PREVALENCE OF THIAMIN DEFICIENCY IN HOSPITALIZED PATIENTS WITH CONGESTIVE HEART FAILURE

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Congestive Heart Failure

1. Normal Heart
2. Enlarged Heart
3. Heart Failure
4. Heart Muscle stiffens and heart weakens
5. Lung capacity decreases
6. Blood backs up in heart, lungs, and veins
7. Creates shortness of breath and edema

This cycle continues as long as the heart's ability to pump blood is compromised.
What are the Main Causes of Heart Failure?

- A viral infection of the heart
- Myocardial infarction (heart attack)
- Chronic high blood pressure
- A heart valve that is not working properly
- Alcohol abuse or other drugs
- Congenital defects
Symptoms of Heart Failure

- Salt and water retention
- Shortness of breath – reduced capacity
- Swelling of the ankles
- Weight gain
- Fatigue
- Loss of appetite – bloated feeling
- Nausea/ vomiting
Health Burden of Heart Failure

- Cancer: 36%
- Infectious disease: 28%
- Diabetes: 15%
- Other: 10%
- Respiratory: 6%
- Accidents/violence: 3%

350,000 Canadians

Heart and Stroke Foundation of Canada, 2003
Management of Heart Failure

- **Pharmacologic**
  Beta blockade, ACE inhibitors, inotropes, calcium channel blockers, statins and DIURETICS

- **Nutritional**
  Sodium and fluid restriction, potassium balance, cholesterol reduction and heart healthy eating

- **Lifestyle**
  Smoking and exercise

- **Dismal Prognosis**
Overall Survival after CHF as Estimated using Kaplan-Meier Methods

Ho et al. JACC 1993
The race continues for new, alternative and complementary strategies
New Paradigm of Nutritional Care

Energy

- Carnitine
- Energy and Protein
- Creatine
- CoQ10

Thiamin

- Vitamin D
- Omega 3

Vitamin E

Vitamin C

Selenium

Antioxidants

Free Radicals

Heart Damage

Taurine

Calcium Balance

Contraction
Thiamin Background

• Thiamin is a water soluble vitamin – B vitamin. It is not stored in the body and is excreted in the urine.

• Thiamin (TPP) is a coenzyme in carbohydrate metabolism - production of ATP for cellular energy.

• Thiamin deficiency manifests as symptoms of CHF (wet beri-beri).
Thiamin Deficiency in Heart Failure

- Inadequate Thiamin Intake
- Diuretic induced urine thiamin excretion
- Disease Severity
- Elderly Age
- Malnutrition
- CHF
- TD
- Kidney Failure
- Decreased Appetite
- Frequent Hospitalization
Proposed Vicious Cycle of Deficiency

- Increased Urinary Losses
- Increased number or dose of diuretic
- Worsening Symptoms of Heart Failure
  - Swelling of ankles
  - Fluid accumulation
- Thiamin Deficiency
Changes in Urinary Thiamin Content before and after treatment with Furosemide

Thiamine Status of Patients with Heart Failure

21/23 deficient

Seligmann Am J Medicine 1991
The Effect of Thiamin Supplementation on Heart Function

Ejection Fraction

0 7 days 7 weeks

* p<0.05 vs baseline  
** p< 0.01 vs baseline

OBJECTIVES

1. To determine the prevalence of TD in a large cross-section of hospitalized CHF patients.

2. To investigate the influence of age, sex, diuretics, urinary thiamin excretion, CHF disease severity, hospitalization, thiamin intake, appetite, malnutrition, decreased renal function, and diabetes on the development of TD.
METHODS: CHF PATIENTS

- 100 CHF patients admitted to St. Michael’s Hospital (April 2001-June 2002).

- 50 age and sex matched healthy control subjects.

- TD was defined as erythrocyte TPP < 78 ng/mL packed cells.

- Approval for this study was obtained from SMH Research Ethics Board.
Patients—Selection Criteria

Inclusion Criteria:

Patients admitted to the cardiology ward or coronary care unit at SMH with a primary diagnosis of CHF
Patients– Exclusion Criteria

- Exclusion Criteria:
  - High-dose thiamin supplementation (200mg/day) for alcohol abuse
  - Experimental medication
  - Inability to give informed consent (because of dementia or inability to speak English)
  - Short anticipated hospital stay
Healthy Controls

• Inclusion Criteria:
  – Age-matched to patients within 5 years

• Exclusion Criteria:
  – Any known conditions affecting thiamin status
  – Use of thiamin-containing supplements.

Spouses, staff members, patients undergoing elective cardiac procedures, cardiac rehab patients
STUDY PROCEDURES FOR CHF PATIENTS

During hospitalization
Information was obtained:
• Diuretics: duration & dose
• FFQ\textsuperscript{a}–estimate thiamin intake
• SGA\textsuperscript{b}, BMI\textsuperscript{c}: nutrition status
• Appetite rating
• CHF severity: LV function\textsuperscript{d}

\textsuperscript{a}FFQ, food frequency questionnaire. \textsuperscript{b}SGA, subjective global assessment. \textsuperscript{c}BMI, body mass index. \textsuperscript{d}LV, left ventricle function.

