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Evaluation of whole blood thiamine pyrophosphate concentrations in critically ill patients receiving chronic diuretic therapy prior to admission to Turkish intensive care units: A pragmatic, multicenter, prospective study

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ABSTRACT

Background/Objectives: Thiamine plays a pivotal role in energy metabolism. The aim of the study was to determine serial whole blood TPP concentrations in critically ill patients receiving chronic diuretic treatment before ICU admission and to correlate TPP levels with clinically determined serum phosphorus concentrations.
Subjects/Methods: This observational study was performed in 15 medical ICUs. Serial whole blood TPP concentrations were measured by HPLC at baseline and at days 2, 5 and 10 after ICU admission.
Results: A total of 221 participants were included. Of these, 18% demonstrated low TPP concentrations upon admission to the ICU, while 26% of participants demonstrated low levels at some point during the 10-day study period. Hypophosphatemia was detected in 30% of participants at some point during the 10-day period of

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observation. TPP levels were significantly and positively correlated with serum phosphorus levels at each time point ($P < 0.05$ for all).

Conclusions: Our results show that 18% of these critically ill patients exhibited low whole blood TPP concentrations on ICU admission and 26% had low levels during the initial 10 ICU days, respectively. The modest correlation between TPP and phosphorus concentrations suggests a possible association due to a refeeding effect in ICU patients requiring chronic diuretic therapy.

1. Introduction

Thiamine (vitamin B1) is a water soluble vitamin and acts as a co-enzyme for carbohydrate and protein energy metabolism [1]. It cannot be synthesized and stored in the human body and is thus an essential micronutrient. [2].

Malnutrition, obesity, artificial nutrition, diets with low thiamine content, processed foods, and alcoholism are common causes of thiamine deficiency [2,3]. Excessive vomiting, gastrointestinal losses, liver diseases, bariatric surgery, cardiovascular diseases, kidney failure, use of loop diuretics, and catabolic conditions also may lead to thiamine deficiency [2]. As a result of serum thiamine deficiency, neurological diseases (e.g Wernicke-Korsakoff syndrome) and cardiovascular diseases (e.g wet and dry beriberi) may occur [4].

In critically ill patients, low thiamine levels are linked to poor prognosis and requires repletion [5,6]. The level of blood thiamine is decreased by inflammation associated with critical illness [5] [7]. It is not clearly known whether the measured low blood thiamine level is due to inflammation or other associated causes in critically ill patients. The frequency of low thiamine levels has been shown to occur in up to 82% in catabolic processes such as severe burns, septic shock, kidney diseases, patients who have undergone surgery, and heart diseases [8,9].

There is no recommendation of thiamine replacement for enterally fed patients in the current ASPEN or ESPEN guidelines on nutrition support in critically ill patients. However, both guidelines recently recommended the administration of thiamine replacement to patients receiving parenteral nutrition [10,11]. More recent ESPEN Guidelines on micronutrients provide recommendations for patients receiving enteral nutrition, parenteral nutrition, and for ICU patients [12]. Low circulating thiamine is likely more common in patients receiving chronic diuretics, such as those with heart failure, cirrhosis of the liver and in catabolic patients admitted to the intensive care unit (ICU). Most of these patients are feed enterally and do not routinely receive additional thiamine support in the ICU.

Gundogan et al. performed a pilot single-center prospective study in Turkey in which low TPP concentrations were found in 96% of critically ill patients admitted with chronic (> 6 months) furosemide treatment before ICU admission [13]. To provide more generalizable data, this larger multicenter study was designed. The aim of this prospective study was to determine whole blood thiamine pyrophosphate (TPP) (the active form of thiamine) concentrations in critically ill adult patients receiving chronic diuretic therapy prior to and during admission to 15 Turkish ICUs.

2. Materials and methods

2.1. Study design

This study was prospectively performed in the 15 Turkish Medical ICUs between 1 April 2017 and 1 April 2020. It was approved by the Erciyes University Ethics Committee (04.01.2017/2017/18). Written informed consent was obtained from all participants or appropriate family members.

