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Serum zinc and copper in people with COVID-19 and zinc supplementation in parenteral nutrition

Francisco Arrieta M.D., Ph.D. [a,b], Victoria Martinez-Vaello M.D. [a], Nuria Bengoa M.D. [a], Lucía Jiménez-Mendiguchia M.D. [c], Marta Rosillo M.D., Ph.D. [c], Angélica de Pablo M.D. [d], Cristina Voguel M.D. [d], Hilario Martinez-Barros M.D. [e], Rosario Pintor M.D. [e], Amaya Belanger-Quintana M.D., Ph.D. [f], Raquel Mateo M.D. [a], Angel Candela M.D. [d], José I. Botella-Carretero M.D., Ph.D., M.B.A. [a,b,*]

[a] *Department of Endocrinology and Nutrition, Hospital Universitario Ramón y Cajal, Madrid, Spain*
[b] *Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición (CIBERobn) & IRyCIS, Madrid, Spain*
[c] *Department of Biochemistry, Hospital Universitario Ramón y Cajal, Madrid, Spain*
[d] *Department of Anesthesiology, Hospital Universitario Ramón y Cajal, Madrid, Spain*
[e] *Department of Pharmacy, Hospital Universitario Ramón y Cajal, Madrid, Spain*
[f] *Department of Pediatrics, Hospital Universitario Ramón y Cajal, Madrid, Spain*

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ABSTRACT

Objectives: Zinc and copper are important to protect cells from oxidative stress and to enhance immunity. An association between low zinc levels and the severity of acute respiratory distress syndrome has been shown for people with COVID-19. We aimed to study serum zinc and copper concentrations in people with severe COVID-19 and zinc supplementation in parenteral nutrition (PN).
Methods: Thirty-five people with COVID-19 in need of PN were studied in a retrospective design. Serum samples were collected at three time points: at the start of PN, between 3 and 7 d after, and at the end of PN.
Results: Participants were on PN for a mean of 14 d, with a mean (± SD) daily supplemental zinc of 14.8 ± 3.7 mg/d. Serum zinc increased during PN administration from 98.8 ± 22.8 to 114.1 ± 23.3 μg/dL (Wilks' λ = 0.751, $F = 5.459$, $P = 0.009$). Conversely, serum copper did not vary from baseline (107.9 ± 34.2 μg/dL) to the end of the study (104.5 ± 37.4 μg/dL, Wilks' λ = 0.919, $F = 1.453$, $P = 0.248$). Serum zinc within the first week after starting PN and at the end of PN inversely correlated with total hospital stay ($r = -0.413$, $P = 0.014$, and $r = -0.386$, $P = 0.022$, respectively). Participants in critical condition presented lower serum copper ($z = 2.615$, $P = 0.007$). Mortality was not associated with supplemental zinc or with serum zinc or copper concentrations at any time of the study ($P > 0.1$ for all analyses).
Conclusions: Serum zinc concentrations during PN support were inversely associated with length of hospital stay but not with mortality. Serum copper concentrations were lower in participants in critical condition but not associated with prognosis.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the coronavirus disease 2019 (COVID-19) pandemic, which has affected more than 200 million individuals and has been the cause of more than four millio deaths worldwide as of this writing [1]. An important proportion of people with COVID-19 may present severe pneumonia requiring hospital admission, some to an intensive care unit (ICU). In these people, an excessive release of inflammatory cytokines, activation of procoagulating factors, and increased oxidative stress may occur [2]. The disease can then progress to acute

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*Corresponding author. Tel.: 34-91-336-8726.
E-mail address: joseignacio.botella@salud.madrid.org (J.I. Botella-Carretero).

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respiratory distress syndrome and other multiple organ failures such as acute cardiac, liver, or kidney injury [3,4]. In this situation, artificial nutrition may be needed to avoid further malnutrition, either as parenteral nutrition (PN) or as enteral nutrition [5,6].

Apart from macronutrients, several micronutrients are usual components of artificial nutrition, based on average requirements. Among these, some trace elements such as zinc and copper are important to protect cells from oxidative stress, especially in patients in critical care [7]. People who are critically ill develop severe stress and a state that may raise the utilization and metabolic replacement of some of these trace elements, especially zinc, depleting their body reserves [8]. In addition, enzymes dependent on trace elements are of great importance in the antioxidant defense mechanisms to protect cells from reactive oxygen species [9]. Accordingly, low serum levels of zinc and copper have been observed at ICU admission, and those with higher serum concentrations have shown significantly lower mortality [10,11].

