Nutrition 45 (2018) 85–89

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Zinc and selenium status in critically ill patients according to severity stratification

Marina Augusta Cirino Ruocco M.Sc. [a,b,*], Evelin Drociunas Pacheco Cechinatti M.D. [b], Fernando Barbosa Jr. Ph.D. [c], Anderson Marliere Navarro Ph.D. [a,d]

[a] Department of Foods and Nutrition – Faculty of Pharmaceutical Sciences, São Paulo State University – UNESP, São Paulo, Brazil
[b] Américo Brasiliense State Hospital, São Paulo, Brazil
[c] Department of Clinical and Toxicological Analyses and Bromatology, Faculty of Pharmaceutical Sciences of Ribeirão Preto – University of São Paulo – FCRP/USP, São Paulo, Brazil
[d] Ribeirão Preto Medical School, University of São Paulo – USP, São Paulo, Brazil

ARTICLE INFO

Article history:
Received 2 February 2017
Accepted 20 July 2017

Keywords:
Zinc
Selenium
SAPS III
Critically ill

ABSTRACT

Objective: The aim of this study was to evaluate the concentrations of zinc and selenium in different biological materials and to associate them with the clinical severity score according to the Simplified Acute Physiology Score (SAPS) III.

Methods: The study was conducted in a 10-bed general intensive care unit of the Américo Brasiliense State Hospital/SP, with 95 patients stratified by the SAPS III score cutoff points (63.5 points) as less or more severe and by the diagnosis of sepsis. Analyses of zinc and selenium concentrations in plasma, erythrocytes, and urine were conducted.

Results: Plasma concentrations were found to be lower than the reference values for both micronutrients (8.4 ± 4 and 0.18 ± 0.06 μmol/L, respectively, for zinc and selenium), and urinary zinc concentration was higher than the reference (38.6 ± 35.8 μmol/24 h). The mean selenium plasma concentration was significantly lower in patients with greater severity, which was not observed for zinc ($P > 0.05$). The mean selenium plasma and erythrocyte concentrations were significantly different between the groups diagnosed with sepsis, which was not observed in the analysis of zinc. Albumin levels ($r = -0.26$; $P = 0.01$) and C-reactive protein ($r = 0.40$; $P < 0.001$) correlated with the SAPS III severity score.

Conclusion: Plasma concentrations of zinc and selenium are low in critically ill patients upon admission to the intensive care unit and may make these patients more susceptible to oxidative stress. The low concentration of erythrocyte selenium may represent an inadequate intake by this population. Additional studies using new biomarkers should be performed with the objective of identifying values for the local population.

Introduction

The importance of the role of micronutrients in critically ill patients is well documented [1,2]. Low zinc concentrations have been reported in patients admitted to the intensive care unit (ICU) [3], and plasma selenium levels are commonly decreased in critically ill patients for various reasons [4,5].

With regard to zinc, the evaluation of nutritional status may include the measurement of food consumption, plasma, erythrocyte and urinary zinc concentrations, and functional indicators such as analysis of the activity of metalloenzymes (carbonic anhydrase, alkaline phosphatase, and carboxypeptidase [6]), but these markers can be difficult to evaluate or interpret [7]. Plasma zinc currently is the most used and accepted nutritional status marker despite weak sensitivity and imperfect specificity [8].

Selenium nutritional status is commonly evaluated directly by measurement of its plasma concentration or indirectly by measuring glutathione peroxidase activity in whole blood, erythrocytes, and plasma [9]. Recent studies have analyzed promising biomarkers, such as selenoprotein-P [10], which accounts for 50% of the selenium in the blood.

Plasma selenium, although not generally considered an ideal biomarker of selenium status, is the most widely used in the

* Corresponding author. Tel./fax: +55-16-339-37800.
E-mail address: macruocco@heab.fmrp.usp.br (M. A. Cirino Ruocco).

http://dx.doi.org/10.1016/j.nut.2017.07.009
0899-9007/

literature. It has been proposed that in the presence of the systemic inflammatory response, erythrocyte selenium, which is not affected by the acute response and presents a technically robust analysis, is the preferred marker for assessing deficiency and toxicity [9].