The inclusion criteria were as follows: ages ≥18 years, expected ICU stay of at least 48 h hours of ICU treatment, and those receiving furosemide, with or without spironolactone therapy for at least 6 months and longer before ICU admission. Patients receiving high-dose oral thiamine (daily 50 mg over at least 14 days) and those with previous history of gastrointestinal surgery were excluded.

The study subject demographic data (age, sex, height, and weight) and severity of illness (Acute Physiology and Chronic Health Evaluation II (APACHE II) score) were documented on ICU admission. We calculated the Modified Nutrition Risk in Critically Ill (mNUTRIC) score [14] according to the standard method. The SOFA score [15] was also daily calculated throughout 10-day study period. The Glasgow coma scale was also determined.

Clinical data (reason for ICU admission, need for mechanical ventilation and vasopressor treatment, presence of co-morbid diseases, sepsis, new infection, need for renal replacement therapy, acute kidney injury (AKI) [16], length of ICU stay and ICU mortality) were recorded during follow-up.

Nutritional data (route of nutrition, daily energy requirement (Harris-Benedict equation), daily energy intake, daily dextrose and insulin intake) were also followed.

Laboratory data (blood glucose, potassium, phosphorus (P), magnesium, calcium, and lactate) were recorded at baseline and during follow up. Hypophosphatemia was defined as serum P level ≤ 2.4 mg/L (0.77 mmol/L). Furosemide and spironolactone use and dosage were recorded.

2.2. Laboratory analysis

Patients were included in the study within the first 24 h after admission to the ICU. Whole blood TPP concentrations were measured at baseline and serially on days 2, 5, and 10 after entry into the study in those who remained admitted to the ICU. Concentrations of TPP were determined using high-performance liquid chromatography (HPLC; Chromsystems Instruments and Chemicals GmbH, Am Haag 1,282,166 Grafelfing, Germany). The reference range for whole blood TPP is 28–85 μg/L (66.5–200 nmol/l) and thiamine deficiency was considered <28 ng/mL [17]. Blood samples were stored at −80 °C until all samples belonging to study subjects were completed and batch laboratory analysis were initiated.

2.3. Statistical analysis

All data analysis was performed with Statistical Package for the Social Sciences SPSS 22.0. Data presented as median (range: minimum maximum) and percentage. For comparison of the two groups, independent-samples *t*-tests were used for parametric continuous data and Mann Whitney U for non-parametric continuous data. The Spearman/Pearson correlation coefficient was calculated to investigate correlations between whole blood TPP levels and serum phosphorus levels in non-renal failure patients ($n = 150$). Categorical variables were compared using Chi-Square Test. Logistic regression analysis was used to investigate the relationship between low TPP concentrations and clinical outcomes involving need for MV support, vasopressor therapy, and RRT, new infection, sepsis, and mortality. Statistical significance was accepted as $p < 0.05$. According to our pilot study, study sample size was calculated with at least 194 participants to detect a mean difference of 16.1% (2.5 ng/mL) and a standard deviation of 10.7 (90% strength and 5% error probability in whole blood TPP concentrations.

3. Results

A total of 234 patients were screened (Supplemental Fig. 1). A total of 221 participants were enrolled into the study from 15 Turkish ICUs (Supplemental Table 1). The median age of study participants was 71 (range, 25–101) years and 51% were female. The mean APACHE II score at ICU admission was 18 ± 7.4. The median modified NUTRIC score was 4 (range, 0–9). The most common reasons for ICU admission were respiratory failure (54%) and metabolic disease (31%). Heart failure (154 patients) and chronic obstructive pulmonary disease (COPD) (67 patients) were the most frequent co-morbid diseases of study participants. Before ICU admission, the median duration of furosemide usage was 24 (range,12–27) months and median furosemide dose was 40 (range 20–120) mg/day. In addition, a total of 17.2% (38 patients) used a median of 25 (range, 25–100) mg/day spironolactone prior to ICU admission. ICU mortality was 26%. Demographic and clinical characteristics of the participants are listed in Table 1. There is no difference in baseline clinical/demographic parameters (age, gender, BMI, APACHE II score, mNUTRIC score, SOFA score, Glasgow Coma score, use duration of diuretic therapy, feeding route, energy intake, presence of CKD) between participants with low and normal TPP concentrations ($p > 0.05$ for all test) (Supplemental Table 2). In addition, there is no statistically significant association between low TPP and poor clinical outcomes (mortality, need for MV, vasopressor, and RRT, new infection, sepsis) ($p > 0.05$ for all test). We have now shown this table as supplemental Table 3.

