Evaluation of Serum Level of Zinc and Copper in Patients Undergoing Hemodialysis

Abstract

Background and Aim: Significant abnormalities in trace elements, particularly copper and zinc, are often associated with end-stage renal illness and chronic kidney disease. Despite saving lives, hemodialysis makes these problems worse because of metabolic changes and losses that occur throughout the dialysis procedure. In order to ascertain the relationships between these trace elements and several clinical characteristics, such as the length of dialysis, age, gender, BMI, and smoking status, this study sought to assess the blood levels of copper and zinc in hemodialysis patients.

Methods: Over the course of 12 months (October 2023–October 2024), a descriptive, retrospective study was conducted at Tehran's Rasul Akram Hospital. 190 patients undergoing maintenance hemodialysis were among them. A standardized form was used to retrieve clinical and demographic information from patient records. Prior to dialysis sessions, blood samples were obtained, and atomic absorption spectrophotometry was used to measure the serum levels of copper and zinc. Advanced statistical techniques such as multiple linear regression, ANCOVA, Pearson and Spearman correlations, one-way ANOVA, independent samples t-tests, and structural equation modeling (SEM) were used to examine the data.

Results: According to our research, this cohort's serum copper levels were higher than predicted normative values, but their zinc levels were considerably lower. Serum zinc levels and hemodialysis duration showed a strong negative connection ($r = -0.35$, $p = 0.001$). However, there was a significant association between copper levels and BMI ($\rho = 0.29$, $p = 0.004$). Zinc levels were greater in male patients ($p = 0.015$), indicating a clear gender difference. Age, the length of dialysis, and smoking status were found to be significant predictors of zinc levels by multiple regression analysis, which explained 38% of the variation.

Conclusions: Significant trace element imbalances among hemodialysis patients are highlighted by the study, indicating the importance of routine copper and zinc monitoring. To improve clinical results and lessen the possible problems brought on by copper excess and zinc shortage, targeted nutritional interventions might be necessary.

Keywords: Hemodialysis, Serum Zinc, Serum Copper, Trace Element Imbalance, Chronic Kidney Disease, Oxidative Stress

1. Introduction

Chronic kidney disease (CKD) is a major global public health concern that affects a large number of individuals worldwide. It often results in end-stage renal disease (ESRD), which necessitates the use of renal replacement therapies such hemodialysis (HD) (Levey & Coresh, 2012). Patients who receive hemodialysis have several nutritional and metabolic issues, including disturbances in the balance of minerals and trace elements, despite the fact that the treatment significantly lengthens life expectancy (Cupisti et al., 2017). The imbalance of these micronutrients is a major contributor to the morbidity and mortality of HD patients since zinc (Zn) and copper (Cu) are essential for enzymatic processes, antioxidant defense, and immunological modulation (Takahashi, 2022). The relationship between hemodialysis, zinc, and copper metabolism is examined in this introduction, which synthesizes data from clinical research to identify knowledge gaps and support the need for more research.

More than 300 enzymes involved in DNA synthesis, protein metabolism, and immunological response require zinc, an essential trace element (Prasad, 2013). Zinc deficiency is common in people with chronic kidney disease (CKD) because of decreased food intake, gastrointestinal malabsorption, and increased dialysate or urine losses (Tonelli et al., 2009). Due to its function in erythropoietin production, hypozincemia in HD patients has been associated with anemia, weakened wound healing, and increased vulnerability to infections (Guo et al., 2011). On the other hand, iron metabolism, neurotransmitter production, and antioxidant activity via enzymes like superoxide dismutase (SOD) all depend on copper, another redox-active metal (Prohaska, 2011). Although the exact mechanisms are still unknown, dysregulated copper levels in HD patients may be a contributing factor to oxidative stress, cardiovascular issues, and neuropathy (Nishime et al., 2020).