Study procedures for control subjects included age and sex matching to CHF patients and obtaining a fasting blood sample for determination of erythrocyte TPP concentration.
## Characteristics of CHF patients and control subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CHF (n = 100)</th>
<th>Control (n = 50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>58 (58%) / 42 (42%)</td>
<td>24 (48%) / 26 (52%)</td>
<td>0.246&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age [mean(SD)]</td>
<td>67.1 (10.1) y</td>
<td>61.1 (11.1) y</td>
<td>0.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI [mean(SD)]</td>
<td>27.3 (5.5) kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>27.2 (4.7) kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.762&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thiamin-containing Supplement use</td>
<td>21 (21%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Other supplement use</td>
<td>41 (41%)</td>
<td>9 (18%)</td>
<td>0.001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pearson Chi-Square, <sup>b</sup> Mann-Whitney, <sup>c</sup> Fisher’s Exact
## Cardiac disease characteristics of CHF patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>Characteristics</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHF Etiology</strong></td>
<td></td>
<td><strong>NYHA Classification</strong></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>40</td>
<td>Class I</td>
<td>6</td>
</tr>
<tr>
<td>Valve disease</td>
<td>18</td>
<td>Class II</td>
<td>18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>Class III</td>
<td>43</td>
</tr>
<tr>
<td>CAD &amp; Valve</td>
<td>11</td>
<td>Class IV</td>
<td>32</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left Ventricle Function</strong></td>
<td></td>
<td><strong>Diuretic Use at Admission</strong></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>21</td>
<td>Furosemide</td>
<td>80</td>
</tr>
<tr>
<td>Grade II</td>
<td>26</td>
<td>Spironolactone</td>
<td>16</td>
</tr>
<tr>
<td>Grade III</td>
<td>27</td>
<td>Metolazone</td>
<td>7</td>
</tr>
<tr>
<td>Grade IV</td>
<td>26</td>
<td>Multiple Diuretics</td>
<td>26</td>
</tr>
</tbody>
</table>
Prevalence of TD in CHF patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>CHF (n = 100)</th>
<th>Control (n = 49)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33.0 %</td>
<td>12.2 %</td>
<td>0.007*</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pearson Chi-Square, * Significant at P < 0.05
Factors Related to the Presence of Thiamin Deficiency

Which are predictive of those at risk?
Relationship Between Diuretic Dose and Urine Thiamin Loss
Relationship between TD and urine thiamin excretion in CHF patients

**Graph:**
- X-axis: Urine Thiamin Excretion (µg/g creatinine)
- Y-axis: Urine Thiamin Excretion
- TD (n=33)
- NTD (n=67)
- P = 0.089

**Caption:**
Mann-Whitney Test
Relationship between Thiamin Intake and Loss

\[ r = 0.314 \]
\[ p = 0.004 \]
\[ y = 71.5x + 175.7 \]

Average Requirement
Relationship between TD and thiamin supplement use in CHF patients

![Bar chart showing the prevalence of NTD and TD in patients with and without thiamin supplements.](image)

Prevalence

Thiamin supplements (n=21) vs. No Thiamin supplements (n=78)

NTD and TD prevalence comparison: 
P = 0.046

Pearson Chi-Square Test
Factors not associated with Thiamin Deficiency in CHF patients

- Age
- Gender
- Hospitalization
- Diabetes
- Furosemide use
- Metolazone use
- multiple diuretics
Factors associated with thiamin deficiency

- Having low urinary thiamin losses
- Not using thiamin containing supplements
- Having good kidney function
- Worsening heart failure
- Having a poor appetite
- Having a thiamin intake that is less than the average requirement
- Having mild or moderate malnutrition
CHF and B Vitamins

• We have demonstrated that 33% of CHF patients at SMH were thiamin deficient (Hanninen et al, 2005).

• Riboflavin and vitamin B6 are water-soluble with no appreciable tissue storage.

• Therefore, as an adjunct study, we investigated the status of riboflavin and vitamin B6 in the same CHF patients.
Role of Riboflavin (B2) and B6 in Metabolism

• Important factor in fatty acid oxidation and glucose metabolism.