From these analyses, the concentrations of zinc and selenium can be correlated with clinical outcomes. Some studies have associated their concentrations with the severity scores of instruments used to predict mortality [3,11].

The Simplified Acute Physiology Score (SAPS) III is the latest scoring system to be published and has particular characteristics, such as data collection in the first hour before or after admission to the ICU and custom equations for different geographic areas [12], that have made its use recommended by the Brazilian Association of Intensive Medicine. The SAPS III score has been shown to exhibit good discrimination, calibration, and best fit [12].

Despite a well-documented association between low levels of zinc and selenium in critically ill patients, studies assessing the concentrations of these micronutrients associated with the outcome, according to severity score from the SAPS III criterion, are scarce. Therefore, the aim of this study was to evaluate the concentrations of zinc and selenium in different biological materials and to associate them to the SAPS III.

Materials and methods

This was a cross-sectional study conducted in a 10-bed general ICU at the Américo Brasiliense State Hospital/SP/Brazil (HEAB). A total of 185 patients were hospitalized between April and September 2014.

The SAPS III score was calculated for all patients admitted to the ICU, excluding those according to the criteria (age less than 18 years, hospitalizations less than 12 hours and readmissions) adopted by the SAPS III researchers in their study [12]. Patients who were <18 y of age, with anuria, and those diagnosed with acute or chronic renal failure on dialysis were excluded (Fig. 1). Patients who had undergone red cell transfusion also were excluded from the study. Considering the exclusion criteria, 95 patients were selected.

The sepsis status of all patients was prospectively classified using the criteria from the American College of Chest Physician/Society of Critical Care Medicine consensus conference [13].

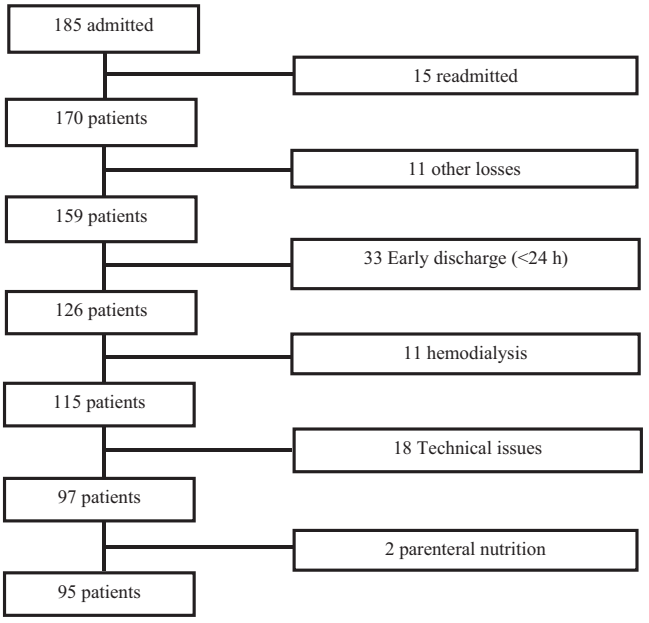

Fig. 1. Flowchart of the selection of the patients, considering the exclusion criteria.

Subsequently, patients were divided into groups according to the SAPS III scoring system and the diagnosis of sepsis. For each group of patients, the plasma, erythrocyte, and urine concentrations of zinc and selenium and laboratory tests (urea, creatinine, C-reactive protein [CRP], albumin) were evaluated. These samples were collected up to 48 h after admission to the ICU.

Severity score

The SAPS III was used to predict the severity of patients admitted to the ICU. The SAPS III score includes 20 variables divided into three subscores related to patient characteristics before admission, the circumstance of the admission, and the degree of physiological derangement within 1 h before or after ICU admission. The total score can range from 0 to 217. SAPS III includes customized equations for prediction of hospital mortality in seven geographic regions: Australasia; Central, South America; Central, Western Europe; Eastern Europe; North Europe; Southern Europe; Mediterranean; and North America. The prognostic performance of the different scores was evaluated in terms of calibration and discrimination. The SAPS III score has been shown to exhibit good discrimination, calibration, and best fit [12].