Median whole blood TPP levels were within the normal range at all time points and slightly increased at day 10. Fig. 1 shows median whole blood TPP concentrations at baseline (ICU admission day) ($n = 221$), day2, day 5 and day10. The proportions of participants with low TPP levels is shown in Fig. 2. The highest ratio was detected at baseline (18%) and in day 5 (16%). A total of 26% of participants exhibited low TPP during one or more time points during the study (Fig. 2).

Table 1
Demographic and clinical characteristics.

Variables	Value
Age, year, median (range)	71 (25–101)
Gender, n (%)	
Male	109 (49)
Female	112 (51)
BMI, kg/m^2, median (range)	26.7 (16.3–50.6)
APACHE II score, mean ± SD	18 ± 7.4
mNUTRIC score, median (range)	4 (0–9)
Reason for ICU admission, n (%)	
Respiratory failure	116 (54)
Metabolic disease	67 (31)
Shock	14 (6)
Neurologic disease	8 (4)
Post-op	8 (4)
Cardiac arrest	2 (1)
Co-morbid diseases, n (%)	
Heart failure	153
Chronic obstructive pulmonary disease	67
Kidney failure	58
Liver cirrhosis	52
Cancer	8
Use duration of furosemide, months, median (range)	24 (12–27)
Dose of furosemide, mg/day, median (range)	40 (20–120)
SOFA score, median (range)	
Baseline	5 (0–13)
Day 2	4 (0–15)
Day 5	4 (0–15)
Day 10	6 (0–15)
Glasgow coma score at admission, median (range)	15 (3–15)
Need for mechanical ventilation, n (%)	63 (30)
Need for RRT, n (%)	24 (12)
Vasopressor, n (%)	73 (34)
New site infection, n (%)	65 (31)
Length of ICU stay, day, median (range)	6 (2–111)
ICU mortality, n (%)	54 (26)

APACHE II: Acute physiology and chronic health evaluation II, BMI: Body mass index, ICU: Intensive care unit, mNUTRIC: modified nutrition risk in critically ill score, range: minimum-maximum, RRT: Renal replacement therapy, SOFA: Sequential organ failure assessment.

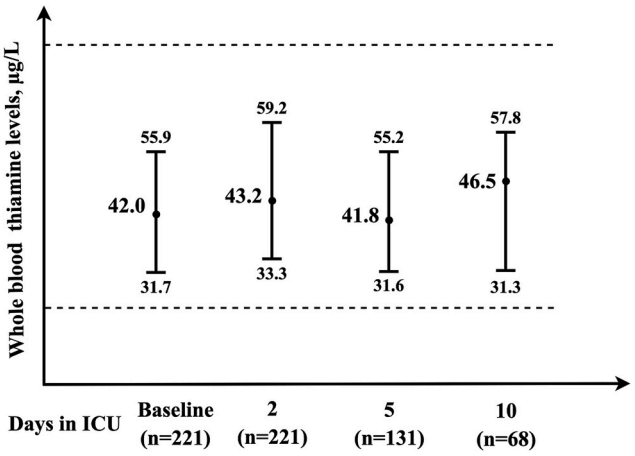

Fig. 1. shows the median and interquartile range (25 th – 75 th percentile) of whole blood TPP concentrations in study participants at baseline and on day 2, 5, and 10. The dashed lines show the normal range for whole blood TPP concentration. To covert µg/L to nmol/L: 1 µg/L = 17.513135 nmol/L.