Recently, an association between low zinc levels and the severity of acute respiratory distress syndrome has been shown for people with severe COVID-19 [12]. Therefore, given this previous knowledge, we aimed to study serum zinc and copper concentrations in people with severe COVID-19 and zinc supplementation in PN, as well as their associations with inflammatory markers and prognosis.

Materials and methods

Participants

Thirty-five COVID-19 patients in need of PN were studied in a retrospective design. Inclusion criteria were confirmation of COVID-19 by the presence of SARS-CoV-2 in respiratory specimens by real-time polymerase chain reaction in pharyngeal swabs, severe pneumonia requiring high-flow oxygen, the need for artificial nutrition in the form of PN, and available serum samples for zinc and copper measurements. The latter were collected at three time points: at the start of PN, between 3 and 7 d after, and at the end of PN. All participants received our standard treatment protocol for COVID-19, including glucocorticoids, low-molecular-weight heparin, and tocilizumab if indicated.

The study protocol was approved by the institutional ethics committee of our center (study code 147/20) and performed according to the Declaration of Helsinki. Written or verbal informed consent was obtained from all participants.

Artificial nutrition therapy

The composition of artificial nutrition administered to the participants was recorded. PN was delivered through a central line as soon as the participant was hemodynamically stable. Individualized formulae were prepared by the hospital pharmacy, and whenever possible, commercial "ready to use" bags were initially used (Olimel N9, Baxter Ltd., Deerfield, IL, USA). Some participants were started on peripheral PN (Periolimel N9, Baxter Ltd., or Isoplasmal, Braun Medical Inc., Melsungen, Germany).

We aimed at 20 to 25 kcal/kg/d, with a proportion of 3 to 6 g/kg/d for glucose, 1.0 g/kg/d for amino acids, and <1 g/kg/d for lipids, with 7 to 10 g/d of essential fatty acids. Vitamins (Cernevit, Baxter Ltd.) and trace elements (Supliven, Fresenius Kabi, Bad Homburg, Germany) were added by the hospital pharmacy. The latter contains 1.05 mg/mL of zinc chloride. Supplemental zinc was also added to PN bags when needed in the form of zinc sulfate (10 mg in 10-mL vials; Oligozinc, Fresenius Kabi) to maintain serum zinc in the normal range. Mean daily zinc doses were calculated during PN from all parenteral sources. For those participants with stays > 7 d and whenever possible, enteral nutrition was started with a standard fiber-free formulation, and PN gradually tapered as enteral nutrition was tolerated and increased. After PN withdrawal, parenteral zinc supplementation stopped. Therefore, the analysis was restricted to the period of PN administration.

Analytical assays

Serum biochemical variables were measured with an Architect c16000/i2000 analyzer (Abbott Diagnostics, City, UK). Serum copper was analyzed by atomic absorption spectrophotometry (AAnalyst 800, Perkin Elmer, City, CA, USA). Serum zinc was analyzed by a colorimetric method (Sentinel Diagnostics, Milano, Italy). The normal ranges were 60 to 150 μg/dL for zinc and 75 to 150 μg/dL for copper. Immunoanalysis was used to measure C-reactive protein, procalcitonin (Abbott Diagnostics, City, ST, US) and D dimer (Siemens, City, Germany), and interleukin-6 and interleukin-12 by enzyme-linked immunosorbent assay (Invitrogen, City, CA, USA). The intra- and interassay coefficients of variation were below 10%.

Statistical analysis

Sample size was calculated with the online calculator GRANMO 7.12 (https://www.imim.es/ofertadeserveis/software-public/granmo/index.html). To find a mean difference of 15 μg/dL in circulating zinc and copper between baseline levels and at the end of follow-up, with an SD of 25 μg/dL, a minimum sample size of 22 participants was needed for a bilateral contrast, with an α of 0.05, $1-\beta$ of 0.20 and no expected losses.

