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The Effects of Enteral Nutritional Support and Inflammation on Plasma Thiamine and Erythrocyte Thiamine Pyrophosphate Concentrations in the Acute Phase of Critical Illness

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ABSTRACT

Objective: Plasma thiamine concentrations are decreased with inflammation, but approximately 90% of thiamine is within erythrocytes. We evaluated the effect of enteral nutritional therapy and inflammation on plasma thiamine and erythrocyte thiamine pyrophosphate (eTPP) concentrations, respectively, in critically ill patients.

Materials and Methods: Blood samples were obtained from participants within the first 24-h of ICU admission, and the second sample was obtained on the discharge day in participants with ICU stay <7 days or on the 7th ICU Day in participants with ICU stay>7 days. Plasma thiamine and eTPP levels were analyzed by high-pressure liquid chromatography (HPLC). Serum C-reactive protein (CRP) concentrations were determined by turbidimetric analysis.

Results: Fifty participants, 57% male, were included, and the median age was 68.0 (range: 52.5–75.5) years. The mean plasma thiamine concentration was 13.6±5.22 nmol/L at the first time point, 15.2±5.06 nmol/L at the second time point (reference range: 8–30 nmol/L). The median eTPP value was 621 (range: 407–922) ng/gHb at the first time point and 588 (range: 338–889) ng/g Hb at the second time point (reference range: 275–675 ng/gHb). Plasma thiamine and eTPP concentrations were significantly lower in orally fed participants versus those receiving enteral tube feeding ($p<0.05$ for both study time points). Multiple linear regression revealed that plasma thiamine and serum CRP levels significantly predicted eTPP value ($F=3.623$, $p=0.020$, $R^2=0.78$).

Conclusion: Participants receiving enteral tube feeding had higher plasma thiamine and eTPP concentrations than those who received an oral diet alone. eTPP concentrations can be predicted by plasma thiamine coupled with serum CRP levels.

Keywords: Critical illness, enteral nutrition, erythrocyte thiamine pyrophosphate, inflammation, plasma thiamine.

INTRODUCTION

Thiamine (vitamin B1) is a water-soluble vitamin that performs the role of a cofactor or coenzyme in numerous metabolic pathways, including glycolysis and the Krebs cycle.[1] Hypermetabolism during critical illness is related to increased catabolic hormones and cytokines, increased thiamine loss (due to renal replacement therapy, diarrhea, etc.), and/or insufficient nutritional intake may cause a decrease in thiamine value in critically ill patients.[2–4] In addition, thiamine deficiency may impair energy metabolism (ATP production) from carbohydrate administration.

Until recently, there was no consensus on daily thiamine intake needs for critically ill patients. In 2022, the European Society of Parenteral and Enteral Nutrition (ESPEN) published micronutrient guidelines for specialized nutritional support. It was recommended that thiamine intake should be approximately 1.5–3.0 mg/day/1500 kcal for enterally fed patients and >2.5 mg/day for patients receiving parenteral nutrition. Moreover, it was recommended that 100–300 mg/day of thiamine intake should be given daily in critical illness.[5]

The determination of thiamine status is an important key to preventing its deficiency/depletion. In critically ill patients, nutritional intake and the presence of inflammation may impact thiamine status.[5,6] Plasma thiamine concentrations are not reliable as a marker of thiamine status in patients with inflammation, and whole-blood thiamine pyrophosphate (TPP) concentrations are recommended.[7,8]

The analysis of plasma thiamine is technically simple and may be determined by a standard HPLC assay to assess thiamine status. Nevertheless, this assay is affected by inflammation in that lower values are observed with higher levels of inflammation.[9,10] Erythrocyte thiamine pyrophosphate (eTPP), which represents an alternative method for assessing thiamine status, is not affected by inflammatory processes.[11] On the other hand, analysis of eTPP is a relatively more difficult technical method and lacks standardization. Moreover, the level of hemoglobin may inversely influence eTPP or whole-blood thiamine levels.[12,13] However, recent ESPEN micronutrient guidelines suggest that either eTPP or whole blood thiamine measurement are the best indices of thiamine status in critical illness.[5]

The objective of the present study was to assess the impact of enteral nutritional support (oral diet with or without oral nutrient supplements or tube feeding) and systemic inflammation on plasma thiamine and eTPP concentrations in critically ill patients. Furthermore, the objective was to establish a correlation between plasma thiamine concentrations and CRP levels in order to estimate eTPP concentrations.

KEY MESSAGES

- Critically ill patients receiving enteral tube feeding had higher plasma thiamine and eTPP concentrations than those who received oral diet alone.
- In the presence of inflammation, eTPP concentrations can be predicted by plasma thiamine coupled with serum CRP levels.
- A total of 26% of study participants demonstrated below normal eTPP levels at least at one time point during the study period.

