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Original article

Prevalence of thiamine deficiency in a stable heart failure outpatient cohort on standard loop diuretic therapy

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SUMMARY

Background & aims: The prevalence of thiamine deficiency in heart failure (HF) patients has been reported to be as high as 50% in outpatient settings and has been found to be as high as 96% in the inpatient setting. Results from previous studies, however, have been inconsistent and further investigation is needed to clarify the true prevalence of thiamine deficiency in patients with chronic HF. The aim of this study was to determine the prevalence of thiamine deficiency in a random sample of stable HF outpatients receiving standard of care loop diuretic therapy.

Methods: A cross-sectional study was conducted in 30 HF patients scheduled for regular follow-up visits in the Mayo Heart Failure Clinic. Whole-blood thiamine diphosphate was measured using high-performance liquid chromatography. Additional clinical and demographic features were collected through review of electronic medical records.

Results: The estimated prevalence of thiamine deficiency in stable HF patients was calculated to be <11.6%. There was no correlation between diuretic dose and thiamine levels ($r = 0.02$, $P = 0.93$) and there was no correlation found between left-ventricular ejection fraction (LVEF) and thiamine levels ($r = 0.147$, $p = 0.44$).

Conclusion: Our findings suggest that the prevalence of thiamine deficiency, based on standard normal values, in a stable outpatient HF cohort on standard loop diuretic therapy is very low. Previous work has demonstrated improvements in myocardial function with high-dose thiamine supplementation regardless of thiamine blood levels, however, suggesting that thiamine may become conditionally essential with HF. Therefore, we suggest that a disease-specific reference range be determined to accurately identify HF patients that would benefit from thiamine supplementation.

1. Introduction

Heart Failure (HF) is the inability of the heart to pump a sufficient amount of blood to adequately perfuse tissues [1]. More than 5.5 million Americans suffer from HF, which carries a high mortality rate of approximately 50% within five years of diagnosis and a high economic burden of 34 billion dollars (recent yearly estimate) [2]. The pathophysiology of HF is complex and has not been fully elucidated, but altered energy metabolism within cardiac tissue is thought to contribute to progression of the disease [3,4].

Thiamine is an essential micronutrient for the normal production of ATP through aerobic glycolysis. Loop diuretics are a widely prescribed therapy for HF symptom management and have been shown to increase the urinary loss of thiamine in humans [5]. Previous research in HF patients has demonstrated an inverse relationship between daily dose of loop diuretics and thiamine concentration [6,7], as well as a direct relationship between thiamine concentrations and left-ventricular ejection fraction (LVEF) [8]. The increased urinary loss of thiamine with loop diuretic use has been hypothesized to potentiate a thiamine deficiency in HF patients – exacerbating their symptoms [9]. This hypothesis is supported by a reported prevalence of thiamine deficiency as high as 96% in blood samples of HF patients [6–8,10–14]. These findings

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are juxtaposed, however, by multiple studies finding no evidence of deficiency, or no difference in thiamine status between HF patients and controls [15–18]. Due to the inconsistency and controversy over findings, we sought to identify the prevalence of thiamine deficiency in a stable outpatient cohort of HF patients receiving standard loop diuretic therapy.

2. Materials and methods

2.1. Study population

A cross-sectional observational study design was undertaken. Patients scheduled for regular outpatient follow-up in the Heart Failure Clinic at Mayo Clinic in Rochester, MN between August 2013 and December 2014 were eligible for inclusion in the study. Electronic medical records were reviewed to identify subjects who met the eligibility criteria (greater than 18 years of age, established diagnosis of HF New York Heart Association class I-IV, and receiving a loop diuretic for greater than six months). Exclusion criteria were the concurrent use of high-dose thiamine supplements (>10 mg/day), chronic alcohol abuse, active eating disorder, history of altered gastrointestinal absorption from disease or surgery, ongoing dialysis therapy, end-stage liver disease, pregnant or lactating females, concurrent chemotherapy or parenteral nutrition. Additional variables such as body mass index (BMI), hemoglobin, and potassium, were recorded to characterize nutritional status. Creatinine was recorded as a measure of renal function. Subject age, sex, daily loop diuretic dose, duration of loop diuretic therapy, duration of HF, LVEF, and the use of spironolactone, and multivitamins were recorded. The loop diuretics prescribed to study participants were Furosemide and Torsemide. Loop diuretic dose was based on "Furosemide Equivalents" (a 1:2 ratio was used for conversion of Torsemide dosing to Furosemide dosing). The study was approved by the Mayo Clinic Institutional Review Board.

