Clinical Nutrition 40 (2021) 3780–3786

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Micronutrient deficiencies in critical illness

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ARTICLE INFO

Article history:
Received 21 February 2021
Accepted 1 May 2021

Keywords:
Vitamins
Trace elements
Selenium
Thiamine
Vitamin C
Vitamin B_6

SUMMARY

Background & aims: Low micronutrient levels in critical illness have been reported in multiple studies. Because of the antioxidant properties of various micronutrients, micronutrient deficiency may augment oxidative stress in critical illness. However, it remains unclear whether micronutrient concentrations in ICU patients are different from those in healthy age-matched controls. It is also unclear whether micronutrient deficiency develops, worsens, or resolves during ICU admission without supplementation.
Methods: We prospectively studied a cohort of adult critically ill patients. Micronutrient levels, including selenium, β-carotene, vitamin C, E, B_1 and B_6 were measured repeatedly during the first week of ICU admission. We compared the micronutrient concentrations at ICU admission to those of healthy age-matched controls. In addition, associations between micronutrient concentrations with severity of illness, inflammation and micronutrient intake were investigated.
Results: Micronutrient blood concentrations were obtained from 24 critically ill adults and 21 age-matched healthy controls. The mean micronutrient levels at admission in the ICU patients were: selenium 0.52 μmol/l, β-carotene 0.17 μmol/l, vitamin C 21.5 μmol/l, vitamin E 20.3 μmol/l, vitamin B_1 129.5 nmol/l and vitamin B_6 41.0 nmol/l. In the healthy controls micronutrient levels of selenium (0.90 μmol/l), β-carotene (0.50 μmol/l), vitamin C (45 μmol/l) and vitamin E (35.5 μmol/l) were significantly higher, while vitamin B_1 (122 nmol/l) and B_6 (44 nmol/l) were not significantly different between patients and controls.
Selenium, vitamin B_1 and vitamin B_6 levels remained stable during ICU admission. Vitamin C levels dropped significantly until day 5 ($p < 0.01$). Vitamin E and β-carotene levels increased significantly on days 5–7 and day 7, respectively ($p < 0.01$).
Micronutrient levels were not associated with severity of illness, CRP or micronutrient intake during the admission.
Conclusions: At admission, ICU patients already had lower plasma levels of selenium, β-carotene, vitamin C and vitamin E than healthy controls. Vitamin C levels dropped significantly during the first days of ICU admission, while β-carotene and vitamin E levels increased after 5–7 days. No association between micronutrient levels and severity of illness, C-reactive protein (CRP) or micronutrient intake was found. Progressive enteral tube feeding containing vitamins and trace elements does not normalize plasma levels in the first week of ICU stay. This was a hypothesis generating study and more investigation in a larger more diverse sample is needed.
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1. Introduction

Low blood micronutrient levels in critical illness have been reported in multiple studies, possibly indicating micronutrient deficiencies. Because of the antioxidant properties of various micronutrients, these micronutrient deficiencies may augment oxidative stress in critical illness. Over the past 20 years, oxidative stress-mediated cell damage has been recognised to play a fundamental role in the pathophysiology of various critical illnesses such

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https://doi.org/10.1016/j.clnu.2021.05.003
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as acute respiratory distress syndrome (ARDS), ischemia-reperfusion injury, and multiple organ dysfunction syndrome (MODS) [1].

If micronutrient deficiency worsens oxidative stress, micronutrient supplementation may be beneficial in critical illness. However, studies investigating micronutrient supplementation effects in intensive care unit (ICU) patients show conflicting results [2,3]. This is further complicated because most studies evaluated micronutrient cocktails rather than the effect of a single nutrient. Aggregation of the results of these heterogeneous studies suggest a reduction of overall mortality [3]. Recent guidelines, therefore, recommend micronutrient supplementation in ICU patients up to 5–10 times the dietary recommended intake (DRI) in healthy adults [4], but the evidence is limited.

