Original Article

Vicious cycle of vitamin B_1 insufficiency and heart failure in cardiology outpatients

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Heart failure is a major manifestation of vitamin B_1 deficiency; beriberi. We have previously reported that even vitamin B_1 insufficiency, milder than deficiency, is a risk for heart failure in the institutionalized elderly. Then in this cross-sectional study, sixty-eight cardiology outpatients were evaluated for their whole blood vitamin B_1 and plasma brain natriuretic peptide (BNP) concentrations, a sensitive marker of heart failure, as well as their dietary intake. Whole blood vitamin B_1 concentration was significantly correlated with plasma BNP level in vitamin B_1-deficient/insufficient patients (whole blood vitamin B_1<28 ng/ml) but not in sufficient patients. Whole blood vitamin B_1 concentration was significantly lower in loop diuretics users than non-users. Multiple regression analysis has identified whole blood vitamin B_1 concentration and eGFR as the significant contributors to log-transformed plasm BNP level, and loop diuretics use, serum albumin level, and eGFR as the contributors to whole blood vitamin B_1 concentration. ROC analysis has shown the significant predictability of whole blood vitamin B_1 for plasma BNP ≥100 pg/ml with the cut-off value of 23.5 ng/ml. Vitamin B_1 insufficiency is a risk of heart failure in the cardiology outpatients, and the therapeutic use of loop diuretics aggravates heart failure and possibly forms a vicious cycle.

***Key Words*: vitamin B_1, vitamin insufficiency, brain natriuretic peptide (BNP), heart failure, diuretics**

Vitamin B_1 (thiamine) is a water-soluble vitamin, and thiamine diphosphate (ThDP) is the biologically active form. ThDP plays the essential roles in energy metabolism. It is a coenzyme in various enzyme reactions including pyruvate dehydrogenase complex, α-ketoglutarate dehydrogenase complex, branched chain α-ketoacid dehydrogenase complex (BCKDH), and 2-hydroxyacyl CoA lyase.[1,2] Namely, ThDP is involved in TCA cycle (tricarboxylic acid cycle), pentose monophosphate pathway, and also in amino acid and fatty acid metabolism. Thus, various aspects of metabolism are disturbed and ATP production is severely impaired in vitamin B_1 deficiency.

Vitamin B_1 deficiency causes beriberi, consisting of wet beriberi with cardiovascular manifestations and dry beriberi involving the nervous system. Beriberi was once extremely prevalent in Asian countries including Japan with lethal outcomes in severe cases, but is now considered to be mostly overcome in developed countries such as Japan. Then, the significance of vitamin B_1 in the health promotion and disease prevention tends to receive far less attention.

Recently, however, vitamin insufficiency has been receiving increasing concern.[3] Vitamin deficiency causes classical deficiency diseases with typical phenotypic changes in the individual patients. Examples with the responsible vitamins in the parentheses include beriberi (vitamin B_1), rickets and osteomalacia (vitamin D), scurvy (vitamin C), and bleeding tendency (vitamin K). Vitamin insufficiency, milder than deficiency, does not cause such classical deficiency diseases with overt abnormality in the affected subjects. Vitamin insufficiency, however, is associated with the increased risk of various diseases. Lack of individualized abnormality make vitamin insufficiency receive inadequately little attention. Regarding vitamin insufficiency, vitamin D has been most extensively studied. Its deficiency causes the bone mineralization defect; rickets and osteomalacia. Vitamin D insufficiency does not cause such diseases, but is associated with increased risk of various diseases such as osteoporotic fracture, sarcopenia, colon cancer, autoimmune disease, cardiovascular disease, and diabetes.[4] Far less attention has been paid, however, on the insufficiency of B vitamins.

We have made a hypothesis that vitamin B_1 insufficiency is a risk of heart failure based on the following considerations. Heart failure is an important manifestation of wet beriberi, which is quite conceivable considering that heart is the organs with high energy consumption, and vitamin B_1 is an essential nutrient in energy metabolism. As the initial step, we have studied the possible involvement of vitamin B_1 in heart failure in the institutionalized elderly, since the prevalence of heart failure is quite high, and the nutritional status of vitamin B_1 has been reported to be poor in the elderly. We have recently reported that whole blood vitamin B_1 concentration, an established marker for vitamin B_1 status, is a significant contributor to plasma brain natriuretic peptide (BNP) concentration, which is a sensitive marker of heart failure after adjusting by possible confounders such as age, sex, body mass index (BMI), and estimated glomerular filtration ratio (eGFR).[5] Then in this paper, we have studied the relationship between the vitamin B_1 status and the index for heart failure in outpatients in the cardiology department to clarify whether the above-mentioned hypothesis is applicable to populations other than the institutionalized elderly.