MATERIALS AND METHODS

Study Design, Population, and Protocol

The observational study was prospectively performed at the medical ICU at Erciyes University, between December 2020 and January 2022. It was approved by the Erciyes University ethics committee (Date: 23.09.2020 and No: 2020/473) and conducted in accordance with the ethical principles set forth in the Declaration of Helsinki. When power analysis is performed via G-power software, considering 95% confidence (1-α), 80% test power (1-β), and d=0.5 effect size, a minimum of 27 patients should be included.

The study included critically ill patients aged ³18 years and deemed to require at least 48 hours of ICU stay or longer. The exclusion criteria were as follows: 1) pregnancy, 2) advanced and metastatic cancer, 3) prolonged diuretic treatment, 4) history of gastric by-pass surgery, 5) gastrointestinal trauma, 6) chronic alcoholism, 7) severe malnutrition, 8) chronic use of the thiamine-containing multivitamins before ICU admission (³ 6 months), 9) administration of parenteral nutrition. Each study participant or legal guardian was provided with the relevant information and gave their consent to take part in the study.

The study protocol consisted of two study time points and is detailed in Figure 1. All study participants were assessed in terms of demographical, clinical, and nutritional status in the first 24 hours in the ICU, defined as the 1st study time point. We considered the first seven days of ICU as the acute phase of critical illness.[14] The second study time point was the day of ICU discharge in participants who stayed in the ICU < 7 days or on day 7 of the ICU admission (Fig. 1).

Demographic, Clinical, and Nutritional Assessment

At ICU Admission

Data on patient demographics (age, body mass index, reason for ICU admission, and the presence of comorbidities were recorded. Clinical illness severity was assessed using the Acute

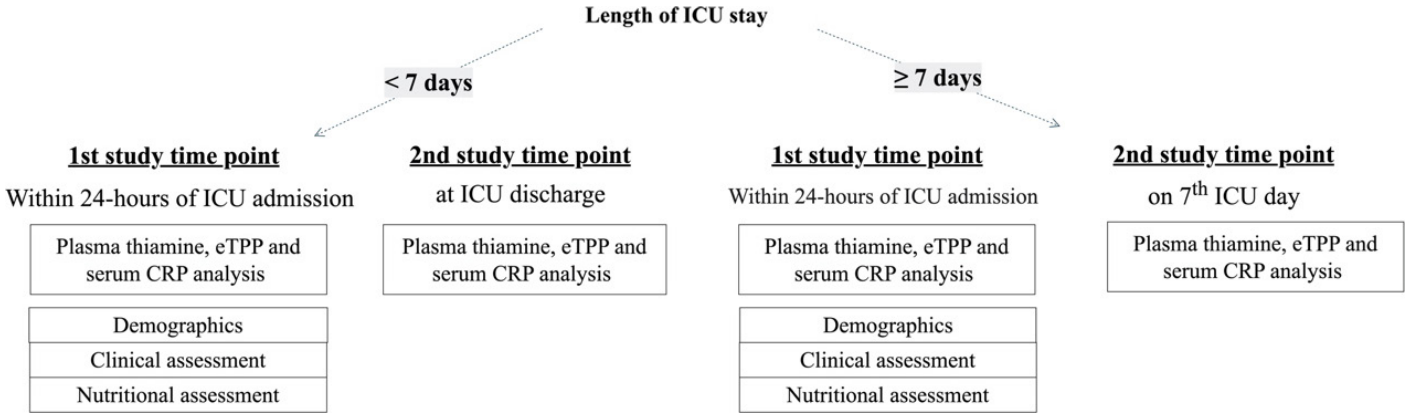

Figure 1. Study protocol. The overall study schema, including times for blood sampling and determinations of demographic and clinical data and enteral nutritional intake.

Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score,[15] the Sequential Organ Failure Assessment (SOFA) score,[16] the Glasgow Coma Scale (GCS) score,[17] and the Charlson Comorbidity Index.[18]

The nutritional status of the patients was evaluated with the modified Nutrition Risk in Critically ill (mNUTRIC) score[19] and the Global Leadership Initiative on Malnutrition (GLIM) criteria.[20] The presence of malnutrition was accepted as mNUTRIC score >4. GLIM is a framework including etiologic criteria (reduced food intake or assimilation, inflammation, or disease burden) and phenotypic criteria (non-volitional weight loss, low BMI, and reduced muscle mass). The non-volitional weight loss and reduced food intake data were obtained from the participant's medical records. The presence of malnutrition was defined by the presence of at least one phenotypic criterion (serum CRP value >5 mg/L),[21] namely non-volitional weight loss (5%–10% within the past 6 months or 10%–20% beyond 6 months) and/or low BMI (less than 20 if aged less than 70 years or less than 22 if aged 70 years or over).[22]

Serial Study Data Collection

The SOFA score, GCS score, and medical ICU treatment (need for mechanical ventilation, vasopressors, renal replacement therapy, insulin therapy) of patients were recorded daily during the study period. The daily energy and protein requirement of patients was calculated as 25–30 kcal/kg per day energy and 1–2 g/kg per day protein using actual/adjusted body weight according to ESPEN[14] and ASPEN[23] guidelines.