In addition, it remains unclear 1) whether low micronutrient levels in critical illness are different from levels in healthy matched controls and 2) what the course of micronutrient levels is during ICU admission in the absence of supplementation. Due to the large differences in micronutrient levels that have been described in healthy people [5], as well as decreasing micronutrient levels with increasing age [6], it is essential to know whether micronutrient levels in critical illness correspond with micronutrient levels of healthy controls of the same age and population, to determine whether they are genuinely lower in patients. Furthermore, it is crucial to know the natural course of micronutrient levels in critically ill patients as this may guide the investigation and application of possible therapeutic interventions.

We performed a prospective cohort study in critically ill patients before implementing the current nutrition guidelines [4,7]. As active micronutrient supplementation was not the standard of care, patients only received micronutrients from the standard composition of enteral nutrition (EN). This study determined the serum micronutrient levels of selenium, β-carotene, vitamin C, vitamin E and blood levels of vitamin B_1 and B_6 during the first week of ICU admission and compared these with the micronutrient concentrations of healthy age-matched controls. We also quantified a possible association between micronutrient levels and severity of illness, inflammation and enteral micronutrient intake during ICU admission.

2. Materials and methods

We performed a prospective observational study in critically ill patients. This study was performed in the mixed medical-surgical adult ICU of Gelderse Vallei Hospital Ede, The Netherlands between July 1st, 2002 and December 1st,2002. Patients were included when they were admitted to the ICU and were >18 years of age. Exclusion criteria were chronic kidney failure (creatinine > 177 μmol/l, peritoneal or haemodialysis), chronic liver failure (portal hypertension, histologically proven hepatic cirrhosis or oesophageal varices), or receiving parenteral nutrition.

We asked 21 volunteers to participate in the control group. To recruit a control group with a similar age and dietary pattern as the patient group, relatives of the patient were asked to participate. If no relatives were available or did not agree to participate, patients with a similar age admitted to the general hospital wards without an underlying illness confounding micronutrient status were recruited. Volunteers were excluded when they had taken fortified foods or supplements in the previous 14 days.

The ethics committee of Gelderse Vallei Hospital (Ede, The Netherlands) and Wageningen University and Research (Wageningen, The Netherlands) approved the research protocol. All volunteers and patients, or in case of impaired consciousness, the patients' relatives, gave written informed consent.

2.1. Clinical management

Patients participating in the study received usual intensive care treatment. According to Gelderse Vallei Hospital-specific standard operational procedures and protocols, the team of physicians, ICU nurses and dieticians performed clinical management, including nutritional support. The Harris-Benedict formula was used to calculate daily energy requirements. No additional vitamins or trace elements supplementation other than enteral nutrition was performed. Our local protocol for enteral nutritional support included four types of standard enteral nutrition with a slightly different composition regarding proteins, fibers and micronutrients and total amount of energy. Changes from one type to another were never based on micronutrient concentrations in the patient nor on the amount of micronutrients in the enteral nutrition.

2.2. Sample size

The number of ICU patients needed to include in this pilot study was estimated at 21, based on a power calculation of the most variable vitamin, vitamin C (between-person-variation 15%; power 0.90; α 0.05) [8].

2.3. Data collection

Baseline characteristics were obtained from a questionnaire (in both patients and volunteers) and the individual patient files. The characteristics assessed by questionnaire were medical history, weight, height, smoking status, alcohol consumption and use of medication and micronutrient supplementation. The patient characteristics obtained from the patient files included type and amount of feeding, daily fluid balance, transfusions (blood and plasma), Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores, Sequential Organ Failure Assessment (SOFA) scores, C reactive protein (CRP), medications and micronutrient supplementation calculated from nutrition intake. Collected data were de-identified and stored on a secure hospital computer.

2.3.1. Laboratory tests

In patients, blood was sampled at 0, 12, 24, 36, 48, 72, 96, 120 and 144 h after ICU admission. The micronutrients selenium, β-carotene and vitamins C and E were measured in serum on every interval. The vitamins B_1 and B_6 were determined in haemolysed EDTA blood at the first, fourth and seventh time point. Besides measurements of the micronutrients in blood in ICU patients, other laboratory measurements were determined. All measurements are shown in supplement A. In the control group, only one sample was drawn to assess micronutrient status.