Materials and Methods

Subjects. This is a cross-sectional study performed between December 2018 and July 2019 including 85 patients visiting the outpatient clinic at Cardiology Department, Hirakata Kosai Hospital. After excluding the patients under vitamin B_1 treatment and those with self-declared use of vitamin B_1 supplementation, additional exclusion criteria were applied as below. First, patients

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whose blood vitamin B_1 concentration or plasma BNP concentration were below [Q1 − (1.5 × IQR)] or above [Q3 + (1.5 × IQR)] were excluded (IQR: interquartile range) to exclude the undeclared supplementation use. IQR was used since whole blood vitamin B_1 concentration or plasma BNP concentration was not normally distributed. Those with their eGFR below 30 ml/min/1.73 m^2 were also excluded. Finally, data from 68 patients were subjected to analysis. Additionally, patients with their energy intake outside the IQR were excluded in the applicable analyses. The study protocol was approved by the Ethical Committee of Hirakata Kosai Hospital (Ethics Approval number: 2018-018), and done complying with the Declaration of Helsinki. Written consent to participate in this study was obtained from each patient after explanation of the objective and protocol of this study.

Methods. Fasting or non-fasting blood was drawn, and kept frozen at −22°C before measurement. Serum concentrations of albumin and total cholesterol were employed as the indices for the overall nutritional status. Whole blood vitamin B_1 concentration was measured by liquid chromatography-mass spectrometer (LC-MS/MS) using LCMS-8040 (Shimadzu, Kyoto, Japan) with the inter-assay and intra-assay variation of 0.62 to 3.99% and 1.46 to 3.36%, respectively. Plasma BNP was measured by chemiluminescent enzyme immunoassay (CLEIA) with the detection limit of 6.8 pg/ml.

Patients were divided into two groups according to the whole blood vitamin B_1 concentration; less than 28 ng/ml (deficiency/insufficiency group) and equal to or higher than 28 ng/ml (sufficiency group).[6] Also, plasma BNP level was dichotomized to less than 100 pg/ml and equal to or higher than 100 pg/ml.[7]

Dietary intake. Dietary intake was evaluated using a brief-type self-administered diet history questionnaire (BDHQ) adjusted by energy density model,[8] and 11-item Food Diversity Score Kyoto (FDSK-11).[9] The latter, devoted to the evaluation of dietary diversity, is composed of four-grade questions on the weekly consumption frequency of 11 food groups. The scores were summated, and converted to the scale of one hundred. These data were available in 57 patients.

Statistical analyses. The normality of distribution was judged by Shapiro Wilk test. The difference between the two independent groups was analyzed by Student's *t* test or Mann Whitney's *U* test. Correlations between two independent variables were analyzed by Pearson's or Spearman's correlation. Variables contributing to the whole blood vitamin B_1 concentration or plasma BNP level were analyzed by the multiple regression analysis. The predictability of whole blood vitamin B_1 concentration for the plasma BNP level equal to or higher than 100 pg/ml was analyzed by receiver operating characteristic (ROC) curve analysis, followed by the determination of cut-off value using Youden's index. Statistical analyses were done using SPSS ver. 23 (IBM Japan, Tokyo, Japan). The significance level of the associations was set at $p<0.05$.

Results

Background profiles of the subjects and data from blood test (Table 1). The patients were older subjects with their average age higher than 70 years old in both genders. However, they were not considered mal-nourished based on their BMI and serum albumin concentration.

Nutrients intake in vitamin B_1-deficient/insufficient and B_1-sufficient groups. There were no significant differences between the vitamin B_1-deficient/insufficient ($n = 17$) and vitamin B_1-sufficient ($n = 40$) groups in the intakes of protein, fat, carbohydrate, or vitamin B_1 (Table 2).