A total of 73% of subjects remained on diuretic therapy during the ICU stay. Diuretic use of the participants throughout the 10-day observation period is shown in Supplemental Table 4. At day 1 (one day after ICU admission), the median daily energy intake of study subjects was 993 (range, 64–2000) kcal/day. Daily energy intake continued to increase and reached a maximum on day 9 (median 1261, range 160–2280 kcal/day). The daily energy intake of participants during the 10-day period of ICU observation is shown in Supplemental Fig. 2. A total of the 62.5% (137 patients) of study sample reached target daily energy intake.

Route of nutrition, carbohydrate administration from tube feeding and parenteral nutrition, and short-acting insulin treatment are shown in Supplemental Table 5. Participants received oral food, enteral tube feeding or parenteral feeding according to standard nutrition support practices in each participating ICU.

4. Relation to renal failure

A total of 71 patients with renal failure [chronic kidney disease stage 3 or greater ($n = 58$)] of which 13 required renal replacement therapy were included in the total cohort. Because renal failure may decrease thiamine levels and increase phosphorus concentrations, we excluded renal failure patients and determined the incidence of hypophosphatemia among the 150 non-renal failure patients.

Mean (range) for serum phosphorus concentration was 3.2 (1.2–8.1) mg/dL at baseline (mean:3.5 mg/dL). The incidence of hypophosphatemia in these individuals was between of 19–37% throughout the 10-day study period (Fig. 3). The highest incidence of hypophosphatemia (37%) was observed on the 5th day. Hypophosphatemia was detected in 30% of participants during at least one point in the 10-day period of observation.

4.1. Correlation analysis

Fig. 4 shows the correlation of whole blood TPP and serum phosphorus concentrations with 95% confidence intervals at baseline and on days 2, 5, and 10 of observation. Whole blood TPP levels were most significantly and positively correlated with serum phosphorus concentrations at day 10 ($r = 0.520$, p:0.001), whereas there was a significant, but weaker, positive correlation at baseline ($r = 0.215$, $p = 0.016$), day 2

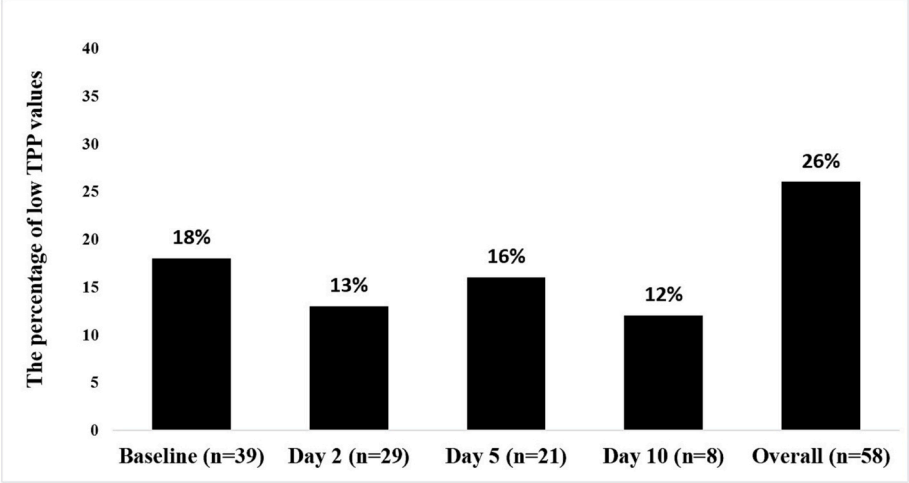

Fig. 2. shows the percentage of participants with low TPP values at baseline and on day 2, 5, and 10, and at any time point.

