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The Role of Zinc and Copper in Anemia and Erythropoietin Responsiveness in Patients on Hemodialysis and Peritoneal Dialysis

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Abstract

Introduction: Imbalance in copper (Cu) and zinc (Zn) homeostasis is a frequent finding in patients undergoing dialysis. These patients have higher serum Cu and lower serum Zn levels compared to controls. This study is designed to investigate the relationship between blood Cu and Zn levels and Cu/Zn ratio and, ESA (erythropoietin stimulating agent) dosage, erythropoietin responsiveness and anemia in dialysis patients.

Methods: Clinical and demographic data for 151 participants (men=79) with a median dialysis vintage of 69.7 months [101 on Hemodialysis (HD), 50 on Peritoneal Dialysis (PD)] and mean age of 56.25±15.6 years was collected in November 2022. Zn and Cu levels were measured with atomic absorption. Erythropoietin responsiveness was evaluated by the erythropoietin resistance index (ERI) and ESA dosing.

Results: In HD patients, mean serum Zn and Cu levels were 61.33 ± 15.77 µg/dL and 95.1 ± 21.1 µg/dL, respectively, with a Cu/Zn ratio of 1.58 ± 0.69. In PD patients, mean serum Zn and Cu levels were 54.8 ± 10.3 µg/dL and 97 ± 20.2 µg/dL, respectively, with a Cu/Zn ratio of 1.72 ± 0.55. In Spearman analyses serum Cu was negatively correlated with hemoglobin (p=0.018), serum iron (p=0.03), transferrin saturation (p=0.019), and iron supplementation (p <0.01) in the HD patient group. Serum Cu was found to be positively correlated with erythropoietin (EPO) dosage (p=0.03), ERI (p=0.04), high sensitive C reactive protein (hsCRP) (p=0.01), and Kt/V (p=0.033). Cu/Zn ratio was positively correlated with EPO dosage (p=0.043), ERI (p=0.051) and hsCRP (p=0.015). Conversely, it was negatively correlated with iron supplementation (p=0.014) and serum albumin levels (p=0.049). Serum Zn levels was solely correlated with albumin level (p=0.039).

In PD, patient's serum Cu level was correlated positively with hsCRP (p=0.036); serum Zn levels correlated positively (p=0.01), and Cu/Zn ratio was correlated negatively with albumin (p=0.042).

Conclusion: This study has shown a possible association between both serum Cu and Cu/Zn ratio, ESA dosage and hsCRP in HD patients.

Keywords: Copper; Zinc; Cu/Zn; Dialysis; Inflammation

Abbreviations: Cu: Copper; Zn: Zinc; HD: Hemodialysis; PD: Peritoneal dialysis; ESA: Erythropoietin stimulating agent; hsCRP: High sensitive C-reactive protein.

Introduction

Among numerous complications which can affect the quality of life in dialysis patients, perhaps the most common is anemia [1,2]. It can also play a significant role in the development of complications of hypotension and heart failure, increase hospitalizations and mortality rates. Therefore providing an optimal management to prevent and treat anemia in this particular patient group is very important. It is shown that the most common cause of anemia in End Stage Kidney Disease (ESKD) patients is the insufficient level of erythropoietin but the effect of alterations in trace element levels on anemia and its correction has not been studied adequately.

In limited studies conducted in patients undergoing hemodialysis (HD) or peritoneal dialysis (PD) alterations in trace element levels have been documented. These changes include increased levels of serum cadmium, copper (Cu), and lead; and decreased levels of selenium, zinc (Zn) and manganese [3,4].

Zn is an important micronutrient which has anti-oxidative and anti-inflammatory effects. Zn finger proteins such as growth factor independent-1b (Gfi-1B) have important effects on various cell stages during erythroid differentiation [5,6]. It has been shown in studies on HD patients that Zn supplementation increases the hemoglobin (Hb) level and decreases the erythropoietin stimulating agent (ESA) need and inflammation [7,8].