The daily feeding methods (oral nutrition (regular diet with/without oral nutritional supplements (ONS)) or enteral tube feeding) and daily intake of energy and protein of study participants were continuously documented throughout the study timeline. Oral food intake was determined daily using 24-hour dietary recall methods by a clinical dietitian. Oral nutrient intake was analyzed using BeBis software developed especially for Türkiye. The present software provides a comprehensive analysis of the macronutrients (carbohydrate, protein, and lipid) and micronutrients (vitamins, minerals, and trace elements) ingested over a period of 24 hours, as determined by a dietary recall.[24] In addition, oral nutritional supplement intake was added to the daily food intake. Participants unable to consume oral diet or supplements were fed via enteral feeding tube using standard formulations of the ICU. The daily energy and protein intake were calculated from enteral product intake according to the manufacturers' data. The thiamine content in enteral products (100 ml): 0.19 mg in the standard product (1.2 kcal/ml), 0.42 mg in the renal product (1.8 kcal/ml), 0.13–0.15 mg in peptide-based products (1 kcal/ml), 0.15–0.16 mg in diabetes-specific products (1.0 kcal/ml), 0.30 mg in immune-modulating (1.0 kcal/ml) product, 0.25 mg in pulmonary specific product (1.5 kcal/mL). According to ESPEN Micronutrient Guideline,[5] 1.5–3 mg/1500 kcal/day enterally thiamine intake was considered sufficient for critically ill adult participants. In addition, the administration of IV thiamine to all study participants was followed.

Blood Sample Collection and Analysis

At the initial and subsequent study time points, blood samples were collected from each study participant, and plasma and serum were obtained. Obtained samples were stored at -80 °C.

Analysis of Plasma Thiamine Concentrations

Plasma thiamine levels were quantified using high-performance liquid chromatography (HPLC). The analysis protocol was performed in accordance with the methodology described by McCann et al.[10] with modifications. HPLC analysis was run at 25°C with Agilent Zorbax Eclipse plus C18 Rapid

Resolution HT column (3.0 x 50 mm, 1.8 µm), a Phenomenex Security C18 cartridge (4 x 2.0 mm). Thiamine standard was purchased from Sigma-Aldrich (Apeldoorn, The Netherlands). The analytes and standard had >99% purity. The reference range of plasma thiamine was considered as 8–30 nmol/L.

Analysis of eTPP Concentrations

eTPP was determined using HPLC according to the protocol of Lu and Frank,[25] with modifications. Analysis was performed at 25°C with Agilent Zorbax Eclipse plus C18 Rapid Resolution HT column (3.0 x 50 mm, 1.8 µm) and a Phenomenex Security C18 cartridge (4 x 2.0 mm). The normal range of eTPP value was accepted as 275–675 ng/g Hb.[12,26]

Serum CRP Analysis

Serum CRP values were measured by the turbidimetric method at both study time points. The presence of inflammation was considered as a CRP value >5 mg/L.

Statistical Analysis

The data were analyzed using RStudio (version 2022.07.1; RStudio, PBC, Boston, MA, USA). Continuous variables are presented as either the mean±standard deviation (SD) or the median (interquartile range (1st quartile–3rd quartile) (IQR)) in accordance with the normality distribution, as determined by the Shapiro-Wilk test. The categorical variables are indicated as numbers (%). The independent continuous data of the two groups was compared using either the Student's t-test or the Mann-Whitney U test, depending on the circumstances. The Chi-Square test was employed to compare the two groups for the categorical variables. A paired sample T-test or Wilcoxon test was conducted to assess the impact of time (1st and 2nd study time point). A Spearman correlation analysis was employed to assess the relationship between two continuous variables.

A multiple linear regression analysis was conducted to examine the correlation between plasma thiamine levels and serum CRP concentrations, with the objective of predicting eTPP values. The analysis included a total of 96 samples from 48 study participants, with the exception of two patients who received intravenous thiamine supplementation in the ICU. The adjusted R2 value was calculated, and a p-value of less than 0.05 was considered statistically significant for all tests.

RESULTS

Study Sample

A total of 389 critically ill patients were screened, and 50 adult participants completed this study (Fig. 2). The median age of study patients was 68.0 (IQR: 52.5–75.5) years, and composed of 57.1% were male. The most prevalent indications for admission to the ICU) were respiratory failure (28%), sepsis/septic shock (18%) and neurological diseases (18%) (Table 1).