Results are expressed as mean ± SD unless otherwise stated. The Kolmogorov–Smirnov statistic was applied to continuous variables. Logarithmic or square-root transformations were used as needed to ensure normal distribution of the variables. To compare discontinuous variables, we used the χ^2 test or Fisher's exact test as appropriate. Unpaired *t* tests or Mann–Whitney *U* tests were used to compare the central tendencies of the different groups, as appropriate. A general linear model repeated-measures test was used to analyze continuous variables measured several times during the study period. Bivariate correlation was used to study the association between two continuous variables, using Pearson's or Spearman's test, as appropriate. Analyses were performed using SPSS 18 (SPSS Inc., Chicago, IL, USA). We considered $P < 0.05$ statistically significant.

Results

The baseline characteristics of the 35 participants are shown in Table 1. Most were male, less than half had hypertension, and less than a third had obesity or previous type 2 diabetes mellitus. Twenty-seven participants were critical ones admitted to the ICU, and the other eight were in respiratory intermediate care. Participants were on total PN for a mean of 14 d, with a mean daily supplemental zinc of 14.8 ± 3.7 mg/d. Only one participant had zinc deficiency at baseline according to our hospital reference range.

At follow-up there was an increase in alanine aminotransferase, γ-glutamyl transpeptidase, and D dimer, whereas serum interleukin-6, interleukin-12, total proteins, and albumin remained stable (Table 2). Serum zinc concentrations increased during PN administration from 98.8 ± 22.8 to 114.1 ± 23.3 μg/dL (Wilks' λ = 0.751, F = 5.459, P = 0.009; Fig. 1). Conversely, serum copper concentrations did not vary from baseline (107.9 ± 34.2 μg/dL) to the end of the study (104.5 ± 37.4 μg/dL, Wilks' λ = 0.919, F = 1.453, P = 0.248; Fig. 1).

Serum zinc at baseline did not correlate with any prognostic variable. Conversely, serum zinc within the first week after starting PN and serum zinc at the end of PN were inversely correlated with total hospital stay (r = −0.413, P = 0.014, and r = −0.386, P = 0.022, respectively; Fig. 2). Mean daily supplemental zinc was inversely correlated with

Table 1
Baseline characteristics of participants (n = 35)

Characteristic	Value
Age, y	65 ± 10
Sex (M/F)	30/5 (86/14)
Obesity	11 (31)
Body mass index, kg/m^2	30.3 ± 8.4
Hypertension	15 (43)
Type 2 diabetes mellitus	9 (26)
Coronary heart disease	4 (11)
Smoking	11 (31)
Systolic blood pressure, mm Hg	129 ± 18
Diastolic blood pressure, mm Hg	79 ± 15
Heart rate, beats/min	96 ± 20
Respiratory rate, respirations/min	28 ± 9
CURB-65 score	1.4 ± 1.1
Oximeter saturation, %	91.1 ± 5.6
Time in PN, d	14.0 ± 8.7
Energy delivered, kcal/d	1143 ± 219
Supplemental zinc, mg/d	14.8 ± 3.7
ICU admission	27 (77)
ICU stay, d	18 ± 16
Total hospital stay, d	47 ± 29
Mortality	14 (40)

CURB-65, pneumonia severity score; ICU, intensive care unit; PN, parenteral nutrition
Data are mean ± SD or n (%)

Table 2
Biochemical and inflammatory variables throughout the study

Variable	Baseline	End of PN	*P*
Glycemia, mg/dL	139 ± 54	151 ± 68	0.105
Creatinine, mg/dL	1.0 ± 0.5	1.1 ± 0.5	0.647
ALT, U/L	63 ± 50	87 ± 93	0.001
AST, U/L	49 ± 35	50 ± 47	0.944
GGT, U/L	109 ± 130	228 ± 240	<0.001
Alkaline phosphatase, U/L	96 ± 70	115 ± 78	0.086
Total cholesterol, mg/dL	173 ± 60	194 ± 65	0.074
Triacylglycerols, mg/dL	379 ± 261	365 ± 252	0.103
Serum total proteins, g/L	6.4 ± 1.1	5.3 ± 0.7	0.633
Serum albumin, g/L	2.9 ± 0.5	2.6 ± 0.6	0.482
CRP, mg/L	172 ± 122	92 ± 66	0.723
Procalcitonin, ng/mL	0.7 ± 1.8	0.6 ± 2.5	0.724
D dimer, μg/mL	5183 ± 11 270	7810 ± 14 534	<0.001
IL-6, pg/mL	417 ± 922	1029 ± 2374	0.660
IL-12, pg/mL	0.8 ± 1.6	1.3 ± 1.2	0.863

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, γ-glutamyl transpeptidase; IL, interleukin; PN, parenteral nutrition
Data are mean ± SD

procalcitonin ($r = -0.338$, $P = 0.047$) but did not reach a statistical significance correlation with total hospital stay ($r = -0.298$, $P = 0.082$).