Cu, which is another micronutrient crucial for normal organ functioning, plays important role in many metabolic processes like hemoglobin synthesis [9]. Along with serum levels of Cu, serum Cu/Zn ratio is also higher in patients on HD [10] and the ratio is shown to be a better predictor for disease severity and/or mortality compared to serum Cu levels [11-13].In patients undergoing PD the Cu/Zn ratio was found to be a useful biomarker for inflammation and nutrition [10].

This study is designed to investigate the relation between serum levels and ratio of Cu and Zn with anemia and erythropoietin responsiveness [ERI and erythropoietin (EPO) dosage] in a group of patients undergoing HD or PD for ESKD.

Materials and Methods

Adult patients over 18 years of age who were on HD or PD therapy for more than 6 months were included in this single center cross-sectional study. Patients were informed in detail about the study design and provided written consent. Those with a history of surgery or serious infection within the last 3 months, those with a definite diagnosis of malignancy, who used Zn supplements or any medication altering Cu or Zn metabolism within the last 3 months and those who refused to participate in the study, were excluded. Data for age, sex, height, dry weight, dialysis vintage, and primary disease for chronic kidney disease (CKD) was recorded as demographic parameters and existing comorbidities.

Patients in the HD group were on HD three times a week using a Braun Dialog$^+$ device (B. Braun Co Ltd, Melsungen, Germany) and an FX 80 high flux polysulfone membrane dialyzer (Fresenius, Frankfurt, Germany) with a membrane area of 1.8 m^2, blood flow rate of 300 ± 25 mL/min, dialysate flow rate of 500 mL/min, and dialysis time of 4 h with ultra-pure water dialysate. The electrolyte concentrations of the dialysate were as follows: Na^+ 138 mmol/L; K^+ 2 mmol/L; Ca^{++} 1.5 mmol/L; Mg^{++} 0.5 mmol/L; Cl^-108.7 mmol/L; CH_3COO^- 4.0 mmol/L; and HCO_3^- 31.1 mmol/L. Patients in the PD group received 44 continuous ambulatory PD and 6 automated PD cycles using 4 or 5 nocturnal cycles.

Local Committee for Science and Research Ethics approved the study on 13.10.2022 (İ09-552-22). The study was designed to meet all the conditions of 1964 Helsinki Declaration and its subsequent revisions. The study was carried out in November 2022 at Ankara University IbniSina Hospital, Ankara, Turkey.

Data Collection

Following an overnight fasting for 12 hours blood samples were drawn in the morning before the HD session. We conducted routine blood tests, blood biochemistry for serum iron level, total iron binding capacity, serum ferritin, intact parathyroid hormone (iPTH) and high sensitive C-reactive protein (hsCRP) testing with automated and standardized methods. An atomic absorption spectroscope (Perkin Elmer Analyst 800) and "WinLab32" program for the atomic absorption method were used in studying the serum levels of Cu and Zn. To avoid mistakes in measurement we generated calibration curves using standard solutions according to the guidelines and made 2 repetitive measurements for each sample [14]. Levels in range of 95-130 µg/dL and 76-110 µg/dL were regarded as normal for Cu and Zn, respectively.

Information regarding the treatment which included dosage of iron and ESA were also collected. We evaluated the EPO responsiveness using the erythropoietin resistance index (ERI) calculated by weekly weight-adjusted (kg) EPO dosage (in IUs) divided by the Hb level (g/dL). HD patients were treated with ferric carboxymaltose and PD patients with 162 mg elemental Fe in the form of ferrous fumarate daily until blood ferritin level achieved 500 ng/ml. We used 0.25-0.75 µg/kg/week ESA (namely darbepoietin alpha) subcutaneously in indicated patients, i.e., in anemic patients with transferrin saturation or ferritin values above 20% and 100 ng/ml, respectively.

Grouping

We divided our study population in two subgroups according to their Hb level and ERI. We used the Hb reference level as 11 g/dL, which is the treatment target level of Hb in dialysis patients with renal anemia. We regarded those with an Hb level of ≥ 11 g/dL as "patients without anemia" and those <11 g/dL as "anemic".