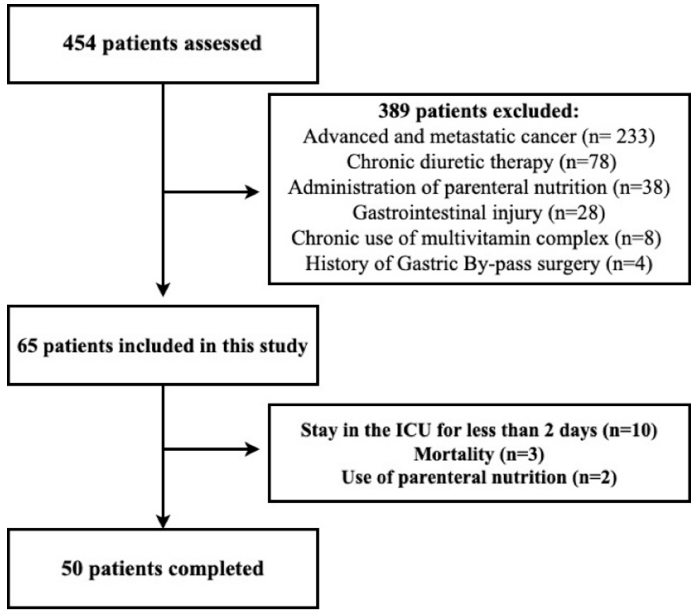

Figure 2. The consort diagram of the study. The diagram illustrates the sequence of events in the study.

At ICU admission, the mean APACHE II score was 14.7±7.4, and SOFA was 4.0±3.0. The median Charlson Comorbidity Index score of patients was 4.0 (IQR: 1.0–5.0). According to mNUTRIC score and GLIM criteria, 22% and 40% of the study participants had malnutrition at study admission, respectively. A total of 52% of participants required MV (invasive or non-invasive) support, and 34% required vasopressor therapy. The ICU mortality rate of study participants was 34% (Table 1).

Some clinical parameters according to nutritional support therapies (oral nutrition or enteral tube feeding) of the participants are documented in Appendix Table 1. Patients receiving enteral tube feeding had significantly higher APACHE II scores, baseline SOFA, and Glasgow coma scale scores than participants receiving oral nutrition ($p<0.05$ for all). Also, tube-fed participants were more malnourished according to both mNUTRIC score and GLIM criteria, respectively, compared to orally fed patients ($p<0.05$ for both) (Appendix Table 1).

Plasma Thiamine and eTPP Concentrations

The mean plasma thiamine level was 13.6±5.22 nmol/L at the 1st study time point (day of ICU admission) and 15.2±5.06 nmol/L at the 2nd study time point, respectively (not significant). At ICU admission, the median eTPP concentration of the study sample was 621.0 (range: 406.9–921.9) ng/g Hb and was 587.8 (range: 338.2–889.4) ng/g Hb at the 2nd study time point (not significant). There was no significant correlation between plasma thiamine levels and eTPP values in participants at either the first or second study time points ($p>0.05$ for all).

Table 1. Patient demographics, clinical and nutritional data

Variables	Total (n=50)	Variables	Total (n=50)
Age, median (IQR)	68.0 (52.5–75.5)	Day 3	4.1±3.6
Gender, n (%)		Day 7	5.0±3.5
Male	28 (57.1%)	Glasgow coma scale score, median (IQR)	
Female	22 (42.9%)	ICU admission	11.0 (4.5–15.0)
BMI (kg/m^2), mean±SD	29.2±6.02	Day 1	11.0 (3.0–15.0)
Reason for ICU admission, n (%)		Day 3	13.5 (3.0–15.0)
Respiratory failure	14 (28.0%)	Day 7	10.0 (3.0–14.0)
Sepsis/septic shock	9 (18.0%)	Charlson comorbidity index score, median (IQR)	4.0 (1.0–5.0)
Neurological diseases	9 (18.0%)	Nutritional assessment	
Metabolic diseases	8 (16.0%)	mNUTRIC score, mean±SD	2.7±2.0
Trauma	6 (12.0%)	Presence of malnutrition, n (%)	
Post-op	4 (8.0%)	According to mNUTRIC score	11 (22.0%)
Comorbidities, n (%)		According to GLIM	20 (40.0%)
Hypertension	19 (38.0%)	Icu treatment protocol	
Malignancy	11 (22.0%)	Need for MV support, n (%)	26 (52%)
Diabetes mellitus	10 (20.0%)	Need for vasopressor treatment, n (%)	17 (34%)
Coronary arter disease	6 (12.0%)	Need for renal replacement therapy, n (%)	5 (10%)
Chronic obstructive pulmonary disease	5 (10.0%)	Need for insulin therapy, n (%)	14 (28%)
Chronic renal failure	5 (10.0%)	Clinical outcomes	
Congestive heart failure	4 (8.0%)	Presence of sepsis, n (%)	21 (42%)
Alzheimer	4 (8.0%)	Length of ICU stay, median (IQR)	10.0 (7.5–19.0)
Clinical assessment		Mortality, n (%)	
APACHE II score, mean±SD	14.7±7.4	ICU	17 (34%)
SOFA score, mean±SD		28-day	20 (40%)
ICU admission	4.0±3.0	90-day	25 (50%)
Day 1	4.0±3.0		