2.4. Data analysis and statistical considerations

Descriptive data are reported as means and standard deviation (SD) or median and interquartile range (IQR) in case of skewed distributions, or as frequencies and percentages when appropriate. A p-value <0.01 was considered statistically significant.

The primary analysis comparing patient baseline micronutrient levels to the controls was performed using an independent-samples t-test in case of a normal distribution and a Mann–Whitney U test in case of non-normality.

The course of micronutrient levels during ICU admission was shown graphically. Differences between time points were analysed separately for each micronutrient through mixed model regression analysis, taking into account the within-subjects' correlation. An autoregressive covariance was used, and the model was adjusted for multiple comparisons by Bonferroni correction.

We also evaluated the associations of SOFA-scores, CRP, and micronutrient intakes in the ICU on micronutrient levels during ICU admission. These associations were analysed separately for each micronutrient through mixed model regression analysis, taking into account the within-subjects' correlations. The dependent variable was divided by median split.

IBM SPSS Statistics for Windows, version 25.0 (IBM Corporation, released 2017, Armonk, New York, USA) was used to perform analyses.

3. Results

During the study period, 106 patients were admitted to the ICU, of whom 24 were included according to the in- and exclusion criteria. Besides, 21 volunteers were willing to participate in the control group; three were excluded because of vitamin supplement intake in the past 14 days.

Baseline characteristics are shown in Table 1. Full baseline laboratory results are shown in supplement B. The median ages were 65.5 and 66.0 years in the patient and control groups, respectively. Most patients and controls were male (66.7% and 54.6%). In the ICU group, median SOFA and APACHE II scores were 7 and 20, respectively. Twelve patients were admitted because of medical reasons (50%) and twelve because of emergency or (complicated) elective surgery (50%). The in-hospital mortality was 37.5%.

3.1. Primary outcome

Baseline micronutrient levels in ICU patients and controls are shown in Table 2. Selenium, β-carotene, vitamin C and vitamin E levels were significantly lower in ICU patients than in controls ($p < 0.001$). Vitamin B_1 and B_6 levels were not significantly different in ICU patients and controls.

3.2. Course of micronutrient levels during ICU admission

Micronutrient levels during the first week of ICU admission are shown in Fig. 1A and F. Selenium levels remained stable and low. β-carotene levels remained below normal values but increased significantly on day 7 ($p < 0.01$). Vitamin C levels remained below normal values and dropped significantly from day 1 until day 5 ($p < 0.01$) of ICU admission. Vitamin E levels remained within normal values and increased significantly on days 5–7 ($p < 0.01$). Vitamin B_1 and vitamin B_6 levels remain stable and within the normal range.

Table 2
Baseline micronutrient levels in ICU patients and controls.

Micronutrient	ICU	Controls	p-value
Selenium (μmol/l)	0.52 ± 0.20	0.90 ± 0.16	<0.0001
β-Carotene (μmol/l)	0.17 [0.08–0.26]	0.50 [0.25–0.57]	<0.0001
Vitamin C (μmol/l)	21.5 [8.5–32.0]	45 [28.8–64.8]	0.001
Vitamin E (μmol/l)	20.3 ± 8.3	35.5 ± 8.3	
Vitamin B_1 (nmol/l)	130 [107–169]	122 [105–132]	0.383
Vitamin B_6 (nmol/l)	41 [37–56]	44 [41–61]	0.497

Abbreviations: ICU: intensive care unit.
Note: Results are depicted as mean ± standard deviation or median [interquartile range] as appropriate.

3.3. Effect of severity of illness on micronutrient levels

Severity of illness was assessed through daily SOFA scores (Fig. 2). No significant associations were found between micronutrient levels and SOFA scores (selenium $p = 0.562$, β-carotene $p = 0.155$, vitamin C $p = 0.528$, vitamin E $p = 0.044$).