Table 1. Background profiles of the subjects and data from blood test

	Total ($n = 68$)	Men ($n = 38$)	Women ($n = 30$)	*p*
Age	72.9 ± 9.2	71.4 ± 9.1	74.7 ± 9.1	0.141
Height (cm)	159.1 ± 10.7	166.5 ± 6.8	149.7 ± 6.5	<0.001
Weight (kg)	60.1 ± 14.4	68.1 ± 13.4	50.0 ± 7.8	<0.001
BMI (kg/m^2)	23 (20.5, 25.8)	23.7 (21.3, 27.6)	21.9 (19.9, 24.4)	0.044
Albumin (g/dl)	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.3	0.958
Total cholesterol (mg/dl)	191.0 ± 32.2	182.8 ± 32.6	201.4 ± 29.0	0.017
HDL cholesterol (mg/dl)	60.6 ± 16.6	55.3 ± 13.8	67.3 ± 17.7	0.002
LDL cholesterol (mg/dl)	101.5 (86.8, 112.3)	100.5 (80.3, 109.8)	102.5 (92.0, 120.8)	0.202
eGFR (ml/min/1.73 m^2)	59.4 ± 15.7	58.0 ± 13.9	61.1 ± 17.7	0.412
Plasma BNP (pg/ml)	38 (15.4, 86.4)	40.6 (15.1, 87.2)	35.9 (15.5, 86.4)	0.946
Whole blood vitamin B_1 (ng/ml)	32.0 ± 8.4	32.5 ± 8.9	31.4 ± 7.9	0.615

Data are shown as mean ± SD or median (Q1, Q3). The *p* value was obtained from Students's *t* test or Mann-Whitney *U* test.

Table 2. Nutrients intake in vitamin B_1-deficient/insufficient and -sufficient groups

	Total ($n = 57$)	Deficiency/insufficiency group ($n = 17$)	Sufficient group ($n = 40$)	*p*
Protein (g/1,000 kcal)	41.6 ± 7.9	41.4 ± 6.5	41.7 ± 8.5	0.888
Animal protein (g/1,000 kcal)	24.7 ± 7.0	24.6 ± 5.1	24.7 ± 7.7	0.962
Vegetable protein (g/1,000 kcal)	16.9 ± 3.1	16.8 ± 3.1	17.0 ± 3.1	0.800
Fat (g/1,000 kcal)	29.1 ± 6.9	30.8 ± 6.2	28.3 ± 7.1	0.209
Animal fat (g/1,000 kcal)	13.9 ± 3.9	14.5 ± 3.5	13.7 ± 4.1	0.497
Vegetable lipid (g/1,000 kcal)	15.1 ± 4.1	16.3 ± 3.9	14.6 ± 4.1	0.146
Carbohydrate (g/1,000 kcal)	132.3 ± 22.0	133.6 ± 16.5	131.7 ± 24.2	0.768
Vitamin B_1 (mg/1,000 kcal)	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.912

Data are expressed as mean ± SD, and *p* value shows the results from Students' *t* test.

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Table 3. Correlation between the nutrient intake, plasma BNP concentration and whole blood vitamin B_1 concentration

	Total	Deficiency/Insufficiency group	Sufficient group
Protein (g/1,000 kcal)	–0.127	0.157	–0.240
Animal protein (g/1,000 kcal)	–0.167	0.074	–0.251
Vegetable protein (g/1,000 kcal)	0.050	0.132	–0.003
Fat (g/1,000 kcal)	–0.201	0.017	–0.112
Animal fat (g/1,000 kcal)	–0.196	–0.237	–0.176
Vegetable lipid (g/1,000 kcal)	–0.198	0.264	–0.026
Carbohydrate (g/1,000 kcal)	0.109	–0.222	0.205
VitaminB_1 (mg/1,000 kcal)	–0.073	–0.001	–0.113
FDSK-11 score	–0.142	–0.266	–0.225
Plasma BNP (log)	–0.237	–0.513*	0.044

The r value denotes the Spearman's correlation coefficient. The asterisk (*) shows the statistical significance (p<0.05).

Table 4. Comparison of whole blood vitamin B_1 concentration between diuretics users and non-users

	User	Non-user	p
Diuretics	30.6 ± 9.8	32.9 ± 7.5	0.282
Loop diuretics	28.9 ± 9.4	33.4 ± 7.7	0.040

Data are expressed as mean ± SD, and the p value shows the results from Students' t test.

Table 5. Variables contributing to the log-transformed plasma BNP concentration

Variables	Total	Deficiency/ Insufficiency group
Whole blood vitamin B_1 (ng/ml)	–0.175	–0.441*
Age	0.265	–0.128
Sex (Reference: men)	–0.066	0.258
eGFR (ml/min/1.73 m^2)	–0.268*	–0.665*
BMI (kg/m^2)	–0.097	0.061
p	0.001	0.042
Adjusted R^2	0.211	0.485

Data indicate the standardized coefficient β, and the asterisk (*) shows the statistical significance (p<0.05).