Statistical Analyses

We expressed normally distributed continuous variables as mean ± standard deviation, those with non-normal distribution as median [25-75% interquartile range (IQR)], and proportions as percentages. We evaluated the differences in mean, median, and percentages between the two groups using Student's t-test, Mann Whitney U test, and X^2 test, respectively. We used Spearman analyses to evaluate correlations between the Cu/Zn ratio and clinical parameters and the SPSS statistical software version 22 (IBM Corp, Armonk; NY, USA) for conducting the statistical analyses. A p value 0.05 was considered statistically significant.

Results

A total of 151 patients (101 on HD, 50 on PD) were enrolled for this study. The mean age was 56.25 ± 15.6 years. Of all patients, 52.3% were male and the median dialysis vintage was 69.7 (15.2-103.4) months. The primary diseases of the patients were hypertension (26.4%), diabetes (23.07%) and Glomerulonephritis (22.5%), in descending order. Clinical characteristics and laboratory data of all-patients, patients in the HD and PD groups are given in table 1. There were statistically significant differences in some of the laboratory parameters like Hb (p <0.001), ferritin (p <0.001), and hsCRP (p=0.017).The dose of iron supplementation was also higher (p=0.001) in the HD group as expected. For all-patients the ERI range was 3.25-28.97 IU/week/kg, with a mean of 11.84 ± 5.72 IU/week/kg.

In all-patients, the mean serum levels for Zn and Cu were 54.8 ± 10.3 µg/dL and 97 ± 20.2 µg/dL, respectively. The Cu/Zn ratio was 1.65 ± 0.28. In HD patients, the mean serum levels of Zn and Cu were 61.33 ± 15.77 µg/dL and 95.1 ± 21.1 µg/dL, respectively. The Cu/Zn ratio was 1.58 ± 0.69. In PD patients, the mean serum levels of Zn and Cu were 54.8 ± 10.3 µg/dL and 97 ± 20.2 µg/dL, respectively. The Cu/Zn ratio was 1.72 ± 0.55. The difference between the two groups was statistically insignificant. We evaluated the correlation of serum levels of Cu and Zn, and Cu/Zn ratio to clinical and laboratory parameters in patients on HD and PD (Table 2,3). In Spearman analyses, serum Cu levels negatively correlated with Hb (r=-0.239, p=0.018), hematocrit level (r=-0.214, p=0.034), serum iron (r=-0.219, p=0.03), transferrin saturation (r=-0.237, p=0.019), and iron supplementation (r=-0.428, p <0.001) in the HD patient group. Serum Cu was found to be positively correlated with dialysis vintage (r=0.217, p=0.033), rHuEPO dosage (r=0.340, p=0.03), ERI(r=0.31, p=0.04), hsCRP (r=0.338, p=0.01), and Kt/V (r=0.216, p=0.033). Serum Zn levels solely correlated with the albumin level (r=0.207, p=0.039). Cu/Zn ratio was positively correlated with rHuEPO dosage (r=0.233, p=0.043), ERI(r=0.21, p=0.042) and hsCRP (r=0.245, p=0.015). Conversely, it was negatively

Table 1: Characteristics of HD and PD patients.