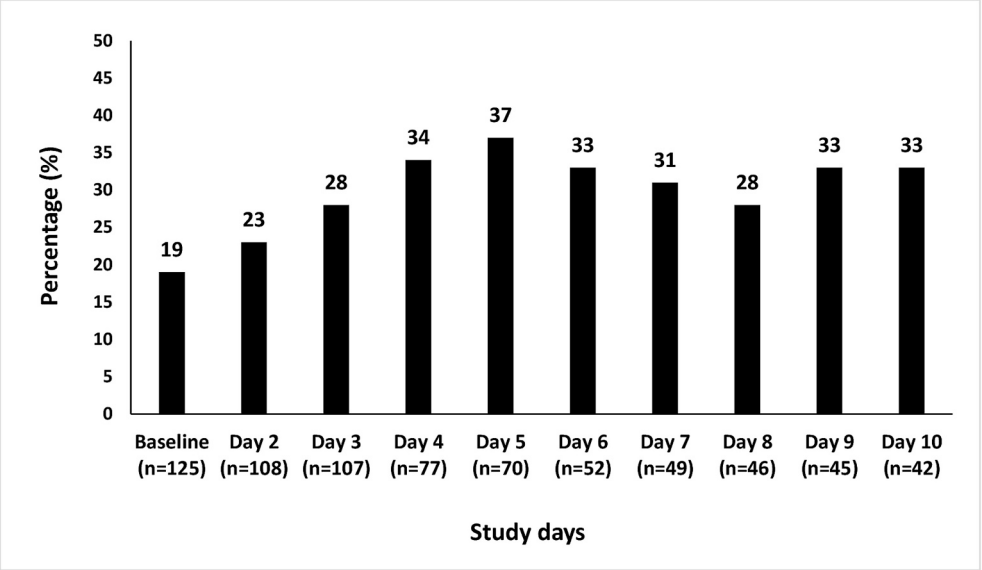

Fig. 3. shows the incidence of hypophosphatemia in the study population was between of 19–37% throughout the 10-day study period in participants without chronic kidney disease.

($r = 0.320$, $p = 0.001$) and day 5 ($r = 0.290$, $p = 0.043$), respectively.

5. Discussion

This multicenter, prospective study evaluated serial whole blood TPP concentrations in critically ill adult patients receiving diuretics therapy prior to ICU admission. A total of 18% of participants exhibited low TPP upon admission to the ICU, while 26% of participants had low concentrations at some point during the 10-day study period. In addition, we found a total of 30% of participants with hypophosphatemia at some point during the 10-day period of observation.

In this study, our participants were on chronic diuretics before ICU admission and thus were likely at risk for thiamine depletion. Gundogan et al. performed a pilot study in patients on loop diuretic treatment for at least 6 months prior to medical ICU admission in a Turkish medical center [13]. Fifty subjects were included (25 subjects in each of the diuretic and control groups) in this study. At baseline, whole blood TPP concentrations of all study participants were 31.2 ± 27.1 ng/mL. In the diuretic group, the baseline TPP level was significantly lower compared to the control group (15.5 ± 10.7 vs 46.8 ± 29.5 ng/mL; $p < 0.001$). On day 2 after ICU admission, whole blood TPP levels remained low (23.2 ± 15.4 ng/mL in the diuretic group vs 49 ± 38 ng/mL in the control group; $P = 0.003$). Low TPP levels were found in 96% and 72% of control group at baseline and on the second day. In the current study, the percentage of participants admitted to 15 Turkish ICUs with low TPP levels was lower than our pilot study at all time points. The reasons for this discrepancy are unclear given that the APACHE II score on admission to the ICU were similar between the current study and our pilot study.

Van Snippenburg et al. conducted a prospective study to evaluate thiamine levels during intensive insulin therapy in mixed medical and surgical ICU patients [18]. Thiamine deficiency was determined in 40% of patients and was significantly associated with the presence of gastrointestinal pathology and also with recent surgery. This study had similar patients with regard to age and clinical characteristics as in our study sample.