3.4. Effect of CRP on micronutrient levels

CRP levels during ICU admission are shown in Fig. 3. No significant associations between micronutrient levels and CRP were found (selenium $p = 0.400$, β-carotene $p = 0.377$, vitamin C $p = 0.064$, vitamin E $p = 0.552$).

Table 1
Baseline characteristics.

		ICU patients (n = 24)	Controls (n = 18)
Gender (female)	N (%)	8 (33.3)	8 (44.4)
Age (years)	Median [IQR]	65.5 [62.5–71.8]	66 [61–72]
BMI on admission (kg/m2)	Median [IQR]	25.1 [22.0–26.9]	25.4 [24.1–29.3]
Malnourished (<18.5)		1 (4.2)	0 (0)
Normal (18.5–24.9)		10 (41.7)	7 (38.9)
Overweight (25–29.9)		11 (45.8)	9 (50.0)
Obese (30–34.9)		2 (8.3)	2 (11.1)
Morbidly obese (>35)		0 (0)	0 (0)
Admission type			
Medical		12 (50.0)	NA
	N (%)	12 (50.0)	NA
Surgical	N (%)		
Smoking status (yes)	N (%)	10 (45.5)*	2 (11.1)
Alcohol consumption (yes)	N (%)	13 (61.9)*	15 (83.3)
Nutrition in ICU			
Enteral nutrition	N (%)	22 (91.7)	NA
Parenteral nutrition	N (%)	0 (0)	NA
No nutrition	N (%)	2 (8.3)	NA
SOFA score on admission	Median [IQR]	7 [4–9.75]	NA
APACHE II score on admission	Median [IQR]	20 [15.8–28.5]	NA
In-hospital mortality	N (%)	9 (37.5)	NA
Mechanical ventilation	N (%)	24 (100)	NA
ICU length of stay	Median [IQR]	5 [3–13]	NA

Abbreviations: ICU: intensive care unit; IQR: interquartile range; n: number; SD: standard deviation; SOFA: sequential organ failure assessment; APACHE: Acute Physiology And Chronic Health Evaluation; NA: not applicable.

