (PPP) serves as a metabolic pathway within the cell to produce fuel and store it in the form of NADPH (reduced nicotinamide adenine dinucleotide phosphate; Figure 2). Thiamin pyrophosphate plays an important role in this central pathway for energy production and the creation of riboses used for RNA and DNA synthesis.[12] Another enzyme within the PPP that TPP functions as a coenzyme with is transketolase. A 2-carbon unit from an α-ketose is transferred to an aldose by transketolase (Figure 2).

Thiamin is found in both the nerves and brain tissue.[8] The role of thiamin in neurophysiology is unclear, but it seems to be important independent of its role as a coenzyme. It appears that TPP is involved in the sodium-dependent and potassium-dependent gradients that stimulate nerve impulses.[11]

Food and Supplemental Sources

Thiamin is widely distributed in foods (Table 1), but its content in most foods is relatively low.[12] As whole grains

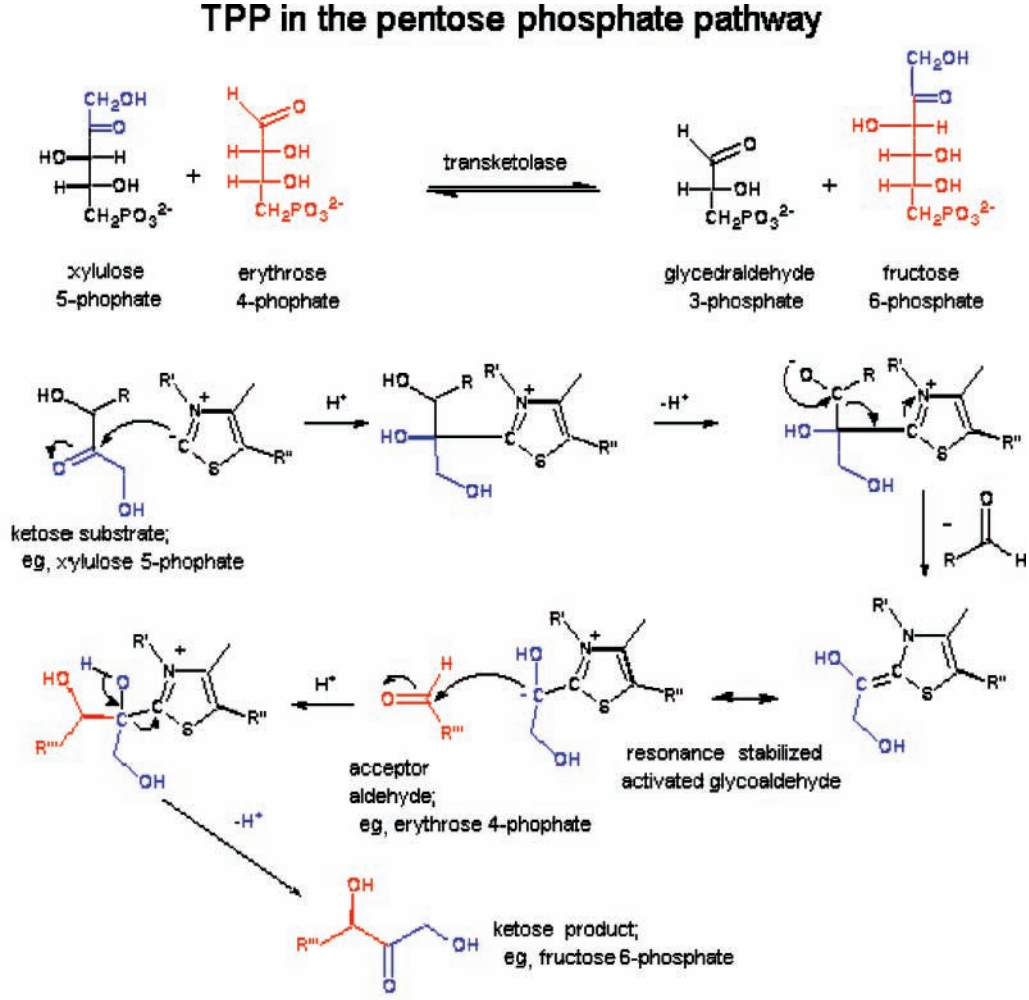

Figure 2. Thiamin pyrophosphate (TPP) in the pentose phosphate pathway.