	HD (n=101)	PD (n=50)	p value
Female gender (%)	43 (42.6)	29 (58)	0.074[a]
Age[+]	56.5 ± 15.3	69.7 ± 68.8	**0.008[b]**
Duration of dialysis[+] (months), n=150	53.6 ± 15.8	50.1 ± 42.1	0.78[b]
CKD etiology*			0.83[a]
Diabetes Mellitus (n %)	23 (23)	11 (22)	
Hypertension (n %)	29 (9)	11 (22)	
Glomerulonephritis (n %)	18 (18)	16 (32)	
Smoking*	19 (18.8)	3 (6)	**0.036[a]**
Iron supplementation*	68 (67.3)	19 (38)	**0.001[a]**
rHuEPO dosage (U/kg per week)[+] n=108	411.8 ± 238.2	369.5 ± 209.8	
ERI, U/kg/week/g/dL	12.76 ± 8.02	10.92 ± 9.1	**0.02**
Hemoglobin[+] (g/L)	10.7 (1.9)	11.3 (2.1)	**<0.001[b]**
Hematocrit[+] (%)	33.1 ± 4.9	34.4 ± 4.9	0.25[c]
RBC[+] (x10^6/L)	3.52 (0.71)	3.65 (0.87)	**<0.001[b]**
White Blood Cell[+] (x10^3/µL)	3.9 (2.0)	4.6 (2.3)	0.19[b]
Calcium[+] (mg/dL)	8.5 (0.8)	8.8 (1)	0.49[b]
Phosphate[+] (mg/dL)	5.03 (1.7)	4.47 (1.14)	0.80[b]
Albumin[+] (g/dL)	4 (0.4)	3.8 (0.7)	0.25[b]
Total cholesterol[+] (mg/dL)	152 (47.5)	174 (69.5)	0.67[b]
Ferritin[+] (ng/mL)	426 (385.5)	319 (328.5)	**<0.001[b]**
Serum iron[+] (µg/dL)	55 (28.5)	59.5 (33)	0.15[b]
Total iron binding capacity[+] (µg/dL)	220 ± 53.5	233.6 ± 45.1	0.13[c]
Transferrin saturation[+] (%)	25 (14.5)	26 (14.3)	0.74[b]
hsCRP[+] (mg/L)	5.1 (11.6)	4.7 (15.5)	**0.017[b]**
Kt/v[+]	1.35 (0.39)	2.28 (0.76)	0.60[b]
Serum copper[+] (µg/dL)	95.1 ± 21.1	97 ± 20.2	0.49[c]
Serum zinc[+] (µg/dL)	61.33 ± 15.77	54.8 ± 10.3	0.54[c]
Copper/Zinc[+]	1.58 ± 0.69	1.72 ± 0.55	0.51[c]

*n (%); [+]Mean ± SD or median (IQR); [a]Chi-Square; [b]Mann-Whitney U Test; [c]Independent-Samples T Test.
CKD=chronic kidney disease; rHuEPO=recombinant human erythropoietin; RBC=red blood cell; hsCRP=high sensitive C reactive protein.

Table 2: Correlations between serum levels of Cu and Zn, and Cu/Zn ratio with laboratory parameters in HD patients.

Hemodialysis patients	Copper		Zinc		Cu/Zn	
	r_s	**p value**	**r_s**	**p value**	**r_s**	**p value**
Age	0.072	0.48	-0.083	0.41	0.160	0.12
Duration of dialysis (months)	0.217	**0.033**	0.068	0.50	0.135	0.19
Iron supplementation (Orally or intravenous)	-0.428	**<0.001**	0.021	0.86	-0.302	**0.014**
rHuEPO dosage (U/kg/week)	0.340	**0.003**	-0.016	0.89	0.233	**0.043**
ERI (U/kg/week/g/dL)	0.310	**0.004**	-0.12	0.87	0.21	0.042
Hemoglobin (g/L)	-0.239	**0.018**	0.032	0.76	-0.151	0.14
Hematocrit (%)	-0.214	**0.034**	0.036	0.72	-0.136	0.18
RBC[+] (x10^6/L)	-0.153	0.13	0.120	0.23	-0.153	0.13
White Blood Cells (x10^3/µL)	0.303	**0.002**	0.045	0.66	0.177	0.082
Calcium (mg/dL)	-0.122	0.23	-0.064	0.53	-0.037	0.72
Phosphate (mg/dL)	-0.070	0.49	-0.035	0.73	-0.009	0.93
Albumin (g/dL)	-0.140	0.17	0.207	**0.039**	-0.200	**0.049**
Total cholesterol (mg/dL)	0.171	0.092	-0.187	0.063	0.258	**0.011**
Ferritin (ng/mL)	0.037	0.72	-0.007	0.95	0.028	0.79
Serum iron (µg/dL)	-0.219	**0.030**	-0.074	0.46	-0.085	0.41
Total iron binding capacity (µg/dL)	0.039	0.70	0.016	0.88	0.012	0.90
Transferrin saturation (%)	-0.237	**0.019**	-0.041	0.68	-0.126	0.22
hsCRP (mg/L)	0.338	**0.001**	-0.043	0.67	0.245	**0.015**
Kt/v	0.216	**0.033**	0.007	0.95	0.146	0.16
Zn	-0.041	**0.69**	-	-	-	-

rHuEPO=recombinant human erythropoietin; RBC=red blood cell; hsCRP=high sensitive C reactive protein.