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II score; BMI: Body mass index; GLIM: Global leadership initiative on malnutrition; mNUTRIC: Modified Nutrition Risk in Critically Ill score; ICU: Intensive care unit; IQR: Interquartile (25th–75th quartile); MV: Mechanical ventilation; SD: Standart devitation; SOFA: Sequential organ failure assessment.

The Prevalence Of Participants with low eTPP Values

A total of 12% and 18% of patients had low eTPP levels at the first and second study time point, respectively. During the study period, 26% of participants demonstrated below-normal eTPP levels at least at one-time point. The eTPP value of 50 study participants was classified according to the reference range (275–675 ng/g Hb) in both study time points, shown in Appendix Figure 1.

No participant received supplemental thiamine on the baseline day. However, two participants received IV thiamine (300 mg/day) daily during follow-up. These individuals had above-normal thiamine concentrations (median eTPP value:1386 and 1256 ng/g Hb at the 2nd study time point). The remaining participants did not receive any thiamine treatment (oral or IV route) during follow-up.

Effect of Inflammation

The median serum CRP value of participants was 135.4 (range: 87.9–172.1) mg/L at the first study time point and 103.5 (range: 38.1–199.9) mg/L at the second study time point (p=0.149, 23.6% reduction). This indicates a high level of inflammation, given that the normal CRP range was 0–5 mg/L. The median serum CRP concentration of study participants receiving oral diet with/without oral supplements was significantly reduced by 45.0% during the study period (median CRP: 116.7 vs

Table 2. Multiple linear regression analysis predicting etpp concentrations from plasma thiamine and serum crp concentrations

	Unstandardized coefficients		Standardized coefficients	p	Collinearity statistics	
	B (95% CI)	Std. error	β		Tolerance	VIF
Constant	444.321 (231.183–657.458)	107.101				
Plasma thiamine	4.916 (2.283–8.594)	1.837	0.297	0.009	0.941	1.013
Serum CRP value	-0.231 (-0.058– -0.425)	0.464	-0.058	0.031	0.941	1.013

This analysis was performed in 96 samples from 48 participants who did not receive any IV thiamine supplementation during the study period. Resume of the model: F=3.623, p=0.020, R^2=0.78. B: Unstandardized coefficient; β: Standardized coefficient; CI: Confidence interval; CRP: C-reactive protein; VIF: Variance inflation factors.

64.2 mg/L, p=0.021). The median CRP values of participants receiving enteral tube feeding were similar between the first and second-time points (Appendix Table 1).

Multiple linear regression data is shown in Table 2. Plasma thiamine and serum CRP concentrations predicted eTPP concentrations using the following model: eTPP concentration=444.321 + (4.916 * plasma thiamine level) - (0.231 * CRP value) (F=3.623, R^2=0.78, p=0.020) (Table 2).

Effect of Nutritional Therapy

The median daily energy and protein requirements of patients were estimated to be 1361 (1201–1523) kcal/day and 65.3 (57.7–73.1) g/day. Participants achieved 18.1±8.03 kcal/kg/day energy (73% of target energy) and 0.78±0.44 g/kg/day protein (74% of target protein amount) by the 3rd study day. Patients receiving oral food with/without oral nutrient supplements achieved 20–64% and 13–47% of daily energy and protein requirements throughout the study period, respectively. Enteral tube-fed participants reached 30–88% of the daily energy target and 33–97% of the daily protein target, respectively. The daily received energy and protein amount of study participants are detailed in Appendix Table 2. Participants receiving enteral tube feeding achieved 2.46–2.83 mg/day/1500 kcal thiamine intake during the study period (Appendix Fig. 2).

Participants receiving enteral nutrition via feeding tube had significantly higher plasma thiamine values than orally fed patients at the two study time points (mean: 11.0 vs. 15.8 nmol/L, p=0.001 and mean: 14.4 vs. 16.1 nmol/L, p=0.029, respectively). Orally fed participants had significantly higher mean plasma thiamine concentrations at the 2nd study time point compared to the 1st study time point (p=0.021) (Fig. 3).