Participants in the ICU had longer hospital stays than those in intermediate care (50 ± 30 d versus 29 ± 16 d, $z = 2.417$, $P = 0.016$), but their serum zinc levels were similar ($P > 0.1$ for all time points of the study). Conversely, participants in critical care presented lower serum copper concentrations at baseline ($z = 2.615$, $P = 0.007$), within the first week after starting PN ($z = 2.986$, $P = 0.002$), and at the end of PN ($z = 2.790$, $P = 0.004$; Fig. 3). Mortality was not associated with supplemental zinc or with serum zinc or copper concentrations at any time of the study ($P > 0.1$ for all analyses).

Discussion

We have shown in the present study that supplementation of zinc in PN produced an increase in serum zinc concentrations in people with severe COVID-19 infection. Serum zinc concentrations during PN support were inversely associated with length of hospital stay but not with mortality. This association was observed in patients in both ICU and intermediate care. In addition, serum copper concentrations were lower in those in the ICU but were not associated with prognosis.

Zinc is a highly abundant element on Earth, and it is an essential micronutrient. After ingestion and absorption through the small intestine, it is bound predominantly to albumin as well as to other proteins, including prealbumin, α_2-macroglobulin, transferrin, ceruloplasmin, haptoglobin, immunoglobulins, and complements. Serum circulating zinc accounts for only 0.1% of total body stores [13]. There are two families of proteins responsible for the movement of zinc across membranes: zinc-importer proteins, which transport it into the cytosol, and zinc transporter family proteins, which transport it outside the cytosol [14]. Most of the body content of zinc is found in muscle and bone, but many other organs—such as the liver, intestine, kidney, skin, lung, brain, heart, and pancreas—also contain significant concentrations. Its role within the human body is extensive in reproduction, immune function, wound repair, and, on the microcellular level, activity of macrophages, neutrophils, natural killer cells, and complements [15].

Notably, major risk groups for COVID-19—older people, men more than women, people who are obese, and people with diabetes—are all at risk of zinc deficiency [16]. Further, people who are critically ill may have elevated utilization of zinc, depleting their body reserves [8] and compromising the antioxidant defense mechanisms that protect cells from reactive oxygen species [9]. The alteration of zinc metabolism is more pronounced in people who are septic than in people who are critically ill but not infected. Specifically, sepsis is associated with lower plasma zinc concentrations [17]. A previous study reports that low serum zinc was very common at the onset of acute respiratory failure in the ICU but had no predictive value for 30-d mortality, ICU length of stay, or time of invasive mechanical ventilation [18]. In another study with a pediatric population, plasma zinc was correlated with measures of inflammation on day 3 and was associated with the degree of multiorgan failure in the ICU [19]. Therefore, zinc supplementation has been suggested as a novel strategy to influence severe COVID-19, as it may enhance the antiviral immune response [20,21]. Indeed, much evidence has accumulated over the past 50 y to demonstrate the antiviral activity of zinc against a variety of viruses and via numerous mechanisms [22]. Although the exact underlying mechanism of zinc-induced antiviral response is not well understood, it has been demonstrated that zinc has the potential to inhibit viral binding to the mucosal cells and eventual replication, possibly by generating antiviral interferon. In addition, it has been proposed that zinc may reduce expression of sirtuin 1-mediated cell-surface angiotensin-converting enzyme 2, the binding site for the SARS-CoV-2 spike protein [23].

Our results, although limited by the nature of a small retrospective study, show some interesting data on zinc supplementation in PN and the prognosis of people with severe COVID-19. Further, some of them are in agreement with recent reported data showing an association between low zinc levels and the severity of acute respiratory distress syndrome in people with severe COVID-19 [12]. The latter study included 269 people with severe COVID-19 admitted to an ICU, mostly men, with a mean age of 70 y and a median body mass index of 30 kg/m^2. The researchers measured serum zinc at admission and found an association of low zinc levels and severe acute respiratory distress syndrome even after adjusting for baseline variables [12]. Although we did not find an association between prognosis and baseline zinc concentrations, we identified only one participant with zinc deficiency, in contrast to the data reported in that previous study, which showed a 79.6% prevalence of low zinc levels. Our study has the advantage of serum zinc measurements at follow-up, and direct quantification of the parenteral zinc administered with PN. We were able to show a dynamic picture of serum zinc changes and an association of serum zinc levels after PN support with the length of hospital stay.