In the present study, these data were collected in the first hour before or after admission to the ICU and the probability of death given by the SAPS III was calculated using the general formula and using the customized formula for Central and South America [14]. The patients were monitored until hospital discharge or death.

In the first part of the study [15], the SAPS III scoring system was validated for this population (area under receiver operating characteristic = 0.83; $\chi^2 = 4.30$; $P = 0.84$) and produced a cutoff of 63.5 points for the classification of severity. This value was used to stratify patients more or less severe.

Biochemical parameters

The admission laboratory tests requested were hematology, electrolytes, renal function, CRP, total protein, and albumin, performed using Labtest kits. The reference value of 4.5 to 11 $\times 10^9$/L was considered for leukocytes, 35 to 55 g/L for albumin, and <6 mg/L for CRP. Regarding renal function, urea of 2.5 to 7.5 mmol/L and creatinine of 50 to 110 μmol/L were considered.

Biological material

Collection and processing of the samples

The venous blood was collected in tubes containing EDTA. The samples were centrifuged (3500*g*, 10 min) to separate the whole blood and obtain plasma and erythrocytes immediately after collection. The samples were stored at −80°C until time of analysis.

Urine samples were collected over 24 h. The volume was measured and an aliquot stored at −20°C for later analysis.

Concentration of minerals

The determination of the concentration of the trace element in the plasma, erythrocytes, and urine was performed using a mass spectrometer with inductively coupled plasma, equipped with a reaction cell (DRC-ICP modelo ELAN DRC II, PERKIN ELMER Sciex, Norwalk, CT, USA), operating with high-purity argon (99.999%, Praxair, Brazil). All samples were diluted in the ratio 1:50 with a solution containing Triton X-100 0.01% (v/v), HNO_3 0.05% (v/v), and 10 mg/L-1 rhodium as an internal standard. The concentration of the analytical calibration standards ranged from 0 to 50 g/L.

Statistical analysis

Comparisons between groups according to SAPS III severity score and sepsis diagnosis, were performed using the Mann–Whitney test. The correlations of age and of the SAPS III score with plasma concentrations of zinc and selenium, albumin, and CRP were performed using Spearman's coefficient. The χ^2 test was used to evaluate the association between severity according to the SAPS III score and the nutritional diagnosis. Significance was considered at $P < 0.05$.

Ethical statement

The study was approved by the Research Committee Ethics (SMS/SP authorization No. 074351/2013).

Results

We enrolled 95 patients in the study. Table 1 presents the characteristics of the study sample. The sample predominantly

Table 1
Characteristics of study patients (N = 95)*

Characteristics	n (%)	Median (range)
Age (y)		65 (17–97)
Sex		
Male	50 (52.6)	
Female	45 (47.4)	
Reason admission (ICD)		
Respiratory	49 (51.6)	
Postoperative	23 (24.2)	
Cardiovascular	7 (7.4)	
Neurologic	8 (8.4)	
Infection	7 (7.4)	
Digestive	1 (1)	
Severe sepsis or septic shock	29 (30.5)	
Hospitalization before ICU (d)		1 (0–103)
ICU stay (d)		8 (1–81)
Clinical outcome		
Discharge	49 (51.6)	
Death	42 (44.2)	
Transferred	3 (3.2)	
Still in the hospital	1 (1)	
SAPS III (point)		61 (23–88)

ICD, International Classification of Diseases; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score
* Patients hospitalized between April and September 2014.

consisted of older adults; however, age was not related to plasma concentrations of zinc ($r = -0.04$; $P = 0.67$) or selenium ($r = 0.04$; $P = 0.69$). The main reason for hospitalization was respiratory problems due to acute respiratory failure and pneumonia. The most prevalent (41.05%) body mass index, according to the World Health Organization classification [16], was eutrophic (18.5–24.9 kg/m^2), with no association found between the nutritional diagnosis and the SAPS III score classification ($P = 0.68$).

The median of the SAPS III score was close to the cutoff calculated for this population. Of the patients with SAPS III >63.5 points, 77.8% died; of those with a score <63.5 points, 16.8% died.