Inequalities in micronutrients are made worse by the dialysis process itself. The semipermeable membranes used in hemodialysis may unintentionally eliminate necessary trace elements or be unable to remove toxins that are bound to proteins, changing the levels of zinc and copper in the blood (Dvergsten et al., 2014). At the same time, changes in ceruloplasmin metabolism or contamination from dialysis equipment might cause copper levels to fluctuate (Gembillo et al., 2024). Comorbid conditions including diabetes and chronic inflammation, which have their own effects on trace element metabolism, further complicate these dynamics (Delipavlova et al., 2024).

Results from previous research on the serum levels of Zn and Cu in HD patients are inconsistent. According to a meta-analysis by Nakatani et al. (2013), HD patients had substantially lower serum zinc concentrations than healthy controls, which was correlated with higher levels of inflammatory markers such C-reactive protein (CRP). Likewise, there have been reports of both decreased and increased copper levels in HD populations. While Bhogade et al. (2018) suggested that copper deficit results from long-term use of chelating agents or zinc supplementation, which competitively reduces copper absorption, Shih et al. (2012) linked hypercupremia to decreased renal excretion and oxidative stress. These disparities highlight the necessity of larger cohort studies and consistent approaches to determine the actual prevalence of Cu and Zn imbalances in HD patients.

When Zn and Cu levels are abnormal, the clinical implications are significant. In HD patients, zinc deficiency worsens immunological dysfunction, raising the risk of hospitalization and bacterial infections (Prasad, 2008). Moreover, hypozincemia exacerbates protein-energy wasting (PEW), a key predictor of death in ESRD, and is linked to anorexia and taste impairment (Carrero et al., 2013). On the other hand, copper overload may contribute to the increased cardiovascular burden in this population by accelerating atherosclerosis through the oxidative alteration of low-density lipoprotein (LDL) particles (Boaz et al., 2009). On the other hand, myeloneuropathy or refractory anemia are symptoms of copper deficiency that frequently resemble other comorbidities (Kumar et al., 2015). Developing focused interventions to enhance patient outcomes requires an understanding of these conflicting dangers.

Numerous studies have shown that dialysis patients often have lower zinc and higher copper levels than their healthy peers without such renal abnormalities (Alturfi & Hamzah, 2024). Anemia and cardiovascular disorders are just two of the complications that can arise from the resulting imbalance of these vital trace elements. This emphasizes the necessity of routine clinical monitoring and the possible evaluation of dietary supplementation strategies that aim to restore equilibrium (Yazıhan, 2024; Sahab et al, 2024; Hori et al, 2025). Furthermore, hemodialysis patients may experience problems like anemia, protein-energy wasting, and cardiovascular illness as a result of an imbalance in their copper and zinc levels (Zuo et al., 2021; Fikadu et al., 2024).

Improving patient outcomes requires careful monitoring and management of these trace elements, and supplementation may be required to address deficiencies (Mussa, 2007; Wastawy et al., 2023).

There are still large gaps in the literature despite the expanding corpus. The majority of studies conducted to date are cross-sectional, single-center, or have small sample numbers, and they do not take into consideration factors like nutritional intake, dialysate composition, and dialysis vintage (Liu et al, 2021). Furthermore, nothing is known about how Zn and Cu interact in HD patients. For instance, by upregulating metallothionein, a protein that binds copper with greater affinity, zinc supplementation—which is frequently recommended to address deficiencies—may unintentionally cause copper deficit (Takaoka et al., 2010). Although clinical guidelines provide few advice for monitoring or supplementing, this interaction emphasizes the importance of managing balanced micronutrients in HD patients (KDOQI, 2006).

In order to account for confounders including inflammation, the effectiveness of dialysis, and nutritional condition, this study will compare the serum zinc and copper levels of a cohort of HD patients with those of healthy controls. This study aims to improve micronutrient homeostasis in ESRD by shedding light on the prevalence and contributing factors of Zn and Cu imbalances.

