Original Article

Prevalence of Thiamine Deficiency in Chronic Heart Failure Patients: Ramathibodi Cardiology Clinic Experience

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Objective: Thiamine deficiency is still a public health concern in developing countries including Thailand. Heart failure is associated with thiamine deficiency especially in patients receiving diuretic therapy. Therefore, we sought to find the prevalence of thiamine deficiency in chronic heart failure outpatients.

Materials and Methods: A cross-sectional descriptive epidemiological study in 50 heart failure patients scheduled for regular follow-up visits at Ramathibodi Cardiology Clinic, Mahidol University, Bangkok, Thailand. Thiamine pyrophosphate effect was used to identify thiamine deficiency. Review of electrical medical records were made in order to collect variable clinical and demographic data.

Results: The mean age was 60±2.1 years, 54% were male. The mean left ventricular ejection fraction was 37±2.5%. The prevalence of thiamine deficiency in a chronic heart failure outpatient was 6% (n=3). Thiamine status was negatively associated with left ventricular ejection fraction (r=-0.283, p=0.047) and thiamine status was positively associated with left ventricular dimension (r=0.462, p=0.001). However, there was no association between the dose of diuretic and thiamine status (r=0.024, p=0.882), duration of heart failure and thiamine status (r=-0.012, p=0.945). In patients with severe thiamine deficiency, there were subsequent serious adverse cardiovascular outcomes (one had cardiac arrest and underwent left ventricular assist device).

Conclusion: We found that the prevalence of thiamine deficiency in chronic heart failure outpatients is low in an urban outpatient setting.

Keywords: Thiamine deficiency; Heart failure; Prevalence

J Med Assoc Thai 2021;104(Suppl.4): S158-64
Website: http://www.jmatonline.com

Heart failure is a clinical syndrome caused by structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intracardiac pressure at rest or during stress. In Thailand, the common cause of heart failure is coronary artery disease and in-hospital mortality rate was as high as 5.5%[1].

Thiamine or vitamin B1 is a water-soluble vitamin found in many foods including pork, beef, poultry, legumes, and whole grain products. The active form of thiamine is thiamine pyrophosphate (TPP) which acts as a cofactor in macronutrients metabolism. It is a cofactor of pyruvate dehydrogenase which converts pyruvate into acetyl-coenzyme A in part of Krebs's cycle. Thiamine deficiency is also related to cardiovascular disease and can cause wet beriberi. Typically, the patient presents with high output cardiac failure, peripheral vasodilation, and cardiogenic shock with metabolic acidosis (Shoshin syndrome). Risk factors for thiamine deficiency in heart failure include diuretic use and high dose of diuretic, severe heart failure, malnutrition, and advanced age[2–6].

The level of thiamine in the body can be measured by either serum or urinary thiamine level however they may not reflect the level of thiamine in the tissues and total body thiamine stores. The erythrocyte transketolase activity (ETKA) assay measures the activity of thiamine-requiring enzyme transketolase. The test needs the addition of thiamine to the erythrocytes in vitro and then measuring the transketolase activity which is called the thiamine pyrophosphate effect (TPPE). TPPE is expressed as the percentage increase in ETKA after addition of TPP to the erythrocyte. TPPE 0 to 14% is considered the normal range, 15 to 24% reflects marginal deficiency and ≥25% reflects severe deficiency[7,8]. The TPPE is a functional test and therefore it is a good indicator of total body thiamine

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How to cite this article:

Manasirisuk W, Srimachai S, Shantavasinkul PC, Warodomwichit D, Chittamma A, Yingchoncharoen T. Prevalence of Thiamine Deficiency in Chronic Heart Failure Patients: Ramathibodi Cardiology Clinic Experience. J Med Assoc Thai 2021;104 (Suppl.4): S158-64.

doi.org/10.35755/jmedassocthai.2021.S04.00082

stores[9]. This is the currently the most reliable measurement to diagnose thiamine deficiency.

Prevalence of thiamine deficiency has been reported varied from 0% to 96% in the out patients setting[2,3,6,10-15] depending on methods/techniques of thiamine measurement, patient's ethnicity and nutritional status. Some studies demonstrated that thiamine supplementation resulted in better left ventricular ejection fraction (LVEF) compared with placebo[13,16]. Since data of thiamine deficiency in heart failure patients in Thailand is lacking, we sought to find the prevalence of thiamine deficiency in chronic heart failure outpatients.