Plasma zinc levels were not associated with the SAPS III score ($P > 0.05$); however, the concentrations of selenium were inversely correlated with SAPS III score ($r = -0.21$; $P = 0.04$; Fig. 2).

Table 2
Determination of zinc and selenium values in all patients (N = 95)

Biological material	Mean	SD	Reference value
Plasma zinc (μmol/L)	8.4	4.0	12–18*
Erythrocyte zinc (μmol/L)	0.13	0.39	1.5–2.1†
Urine zinc (μmol/24 h)	38.6	35.8	4.5–18†
Plasma selenium (μmol/L)	0.18	0.06	0.9–2.0*
Erythrocyte selenium (μmol/L)	0.90	0.35	1.1–2.4‡
Urine selenium (μmol/24 h)	0.46	0.4	–

* See Ghashut et al. [17].
† See Lima et al. [18].
‡ See Cardoso et al. [19].

Plasma zinc and selenium concentrations were below the lower limit of the reference interval for the healthy population (Table 2) in 84.2% and 100% of the patients, respectively. Erythrocyte selenium content below the lower level of the reference range (Table 2) was observed in 82.6% of the patients.

For the groups formed by severity according to the SAPS III score, 39 of the 95 patients were considered more severe, with significantly lower selenium plasma concentrations, worse kidney function ($P < 0.05$), and significantly higher CRP mean values (Table 3).

A diagnosis of sepsis was given in 29 of the 95 patients. Mean concentrations of plasma and erythrocyte selenium were significantly different between the groups, as were the urea, CRP, and albumin concentrations (Table 4).

Albumin and CRP levels ($r = 0.40$; $P < 0.001$) correlated with the SAPS III severity score, with albumin being negatively correlated ($r = -0.26$; $P = 0.01$).

Plasma concentrations of selenium and zinc correlated with albumin ($r = 0.41$; $P < 0.0001$ and $r = 0.22$; $P = 0.03$, respectively). Plasma concentrations of selenium were negatively associated with CRP ($r = -0.28$; $P < 0.01$), which was not observed for zinc ($P > 0.05$).

Discussion

In the present study, low plasma concentrations of zinc were observed in all patients, as well as high urinary excretion