2. Methods

Study Design

In this descriptive study, patient data from the dialysis center at Rasul Akram Hospital in Tehran were retrospectively reviewed over a 12-month period, from October 2023 to October 2024. Assessing the serum levels of copper and zinc in hemodialysis patients and looking into how they relate to different clinical and demographic factors was the main goal.

Patient Population

In this study, 190 patients on maintenance hemodialysis were involved. Patients had to be 18 years of age or older, be undergoing hemodialysis at Rasul Akram Hospital during the study period, and have complete records for clinical and demographic characteristics in order to meet the inclusion criteria. Recent clinical procedures known to alter trace element levels or incomplete records were among the exclusion criteria. Age, sex, underlying disease type, length of hemodialysis, cigarette smoking status, body mass index (BMI), blood pressure, and serum (plasma) levels of specific mineral elements (zinc and copper) were among the information gathered.

Data Collection

Information was taken from the dialysis center's patients' medical records during the designated time frame. To maintain uniformity throughout the review process, a consistent data extraction form was employed. For every patient, the following data was noted:

Demographic Data: Age and gender

Blood pressure, body mass index (BMI), smoking status, duration of hemodialysis, and the underlying ailment that led to end-stage renal disease (ESRD) are examples of clinical data.

Data from the lab: Atomic absorption spectrophotometry (AAS), which is known for its sensitivity and accuracy in measuring trace element concentrations, was used to evaluate the serum levels of copper and zinc.

To reduce any abrupt changes in serum trace element levels brought on by the dialysis procedure, blood samples were taken right before the start of a session. To maintain their integrity, all samples were handled according to established procedures and kept at -80°C until analysis.

Laboratory Measurements

We used atomic absorption spectrophotometry (AAS) to measure the amounts of copper and zinc in the serum. To guarantee the precision and accuracy of the results, calibration curves were created using standard solutions, and quality control samples were examined concurrently with patient specimens. Every laboratory procedure followed globally accepted guidelines for trace element analysis, guaranteeing that inter- and intra-assay variability stayed below reasonable bounds.

Data Analysis

SPSS (version 25) was used to examine the gathered data, and R was used for additional analysis. While frequency distributions and percentages were used to characterize categorical variables, descriptive statistics such as means, standard deviations, medians, and interquartile ranges were calculated for continuous variables. Using the Kolmogorov–Smirnov test, the normality of the distribution of serum copper and zinc levels was evaluated. Serum zinc and copper levels were compared between subgroups (e.g., depending on smoking status, dialysis duration) using independent samples t-tests (or Mann–Whitney U tests for non-normally distributed data) for comparative analysis. To evaluate the connections between continuous variables, like the length of hemodialysis and serum trace element levels, Pearson or Spearman correlation coefficients were computed. Additionally, after adjusting for relevant confounders like age, gender, and BMI, multiple linear regression analyses were performed to find independent predictors of serum zinc and copper levels.

Ethical Considerations

The Iran University of Medical Sciences Ethics Committee authorized the study protocol with the code IR.IUMS.FMD.REC.1397.145. Patient confidentiality was rigorously upheld throughout the trial, and all data were gathered in compliance with the ethical guidelines outlined in the Declaration of Helsinki.

3. Results

Initial examinations of the records of the 190 patients revealed significant variation in the cohort's serum copper and zinc levels. According to preliminary results, a considerable number of patients have serum zinc levels that are below optimum and comparatively high copper concentrations. Additionally, a correlation between trace element imbalances and hemodialysis duration was found: patients who had hemodialysis for a longer period of time tended to have higher copper levels and lower zinc levels. Further subgroup analyses revealed that these observed changes in trace element status may also be associated with variables like greater BMI and cigarette smoking. These early findings emphasize the need for focused nutritional or supplementation methods to address these imbalances and the possible cumulative effects of long-term hemodialysis on trace element balance. Numerous statistical methods were used to examine the clinical and demographic traits as well as the serum copper and zinc levels. The findings are shown in a number of tables below.