Copper is a component of the Cu/Zn superoxide dismutase and serves as a free radical scavenger [7]. In relatively small amounts, it is an essential cofactor of a broad array of molecules [24]. Common dietary sources of copper are meat, shellfish, seeds, legumes, nuts, whole grains, potatoes, and chocolate. After intestinal absorption, it circulates mainly bound to serum albumin and is carried to the liver. A small amount of copper is excreted in bile, and the rest binds to ceruloplasmin—a copper-dependent ferroxidase—and is released back into the bloodstream [25]. Increased serum copper concentrations during ICU care were associated with significantly lower mortality in a recent study [10]. Another previous study showed that copper supplementation produced significantly fewer 30-d infectious episodes and a significantly shorter length of stay in people with major burns, but a deep analysis showed that the results were associated not with copper levels but with the increased amount of supplemented selenium [26,27]. To our knowledge, there have been no reports of studies dealing with copper supplementation in people with COVID-19, although it has been recently proposed as an adjunct therapy in these patients from a theoretical point of view [28]. Ours, then, are novel data that show an association of lower serum copper concentrations with critical COVID-19 illness.

It has been suggested that the altered plasma concentrations of zinc, selenium, and copper in people with critical illness may be primarily due to the effects of the systemic inflammatory response and may not reliably indicate their status [29]. We did not measure zinc and copper in red blood cells, so this could be a limitation of