Materials and Methods

Study population

The study design was a cross-sectional descriptive epidemiological study. The present study was approved by the ethic committee for Research, Faculty of Medicine Ramathibodi Hospital Mahidol University (MURA2019/70). Patients were scheduled for regular follow-up visits at the Cardiology Clinic Ramathibodi Hospital, Mahidol University, Bangkok, Thailand between January 2018 and November 2018. Inclusion criteria were all patients with the diagnosis of heart failure (New York Heart Association (NYHA) functional class I-IV). We excluded patients with severe malnutrition, chronic alcohol use, active malignancies, post-bariatric surgery or short bowel syndrome, pregnancy, thyrotoxicosis (hyperthyroid state), end-stage renal disease that requires hemodialysis, end-stage liver disease, thiamine supplements (>10 mg/day), and recent blood transfusion within the past three months. Nutritional status was measured by body mass index (BMI). The clinical variables including gender, age, weight, height, blood pressure, heart rate, smoking, functional class, 6-minute walk test, furosemide dose and duration, heart failure medications, etiology of heart failure, and duration of heart failure were collected. Laboratory data including creatinine, hemoglobin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), glucose, lipid status, device and echocardiogram including left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), early mitral inflow velocity, and mitral annular early diastolic velocity ratio (E/E'), maximal tricuspid regurgitation velocity (TRV max), left ventricular dimension (LV dimension), left atrium volume (LA volume), and pulmonary artery systolic pressure (PASP) were collected.

Outcome

The primary aim of the present study was to find the prevalence of thiamine deficiency in chronic heart failure patients. The secondary aim was to find baseline characteristics that associate with thiamine deficiency in heart failure patients.

Laboratory measurements

All included patients gave informed consents before the study initiation. Five milliliters of blood were collected from the patients. TPPE was measured by the standard method which was adapted from Pierre M. Dreyfus[17] at the Faculty of Medicine Ramathibodi Hospital in collaboration with the Faculty of Tropical Medicine, Mahidol University. The blood samples from the first 23 patients were sent to the laboratory in the Faculty of Tropical Medicine, Mahidol University, while the rest were sent to Ramathibodi laboratory (27 patients). The results from the Ramathibodi laboratory were compared with a result from the Faculty of Tropical Medicine for validation. Thiamine deficiency was defined by TPPE ≥25% which indicated severe thiamine deficiency, TPPE 15 to 24% which indicated marginal thiamine deficiency. Age, blood pressure, heart rate, weight and height, functional class that were recorded on the same visit as blood draw were retrieved and collected as the last plan of care of blood testing. Other data including complete blood count, creatinine, electrolyte, NT-proBNP, blood glucose and lipid status, and 6-minute walk test were performed on the same visit.

Echocardiogram was performed by experienced sonographers using standard echocardiography (Philips Medical System, NA) and interpreted by cardiologists. The LV dimension, right ventricular function, systolic and diastolic function as well as other Doppler parameters measurement were performed according to the recommendation of the American Society of Echocardiography[18]. LVEF was measured by the biplane Simpson method[19].

Subtypes of heart failure was classified according to LVEF into heart failure with reduce ejection fraction (HFrEF), defined as LVEF <40%, heart failure with mid-range ejection fraction (HFmrEF), defined as LVEF 40 to 49%, and heart failure with preserve ejection fraction (HFpEF), defined as LVEF ≥50%[20].

Statistical analysis

Continuous data in the present study were expressed as mean±standard error of the mean. A p-value <0.05 was considered statistically significant. Spearman correlation was determined to assess relations between continuous data. Statistical analyses were performed using Statistical Package for Social Science version 21 (SPSS, IBM Corporation, Chicago, IL, USA).

Results

A total of 50 individuals were included in the study. Clinical characteristics and demographic data are shown in Table 1. The mean age of our patient population was 60±2.1 years with 54% male (27 patients). Most of the patients were classified as having NYHA functional class 2, corresponding to 28 patients (56%). The mean duration of heart failure was 58.1±9.1 months that the most common etiology of heart failure is ischemic cardiomyopathy (24 patients, 48%). The mean dose of furosemide was 62.7±12.2 mg and the mean duration of furosemide was 34.7±8.2 months. Other medication is shown in Table 1. The mean LVEF was 37.1±2.5% with range of 10 to 78%. Thirty-three patients had HFrEF, seven patients had HFmrEF, and ten patients had HFpEF. Mean creatinine was 1.2±0.1 mg/dL (23 patients

Table 1. Clinical and demographic characteristics of chronic heart failure patients