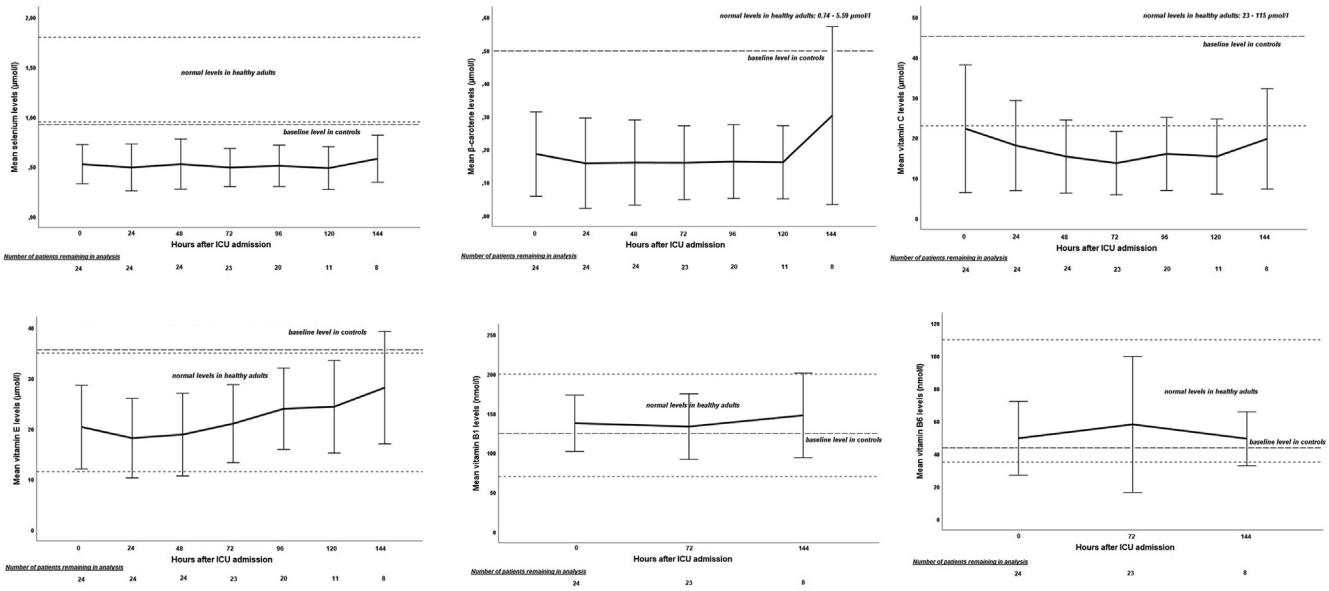

Fig. 1. Mean micronutrient levels during ICU admission. A. Mean selenium levels during ICU admission. B. Mean β-carotene levels during ICU admission. C. Mean vitamin C levels during ICU admission. D. Mean vitamin E levels during ICU admission. E. Mean vitamin B_1 levels during ICU admission. F. Mean vitamin B_6 levels during ICU admission. Abbreviations: ICU: intensive care unit. Note: error bars represent ± one standard deviation.

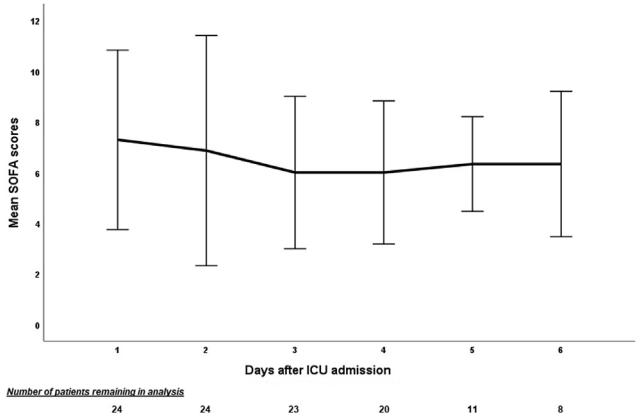

Fig. 2. Mean SOFA scores during ICU admission. Abbreviations: SOFA: sequential organ failure assessment.

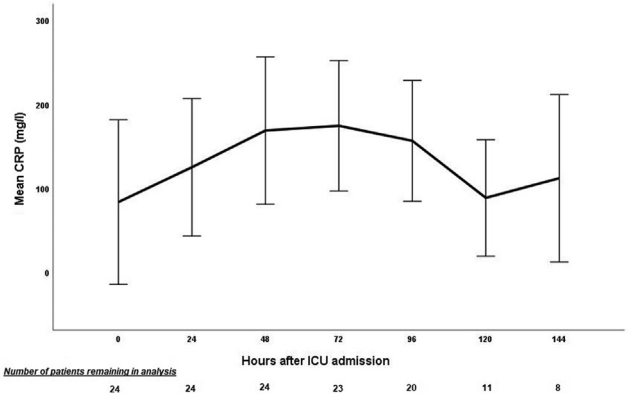

Fig. 3. Mean CRP levels during ICU admission.

3.5. *Effect of micronutrient intake in the ICU on micronutrient levels*

Micronutrient intake during ICU admission is shown in fig. 4A and F. The micronutrients were part of standard enteral nutrition (no additional supplements were used during the study period). No associations between individual micronutrient intake and blood micronutrient concentrations were observed over time (selenium $p = 0.621$, β-carotene $p = 0.708$, vitamin C $p = 0.255$, vitamin E $p = 0.792$, vitamin B1 $p = 0.694$, vitamin B6 $p = 0.964$).

4. Discussion

We prospectively studied micronutrient blood levels in 24 critically ill adults and compared those with micronutrient levels in 21 healthy age-matched controls (Table 2). The micronutrient levels of selenium, β-carotene, vitamin C and vitamin E were significantly lower in ICU patients than in healthy controls. Vitamin B_1 and B_6 levels were within normal range and not significantly different between the patient and control groups.