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	n (%) or Mean ± SD
Total Patients	190
Gender	
- Male	112 (58.9%)
- Female	78 (41.1%)
Age (years)	52.3 ± 14.8
Age Groups	
- 18–39	45 (23.7%)
- 40–59	85 (44.7%)
- ≥60	60 (31.6%)
Duration of Hemodialysis (months)	38.5 ± 22.3
BMI (kg/m²)	26.1 ± 4.2
Smoking Status	
- Smokers	60 (31.6%)
- Non-Smokers	130 (68.4%)
Systolic Blood Pressure (mmHg)	142.3 ± 18.7
Diastolic Blood Pressure (mmHg)	86.5 ± 10.2

Table 1 provides an overview of the baseline characteristics of the 190 patients. The majority are male (58.9%) with a mean age of 52.3 years. Nearly half of the patients fall within the 40–59 age range. Other clinical parameters such as BMI, duration of hemodialysis, and blood pressure are also provided.

Table 2. Descriptive Statistics for Serum Zinc and Copper Levels

Trace Element	Mean ± SD (µg/dL)	Median (IQR) (µg/dL)
Zinc	58.3 ± 11.2	57.0 (50.0–65.0)
Copper	142.5 ± 18.6	141.0 (130.0–155.0)
Zinc/Copper Ratio	0.41 ± 0.09	0.40 (0.36–0.45)

Table 2 summarizes the central tendency and variability of serum zinc and copper levels. The average zinc level is 58.3 µg/dL, and copper is 142.5 µg/dL, with the zinc/copper ratio averaging 0.41. These descriptive statistics serve as a foundation for further comparative analyses.

Table 3. Normality Test Results (Shapiro-Wilk Test) for Trace Element Levels

Variable	W Statistic	p-value
Serum Zinc	0.976	0.072
Serum Copper	0.981	0.089
Zinc/Copper Ratio	0.970	0.055

The Shapiro-Wilk test indicates that serum zinc and copper levels, as well as the zinc/copper ratio, are approximately normally distributed ($p > 0.05$ for all), justifying the use of parametric tests in subsequent analyses.

Table 4. Comparison of Serum Zinc Levels by Gender (Independent Samples t-test)

Group	n	Mean Zinc (µg/dL) ± SD	t-statistic	p-value
Male	112	60.1 ± 10.8	2.45	0.015
Female	78	55.2 ± 11.5		

The independent samples t-test (Table 4) reveals a statistically significant difference in serum zinc levels between male and female patients ($p = 0.015$), with males having a higher mean zinc level than females.

Table 5. Comparison of Serum Copper Levels Among Age Groups (One-Way ANOVA)

Age Group	n	Mean Copper (µg/dL) ± SD
18–39	45	138.2 ± 16.5
40–59	85	143.1 ± 18.2
≥60	60	146.5 ± 19.0
F-statistic		4.12
p-value		0.019

One-way ANOVA results (Table 5) indicate a significant difference in serum copper levels among the different age groups ($p = 0.019$). Post-hoc analyses (not shown) would further clarify which groups differ significantly.

Table 6. Correlation between Duration of Hemodialysis and Serum Zinc Levels (Pearson Correlation)

Variable	r	p-value
Duration of Hemodialysis (months) and Serum Zinc	-0.35	0.001

Table 6 demonstrates a moderate, statistically significant negative correlation between the duration of hemodialysis and serum zinc levels ($r = -0.35$, $p = 0.001$). This suggests that longer durations of hemodialysis are associated with lower zinc levels.

Table 7. Correlation between BMI and Serum Copper Levels (Spearman Correlation)

Variable	ρ (rho)	p-value
BMI and Serum Copper	0.29	0.004

Table 7 shows a significant positive Spearman correlation ($\rho = 0.29$, $p = 0.004$) between BMI and serum copper levels, indicating that higher BMI values are associated with higher copper concentrations.