The median eTPP values were similar in participants receiving oral food/supplements or enteral tube feeding at the first and second-time points (Fig. 3). However, participants receiving enteral tube feeding had significantly higher eTPP values than orally fed participants during the study period (p=0.021 and p=0.034, first and second-time points, respectively) (Fig. 3).

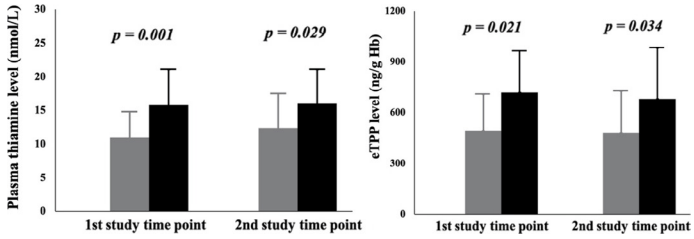

Figure 3. Plasma thiamine and eTPP concentrations of participants receiving oral and enteral nutrition during the study period. The median plasma thiamine and eTPP concentrations of participants as a function of oral nutrition /supplements and enteral tube feeding are shown. Both plasma thiamine and eTPP concentrations were significantly higher in enteral tube-fed participants compared to those receiving an oral diet with or without oral nutrient supplements at the first and second study time points. Grey indicates patients receiving oral diet/supplements, while black denotes patients receiving enteral tube feeding.

DISCUSSION

To our knowledge, this is the first investigation of the effects of enteral nutrition and inflammation on plasma thiamine and concomitant eTPP concentrations in critically ill adult patients. The results demonstrate that mean plasma thiamine and eTPP concentrations were within the reference range for our institution. There was not a significant correlation between plasma thiamine and eTPP values. A total of 26% of participants demonstrated low thiamine concentrations during the period of observation. Patients receiving enteral tube feeding had significantly higher plasma thiamine and eTPP values than orally fed patients. Plasma thiamine concentrations were significantly and inversely related to serum CRP concentrations in orally fed patients. Plasma thiamine and serum CRP levels significantly predicted eTPP concentrations in the 48 participants who did not receive IV thiamine supplementation.

In our study, eTPP and plasma thiamine values were within the reference range of our institution. Similarly, Ghashut et al.[26] determined eTPP values in 553 patients with inflammation

(median CRP: 14 mg/L) at risk of malnutrition and multiple diseases from routine laboratory analysis. The median eTPP values in that study were 613 ng/g Hb and in the normal range, comparable with our data. In addition, it was reported that erythrocyte TPP was not affected by inflammation and may be a suitable marker of thiamine status in the inflamed population. Heming et al.[27] prospectively analyzed eTPP concentrations in 28 critically ill septic patients on the day of sepsis diagnosis and 2 and 7 days after sepsis diagnosis. The median eTPP concentrations were in the reference range (126–250 nmol/L), similar to our study results. Quasim et al.[28] conducted a study investigating eTPP value in 49 healthy adults and 41 critically ill adult patients. A total of 23 critically ill patients were supplemented with an oral B-vitamin complex product containing 250 mg of thiamine. The median eTPP concentrations in the non-B vitamin complex supplemented critically ill group (n=18) was in the normal range 600 (320–1252) ng/g Hb, but thiamine supplementation significantly increased eTPP levels in the supplemented group [906 (390–2420) ng/g Hb]. In our study, only 2 participants received thiamine supplementation and exhibited above normal eTPP levels.

There was not a statistically significant correlation between plasma thiamine and eTPP values in our cohort. Serum CRP concentrations of study participants decreased by 23.6% over the course of the study. Serum CRP values in our participants receiving oral nutrition decreased significantly over time, while plasma thiamine concentrations increased significantly. Our results are consistent with the hypothesis that plasma thiamine concentrations are reduced as a component of the systemic inflammatory response.[5,10] Furthermore, multiple linear regression revealed that eTPP values were significantly associated with plasma thiamine concentrations and serum CRP concentrations in our study participants who did not receive IV thiamine supplementation. This regression-based model can explain 78% of the variance in eTPP concentrations in our cohort (Table 2). Therefore, in clinical settings where only plasma thiamine determinations are available, this model may be useful to estimate eTPP concentrations in inflamed critically ill adult patients. Thus, the difficulty and high cost of measuring eTPP concentration by the HPLC method can be overcome. It is hypothesized that the equation has the potential to be of use in the medical management of ICU patients who exhibit a comparable degree of illness severity to that observed in the study sample. However, it is imperative to consider the potential limitations of the study, which are detailed in the limitations section. Patients in this category may be receiving enteral tube feeding or a regular diet.