Table 1. Thiamin Food Sources

Grains—wheat, wheat germ, dried yeast, oats, rice, cereal products, bread, pasta
Meats—pork, beef, lunch meat, sausage, bacon, liver
Poultry
Fish
Eggs
Milk and milk products
Orange and tomato juice
Pizza
Vegetables—beets, green leafy vegetables, potatoes
Legumes—lentils, soy beans, nuts, and seeds

are processed, they lose their naturally occurring thiamin content. However, the enrichment of refined flour allows the nutrition quality to be returned to original levels.

Thiamin supplements are available in several forms with the most common being thiamin hydrochloride and thiamin mononitrate, both of which are water-soluble. *S*-benzyolthiamine-*O*-monophosphate is a synthetic derivative of thiamin that is fat-soluble. Although not commonly used in practice, *S*-benzyolthiamine-*O*-monophosphate is more bioavailable and physiologically active than other sources of thiamin and may induce a better thiamin response in patients than other forms. Typically, thiamin supplements are manufactured and distributed in 50 or 100 mg doses even though the recommended dietary intake (RDI) is much lower (Table 2).

Thiamin Absorption

Thiamin is absorbed in the jejunum of the small intestine by an active transport process that is likely carrier-mediated against a concentration gradient at low concentrations.[12] At high concentrations, absorption takes place by passive diffusion.[12] Phosphorylation takes place in the jejunal mucosa to yield TPP. Maximum absorption of thiamin by the gut is 5 mg (Table 2). Thiamin is carried by portal

Table 2. Thiamin Supplementation Considerations

Recommended dietary intake	1-1.5 mg/day
Maximum jejunal absorption	5 mg/day
Storage capacity	30 mg
Standard dose in multivitamin	1 mg/day
Standard dose in single vitamin	50-200 mg/day
Estimated cost of intravenous thiamin	$0.25/100 mg dose
Estimated cost of oral thiamin	$0.03/100 mg dose
Risk of toxicity	Low

blood to the liver and transported into red blood cells (RBCs) by a facilitated diffusion process.[12] Thiamin has a quick turnover rate and is not stored in large amounts; therefore, a continuous supply is necessary.[12] Approximately 30 mg of thiamin are stored in the body (Table 2) with 80% as TPP and the rest as TMP. About 50% of the body stores are found in skeletal muscles with the remainder in the heart, liver, kidney, and tissue of the nervous system, including the brain.[10]

Thiamin Excretion

Thiamin, in excess of systemic tissue demand and storage capacity, is excreted in the urine.[10] As thiamin deficiency develops, there is a rapid loss of the vitamin from all tissues except the brain. The decrease of TPP in RBCs roughly parallels the decrease of this coenzyme in other tissues. During this time, urinary excretion of thiamin falls close to zero in order to preserve endogenous stores.

Signs and Symptoms of Thiamin Deficiency

Specific signs and symptoms observed in thiamin-deficient patients represent alterations in the biochemistry of thiamin that result in impaired oxidative phosphorylation, increased levels of proximal metabolites (pyruvate), and decreased transketolase activity in RBCs, liver, heart, and other organs.[12]

Thiamin deficiency manifests as dry or wet beriberi. Dry beriberi involves peripheral neuropathy that can be permanent even following thiamin repletion.[14,15] Neurological side effects of thiamin deficiency can progress to Wernicke–Korsakoff syndrome. In general, patients with thiamin deficiency experience the "classic triad" of symptoms, including oculomotor abnormalities, gait disturbance, and global confusion.[14] However, all these symptoms do not need to be present to make a diagnosis of Wernike–Korsakoff syndrome.