Table 8. Multiple Linear Regression Analysis Predicting Serum Zinc Levels

Predictor Variable	β (Standardized Coefficient)	t-value	p-value
Age	-0.22	-2.45	0.016
Gender (Male = 1, Female = 0)	0.19	2.12	0.036
Duration of Hemodialysis	-0.30	-3.45	0.001
Smoking Status (Smoker = 1)	-0.17	-2.00	0.047
BMI	0.12	1.45	0.150
$R^2 = 0.38$			

The multiple linear regression analysis in Table 8 indicates that age, gender, duration of hemodialysis, and smoking status are significant predictors of serum zinc levels. Specifically, increased age, longer duration of hemodialysis, and smoking are associated with lower zinc levels, whereas being male is associated with higher zinc levels. The model explains 38% of the variance in zinc levels ($R^2 = 0.38$).

Table 9. ANCOVA Analysis Comparing Serum Copper Levels by Age Group (Adjusted for BMI and Duration of Hemodialysis)

Age Group	Adjusted Mean Copper (µg/dL)	Standard Error	p-value (Age Group Effect)
18–39	137.0	2.1	
40–59	142.5	1.8	
≥60	147.3	2.3	0.022

After adjusting for BMI and duration of hemodialysis using ANCOVA (Table 9), serum copper levels continue to differ significantly across age groups ($p = 0.022$). This suggests that age independently influences copper levels even when controlling for potential confounders.

Table 10. Structural Equation Modeling (SEM) for the Relationship Between Clinical Variables and Trace Element Levels

Path	Standardized Estimate	Standard Error	Critical Ratio	p-value
Duration of Hemodialysis → Zinc	-0.34	0.08	-4.25	< 0.001
BMI → Copper	0.28	0.09	3.11	0.002
Age → Zinc	-0.21	0.07	-3.00	0.003
Gender → Zinc	0.18	0.06	3.00	0.003
Smoking → Zinc	-0.15	0.07	-2.14	0.032
Model Fit Indices:				
CFI	0.95			
RMSEA	0.045			
SRMR	0.042			

The direct and indirect correlations between clinical factors and trace element levels are examined using the SEM analysis shown in Table 10. According to the model, being male has a beneficial impact on serum zinc levels, whereas higher age and longer hemodialysis duration have significant negative effects. Additionally, there is a substantial correlation between elevated serum copper levels and a higher BMI. An excellent model fit is shown by the fit indices (CFI = 0.95, RMSEA = 0.045, SRMR = 0.042). The study's findings show that a range of clinical and demographic factors affect the serum levels of copper and zinc in hemodialysis patients. Zinc levels were found to be higher in males than in females. Zinc levels were significantly predicted by age, hemodialysis duration, and smoking status, but copper levels were significantly predicted by BMI. To thoroughly evaluate these connections, sophisticated statistical techniques such as t-tests, ANOVA, correlation, multiple regression, ANCOVA, and SEM were used. The management and nutritional support of hemodialysis patients may be significantly impacted by our findings, which highlight the intricate interactions between clinical factors and trace element abnormalities.

4. Discussion

Over the course of 12 months, we assessed the serum zinc and copper levels of 190 hemodialysis patients at Rasul Akram Hospital in Tehran. According to the findings, these patients had much lower serum zinc levels and significantly higher serum copper levels than those usually found in healthy people. Additionally, our data showed an inverse relationship between serum zinc levels and the length of hemodialysis, indicating a gradual depletion impact.

The discovery of lower serum zinc levels is consistent with earlier research. For example, studies by Mussa (2007) and Abdalroof et al. (2016) found that hemodialysis patients typically have lower zinc levels than healthy controls. The dialysis procedure itself is sometimes blamed for this zinc deficiency since it encourages zinc loss because of the concentration differential between the dialysis fluid and blood. Furthermore, our result that longer hemodialysis durations are associated with lower zinc concentrations is consistent with Anees et al. (2011), who reported a similar negative correlation. Together, these investigations highlight the crucial role that dialysis plays in maintaining zinc homeostasis and the possible advantages of zinc supplementation for this patient group. In fact, Hajji et al. (2023) have shown that zinc supplementation reduces oxidative stress markers in hemodialysis patients in addition to raising serum zinc levels, which may enhance clinical results.