A total of 26% of patients demonstrated low thiamine status (reflected by eTPP concentrations) at the first and/or second study time points. Thiamine deficiency has been reported in 10–71% of septic ICU patients using different indices (serum thiamine, plasma thiamine, or whole blood thiamine).[29–31] A total of 42% of our participants developed sepsis during the study period. The differences between the rate of low thiamine status in our study compared to other published cohorts may reflect our use of eTPP as the index of thiamine nutriture.

Gundogan et al.[2] conducted a prospective observational study investigating whole-blood thiamine status in critically ill patients receiving chronic diuretic therapy. It was reported that 96% of patients had thiamine deficiency at ICU admission. However, in this study, patients undergoing chronic diuretic therapy and at risk of thiamine deficiency were excluded from the study in order to ascertain the impact of the acute phase of critical illness on thiamine status.

The results indicated that the median plasma thiamine and eTPP concentrations were significantly elevated in enterally tube-fed patients compared to participants receiving only oral nutrition. While participants receiving enteral tube feeding achieved 88% and 97% of daily energy and protein targets, respectively, our orally fed participants achieved only 64% and 47% of daily energy and protein recommendations. In addition, our tube-fed patients achieved adequate dietary thiamine intake according to the ESPEN micronutrient guideline recommendations. We did not analyze the daily thiamine intake of orally fed participants. Participants who received a regular oral diet and were not consuming adequate amounts were given oral liquid nutritional products based on our hospital protocol.

It should be noted that this study is not without limitations, including its observational nature, relatively small sample size, and the fact that it was conducted in a single hospital medical ICU. It is, therefore, not possible to generalize the data to all medical ICU patients. In addition, we did not have a control group (e.g., healthy control population or non-ICU patients). Also, we did not analyze whole blood thiamine levels. Furthermore, eTPP status may be influenced by the presence of anemia. To better understand the implications of these results, future studies could address relationships between whole blood thiamine, plasma thiamine, and eTPP levels in larger prospective studies in critically ill patients. To the best of our knowledge, this is the first study to assess thiamine status using eTPP values and, in comparison, to plasma thiamine concentrations in critically ill patients according to enteral feeding methods. In addition, we were able to calculate an estimation of eTPP using plasma thiamine and a common marker of inflammation (CRP). Moreover, participants who received chronic diuretic treatments or had an advanced cancer diagnosis and were at particular risk for thiamine deficiency were not included in this study. Further longitudinal research is needed to determine the effects of both acute and chronic phases of critical illness on the thiamine status of ICU patients.

CONCLUSION

We found that plasma thiamine and eTPP concentrations were significantly lower in orally fed participants compared to those receiving enteral tube feeding. Multiple linear regression revealed that plasma thiamine and serum CRP levels predicted eTPP concentrations. A total of 26% of participants demonstrated below normal eTPP levels at least at one time point during the period of observation. The multiple linear regression model provides new insight into the relationship between eTPP, plasma thiamine, and inflammation in critically ill medical ICU patients.

Ethics Committee Approval: The Erciyes University Ethics Committee granted approval for this study (date: 23.09.2020, number: 2020/473).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Conflict of Interest: The authors have no conflict of interest to declare.

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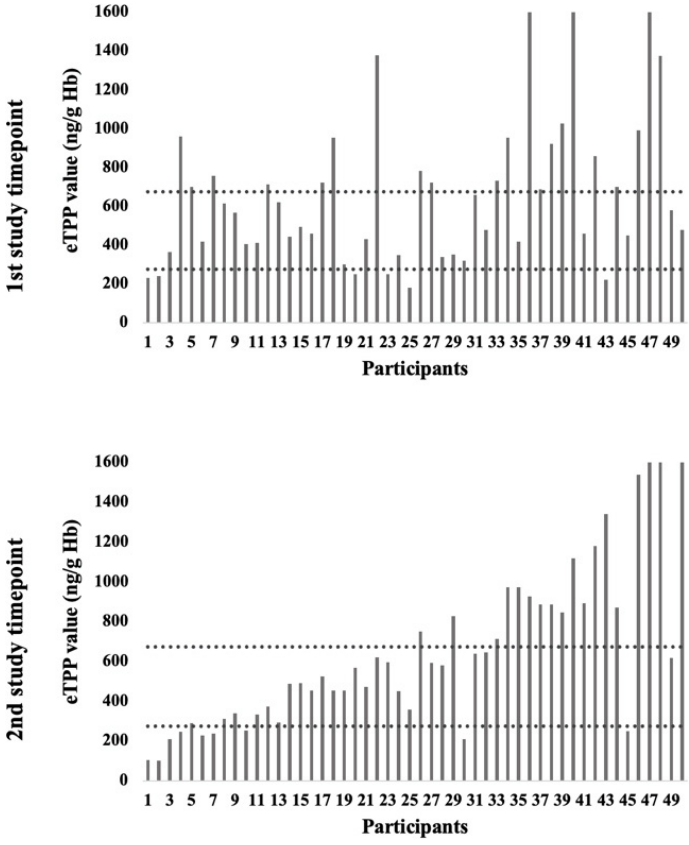
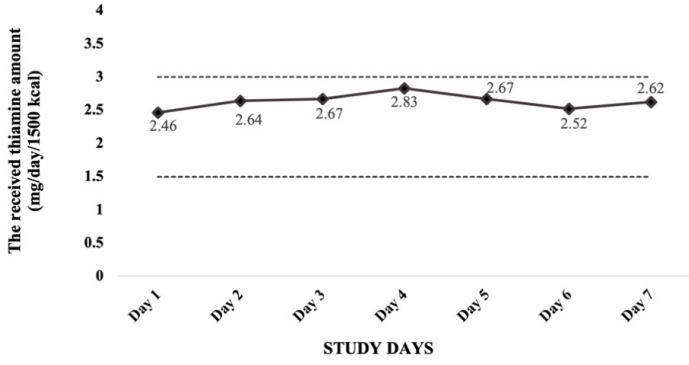
Appendix Table 1. Clinical and nutritional data according to nutritional therapies of critically ill patients