Wet beriberi impairs cardiac performance and typically presents as peripheral dilation, high-output cardiac failure, biventricular low-output failure, and sodium and water retention.[7] This syndrome mimics the signs and symptoms of HF; therefore, thiamin deficiency may actually exacerbate underlying HF. In fact, research has shown that when thiamin deficiency is corrected, LVEF improves.[6,16-18] Ejection fraction is one of the most widely used predictors of prognosis; patients with reduced LVEF typically have poor outcomes. The presumed mechanism by which thiamin deficiency exacerbates HF is through the inhibition of the pyruvate dehydrogenase complex.[19,20] Inhibition of pyruvate dehydrogenase complex has been theorized to decrease the efficiency of adenosine triphosphate production, increase cellular acidosis, and increase free fatty acid levels in circulation.[19,20]

Thiamin deficiency can occur within 14 days of inadequate status.[10] Although rare, the most extreme and life-threatening form of thiamin deficiency is shoshin beriberi, a fulminant form of wet beriberi that can ensue quite rapidly resulting in acute cardiovascular collapse, metabolic acidosis, and death within hours.[13] Rapid recovery is achieved within hours following intravenous thiamin administration.[20,21] Therefore, thiamin deficiency should routinely be considered during diagnostic evaluations.

Mechanisms Contributing to Thiamin Deficiency in HF Patients

There are several mechanisms that can contribute to thiamin deficiency in HF patients (Table 3). Subclinical thiamin deficiency may occur with age or during situations that cause hypermetabolism, that is, trauma, surgery, or fever.[22] Other high-risk populations include the elderly, alcoholics, people with HIV/AIDS, homeless individuals, patients with frequent hospitalizations, and those with persistent vomiting, diarrhea/malabsorption syndromes, and dietary inadequacy.[7,8,10]

The issue of age as a factor contributing to the prevalence of thiamin deficiency was evaluated by Levy et al[16] who conducted a prospective trial of patients with a mean age of 47 ± 10 years, mean New York Heart Association (NYHA) functional class of 2.5 ± 0.6 on a scale of I-IV, and mean LVEF of 22 ± 9% (normal LVEF >50%[8]). The mean dosage of loop diuretics (mainly furosemide) was 184 mg/day. Thiamin status was measured by erythrocyte transketolase activity. No evidence of thiamin deficiency was found in their population of HF patients.[16] Given the relatively young age of the subjects used in this study, it may be that other factors in an older HF population contribute to the risk of thiamin deficiency such as disease severity, comorbidity, dietary inadequacy, and drug–nutrient interactions.

A drug–nutrient interaction has been shown to occur between loop diuretics and thiamin. Historically, loop diuretics were approved for the general treatment of edematous disorders. Even though they have never been primarily evaluated for the treatment of HF, loop diuretics are used to counteract HF through the renal excretion of

Table 3. Mechanisms Contributing to Thiamin Deficiency in Heart Failure Patients

Urinary wasting from diuretics or dialysis
Diarrhea
Dietary inadequacy
Malabsorption syndromes
Gastroplasty/gastric bypass surgery
Alcoholism
Thiaminases in certain foods (eg, tannins in tea)
Magnesium deficiency
Hyperthyroidism

sodium, chloride, and water along with other water-soluble molecules, including potassium, magnesium, vitamin C, and vitamin B-complex vitamins, such as thiamin.[10] Increased losses of thiamin secondary to loop diuretic therapy was first described in 1980 by Yiu et al.[23] Since then, several other studies have replicated these findings suggesting that loop diuretic therapy can lead to thiamin deficiency secondary to hyperexcretion.[6-9]

Inadequate caloric and protein intake is common in HF patients[8,24] and the diets of patients with HF often do not contain adequate amounts of thiamin-rich foods.[7,8] Kwok et al[22] reported that poor appetite is a reliable indicator of compromised thiamin status in elderly patients with HF. Reasons that oral intake in HF patients may be marginal include early satiety, a sensation of fullness, cachexia, changes in the thirst mechanism, sodium-restrictive and fluid-restrictive diets that may result in the avoidance of thiamin-rich foods, lack of motivation, malaise, and poor mobility.