Table 3: Correlations between serum levels of Cu and Zn, and Cu/Zn ratio with laboratory parameters in PD patients.

Peritoneal dialysis patients	Copper		Zinc		Cu/Zn	
	r_s	p value	r_s	p value	r_s	p value
Age	0.176	0.24	-0.065	0.66	0.071	0.64
Duration of dialysis (months)	-0.118	**0.43**	-0.098	0.50	-0.094	0.53
rHuEPO dosage (U/kg/week)	-0.333	**0.089**	-0.056	0.77	-0.222	**0.27**
ERI (U/kg/week/g/dL)	-0.21	0.076	-0.31	0.81	-0.26	0.082
Hemoglobin (g/L)	0.078	0.60	0.128	0.38	-0.078	0.60
Hematocrit (%)	0.197	0.19	0.138	0.34	0.021	0.89
RBC$^+$ (x10^6/L)	0.134	0.37	0.223	0.12	-0.114	0.45
White Blood Cells (x10^3/µL)	0.111	0.46	<0.001	>0.99	0.153	0.31
Calcium (mg/dL)	-0.107	0.48	0.080	0.58	-0.081	0.59
Phosphate (mg/dL)	-0.170	0.25	0.047	0.74	-0.095	0.53
Albumin (g/dL)	0.009	0.95	0.456	**0.001**	-0.298	**0.042**
Total cholesterol (mg/dL)	-0.061	0.69	0.032	0.83	0.065	**0.67**
Ferritin (ng/mL)	-0.078	0.60	0.061	0.68	-0.074	0.62
Serum iron (µg/dL)	0.009	0.95	0.033	0.82	-0.081	0.59
Total iron binding capacity (µg/dL)	-0.018	0.91	0.131	0.37	-0.031	0.84
Transferrin saturation (%)	-0.018	0.90	-0.007	0.96	-0.112	0.45
hsCRP (mg/L)	0.306	**0.036**	-0.098	0.50	0.276	0.061
Kt/v	0.026	0.87	0.132	0.39	-0.054	0.74
Zn	0.143	0.34	-	-	-	-

rHuEPO=recombinant human erythropoietin; RBC=red blood cell; hsCRP=high sensitive C reactive protein.

correlated with iron supplementation (r=-0.302, p=0.014) and serum albumin level (r=-0.20, p=0.049) (Figure 1).

In the PD patients, serum Cu levels correlated positively with hsCRP (r=0.306, p=0,036); serum Zn levels correlated positively with albumin (r=0.456, p=0.01), and Cu/Zn ratio correlated negatively with albumin (r=-0.298, p=0.042) (Table 3).

We grouped our patients (all-patients, HD and PD patients) in two groups according to their Hb level (≥ 11 g/dL or <11 g/dL) and studied a possible similar relation. We could not observe a correlation between levels of Hb and Cu or Zn, or Cu/Zn ratio in these groups.

Results of multivariate linear regression analyses demonstrated in the HD patient group that the serum levels of Cu were independently associated with rHuEPO dosage (β=0.342, p=0.002), ERI (β=0.329,p=0,047),iron supplementation (β=0.340, p=0.004), and hsCRP (β=0.339, p=0.003) as covariates, which were significantly different according to the univariate analysis; Cu/Zn ratio was independently associated with rHuEPO dosage (β=0.528, p <0.001), ERI(β=0.49, p <0.001), iron supplementation (β=0.521, p <0.001), and hsCRP (β=0.514, p <0.001) as covariates, which were significantly different according to the univariate analysis. For PD patients, there was no independent association between the serum level of Zn and albumin, as well as the serum level of Cu and hsCRP.

Discussion

In this study there was no statistically significant difference between patients in the HD and PD groups in terms of serum levels of Cu and Zn, and Cu/Zn ratio. In the HD patient group, serum Cu levels and Cu/Zn ratio correlated positively with rHuEPO dosage, ERI and hsCRP, but negatively with iron supplementation and serum albumin levels. Serum levels of Zn solely correlated positively with the albumin levels. Based on multivariate linear analyses there were independent associations between a higher serum Cu/Zn ratio and hsCRP, rHuEPO dosage, ERI and iron supplementation, along with independent associations between serum Cu levels and rHuEPO dosage, ERI and Fe supplementation in the HD patient group.