Vitamins and trace-elements have numerous essential functions throughout the body, as described in our earlier reviews [1,9]. Therefore, low blood levels may manifest the critical illness (patho) physiology, rather than intake deficiency. Low micronutrient levels in critical illness may be caused by redistribution, altered protein binding, increased losses through bodily fluids (urine, blood, sweat, ascites, pleural fluid), increased metabolic use, and dilution secondary to fluid resuscitation [1].

4.1. *Selenium*

Selenium levels on ICU admission were significantly lower than in healthy controls in this study. Other studies report similar findings [10,11]. The low selenium levels are the result of changes in selenium metabolism in critical illness. Selenium and selenoproteins are redistributed to tissues involved in protein synthesis and immune cell proliferation. Capillary leakage and no urinary excretion reduction, despite low serum levels, lead to an additional loss of selenium [1,10]. Selenium supplementation, in low and high

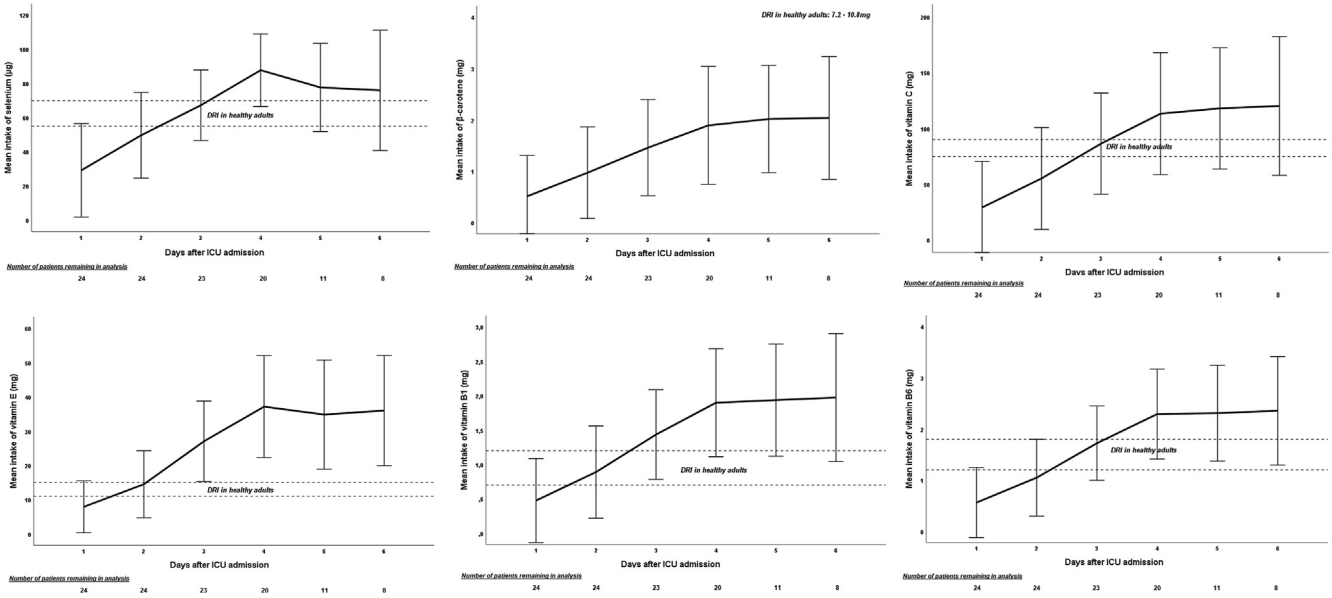

Fig. 4. Mean micronutrient intake during ICU admission. A. Mean selenium intake during ICU admission. B. Mean β-carotene intake during ICU admission. C. Mean vitamin C intake during ICU admission. D. Mean vitamin E intake during ICU admission. E. Mean vitamin B_1 intake during ICU admission. F. Mean vitamin B_6 intake during ICU admission. Abbreviations: DRI: dietary reference intake; ICU: intensive care unit.

dosages, as monotherapy or part of a combination of micronutrients, has been studied in large randomized trials [12,13]. However, no beneficial effects on mortality, ICU length of stay, ventilation duration or infectious complications have been found in these trials nor in a meta-analysis of 21 trials studying selenium supplementation in ICU [14].