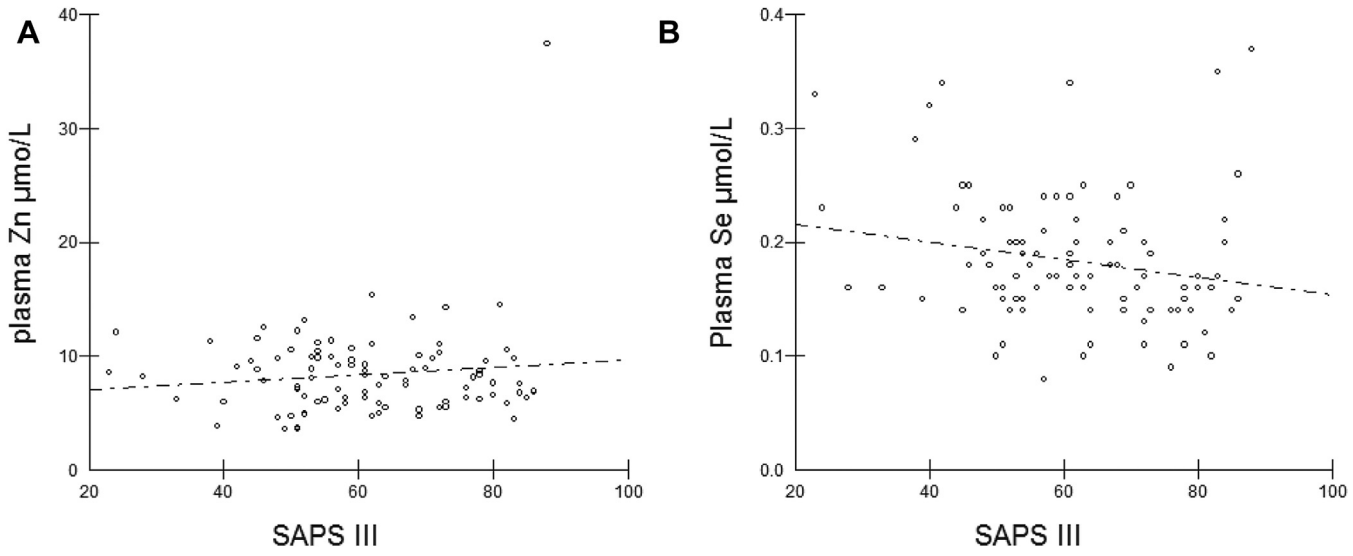

Fig. 2. (A) Relation between plasma zinc and SAPS III ($r = -0.01$; $P = 0.90$); (B) Relation between plasma selenium and SAPS III ($r = -0.21$; $P = 0.04$). SAPS III, Simplified Acute Physiology Score; Se, selenium; Zn, zinc.

Table 3
Comparison of patients according to SAPS III severity score in relation to the concentrations of the minerals and laboratory tests

Variable	SAPS III				*P*-value
	<63.5 (n = 56)		>63.5 (n = 39)		
	Mean	SE	Mean	SE	
Plasma zinc (μmol/L)	8.1	2.7	8.8	5.3	0.92
Erythrocyte zinc (μmol/L)	1.6	0.34	1.74	0.45	0.13
Urine zinc (μmol/24 h)	43.8	42.9	31.2	20.7	0.13
Plasma selenium (μmol/L)	0.19	0.06	0.17	0.06	0.02
Erythrocyte selenium (μmol/L)	0.9	0.34	0.89	0.36	0.75
Urine selenium (μmol/24 h)	0.6	0.4	0.4	0.3	0.12
Leukocytes ($\times 10^9$/L)	25.6	50.4	24.5	42.5	0.73
Urea (mmol/L)	8.7	6.5	12.3	5.2	<0.01
Creatinine (μmol/L)	86.6	43.3	139.7	84.0	<0.01
CRP (mg/L)	69.8	56.5	102.5	49.3	<0.01
Albumin (g/L)	28.8	7.1	26.5	5.4	0.12

CRP, C-reactive protein; SAPS III, Simplified Acute Physiology Score
The comparison between the groups was performed using the Mann–Whitney test, $\alpha = 0.05$

associated with the initial inflammatory response. The decrease in total serum zinc in response to systemic inflammation previously was observed in the context of sepsis, surgical stress, and severe trauma [11,20]. However, there was no significant difference when patients were analyzed according to the presence of sepsis. It has been shown that zinc is redistributed from tissues, particularly to the liver, where it is necessary for the synthesis of acute-phase proteins [21], neutralization of reactive oxygen and nitrogen species, and prevention of microbial invasion [22].

In relation to selenium plasma concentrations, all patients presented levels below normal. Levels were significantly lower in the septic patients, in agreement with other studies [23,24].

Patients with severe sepsis or systemic inflammatory response syndrome have demonstrated decreases in plasma selenium concentrations that could be associated with a reduction in antioxidant defenses [25]. Manzanares et al. showed that a lower level of serum selenium after ICU admission was a predictor of systemic inflammatory response syndrome [26] and Sakr et al. showed that, in critically ill surgical patients, plasma selenium concentrations were generally low and were associated with greater tissue damage and increased ICU mortality [4].

The mean erythrocyte zinc concentrations were normal, whereas selenium presented lower values compared with the reference values. Erythrocyte selenium concentration was not affected by the inflammatory response [9] and in this study might reflect an inadequate intake before the hospitalization. There is considerable variation in the intake of this micronutrient in different parts of the world. Some studies conducted in Brazil have demonstrated that variations in the mineral content of the soil have a direct effect on the dietary intake of selenium. Considering these results, it can be assumed that the Brazilian population is susceptible to selenium deficiency [27]. In a recently published Brazilian study [28], conducted with healthy adults, mean plasma selenium and erythrocyte selenium values were 53.2 (0.67 μmol/L) and 53.3 μg/L (0.67 μmol/L), respectively. These results suggest that these healthy Brazilians present a marginally inadequate selenium status. Selenium urine concentration in critically ill patients is rarely measured. The lack of consistency between the units used for the measurements (e.g., urinary selenium measured either in μmol/d or in μmol/g creatinine) makes it difficult to compare the existing data [10]. In the present study, low urinary selenium excretion was observed in patients with sepsis, as previously observed by Angstwurm and co-workers [29]. However, according to references used by the same author, the values are within the reference values (in 24-h urine samples 0.02–0.79 μmol/L).