In the PD patient group, serum Cu levels correlated positively with hsCRP; serum Zn levels correlated positively with albumin levels; and Cu/Zn ratio correlated negatively with albumin. There was no independent association between Cu levels or the Cu/Zn ratio and rHuEPO, ERI or iron supplementation in the PD patient group.

Patients with ESKD undergoing dialysis have a higher serum level of Cu and a lower serum level of Zn compared to healthy controls [3,15]. It has been proposed that rather than analyzing serum Zn levels, serum Cu/Zn ratio reflects the severity of Zn deficiency [16]. These patients were reported to be more prone to Zn deficiency due to decreased dietary Zn intake and gastrointestinal absorption and increased Zn clearance during dialysis [17].

Serum albumin is the major Zn binding protein. Hypoalbuminemia caused by protein restricted diet and proteinuria were found to be strongly associated with a lower serum Zn level [18]. Zinc deficiency can decrease the Zn content in the erythrocyte membrane, increase erythrocyte fragility, and reduce membrane fluidity. Its deficiency is proposed to be responsible for the decrease in erythrocyte survival in patients undergoing dialysis [19]. Unlike previous studies [19], we did not observe an association between Zn level and Hb, presence of anemia (Hb <11 g/dL), rHuEPO need, and ERI in HD and PD patients. Serum Zn levels solely correlated with serum albumin levels, both in HD and PD patients.

Cu is a part of ceruloplasmin and reflects the inflammatory status. In patients undergoing dialysis, serum Cu levels were higher than healthy controls. This finding is probably associated with increased oxidative stress and may be a consequence of the inflammatory status and release Cu from the dialyzer membrane [17,20,21]. Serum levels of