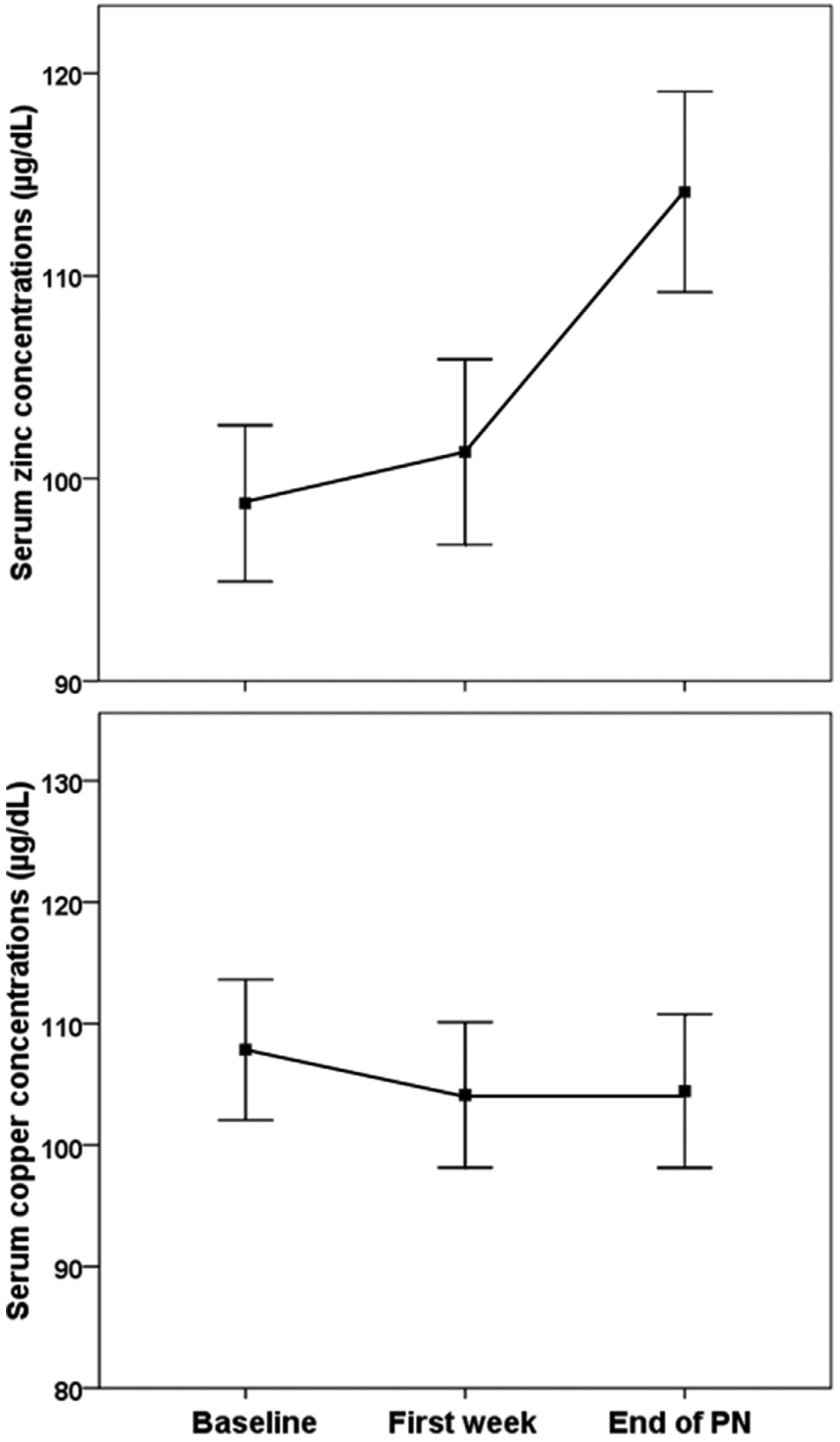

Fig. 1. Serum concentrations of zinc and copper throughout the study. Squares represent mean serum concentrations, and error bars represent standard error of the mean. *$P < 0.01$. PN, parenteral nutrition.