A prospective, multicenter, observational study was performed in critical care units in Spain and the United Kingdom [19]. Thiamine values were analyzed by erythrocyte transketolase activity. In this study, a total of 72 and 76% of the adult patients were thiamine deficient at the

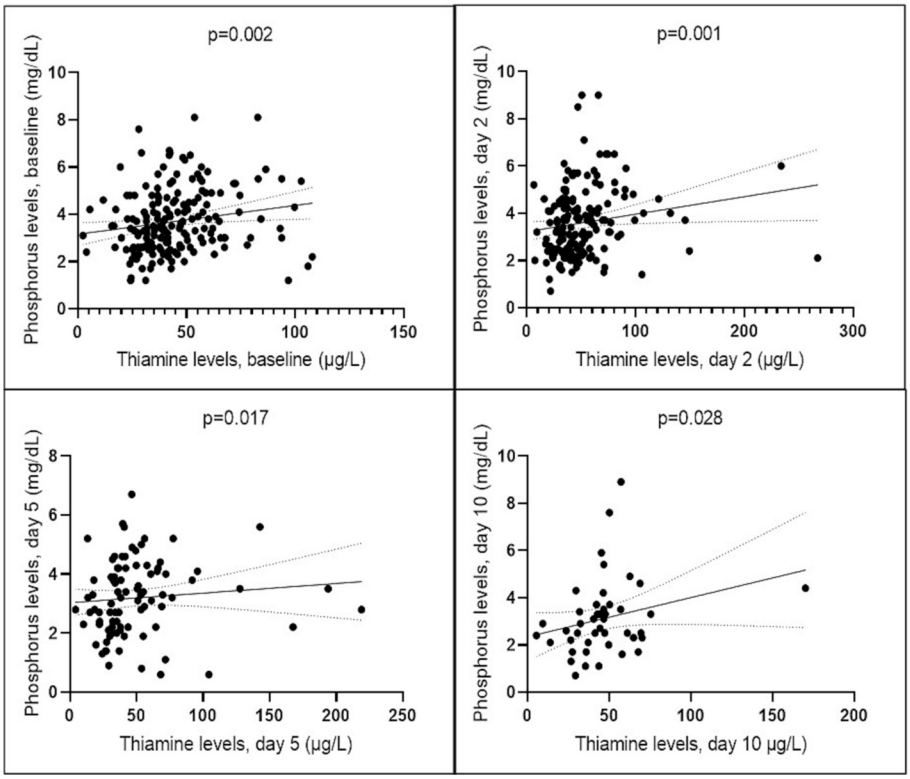

Fig. 4. shows the correlation of whole blood TPP and serum phosphorus concentrations with 95% confidence intervals at baseline and on day 2, 5, and 10. Whole blood TPP levels were moderately correlated with serum phosphorus concentrations at day 10 ($r = 0.520$, p:0.001), whereas there was a significant, but weaker, correlation at baseline ($r = 0.215$, $p = 0.016$), day 2 ($r = 0.320$, $p = 0.001$) and day 5 ($r = 0.290$, $p = 0.043$).

day of admission and on day 7 after ICU admission, respectively.

Another study performed by Donnino et al. [20] prospectively assessed plasma thiamine levels in 60 critically ill adult patients (30 with sepsis and 30 without sepsis). Plasma thiamine concentrations were measured on ICU admission and at 24, 48, 72, and 162 h after admission. Thiamine deficiency in septic patients was found in 10% at baseline and 20% within 72 h after ICU admission, compared to no deficiency in the non-septic control group. Our TPP results are likely not directly comparable to this study of plasma thiamine in ICU patients.

Heming et al. performed a study in 28 critically ill septic patients [21]. Thiamine deficiency was observed 29% of study participants. Total thiamine and TPP concentrations were significantly higher in ICU survivors than in non-survivors. In our study, there was no significant association between low TPP levels and whole blood lactate concentrations (not shown). Also, there was no significant difference in mortality between patients with normal and low thiamine levels at any time period.