Correlation between the nutrient intake, plasma BNP concentration and whole blood vitamin B_1 concentration. Whole blood vitamin B_1 concentration was not significantly correlated with nutrients intake including vitamin B_1, FDSK-11 score, or log-transformed plasma BNP concentration in the total group and sufficiency group. In contrast, whole blood vitamin B_1 concentration was significantly correlated with plasma BNP concentration ($p = 0.015$) in the deficiency/insufficiency group (Table 3).

Comparison of whole blood vitamin B_1 concentration between diuretics users and non-users. Of the 68 patients, 26 subjects were under diuretics treatment, 21 of whom were receiving loop diuretics. There was no significant difference in the whole blood vitamin B_1 concentration between the diuretic users and non-users. However, it was significantly lower in patients under loop diuretics treatment than those without it (Table 4).

Variables contributing to the log-transformed plasma BNP concentration. Variables contributing to the log-transformed plasma BNP concentration were analyzed by multiple regression analyses (Table 5). In an analysis including the total patients, eGFR was the only significant contributor. In the deficiency/ insufficiency group, however, whole blood vitamin B_1 concentration as well as eGFR were the significant contributor.

Table 6. Variables contributing to the whole blood vitamin B_1 concentration

Variables	Total
Age	–0.142
Sex (Reference: men)	–0.061
Loop diuretics (Reference: not using)	–0.293*
Vitamin B_1 intake (mg/1,000 kcal)	–0.029
Albumin	0.327*
eGFR (ml/min/1.73 m^2)	–0.342*
p	0.029
Adjusted R^2	0.241

Data indicate the standardized coefficient β, and the asterisk (*) shows the statistical significance (p<0.05).

Variables contributing to the whole blood vitamin B_1 concentration. Contributing factors to whole blood vitamin B_1 concentration were analyzed by multiple regression analyses (Table 6). Loop diuretics use, serum albumin concentration, and eGFR were the significant contributing variables.

ROC analysis. The predictability of whole blood vitamin B_1 concentration for the plasma BNP level equal to or higher than 100 pg/ml was analyzed by ROC analysis. Area under the curve (AUC) was 0.689 (95% CI: 0.510, 0.868). Analysis with Youden's index yielded the cut-off value of 23.5 ng/ml.

Discussion

In his famous lecture given in Massachusetts Medical Society in 1997, Braunwald has listed heart failure and atrial fibrillation as the newly emerging two epidemics of cardiovascular diseases.[10] He has pointed out that the admission due to heart failure has steadily increased and become the single most frequent cause of hospitalization in persons 65 years of age or older, and the prognosis of heart failure is poor despite the development of many effective therapeutic drugs.[10] Since then, the clinical and societal significance of heart failure has further increased. Cardiovascular diseases have been and even now the leading cause of mortality in the United States, but mortality due to cardiovascular disease has markedly declined between 1980 and 2000 in the USA due to the development of novel therapeutic drugs with robust evidence, and the populational risk reduction through the lifestyle modification.[11,12] After 2011, however, age-adjusted cardiovascular mortality as a whole has exhibited a gradual increase.[13] In contrast to the continued decrease of

morality due to ischemic heart disease, mortality due to heart failure has increased.[14] In Japan also, the prevalence of heart failure is increasing. Zhang *et al.*, from the analysis of Medical Data Vision (MDV) data between 2014 and 2019, have reported that the crude prevalence of heart failure per 1,000 persons was 58.09 in 2014 and 77.18 in 2019.[14] Of the patients with heart failure in 2019, 1.65%, 3.52%, 16.63%, 25.31%, and 52.90% of the subjects were 0–18, 18–44, 45–64, 64–74, and equal to or over 75 years old, respectively. Since aging is closely associated with the development of heart failure, and the percentage of the elderly population is rapidly increasing in Japan, it is quite natural that the number of patients with heart failure has markedly increased.[15] Indeed, the number of hospitalized patients due to heart failure has increased by 22% between 2012 and 2016.[16] Such critical epidemiological condition is called "heart failure pandemic".