Treatment of Thiamin Deficiency

The U.S. RDI is 1 mg/day for women and 1.2–1.5 mg/day for men, but thiamin requirements are contingent on energy expenditure and carbohydrate intake. Typical repletion regimens in the acute clinical setting range from 50–200 mg/day intravenously or orally (Table 2) with rapid clinical improvement following supplementation.[10,13] For mild neuropathy, 10–20 mg oral thiamin per day is recommended for 2 weeks.[25] Moderate or advanced neuropathy can be treated with a dose of 20–30 mg/day for several weeks after symptoms disappear.[25] For edema and congestion due to wet beriberi, 100 mg intravenous (IV) thiamin per day is given for several days.[25] For Wernicke–Korsakoff syndrome, 50–100 mg intramuscular or IV thiamin should be given twice daily for several days followed by 10–20 mg per day until a therapeutic response is observed.[25] Improvement in patients with Korsakoff psychosis may take 1–3 months, and recovery from neurologic deficits is often incomplete.[25]

The cost of thiamin supplementation is low as is the risk of toxicity (Table 2).[13] In general, thiamin is considered safe and relatively nontoxic even at high doses. An upper level of tolerance has not been established. Large doses can result in fatigue or muscle relaxation, but dermatitis or anaphylactic reactions rarely occur.[26] Thiamin injections may cause a burning sensation, which can often be avoided by slow administration into larger veins.[26]

Assessment of Thiamin Status

Serum and Urinary Thiamin Levels

The half-life of serum thiamin is short and only reflects immediately preceding oral intake. This inhibits its use as a reliable indicator of thiamin status. Thiamin urinary excretion, even when normalized for urinary creatinine concentration, also has limitations as a sensitive indicator of thiamin status because, aside from its cumbersome nature due to a required loading dose and 24-hour urine collection, urinary thiamin concentrations reflect recent oral intake. If urinary thiamin levels increase following the loading dose, as measured with high-performance liquid chromatography (HPLC) using the methods of Botticher and Botticher,[27] status is intact. If no change in urinary thiamin content is observed, this is suggestive of the body's need for it and the risk of subclinical deficiency exists. One urinary thiamin metabolite that may be measured is thiochrome, but this method is no longer commonly used in clinical practice.[12]

Erythrocyte Transketolase Activity Assay

The best measure for differentiating normal status from subclinical thiamin deficiency is a functional enzymatic test called the erythrocyte transketolase activity (ETKA) assay. Erythrocytes, or RBCs, are used because they are the first cells to reflect thiamin deficiency.[10] The ETKA assay is a thiamin-dependent enzymatic assay that measures ETKA and TPP effect (TPPE) through an in vitro analysis of transketolase enzyme function. Exogenous TPP is added, and if it has an effect on ETKA, the response expressed as a percentage indicating normal, mild, or severe thiamin deficiency proves whether endogenous thiamin levels were deficient or not (Table 4). High-performance liquid chromatography is also used in the research setting to evaluate ETKA and is probably more sensitive than the ETKA functional enzymatic assay, but it is not as practical.[28]

Erythrocyte Thiamin Pyrophosphate Analysis

The erythrocyte TPP analysis method directly measures TPP using HPLC on an amino acid column.[8,29] According to Hanninen et al,[8] this method is more specific than indirectly measuring thiamin-dependent enzyme activity such as ETKA. They defined thiamin deficiency as TPP < 78 ng/mL

Table 4. Thiamin Pyrophosphate Effect

0%–15% improvement = no deficiency
16%–25% improvement = mild deficiency
>25% improvement = severe deficiency

packed cells based on the correlation between TPP and the TPP effect.[8,10]

In clinical practice, the measurement of thiamin status is unnecessary because a reliable test to measure thiamin status is not readily available. Routine prophylactic thiamin supplementation in HF patients is appropriate because it offers protection from thiamin deficiency, and it is safe and inexpensive with a low risk of side effects or toxicity.[30]

Prevalence of Thiamin Deficiency in HF Patients

Animal Data—Review of Evidence

In 1980, Yiu et al[16] first described the hyperexcretion of thiamin as a consequence of loop diuretic therapy. Using a rat model, they showed that the administration of loop diuretics increased urinary thiamin excretion after 4 weeks of therapy and concluded that long-term diuretics could induce deficiency. In a subsequent study also using a rat model, loop diuretic therapy resulted in thiamin deficiency in a dose-dependent response and was attributed to urinary hyperexcretion of this nutrient.[31]

Human Data—Review of Evidence

A wide range (21%–98%) in the prevalence of thiamin deficiency has been documented in human subjects with HF.[6-9] The breadth of this range reflects variations in the underlying nutrition status of subjects, presence of comorbid conditions, concurrent use of medications, including the type and dose of diuretics, reported use of nutrition supplements, and measurement techniques for the assessment of thiamin status.