Variable	Patients, (n=50) [1]
Age, years	60±2.1
Male	27 (54)
BMI, kg/m^2	23.6±0.7
Systolic blood pressure, mmHg	114.8±3.3
Diastolic blood pressure, mmHg	69.4±1.5
Mean arterial blood pressure, mmHg	84.3±1.9
Heart rate, bpm	74.5±2.2
Heart failure risk factor	
Smoking	7 (14)
Diabetes	14 (28)
Hypertension	21 (42)
Dyslipidemia	19 (38)
Atrial fibrillation	23 (46)
Chronic kidney disease	
Stage 3	19 (38)
Stage 4	4 (8)
Stage 5	0
History of cerebrovascular disease	7 (14)
Valvular heart disease	8 (16)
Etiology of heart failure	
Cardiomyopathy	
Ischemic	24 (48)
Hypertrophic	3 (6)
Restrictive	0
Arrhythmogenic right ventricular dysplasia (ARVD)	0
Dilated	12 (24)
Others	11 (22)
Duration of heart failure, mean±SE (months)	58.1±9.1
NYHA	
I	19 (38)
II	28 (56)
III	3 (6)
IV	0
Severity	
6 minutes walks, meters	307±14.2
HFrEF	33 (66)
HFmrEF	7 (14)
HFpEF	10 (20)

[1] Values are n (%) or mean±SE (unless otherwise stated)
ACEI = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor blocker/neprilysin inhibitor; BMI = body mass index; E/E' = Early mitral inflow velocity and mitral annular early diastolic velocity ratio; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserve ejection fraction; HFrEF = heart failure with reduce ejection fraction; LA volume = left atrium volume; LV dimensions = left ventricle dimensions; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion; TPPE = thiamine pyrophosphate effect; TRV max = maximal tricuspid regurgitation velocity.

Table 1. Cont.

Variable	Patients, (n=50) [1]
Medications use	
Furosemide	40 (80)
Dose of furosemide, mg	62.7±12.2
Duration, months	34.7±8.2
Spironolactone	32 (64)
Dose of spironolactone, mg	23.4±2.8
Beta blocker	45 (90)
ACEI	13 (26)
Ivabradine	4 (8)
Angiotensin II receptor blockers	9 (18)
Isosorbide dinitrate	4 (8)
Digoxin	8 (16)
ARNI	17 (34)
Echocardiographic data	
LVEF, %	37.1±2.5
E/E'	18.6±1.3
TAPSE, mm	1.7±0.1
TRV max, m/s	3.0±0.4
LV dimensions, mm	5.9±0.2
LA volume, ml	62.8±6.0
PASP, mmHg	36.8±1.7
Biochemical measures	
Hemoglobin, g/dL	12.8±0.3
Serum creatinine, mg/dL	1.2±0.1
NT-proBNP, pg/ml	5,349.3±1067.1
TPPE, %	4.6±2.4

[1] Values are n (%) or mean±SE (unless otherwise stated)
ACEI = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor blocker/neprilysin inhibitor; BMI = body mass index; E/E' = Early mitral inflow velocity and mitral annular early diastolic velocity ratio; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserve ejection fraction; HFrEF = heart failure with reduce ejection fraction; LA volume = left atrium volume; LV dimensions = left ventricle dimensions; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion; TPPE = thiamine pyrophosphate effect; TRV max = maximal tricuspid regurgitation velocity.

had chronic kidney disease (CKD), most patients had CKD stage 3).

The prevalence of thiamine deficiency in the present study is 6% and mean of TPPE was 4.64±2.42. We found that two patients (4%) had TPPE ≥25% which indicated severe thiamine deficiency and one patient had TPPE 15 to 24% which indicated marginal thiamine deficiency. In patients with severe thiamine deficiency, there was subsequent serious adverse cardiovascular outcomes (One had cardiac arrest and underwent left ventricular assist device). The clinical characteristics and outcomes of these patients with thiamine deficiency were summarized in Table 2. Thiamine status (TPPE) was negatively associated with left ventricular ejection fraction (r=-0.283, p=0.047) and thiamine status was positively associated with left ventricular dimension (r=0.462, p=0.001). However, there was no association between the dose of diuretic and thiamine status (r=0.024, p=0.882), duration of heart failure and thiamine status (r=-0.012, p=0.945).