These considerations have prompted us to study the possible contribution of vitamin B_1 insufficiency in the pathophysiology of elderly heart failure, since identifying and minimizing its risk factors would be of great clinical and societal significance. As described in the Introduction, we have recently reported the possibility that vitamin B_1 insufficiency is a risk of heart failure in the institutionalized elderly.[5] In brief, their whole blood vitamin B_1 concentration, which was not so severely decreased as to cause the vitamin B_1 disease, was negatively correlated with plasma BNP concentration. Whole blood vitamin B_1 concentration was a significant contributor to plasma BNP concentration after adjusting for the possible confounding variables such as age, sex, BMI, and eGFR. Then it was considered quite likely that vitamin B_1 insufficiency is a risk factor of heart failure. These data were obtained, however, in the institutionalized elderly, and we have considered it necessary to examine whether the above hypothesis can be generalized, and studied the possibility of vitamin B_1 as a risk for heart failure in patients visiting the outpatient cardiology clinic in the present study.

As a whole, the subjects' average BMI was 23.0 kg/m^2, and their mean serum albumin level was 4.2 g/dl, indicating that the subjects were not malnourished although their mean age was over 70. Whole blood vitamin B_1 concentration was 32.0 ± 8.4 ng/ml with no gender difference. Although no gold standard exits and data are extremely scarce in Japan regarding the reference value of whole blood vitamin B_1 concentration, Ihara *et al.*[6] have defined the whole blood vitamin B_1 concentration of less than 20 ng/ml, 20 to 27 ng/ml, and equal to or above 28 ng/ml to be vitamin B_1 deficient, insufficient, and sufficient, respectively. Thus, the current study subjects were considered to be at least not severely vitamin B_1 deficient. Based on the whole blood vitamin B_1 concentration, we subdivided the subjects into sufficiency group (equal to or above 28 ng/ml) and deficiency/insufficiency group (less than 28 ng/ml). Nutrients intake, including that of vitamin B_1, was no different between the two groups.

There was a significant and negative correlation between the whole blood vitamin B_1 concentration and plasma BNP level in the deficiency/insufficiency group, but not in the sufficiency group. Additionally, in the multiple regression analyses (Table 4), whole blood vitamin B_1 concentration was a significant contributor to the log-transformed plasma BNP concentration after adjustment by age, sex, eGFR, and BMI in the deficiency/insufficiency group, but not in the sufficiency group. From these results, vitamin B_1 was considered to be a risk of heart failure only in those with its deficiency/insufficiency.

Vitamin status in the study population profoundly affects the relationship between the vitamin status and the disease risk. In a prospective, multicenter, double-blind, placebo-controlled randomized trial, ambulatory patients were randomly assigned into vitamin B_1 oral supplementation group (200 mg daily) or placebo group. After 6 months intervention, markers of vitamin B_1 status; erythrocyte vitamin B_1 activity coefficient and urinary vitamin B_1 levels were higher in the intervention group, but there were no differences in LVEF (left ventricular ejection fraction) or other indicator of heart failure; Minnesota Living with Heart Failure score, distance walked in 6 min, or N-terminal prohormone of BNP concentration.[17] Their negative results, however, do not preclude the possible involvement of vitamin B_1 in heart failure. Their initial protocol was to recruit only vitamin B_1-deficient patients, which, however, was abandoned because of the low prevalence of vitamin B_1 deficiency in the population, and the protocol was revised to include vitamin B_1 sufficient patients also.[17,18] In a systematic review and meta-analysis, data from 8 studies including 384 patients were analyzed.[19] Vitamin B_1 supplementation improved none of the parameters including LVEF, NYHA (New York Heart Association) class, plasma BNP, vitamin B_1 status, symptom changes, or quality of life. The authors have concluded that more well-designed RCTs with large sample sizes are required, but we believe that RCTs targeting vitamin B_1 deficient subjects, in addition to the larger-scale RCTs, are required. Thus, it is quite likely that vitamin B_1 status is a contributor to the heart failure risk and the intervention with vitamin B_1 would decrease the heart failure risk in vitamin B_1 deficient subjects, but not in vitamin B_1 sufficient subjects.

Such phenomena are not limited to vitamin B_1, but are widely observed in clinical vitaminology. Let us take an example of vitamin C. In a systematic review and dose-response meta-analysis of prospective studies, plasma vitamin C concentration, which is a good indicator of vitamin C status, less than 50 μmol/L was demonstrated to be a significant risk of various diseases such as coronary heart disease, cerebrovascular disease, cancer, and total mortality.[20] Similar results have also been reported in another systematic review and dose-response meta-analysis of prospective observational studies.[21] In sharp contrast, is the results of the Physicians' Health Study II, which is the largest scale study of vitamin C intervention. The subjects were randomly assigned to vitamin C intervention group (500 mg daily) and placebo group, and more than 7,000 subjects in each group were followed for 8 years. There was no significant difference in any of the outcomes such as myocardial infarction, cerebrovascular infarction, cerebral hemorrhage, congestive heart failure, and total mortality.[22] Such results were confirmed by the Cochrane Review.[23] The basis of the discrepancy is that most participants in the intervention study are vitamin C sufficient and vitamin intervention to deficient subjects is effective, but ineffective to sufficient subjects.[24]