Table 4
Comparison of patients according to sepsis diagnosis in relation to the concentrations of the minerals and laboratory tests

Variable	Sepsis				*P*-value
	No (n = 66)		Yes (n = 29)		
	Mean	SE	Mean	SE	
Plasma zinc (μmol/L)	8.3	2.6	8.7	6.1	0.32
Erythrocyte zinc (μmol/L)	1.69	0.35	1.60	0.48	0.46
Urine zinc (μmol/24 h)	40.6	40.8	34.1	20.6	0.86
Plasma selenium (μmol/L)	0.19	0.05	0.17	0.07	0.02
Erythrocyte selenium (μmol/L)	0.92	0.33	0.84	0.39	0.05
Urine selenium (μmol/24 h)	0.46	0.4	0.46	0.3	0.68
Leukocytes ($\times 10^9$/L)	29.8	55.7	14.5	8.1	0.90
Urea (mmol/L)	9.0	5.61	12.9	6.9	0.001
Creatinine (μmol/L)	102.5	68.9	121.1	66.3	0.09
CRP (mg/L)	72.3	56.2	108.1	47.2	<0.01
Albumin (g/L)	29.3	6.8	24.4	4.2	<0.01

CRP, C-reactive protein.
The comparison between the groups was performed using the Mann–Whitney test, $\alpha = 0.05$

Numerous studies have shown that the initial stress response results in increased urinary excretion of zinc [30], regardless of its intake, which indicates that the zinc homeostasis control mechanisms may be impaired [23]. A recent study with experimental models also observed an increase in the urinary excretion of zinc in the early inflammatory response, which declined over time [31].

It has been reported that in both infected and uninfected patients evaluated after ICU admission, low plasma concentrations of zinc [11] and selenium [25] are associated with high severity scores. This study found that in patients classified as more severe by the SAPS III scoring system, only plasma selenium values were lower.

It was observed that although there was no significant correlation between clinical severity and albumin concentrations, the mean values were below normal and were significantly lower in the septic patients. Studies show that low serum albumin levels are associated with an increase in hospital complications, length of hospitalization, and hospital mortality [32,33].

The plasma concentrations of zinc in the presence of hypoalbuminemia should be interpreted with caution [34]. Additionally, Duncan et al. [35] recommend that the clinical interpretation of plasma micronutrients be made considering the concentration of CRP because of its effect on plasma concentrations of a variety of micronutrients. The association of plasma concentrations of zinc and selenium with the concentrations of CRP and albumin has been evaluated in recent studies, suggesting that patients with low plasma zinc and selenium who have concentrations of albumin and CRP within normal limits can be susceptible to deficiency [17]. This same author showed that plasma concentrations of zinc and selenium are associated with CRP and albumin, which also was observed in the present study, although only for albumin in relation to zinc.

Among the limitations of the study, obtaining urine over 24 h required care to avoid losses and inadequate collection. This makes the measurement of the urinary concentration of zinc and selenium a less useful parameter. Even in ICU patients who have diuresis collection bags, complete collection is difficult because the collection is performed during each shift by several nursing technicians. In the present study, there was a risk of contamination if inadequate tools were used to transfer the diuresis into the collection bottle. Furthermore, when the zinc and selenium

values were corrected for urinary creatinine over 24 h, the occurrence of a reduction in urinary filtration rate with age was suggested. A new measurement of plasma selenium at another time during hospitalization would confirm whether patients had lower values previously.

New biomarkers, such as selenoprotein-P, a marker for septic shock and for endothelium protection, need to be studied further [36]. Hoeger et al. [31] identified free serum zinc and zinc-binding capacity as promising tools for diagnosing the initial stages of sepsis and for developing controlled zinc supplementation strategies in septic patients. However, further research is needed to evaluate potential biomarkers and to assess the limitations of their applicability in different populations.