Discussion

In the present study, we found that the prevalence of thiamine deficiency in chronic heart failure outpatients was only 6% which lower than other previously published

Table 2. Details of thiamine deficiency patients

Gender	Age (years)	Underlying disease	LVEF	TPPE	Progression	The Seattle Heart Failure models	
						Anticipated 1-year Survival	Anticipated 5-year Survival
Male	64	-Ischemic cardiomyopathy on cardiac resynchronization therapy -History of ventricular fibrillation arrest on ECMO support	19%	118%	-Readmission in 7 months -Cardiac arrest and underwent LVAD	87.6%	51.6%
Female	48	-Hypertrophic obstructive cardiomyopathy -Severe mitral regurgitation and severe tricuspid regurgitation	40%	25%	-No readmission	92.7%	68.3%
Male	53	-Triple vessel disease with ischemic cardiomyopathy on AICD	38%	18%	-No readmission	98.6%	93.1%

AICD = automated implantable cardioverter-defibrillation; ECMO = extracorporeal membrane oxygenation; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; TPPE = Thiamine pyrophosphate effect

studies[3,11-15]. The low prevalence can be explained by the fact that we excluded patients with severe malnutrition and at-risk patient population such as chronic alcohol use, history of bowel resection and hyperthyroidism. Moreover, different techniques to identify thiamine level, different ethnicity & environment may affect the thiamine status. Furthermore, our cardiology clinic at Ramathibodi Hospital is a multidisciplinary clinic in which all patients with chronic heart failure have a dietary advise to have nutrient-dense food by registered dietitian at the first visit and as needed in the follow-up visit. We found that the patients in our study were able to afford healthy and nutrient-dense food.

The population of this study suffered from severe heart failure (mean LVEF=37.1%) but most patients (94%) have NYHA functional class 1 and 2. This implied that the subjects in the present study are well treated in an academic medical center in urban area (mean duration of heart failure is 58.1±9.1 months).

The patients who had thiamine deficiency portend bad prognosis in our study, predicted by The Seattle Heart Failure models, we found that 1- and 5-year survival rate in patients with severe thiamine deficiency (TPPE ≥25%) is 87.6%, 51.6% in the first person and 92.7%, 68.3% in the second person, respectively (1 had cardiac arrest and underwent left ventricular assist device). This finding may indicate that severe thiamine deficiency, though not as common as expected, may be a prognostic marker of end-stage heart failure. Unfortunately, due to small sample size and limit in research methodology, this result does not yet confirm that thiamine deficiency associate with severity of heart failure patients. Further cohort study with a large sample size and sufficient follow-up duration would need to confirm this finding.

In our study, we found that thiamine status was negatively associated with LVEF, which was different from Teigen, et al[15], and Azizi-Namini, et al[10]. The difference may be due to the severity of heart failure in our study are more severe. Furthermore, techniques and time to estimate LVEF are difference. Our study had mainly HFrEF patients (66%). The result was similar to previous studies[3,11] that mostly include severe heart failure patients, and result by Brady, et al[2] is tend to have thiamine deficiency in severe heart failure (p=0.7).

Thiamine supplement in chronic heart failure patients may be beneficial to improve LVEF[21]. The results showed heterogeneity because of variation in the prevalence of thiamine deficiency. The latest randomized controlled trial of thiamine supplementation does not improve LVEF due to the low prevalence of thiamine deficiency[22]. Based on the result from our study, the measure of thiamine status before routine thiamine supplement may be beneficial.

To the best of our knowledge, this is the first study to report the prevalence of thiamine deficiency in chronic heart failure patients in Thailand. The strength of the study was that we use the TPPE assay which is the best available biochemical test to diagnose thiamine deficiency. We acknowledge some limitations including this study consisted of a small number of subjects due to many exclusion criteria that may affect thiamine level. In addition, the majority of patients had been categorized as having functional class 1 to 2 which reflects relatively mild disease severity. The study was performed in single and tertiary care settings that may

not represent the whole heart failure patients in Thailand. Future studies that include more severe heart failure in remote areas of the country would provide more information on these patients. Moreover, the cut-off value of thiamine deficiency that we used in the present study was derived from general population[23]. Adequate thiamine level in heart failure patients remains to be determined.

Conclusion

We found that the prevalence of thiamine deficiency in chronic heart failure outpatients is low in urban outpatient settings. However, the patients who had thiamine deficiency portend bad prognosis in our study.

What is already known on this topic?

Heart failure patients and chronic diuretic used are a risk factor for thiamine deficiency. Overall studies showed the prevalence of deficiency varied from 0% to 96%.

What this study adds?

The prevalence of thiamine deficiency in chronic heart failure outpatients in Thailand is low.

Acknowledgements

The present study was supported by the Faculty Research fund, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. We thank Dr. Sriwatana Songchitsomboon for technical support.

This manuscript was supported by a grant from the Khon Kaen University, Faculty of Medicine, Department of Medicine (Thailand).

Potential conflicts of interest

The authors declare no conflict of interest.

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