Then, the next issue of concern is the basis for vitamin B_1 insufficiency. Vitamin B_1 intake was no different between the deficient/insufficient group and the sufficient group, whereas whole blood vitamin B_1 concentration was significantly lower in patients under loop diuretics treatment than those without it. From these results, loop diuretics use, rather than insufficient intake, was considered to be responsible for the vitamin B_1 insufficiency in these patients. In a recent review, loop diuretics use was reported to be associated with vitamin B_1 deficiency.[25] Since vitamin B_1 is a water-soluble vitamin without any specific binding protein and filtered in the glomeruli, it is easily excreted in the urine. Loop diuretics inhibits the Na/K/2Cl co-transporter (NKCC2) at the thick ascending limb of Henle's loop and enhances the urinary excretion of sodium and potassium. Because of its strong diuretic potency, loop diuretics are quite often prescribed to patients with heart failure.[26] Reports on the association of vitamin B_1 with diuretics use are almost exclusively limited to those on loop diuretics, and our results that whole blood thiamine concentration was no different between the diuretics users and non-users as a whole are compatible with the previous papers. Thus, a vicious cycle is likely to occur as below.[5] Loop diuretics treatment increased the urinary loss of thiamine and causes thiamine deficiency, which would further aggravate the heart failure.

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Potential usefulness of thiamine supplementation is mentioned in some guideline on heart failure. The 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure states that many nutritional supplements including thiamine have proposed but points out that most studies are limited by methodological problems such as small sample size, surrogate endpoint, or non-randomized design.[27] A Scientific Statement from the American Heart Association states that many patients with heart failure have a relative thiamine deficiency from micronutrient depletion associated with chronic diuretic use, dietary factors, advancing age, and other comorbid conditions, but conclude that thiamine supplementation in patients with heart failure without clinically significant thiamine deficiency may not be efficacious based on the negative results from the intervention studies.[28] Thus, intervention studies targeting the patients with thiamine deficiency is necessary.

Recently, New York Academy of Sciences (NYAS) have proposed a novel concept of vitamin B_1 deficiency "thiamine deficiency disease" (TDD).[29,30] Whereas the number of subjects with thiamine deficiency is large, most of them lack the signs and symptoms observed in the classical beriberi or Wernicke's encephalopathy, and have nonspecific manifestation alone such as gastrointestinal one or fatigue, which can be observed in other conditions. Thus, they argue that TDD should be diagnosed by the compromised biomarker levels for vitamin B_1 status rather than the signs and symptoms. Thiamine status in the current subjects was not so low as to cause beriberi, but it was associated with the increased risk of heart failure. Then, our results could be understood in the context of TDD.

Our study has some limitations. First, the study design is a cross-sectional one. Additionally, the number of study subjects remain modest. One of the strengths would that vitamin B_1 status was assessed by both dietary intake and whole blood thiamine concentration, which helped us discussing the basis of thiamine deficiency in the study subjects. Additionally, despite the increasing number of patients with heart failure in Japan with the rapidly aging society,[15] previous reports the possible involvement of thiamine deficiency in patients with heart failure have been extremely scarce in Japan. Thus, we believe that our paper would of clinical and societal relevance.

In conclusion, we have shown that whole blood thiamine concentration is a significant contributor to plasma BNP concentration in vitamin B_1-deficient patients with heart failure, and suggested that vitamin B_1 deficiency/insufficiency could be a worsening factor of heart failure.

Author Contributions

MA was the principal investigator and contributed to the conception and the design of the study with TM and KTanaka. KTakabayashi, RT, and RF recruited the subjects and were engaged in their clinical evaluation. MA was responsible for the evaluation of the subjects' nutritional status. MA, TM, and KTanaka were responsible for statistical analyses. All authors have critically reviewed the final version of the manuscript and approved it.

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Abbreviations

AUC	area under the curve
BDHQ	brief-type self-administered diet history questionnaire
BMI	body mass index
BNP	brain natriuretic peptide
CLEIA	chemiluminescent enzyme immunoassay
eGFR	estimated glomerular filtration rate
LC-MS/MS	liquid chromatography-mass spectrometer

Conflict of Interest

No potential conflicts of interest were disclosed.

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