Seligmann et al[6] reported that 96% of patients (21 of 23) with HF receiving loop diuretic therapy (daily dose: 80–240 mg furosemide) developed thiamin deficiency. Thiamin status was measured by TPPE and urinary thiamin excretion. Increased urinary losses of thiamin were noted in 15–23 patients. The investigators also evaluated the effect of thiamin supplementation on LVEF and reported significant improvements in cardiac function following thiamin repletion.[6]

Brady et al[7] found that 21% of HF patients (8 of 38) with NYHA class III/IV disease (mean LVEF 22 ± 8%) receiving loop diuretic therapy (mean furosemide dose: 242 ± 216 mg/day) had thiamin deficiency based on ETKA.[7] They concluded that thiamin deficiency is prevalent in outpatients with chronic HF but did not address urinary thiamin excretion. Dietary assessment of thiamin intake was conducted using a validated semiquantitative food frequency checklist containing thiamin-rich foods to estimate usual thiamin intake. Adequate thiamin intake was defined as >30 servings/week; mild thiamin intake inadequacy, 20–30 servings/week; and severe thiamin intake inadequacy, <20 servings/week.[7] They concluded that marginal oral intake may increase the likelihood of thiamin deficiency in HF patients.

Hanninen et al[8] discovered that thiamin deficiency is even more common in HF inpatients compared with the rate observed in chronic HF outpatients.[8] Their study was the largest study (n = 100) available using hospitalized patients with a wide range of disease severity and variability in diuretic therapy (median dose of furosemide in outpatients: 60 mg/day). Evidence of thiamin deficiency was observed in one-third of subjects who acknowledged the consumption of thiamin supplements.[8] The prevalence of thiamin deficiency was positively correlated with severity of disease. A total of 40% of patients with advanced HF (NYHA class III/IV; LVEF <35%) were thiamin deficient compared with 25% of patients with NYHA class I/II HF (LVEF >35%). This difference in prevalence of thiamin deficiency was even higher when supplement users were excluded with deficiency being present in 49% of patients with LVEF <35% vs 24% of patients with LVEF >35%.[8]

In contrast to the findings of Seligmann et al[6] who found that urinary excretion of thiamin was elevated in HF patients on loop diuretics, Hanninen et al[8] did not detect a relationship between the development of thiamin deficiency and diuretic use or urinary thiamin excretion. Hanninen et al concluded that thiamin supplementation is indicated, but that the thiamin content of a standard multivitamin may be sufficient to protect against thiamin deficiency.[8]

Conclusion

Although animal and human research related to the role of thiamin in the management of HF is clinically significant, studies have been limited by their small sample sizes, varied use of measures of thiamin status, and inconsistencies in the assessment of adequate intake. However, the relevance of thiamin to cardiac function and cellular metabolism is convincing.

Thiamin deficiency is prevalent in patients with HF and yet this problem is underrecognized, preventable, and easily treatable. Long-term routine thiamin supplementation may be protective against the manifestations of thiamin deficiency, which mimics signs and symptoms of HF exacerbation. Adequacy of thiamin intake should be assessed in each HF patient. Measurement of thiamin status is unnecessary. Minimally, NYHA class III and IV

HF patients with LVEF <50% on long-term loop diuretic therapy should consume a multivitamin daily to promote thiamin intake at the RDI level. Long-term use of higher doses of thiamin, those of which are already commercially available in 50–200 mg per dose amounts, deserve further study. However, this dose of thiamin appears to be safe and effective in the prevention of thiamin deficiency with low risk of adverse side effects or toxicity at minimal expense to both the patient and the healthcare system.

More research related to the safety and efficacy of thiamin supplementation in HF patients is needed to determine optimal dosing, duration of therapy, and clinical outcomes. However, if the prophylactic administration of thiamin supplements can decrease the prevalence of thiamin deficiency, increase LVEF, and improve QOL, it should be given without reservation to HF patients who meet criteria in order to slow the progression of this devastating disease.

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