Conclusions

Changes in the plasma concentrations of zinc and selenium are common in critically ill patients after admission to the ICU. Previous selenium deficiency, suggested by low erythrocyte selenium concentration, may further favor plasma selenium lowering observed in severe ICU and especially septic ICU patients.

Low selenium status should be carefully considered because it can be influenced by the great variability between countries. Additional studies using new biomarkers should be performed with the objective of identifying values for the local population.

References

[1] Manzanares W, Hardy G. Suplementacion con selenio en el paciente critico: aspectos farmacologicos y evidencia actual [Selenium supplementation in critical patient: pharmacological aspects and current evidence]. Nutr Hosp 2009;24:429–36.

[2] Heyland DK, Jones N, Cvijanovich NZ, Wong H. Zinc supplementation in critically ill patients: a key pharmaconutrient? JPEN J Parenter Enteral Nutr 2008;32:509–19.

[3] Cander B, Dundar ZD, Gul M, Girisgin S. Prognostic value of serum zinc levels in critically ill patients. J Crit Care 2011;26:42–6.

[4] Sakr Y, Reinhart K, Bloos F, Marx G, Russwurm S, Bauer M, et al. Time course and relationship between plasma selenium concentrations, systemic inflammatory response, sepsis and multiorgan failure. Br J Anaesth 2007;98:775–84.

[5] Salama A, Sakr Y, Reinhart K. The role of selenium in critical illness: basic science and clinical implications. Indian J Crit Care Med 2007;11:127–38.

[6] Marreiro DN, Fisberg M, Cozzolino SMF. Considerações sobre o estado nutricional relativo ao zinco na obesidade. Cad Nutr 1998;6:31–40.

[7] Hambidge M. Human zinc deficiency. J Nutr 2000;130(suppl):1344–9.

[8] Hambidge M. Biomarkers of trace mineral intake and status. J Nutr 2003;3:948–55.

[9] Stefanowicz FA, Talwar D, O'Reilly DS, Dickinson N, Atkinson J, Hursthouse AS, et al. Erythrocyte selenium concentration as a marker of selenium status. Clin Nutr 2013;32:837–42.

[10] Ashton K, Hooper L, Harvey LJ, Hurst R, Casgrain A, Fairweather-Tait SJ. Methods of assessment of selenium status in humans: a systematic review. Am J Clin Nutr 2009;89:2025S–39S.

[11] Besecker BY, Exline MC, Hollyfield J, Phillips G, Disilvestro RA, Wewers MD, et al. A comparison of zinc metabolism, inflammation, and disease severity in critically ill infected and noninfected adults early after intensive care unit admission. Am J Clin Nutr 2011;93:1356–64.

[12] Moreno PG, Metnitz PGH, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3–from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med 2005;31:1345–55.

[13] Members of the American College of Chest Physicians/Society of Critical Care Medicine. Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–73.

[14] Moreno RP, Metnitz PGH. The SAPS 3 outcome research group, 2014. Available at: http://www.saps3.org. Accessed July 28, 2017.

[15] Ruocco MAC. Concentrações de zinco e selênio em pacientes críticos segundo estratificação de gravidade [Concentration of zinc and selenium in critical patients according to severity stratification]. Available at: http://www.fcfar.unesp.br/arquivos/link/20160105171958marina_augusta_cirino_ruocco__me.pdf, Universidade Estadual Paulista, Araraquara, Sao Paulo, Brazil.

[16] World Health Organization. Obesity: preventing and managing the global epidemic. Geneva, Switzerland: WHO; 1997.

[17] Ghashut RA, McMillan DC, Kinsella J, Vasilaki AT, Talwar D, Dincan A. The effect of the systemic inflammatory response on plasma zinc and selenium adjusted for albumin. Clin Nutr 2016;35:381–7.

[18] Lima AS, Cardoso BR, Cozzolino SF. Nutrition status of zinc in children with Down syndrome. Biol Trace Elem Res 2010;133:20–8.