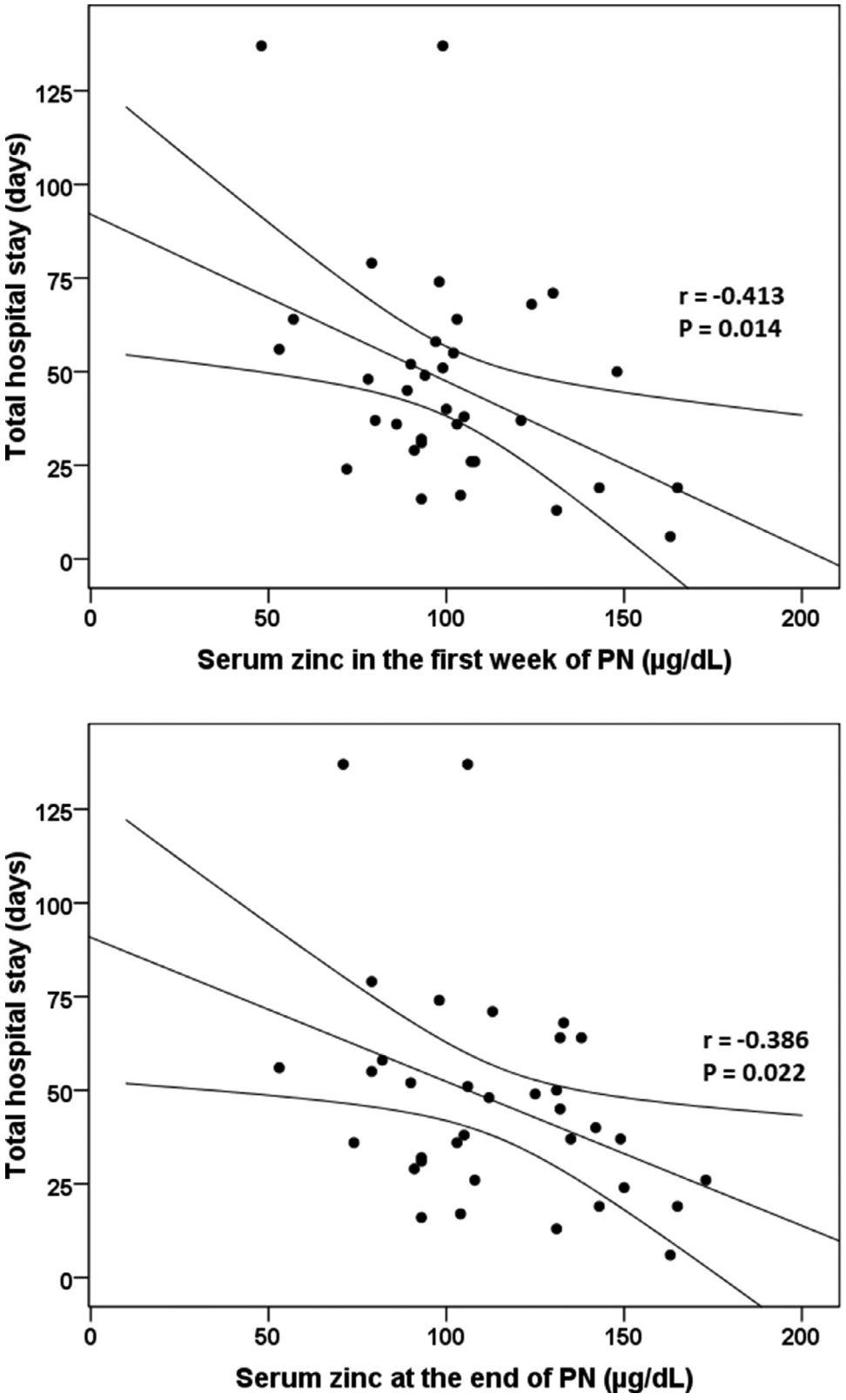

Fig. 2. Correlations of serum zinc concentrations within the first week after starting parenteral nutrition and at the end of infusion with hospital stay.

our study. However, erythrocyte concentrations of trace elements may reflect the sufficiency or deficiency status at baseline but may not be sensitive enough to detect rapid changes as they occur in people who are critically ill [10,11].

In conclusion, serum zinc concentrations during PN support were inversely associated with length of hospital stay but not with mortality in people with severe COVID-19. In addition, serum copper concentrations were lower in participants in the ICU but were not associated

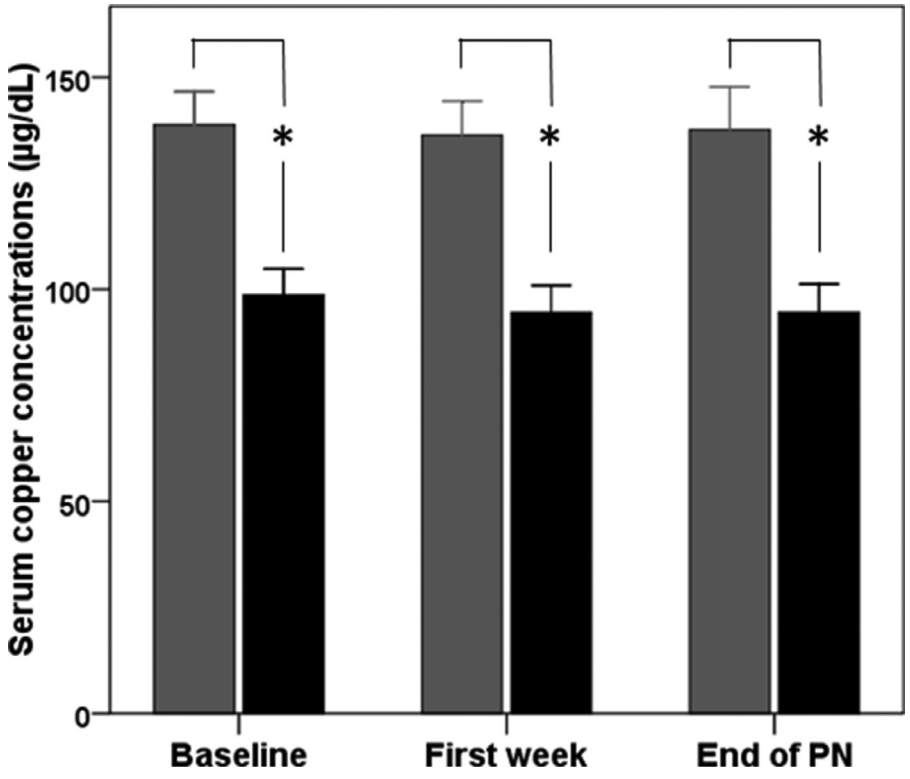

Fig. 3. Serum copper concentrations of participants in the intensive care unit (black bars) versus those in intermediate care (gray bars). Bars represent means and error bars represent standard error of the mean. $^*P < 0.05$. PN, parenteral nutrition.

with prognosis. Therefore, from the clinical experience, prophylactic supplementation of PN with zinc could be considered in these patients. Future clinical trials are needed to unravel the role of zinc and copper supplementation in people with severe COVID-19.

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