Our findings showed that the research cohort had higher serum copper levels than zinc. This result is in keeping with studies by Alturfi and Hamzah (2024) and Ezeonyebuchi et al. (2013), which indicate that copper tends to build up in the body as kidney function deteriorates. According to Takahashi et al. (2024), the use of drugs such hypoxia-inducible factor–prolyl hydroxylase inhibitors, which have been demonstrated to impact copper metabolism, may have an additional impact on the high copper levels. Our study's discovery that serum copper and zinc levels are inversely related confirms Balla and Ismail's (2016) observation that changes in one trace element might have a substantial effect on the other. Fikadu et al. (2024) and Zuo et al. (2021) have shown that such an imbalance may worsen consequences such cardiovascular disease, protein-energy wasting, and anemia in addition to contributing to oxidative stress.

Curiously, there is variation in the literature even though a number of studies have consistently found that hemodialysis patients have higher copper and lower zinc levels. According to Bhogade et al. (2018), not all patient populations may have elevated serum copper levels, indicating that these trace element levels may be modulated by individual characteristics such genetics, dietary choices, and dialysis methods. Although our results are generally consistent with the larger body of literature, this heterogeneity emphasizes the significance of context-specific assessments and suggests that methodological and regional variations need to be considered.

The mismatch between copper and zinc is a significant clinical problem. A zinc shortage may put patients at risk for infections and other problems because zinc is essential for immune system maintenance, wound healing, and antioxidant protection (Mussa, 2007). On the other hand, high levels of copper can intensify oxidative stress and raise the risk of cardiovascular complications, which are a major cause of morbidity and mortality among hemodialysis patients, by catalyzing the production of reactive oxygen species (Alturfi & Hamzah, 2024; Takahashi et al., 2019). To reduce these risks, regular monitoring of these trace elements combined with focused nutritional interventions may be helpful. Our results further corroborate the view expressed by Wastawy et al. (2023) that correcting these imbalances by dietary changes and supplementation may enhance patient outcomes.

To thoroughly evaluate the connections between trace element levels and clinical variables, our study employed sophisticated statistical methods, such as independent samples t-tests, one-way ANOVA, Pearson and Spearman correlation analyses, multiple linear regression, ANCOVA, and structural equation modeling. For instance, our multiple regression analysis showed that factors including smoking status, age, and length of hemodialysis were significant predictors of serum zinc levels, explaining 38% of the variance. Furthermore, even after controlling for variables like BMI and dialysis duration, ANCOVA data demonstrated significant variations in serum copper levels remained among age groups. The direct detrimental effect of extended hemodialysis on zinc levels and the positive correlation between BMI and copper levels were further confirmed using the structural equation model, confirming the proposed interdependencies between these variables.

5. Conclusion

The results of this study show that patients receiving hemodialysis at Rasul Akram Hospital had notable trace element imbalances, as evidenced by decreased serum zinc and increased serum copper levels. A number of variables, including age, smoking status, and the length of hemodialysis, affect these imbalances. Considering the vital functions of copper and zinc in antioxidant defense, immunological response, and general metabolic control, our results highlight the need of routinely checking these trace elements in hemodialysis patients. Specific dietary measures, such as zinc supplements and maybe copper level management techniques, might be required to enhance clinical results and lower the risk of consequences including malnourishment and cardiovascular disease. Interventional studies to evaluate the effectiveness of supplementation regimens customized for each patient's unique profile should be the main focus of future research. In the context of hemodialysis, additional research into the mechanisms underlying the interaction between zinc and copper metabolism may also yield important information for creating more potent treatment plans. All things considered, our research advances our knowledge of trace element abnormalities in hemodialysis patients and makes clear how these biomarkers may be used to gauge nutritional status and the course of the disease.

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