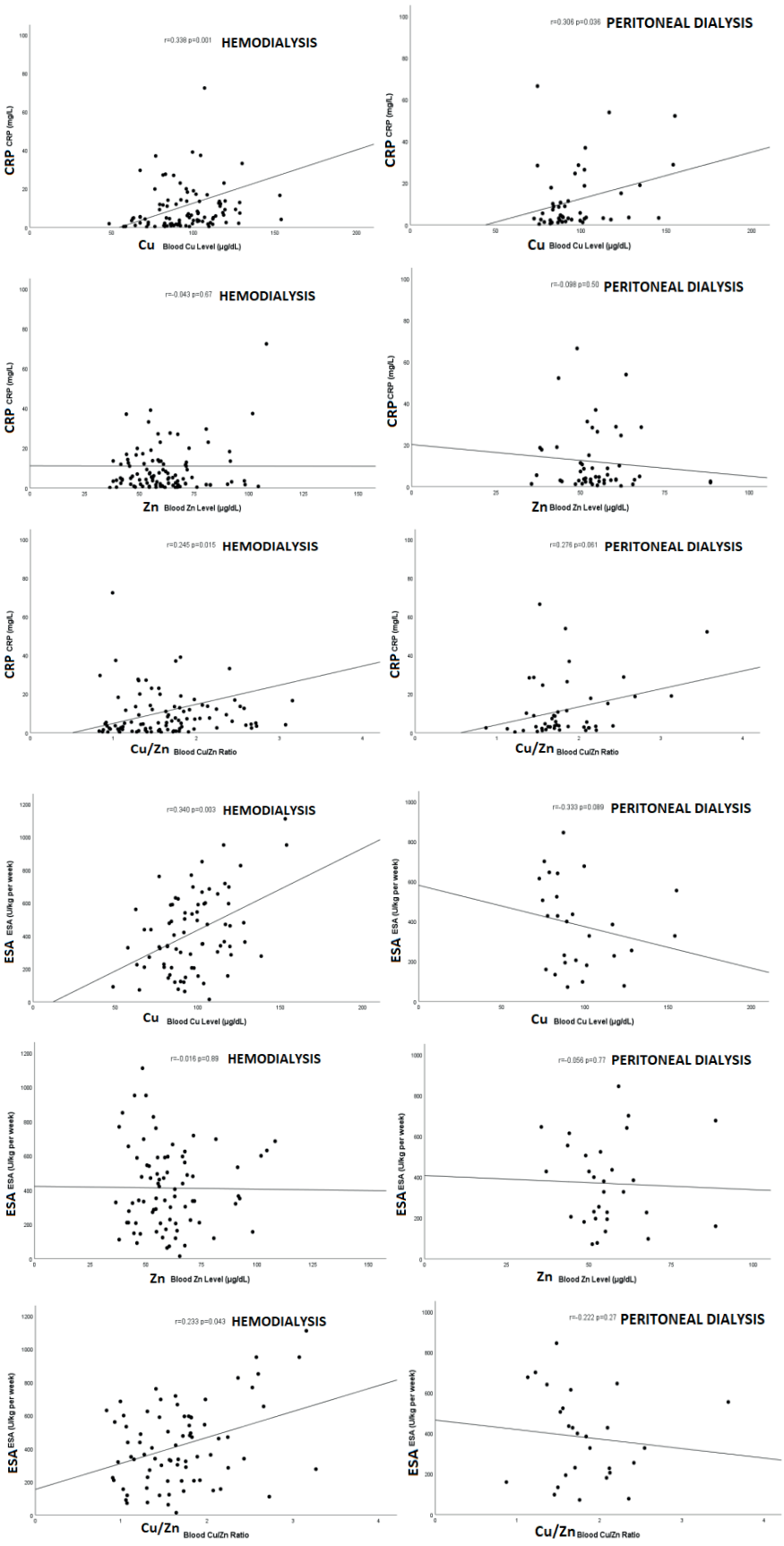

Figure 1: Graphics depicting correlation of serum Cu, Zn, and Cu/Zn ratio with CRP, and ESA.

Cu and Cu/Zn ratio correlated positively with erythropoietin dosage, ERI and hsCRP in our HD patients. PD patients, though serum Cu levels were found to correlate with hsCRP levels, there was not an independent association between the two levels. We attributed this difference to be a result of higher inflammatory status in HD patients compared to PD patients.

As a conclusion we found that increases in serum Cu and Cu/Zn ratio showed a pro inflammatory status in patients on HD. In HD patients, serum Cu levels and Cu/Zn ratio showed a relationship with hsCRP levels, increased rHuEPO need, ERI, and iron supplementation. Therefore especially for this specific group of patients the impact of Zn supplementation on anemia is controversial and requires further studies in larger patient cohorts.

Our study has some limitations. First, though there was an association between serum Cu levels or Cu/Zn ratio and hsCRP or rHuEPO dosage, and ERI; we still cannot conclude on causality. Secondly, the sample size is relatively small. Thirdly, the residual renal function and proteinuria is not evaluated.

Conclusion

We found serum Cu levels and Cu/Zn ratio to be correlated independently with rHuESA need, ERI, Fe supplementation and hsCRP in HD patients. We attributed this correlation to be a consequence of inflammation as it related to an increase in the serum Cu levels. We did not observe a correlation between serum Zn levels and low Hb or rHuESA need. Prospective multicenter studies with larger groups are needed to evaluate the association between serum Cu levels or Cu/Zn ratio and anemia, ESA dosage and inflammation.

Ethics Approval and Consent to Participate

Ankara University Institutional Committee for Science and Research Ethics approved the study on 13.10.2022 (İ09-552-22). We obtained written informed consent from all participants after explaining the protocol in detail. The study was designed to meet all the conditions of 1964 Helsinki Declaration and its subsequent revisions.

Consent for Publication

All authors have approved the submitted version of the manuscript and give consent for publication.

Availability of Data and Material

The data used in this study is available on request from the corresponding author. The datasets supporting the conclusions of this article are included within the article, tables and figure.

Competing Interests

There are no competing interests to declare. The authors do not have a conflict of interest to disclose.

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Authors' Contributions

All authors have made substantial contributions to the conception and design of the work; the acquisition, analysis, interpretation of data; have drafted the work and substantively revised it.

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