Leite et al. reported that 30% of 202 critically ill children in Brazil exhibited thiamine deficiency within the first 10 ICU days [22]. Gonçalves et al. performed a cross-sectional study in critically ill adult with diabetes infected by SARS-CoV-2 [23]. The median whole blood thiamine value was 54 (range, 38–72) µg/L. Of these, 16% of participants exhibited thiamine deficiency.

In our study, the frequency of hypophosphatemia was 30% during the 10-day observation period. Hypophosphatemia in critically ill patients may be multifactorial including refeeding syndrome. A total of 80% of our study sample started to be fed on the first day of ICU admission (Supplemental Table 5). Participants reached a mean intake of 1025 kcal/day on by day 3. Whole blood TPP levels were also positively correlated with serum phosphorus levels during the study (Fig. 4). Therefore, we believe that hypophosphatemia may reflect a possible association with refeeding syndrome in our cohort. A study performed in the same Turkish ICU by Coskun et al. reported that the incidence of refeeding hypophosphatemia was 52% in critically ill adult patients [24].

Our study had some limitations. The relationship between TPP and phosphorus levels was modest overall. In addition, we did not find a correlation between TPP levels and clinical outcomes. However, these were not the focus of our investigation, which will likely require a much larger number of participants in a prospective study. Although baseline correlations do not reflect feeding in our ICU, patients may have arrived from other clinics, hospitals or from our general hospital wards. Therefore, the baseline correlation may possibly still reflect a refeeding response. In critically ill patients, blood thiamine levels may be affected by inflammation and inflammatory biomarkers were not measured in our study. The inflammation marker C-reactive protein (CRP) was not measured. Although our rate of low TPP concentrations was less than some studies [17,18], but was similar to other studies in critically ill patients [19-21]. It is possible that the nutritional intake that occurred at the day of the baseline blood sample (see supplemental Table 5) contributed to the TPP blood levels. In addition, the absence of data on thiamine and phosphate supplementation and on the

temporal relationship between feeding intake, TPP and phosphate concentrations are limitations precluding casual relationships.

To our knowledge, this multi-center study is the largest to date that has investigated whole blood TPP concentrations in critically ill patients receiving diuretics prior to and during ICU admission.

In conclusion, the current study investigated consecutive whole blood TPP levels in critically ill adult patients receiving chronic diuretic treatment prior to ICU admission. We found that 18% of participants demonstrated low TPP at ICU admission and 26% exhibited low levels at some point during the 10-day period of observation after admission, respectively. The correlation pattern between TPP and phosphorus levels suggests a possible association with refeeding in adult medical ICU patients requiring chronic diuretic therapy. While phosphorus repletion should be guided by frequent blood monitoring, it may be

prudent in many cases to empirically supplement thiamine in ICU patients when deficiency is clinically suspected, with serial blood monitoring of thiamine status to guide repletion over time.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2023.154326.

Author contributions

Conceived and designed the study: KG, MS, DPG, TRZ. Performed the study: GGS, SS, NTO, ST, TA, HY,OSD, ZS, KA, RU, AZ, HCD, EA, EO, NA, KG, NY, AT, GT, OE, BE, FDA, IHA, RE, RCY, MS. Analyzed the data: KG, GGS, SSE, NTO. Wrote the manuscript: KG, TRZ. Reviewed the manuscript: KG and TRZ. All authors approved the final version of the manuscript.

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Author statement

Conceived and designed the study: KG, MS, DPG, TRZ. Performed the study: GGS, SS, NTO, ST, TA, HY, OSD, ZS, KA, RU, AZ, HCD, EA, EO, NA, KG, NY, AT, GT, OE, BE, FDA, IHA, RE, RCY, MS. Analyzed the data: KG, GGS, SSE, NTO. Wrote the manuscript: KG, TRZ. Reviewed the manuscript: KG and TRZ. All authors approved the final version of the manuscript.

Declaration of Competing Interest

Authors have declared no conflict of interest.

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