2.2. Laboratory measurements

Patients who met the inclusion/exclusion criteria and signed consent to participate in the study received a one-time blood draw of 4 mL. Whole-blood thiamine diphosphate (TDP) was measured using high-performance liquid chromatography (HPLC) performed by Mayo Medical Laboratories (Andover, MA). The HPLC method used by Mayo Medical Laboratories relies on thiochrome formation and quantitation by fluorometry [19,20]. Results were compared to standard normal values (70–180 nmol/L). Additional laboratory measures, which were collected as part of the standard plan of care on the morning of the patients' thiamine blood draw, were obtained through review of electronic medical records as available. These measures included creatinine, potassium, and hemoglobin. Participants' height, weight, and BMI were recorded as part of the standard plan of care prior to the outpatient heart failure clinic appointment during which consent for the study was obtained. These data were collected by investigators at a later date through review of electronic medical records.

2.3. Statistical analysis

Data were assessed for normality and found to be appropriately distributed. Continuous variables were expressed as means ± standard error of the mean. A 95% confidence level was used and a p-value <0.05 was considered significant. The interval for binomial proportions was calculated using the Pearson-Klopper method. A two-sample t-test was used to compare differences between means. Linear regression was used to assess relationships between continuous variables. The data analysis for this paper was generated using SAS software (Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA).

3. Results

Thirty individuals agreed to participate in the study (25 males and 5 females) and their clinical characteristics and demographics are shown in Table 1. The low accrual numbers over 15 months are due to logistical issues (i.e. the inpatient care roles of the authors and difficulty appropriating the time required to travel to the outpatient heart failure clinic and obtain consent). The mean age of the cohort was 74.8 years, with a gender distribution of 17% female and 83% male. The mean BMI of the participants was 31.1 kg/m^2 with mean hemoglobin and potassium within normal limits indicating a generally adequately-nourished cohort. The mean daily loop diuretic dose was 76.7 mg with a mean duration of therapy of 61.2 months. There were eighteen individuals prescribed Furosemide as their loop diuretic and twelve individuals prescribed Torsemide as their loop diuretic. The mean serum creatinine was 1.6 mg/dL indicating chronic kidney disease, Stage 2. The mean LVEF was 40.4% with a range of 15–74%. Twelve individuals had EFs >40% and seven of those individuals had EFs >50%.

None of the 30 individuals was found to be thiamine deficient by blood level assessment. The calculated confidence bound suggests that the true proportion of stable HF patients on routine loop diuretic therapy with thiamine deficiency would be estimated at <11.6%. The mean blood thiamine concentration was 147.9 nmol/L (range 89–197 nmol/L). A box plot of thiamine values demonstrates that the mean blood thiamine value was not driven by outliers (Fig. 1). Although not statistically significant, there was a notable difference between mean thiamine values of individuals taking a thiamine containing multi-vitamin supplement (n = 12) and the remaining individuals not taking a thiamine containing supplement (n = 18) (p = 0.052); the mean thiamine concentrations in these sub-groups were 161.5 nmol/L and 139 nmol/L, respectively. The mean thiamine content of the thiamine-containing multivitamin supplements was 1.7 mg/day. No significant association was shown between daily dose of loop diuretics and thiamine values (r = 0.02, P = 0.93) (Fig. 2). Also, no significant association was shown between thiamine concentrations and LVEF (r = 0.147, p = 0.44) (Fig. 3), or thiamine concentrations and creatinine (r = 0.24, p = 0.21).

Table 1
Clinical and demographic characteristics of HF patient cohort (N = 30).

Age, mean ± SE (years)	74.8 ± 1.8
Sex (F/M)	5/25
BMI, mean ± SE (kg/m^2)	31.1 ± 1.0
LVEF, mean ± SE (%)	40.4 ± 3.0
Duration of HF, mean ± SE (months)	71.2 ± 12.4
Creatinine, mean ± SE (mg/dL)	1.6 ± 0.1
Potassium[b], mean ± SE (mmol/L)	4.66 ± 0.1
Hemoglobin[a], mean ± SE (g/dL)	12.6 ± 0.74
Spironolactone (Y/N)	9/21
Beta blocker (Y/N)	23/7
Prescribed loop diuretic (Furosemide/Torsemide)	18/12
Loop diuretic daily dose equivalent, mean ± SE (mg)[c]	76.7 ± 5.1
Duration of loop diuretic therapy, mean ± SE (months)	61 ± 8
Thiamine level, mean ± SE (nmol/L)	147.9 ± 5.7
Thiamine containing multivitamin (Y/N)	12/18
Thiamine content of multivitamin, mean ± SE (mg)	1.7 ± 0.25

[a] n = 8.
[b] n = 17.
[c] Conversion factor of 1:2 was used to conver Torsemide doses to Furosemide equivalents.

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