	Oral nutrition (n=24)	Enteral tube feeding (n=26)	p
APACHE II score, median (IQR)	7.5 (5.0–19.0)	15.0 (9.0–22.0)	**0.043**
Baseline SOFA score,±SD	3.2±2.9	4.7±2.9	**0.019**
Baseline Glasgow coma scale score, median (IQR)	14.0 (11.0–15.0)	7.5 (3.0–11.5)	**0.001**
Charlson comorbidity index score, median (IQR)	3.0 (1.0–5.0)	4.0 (0.8–5.3)	0.992
mNUTRIC score, mean±SD	2.1±1.83	3.3±1.96	**0.040**
Presence of malnutrition, n (%)			
According to mNUTRIC score	2 (18.2)	9 (81.8)	**0.009**
According to GLIM	7 (35.0)	13 (65.0)	**0.038**
CRP (mg/L), median (IQR)			
1st study time point	116.7 (61.2–153.3)	136.5 (103.2–186.7)	0.203
2nd study time point	64.2 (32.4–113.4)	115.2 (57.3–221.7)	**0.046**

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation II score; GLIM: Global leadership initiative on malnutrition; mNUTRIC: Modified Nutrition Risk in Critically Ill score, IQR: Interquartile (25th–75th quartile); SD: Standart devitation; SOFA: Sequential organ failure assessment.



Appendix Figure 1. The eTPP concentrations of participants according to reference range. The figure depicts the eTPP concentrations of all study participants, classified according to the reference range (275–675 ng/gHb) at the initial and subsequent study time points.



Appendix Figure 2. Daily thiamine intake of enterally fed participants (n=26). The figure illustrates the daily intake of thiamine (mg/day/1500 kcal) among patients who received enteral tube feeding during the study period.

Appendix Table 2. Daily energy and protein intake of patients receiving oral food/supplements and enteral tube feeding of critically ill patients receiving oral/food supplements and enteral tube feeding

	Total (n=50)				Oral food/supplements (n=24)				Enteral tube feeding (n=26)			
	Energy		Protein		Energy		Protein		Energy		Protein	
	kcal/kg/day	%	g/kg/day	%	kcal/kg/day	%	g/kg/day	%	kcal/kg/day	%	g/kg/day	%
Day 1	6.3±3.69	25	0.19±0.03	23	5.1±3.32	20	0.11±0.04	13	7.4±3.94	30	0.26±0.13	33
Day 2	11.4±6.31	46	0.50±0.24	41	9.9±4.54	39	0.30±0.12	25	12.9±7.81	51	0.68±0.17	57
Day 3	18.1±8.03	73	0.78±0.44	65	15.4±5.38	62	0.44±0.19	37	20.5±9.65	82	1.08±0.52	89
Day 4	19.6±8.49	78	0.88±0.51	74	16.1±7.00	64	0.45±0.24	38	21.9±8.97	88	1.16±0.56	97
Day 5	19.4±9.00	78	0.89±0.52	75	14.5±6.53	58	0.43±0.18	35	22.1±9.55	88	1.16±0.56	97
Day 6	19.3±8.62	77	0.88±0.43	73	15.5±6.65	62	0.54±0.33	45	21.6±9.27	87	1.07±0.50	90
Day 7	18.8±8.27	75	0.82±0.43	69	15.7±5.88	63	0.57±0.33	47	20.5±9.29	82	0.96±0.45	80

% shows the mean daily adequacy of energy and protein requirements. Kcal/kg/day: Energy intake(calorie)/body weight (kg)/day.