• B2 and B6 participate in the production of energy

• B2 required to form active B6

• B6 is needed for red blood cell formation (heme) and plays a role in homocysteine metabolism
The Prevalence of B6 and B2 Deficiency in CHF Patients and Controls
Discussion: Inter-relationships Between B Vitamin Deficiencies

Riboflavin

- Riboflavin deficiency was significantly related to thiamin deficiency
- EGRAC correlated significantly with total riboflavin intake

Vitamin B6

- No relationship between B6 deficiency and thiamin deficiency

Thiamin

- B6 deficiency significantly related to riboflavin deficiency
- Plasma B6 significantly correlated with total riboflavin intake

- Riboflavin deficiency was significantly related to thiamin deficiency
- EGRAC correlated significantly with thiamin intake even when supplement users excluded
The Overall Prevalence of B vitamin Deficiency in CHF Patients

Percent of patients at risk of deficiency

- 0% no vitamin deficiency
- 20% 1 vitamin at risk
- 40% 2 vitamins at risk
- 60% 3 vitamins at risk

all CHF | CHF No Supplements | controls
CONCLUSIONS

• The prevalence of B vitamin deficiency in our hospitalized CHF patients is high (71%).

• Development of deficiency is complex – not simply related to the dose or duration of furosemide (diuretic) use

• Dietary intake meeting requirement for healthy population yet deficient - Conditional Nutrient Deficiency? Paucity of data – NIH call
Our Research Team

Stacy Douglas-Hanninen
Mary Keith
Pauline Darling
Michael Sole
Aiala Barr

CFDR funds allowed the completion of the biochemical analysis of B vitamin status
Study Methodology

- Same population as B1 study

- Plasma riboflavin was assessed by enzymatic activity assay (*Sauberlich, 1999*)

- Deficiency was defined as erythrocyte glutathione reductase activity coefficient (EGRAC) > 1.2

- Vitamin B6 concentrations were determined by radioimmunoassay (RIA) measures PLP-5’

- Deficiency was defined as < 20 nmol/L plasma
Implications for Practice
What about routine supplementation?

• Thiamin status was significantly improved in those taking a multi-vitamin (low dose B1 – 1.5 mg/day) or B complex supplement
• B6 status was also improved (p=0.09) in those taking a multi-vitamin or B complex supplement
• Evidence of benefit difficult to obtain – do the potentials benefit outweigh the risks?
• How can we measure success?
Micronutrient Supplementation in Elderly Patients with CHF

- 32 patients with age >70 years
- Stable – reduced heart function
- Quality of Life, cytokines, six minute walk test and cardiac magnetic resonance imaging
- Randomized, double blind study
- Multi-micronutrients – 9 months

Witte et al. European Heart Journal, 2005
### Multi-Nutrient Supplement for Heart Failure

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Daily dose (four capsules)</th>
<th>RDI</th>
<th>Upper safe limit for total daily intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>250 mg</td>
<td>800 mg</td>
<td>2500 mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>150 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>300 mg</td>
<td>700 mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>15 mg</td>
<td>15 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Copper</td>
<td>1.2 mg</td>
<td>1.2 mg</td>
<td>9 mg</td>
</tr>
<tr>
<td>Selenium</td>
<td>50 μg</td>
<td>65 μg</td>
<td>450 μg</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>800 μg</td>
<td>800 μg</td>
<td>3300 μg</td>
</tr>
<tr>
<td>Thiamine</td>
<td>200 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.4 mg</td>
<td>No limit</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>2 mg</td>
<td>1.5 mg</td>
<td>No limit</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;6&lt;/sub&gt;</td>
<td>200 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Folate</td>
<td>5 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>200 μg</td>
<td>No limit</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>200 μg</td>
<td>1 μg</td>
<td>No limit</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>500 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60 mg</td>
<td>2000 mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>10 μg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 μg</td>
<td>25 μg</td>
</tr>
<tr>
<td>Co-enzyme Q10</td>
<td>150 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 mg</td>
<td>No limit</td>
</tr>
</tbody>
</table>

<sup>a</sup>Doses taken from previous work<sup>8</sup> or RDI.
Clinical Outcomes Following Micro-Nutrient Supplementation

Figure 1  Change in left ventricular end-diastolic volume with placebo (unfilled circles and dashed line) and micronutrient supplementation (filled circles and solid line), (error bars are SD).

Figure 2  Quality of life score (percentage of maximum) during study period for patients taking placebo (unfilled circles and dashed line) or micronutrient supplementation (filled circles and solid line), (error bars are SD).
NORVIT Study

- Large trial post MI - 3749 patients
- Gave 0.8mg folic acid, 0.4 mg B12, 40mg B6
- Looked at homocysteine lowering and cardiovascular risk over 4 years
- Composite endpoint – fatal MI and non-fatal MI, stroke and sudden death due to heart disease.

Bonna et al. NEJM 2006
Bonna et al. NEJM 2006

N=3749

0.8 mg folic acid
0.4 mg B12
40 mg B6
Implications for Practice

• NIH call recognizing paucity of data
• Routine supplementation of B1 appears safe and justifiable
• Supplementation with B6 requires additional investigation to determine:
  the impact of deficiency status
  the impact of dose (high or low)
Continue to investigate the impact of specific disease states on nutritional requirements