Mean selenium levels in healthy controls in this study are also lower than the international reference range for selenium, and this is per other studies of selenium status in the Dutch population [5].

4.2. β-carotene

β-Carotene levels were relatively low in this study with a mean of 0.17 μmol/l in critically ill patients and 0.50 μmol/l in healthy controls. The normal range of β-carotene serum levels has been reported to be 0.04–2.26 μmol/l [15].

Low levels of β-carotene have been earlier reported in patients with ARDS (mean 0.08 μmol/l vs 1.22 μmol/l in healthy controls [16]). The conversion of carotenoids to retinol is increased in patients with vitamin A deficiency; so low plasma values may indicate real vitamin A deficiency [17]. In addition, vitamin A metabolism is altered in critical illness; significant amounts of retinol and retinol-binding protein are excreted in urine (while it usually is mainly excreted in bile) [1]. Stephensen et al. reported 33% of patients with acute infection excreted >50% of the DRI of vitamin A [18]. Few studies have been performed on vitamin A supplementation (monotherapy), one study by Matos et al. showed a reduction in mortality and ICU length of stay [19].

4.3. Vitamin C

We found a significant decline in vitamin C levels during the first four days of ICU admission. This is in accordance with other studies reporting a rapid decline in vitamin C levels after initial injury [20,21].

Vitamin C supplementation has been studied in large trials, both as single interventions and combined with other vitamins and steroids [22,23]. In the Metaplus trial, enteral supplementation of vitamin C did not lead to normalization of plasma levels [23]. However, high dose intravenous supplementation (up to 200 mg/kg/day) has shown to increase plasma levels to normal and supranormal levels in a small phase I trial [24]. . More importantly, no improvements in significant clinical endpoints have been reported in recent randomised trials [22–25].

4.4. Vitamin E

Vitamin E levels remain within normal range; however, are significantly lower than in healthy controls in this study. A decrease in vitamin E serum levels has been frequently reported in critically ill patients [1,26]. However, when standardised for serum lipids changes, no decrease or even an increase in vitamin E levels was found [27]. Concurrent with these findings, we observed an increase in vitamin E levels during the first week of ICU admission.

4.5. Vitamin B_1

The incidence of thiamin deficiency in critically ill patients is supposedly 10–30% [9,28–30]. However, none of the patients included in our study, nor the healthy controls, had any sample with a thiamin level below the normal value (<70 nmol/l). A lower mortality rate has been reported in ICU patients with severe thiamine deficiency (<7 nmol/l) receiving thiamin supplementation. In patients with no deficiency, no benefit of thiamin has been shown [28].

4.6. Vitamin B_6

Only one previous study has investigated vitamin B_6 intake and status in critically ill patients [31]. Vitamin B_6 levels were measured prospectively in 94 critically ill patients on day 1 and 14 of ICU admission. In accordance with our findings, the authors of this study found vitamin B_6 status to be within normal values on ICU admission (42 nmol/l). However, a significantly lower vitamin B_6 level was found on day 14 than on day 1, although intake was high and even increased during ICU admission (>10× DRI). Also, urinary

excretion of vitamin B_6 was significantly higher on day 14, although blood levels were lower. We found no significant change in vitamin B_6 levels during the first week of ICU admission in this study, but we have no measurements after 14 days. Our findings may thus not be contradictory, as vitamin B_6 levels may decline only after the first week of ICU admission.