[19] Cardoso BR, Ong TP, Jacob-Filho W, Jaluu O, Freitas MI, Cozzolino SM. Nutritional status of selenium in Alzheimer's disease patients. Br J Nutr 2010;103:803–6.

[20] Kelly E, Mathew J, Kohler JE. Hemorrhagic shock and surgical stress alter distribution of labile zinc within high- and low-molecular-weight plasma fractions. Shock 2012;38:314–9.

[21] Liuzzi JP, Lichten LA, Rivera S, Blanchard RK, Aydemir TB, Knutson MD, et al. Interleukin-6 regulates the zinc transporter Zip14 in liver and contributes to the hypozincemia of the acute-phase response. Proc Natl Acad Sci U S A 2005;102:6843–8.

[22] Kim S, Watanabe K, Shirahata T, Watarai M. Zinc uptake system (znuA locus) of *Brucella abortus* is essential for intracellular survival and virulence in mice. J Vet Med Sci 2004;66:1059–63.

[23] Mertens K, Lowes DA, Webster NR, Talib J, Hall L, Davies MJ, et al. Low zinc and selenium concentrations in sepsis are associated with oxidative damage and inflammation. Br J Anaesth 2015;114:990–9.

[24] Jang JY, Shim H, Lee SH, Lee JG. Serum selenium and zinc levels in critically ill surgical patients. J Crit Care 2014;29:317.e5–8.

[25] Forceville X, Vitoux D, Gauzit R, Combes A, Lahilaire P, Chappius P. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. Crit Care Med 1998;26:1536–44.

[26] Manzanares W, Biestro A, Galusso F, Torre MH, Manay N, Pittini G, et al. Serum selenium and glutathione peroxidase-3 activity: biomarkers of systemic inflammation in the critically ill? Intensive Care Med 2009;35:882–9.

[27] Cominetti C, Cozzolino SMF. Funções Plenamente Reconhecidas de Nutrientes [Fully recognized functions of nutrients zinc – selenium]. Sao Paulo, Brazil: International Life Sciences Institute of Brazil; 2009.

[28] Donadio JLS, Guerra-Shinohara EM, Rogero MM, Cozzolino SMF. Influence of gender and SNPs in GPX1 gene on biomarkers of selenium status in healthy Brazilians. Nutrients 2016;8:81.

[29] Angstwurm MWA, Engelmann L, Zimmermann T, Lehmann C, Spes CH, Abel P, et al. Selenium in intensive care (SIC): results of a prospectiverandomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med 2007;35:118–26.

[30] Boosalis MG, Solem LD, Cerra FB, Konstantinides F, Ahrenholz DH, McCall JT, et al. Increased urinary zinc excretion after thermal injury. J Lab Clin Med 1991;118:538–45.

[31] Hoeger J, Simon TP, Doemming S, Thiele C, Marx G, Schuerholz T, et al. Alterations in zinc binding capacity, free zinc levels and total serum zinc in a porcine model of sepsis. Biometals 2015;28:693–700.

[32] De Luis DA, Izaola O, Cuellar L, Terroba MC, Cabezas G, Rojo S, et al. Nutritional assessment: predictive variables at hospital admission related with length of stay. Ann Nutr Metab 2006;50:394–8.

[33] Gariballa S, Forster S. Effects of acute-phase response on nutritional status and clinical outcome of hospitalized patients. Nutrition 2006;22:750–7.

[34] Hambidge KM, Krebs NF, Lilly JR, Zerbe GO. Plasma and urine zinc in infants and children with extrahepatic biliary atresia. J Pediatr Gastroenterol Nutr 1987;6:872–7.

[35] Duncan A, Talwar D, McMillan DC, Stefanowicz F. OReilly Denis St. Quantitative data on the magnitude of the systemic inflammatory response and its effect on micronutrient status based on plasma measurements. Am J Clin Nutr 2012;95:64–71.

[36] Forceville X. Effects of high doses of selenium, as sodium selenite, in septic shock patients a placebo-controlled, randomized, double-blind, multicenter phase II study – selenium and sepsis. J Trace Elem Med Biol 2007;S1:62–5.