4.7. Inflammation, the severity of illness and micronutrient levels

We observed no associations between CRP nor SOFA scores and micronutrient levels in this study. However, previous studies on vitamin C supplementation show low plasma concentrations associated with severity of illness, inflammation and mortality [1,21]. Also, selenium levels were negatively correlated with CRP [32] and associated with mortality, organ failure and sepsis severity scores in other studies. Our measurements may have been too early to see an effect of declining inflammation (as CRP and SOFA scores were still high at the end of the study). In addition, our study was not primarily powered for these analyses. Therefore the study population may have been too small to observe such an effect.

No previous studies have investigated the association between CRP nor severity of illness and vitamin E or β-carotene levels.

4.8. Micronutrient intake and micronutrient levels

We observed no associations between micronutrient intake and micronutrient levels during ICU admission. It is possible that the micronutrient intake from EN in this study was too limited to influence actual serum micronutrient levels in ICU patients (i.e., the daily dose of micronutrients is too low to normalise levels). However, multiple studies with high dose micronutrient supplementation have also been unable to normalise micronutrient blood levels [22,31]. This may indicate that micronutrient blood levels are mainly influenced by other processes (i.e., increased metabolic use, redistribution, increased losses), and intake may play a minor role [1].

4.9. Strengths and weaknesses

Micronutrient status of critically ill patients was compared with healthy age-matched controls from the same geographical area. As micronutrient levels in healthy adults decline with age and differ widely between geographical regions, matching patients accordingly reduces the risk of falsely interpreting micronutrient levels in ICU patients as (ab)normal.

We were also able to show the course of micronutrient levels during the first week of ICU admission in the absence of supplementation. This “natural” course has not been extensively investigated before.

However, our study has several limitations. The study population was small and from a single-centre, resulting in low statistical power for our secondary analysis. Therefore, this study should be seen as a hypothesis generating study. Secondly, vitamin E levels were not standardised for serum lipid status. As serum triglyceride levels were lower in patients on ICU admission than in controls, the significant difference between mean vitamin E levels may be (partially) explained by this. Finally, the study was performed in 2002 thus indicating a long delay in manuscript preparation. Recently, the relevance of the data was reconsidered as this study was performed without additional micronutrient supplements and therefore shows the “natural course” of micronutrient concentrations in ICU patients. Nowadays, as many ICUs use additional micronutrients this study would be hard to perform in 2021. We do not think the delay has influenced the validity of our results.

5. Conclusion

Patients already showed lower plasma levels of selenium, β-carotene, Vitamin C and Vitamin E than healthy controls on ICU admission. Vitamin C levels dropped significantly during the first days of ICU admission, while β-carotene and vitamin E levels increased after 5–7 days. Selenium levels remained stable. Vitamin B_1 and B_6 levels on ICU admission were comparable with healthy age-matched controls and remained stable. No associations between micronutrient levels and severity of illness, CRP or micronutrient intake were found. Progressive enteral tube feeding containing vitamins and trace elements does not normalize plasma levels in the first week of ICU stay. When treatment objectives are to normalise plasma concentrations of the studied micronutrients only tube feeding is not sufficient and pharmacological supplementation should be considered.

Statement of authorship

Dr. Van Zanten had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and designing: Van Zanten, Hettinga, de Vries.

Acquisition of data: Hettinga.

Statistical analysis and interpretation of data: Koekkoek, Van Zanten.

Drafting the manuscript: Koekkoek.

Critical revision of the manuscript for important intellectual content: Koekkoek, Van Zanten, Hettinga, De Vries.

Study supervision: Van Zanten.

Conflict of interest statement and funding sources

Prof. Dr. Van Zanten reported having received honoraria for advisory board meetings, lectures, research, and travel expenses from Abbott, Baxter, BBraun, Cardinal Health, Danone-Nutricia, Fresenius Kabi, Mermaid, Lyric, and Nestlé-Novartis. Inclusion fees for patients in clinical trials were paid to the local ICU research foundation. The remaining authors have disclosed that they do not have any conflicts of interest. There was no funding source for this work.

Acknowledgements

Roel van Vugt, Olga Souverein (statistical considerations), Gerbrich Folkersma, Ben de Jong.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.05.003.

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