Al-Azhar International Medical Journal

Volume 4 | Issue 3 Article 14

2023

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How to Cite This Article

Ahmed, Safwat Farrag; Rashed, El-Said Mohamed; Mohamed, Hala Ibrahim; and EL-Hussieny, Mahmoud Mohamed Al-Shahat (2023) "Relation between serum zinc and Erythropoietin responsiveness in prevalent Hemodialysis patients," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 3, Article 14.
DOI: https://doi.org/10.58675/2682-339X.1691

ORIGINAL ARTICLE

Relation Between Serum Zinc and Erythropoietin Responsiveness in Prevalent Hemodialysis Patients

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Abstract

Background: **Hemodialysis (HD) is a blood purification treatment that mainly aims to equilibrate the composition of the patient's sera and the dialysate over a semipermeable dialyzer membrane in order to eliminate metabolic waste products. The equilibrium of solutes across the dialyzer membrane is affected by a wide variety of parameters. Due to zinc elimination during HD, decreased serum albumin levels, insufficient nutritional intake, and poor gastrointestinal absorption of zinc, patients on HD have been observed to have low blood concentrations of zinc.**

Patients and methods: **This cross-sectional study was recruited 50 patients with chronic kidney disease who attended outpatient department of Nephrology in National Institute of Nephrology & Urology. The duration of the study ranged from 6 to 12 months. All patients were subjected to full history taking, clinical examination, medication use, and Laboratory Investigations. Zinc and Ferritin were measured.**

Results: **Mean age 52.16 ± 11.91 years, 66% of the patients were females and 34% of the males with 25.45 ± 3.61 kg/m2. Mean hemoglobin was 9.95 ± 1.25 g/dl, and mean CRP was 8.21 ± 2.14 U/l. Mean ferritin was 521.49 ± 143.05 ng/ml, mean TIBC was 308.56 ± 44.35 µg/dl, and mean T-sat was 36.05 ± 8.98%. mean HD duration was 49.3 ± 55.17 months, mean KT/V was 1.26 ± 0.245, median EPO dose was 8000 IU per week, and mean ERI was 9.42 ± 4.77 There was a negative significant correlation between zinc with disease duration, ferritin, TIBC, CRP, and ERI.**

Conclusion: **In conclusion, there was a negative significant correlation between zinc with disease duration, ferritin, TIBC, CRP and ERI. Zinc and HD duration found to be independent factors that influencing ERI in HD patients.**

Keywords: Erythropoietin, Hemodialysis, Zinc

1. Introduction

Renal function and/or structure are permanently altered in patients with chronic kidney disease (CKD), a condition that worsens over time. Morbidity and death rates are higher among those who have chronic renal disease, particularly those who also have cardiovascular disease.[1]

Predictive Factors of Renal Injury Renal imaging alterations and albuminuria Renal biopsy alterations include hemorrhage and a rise in white blood cells in the urine, as well as chronic shifts in blood volume and electrolyte balance[2]

The prevalence of CKD in the population at large is high. The estimated frequency among adults in the United States is 13.1% and rising. According to the Global Burden of Disease survey, among nations with an average socioeconomic status, CKD ranks as the tenth largest cause of mortality.[3]

More than 1.4 million people throughout the world are on renal replacement treatment, and that figure is rising at an annual incidence rate of 8%.[4]

The prevalence of end-stage renal disease (ESRD) in Egypt increased to 483 people per million in 2016, according to the 9th Annual Report of The Egyptian Renal Registry published by the Egyptian Society of

Accepted 9 October 2022.
Available online 12 June 2023

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https://doi.org/10.58675/2682-339X.1691

Nephrology and Transplantation. Roughly 49.8 years old on average, give or take 19. Males accounted for 55.2% of the total, while females made up just roughly 44.8%.[5]

An erythropoiesis-stimulating agent (ESA) and iron supplements are the major therapy options for anemia in ESRD. The problem of considerable variation in the ESA dose needed to attain target hemoglobin concentration among ESRD patients is crucial in the treatment of this kind of anemia. Factors including iron insufficiency, chronic blood loss, inflammation, vitamin deficiencies, erythropoietin antibodies, and hyperparathyroidism have been linked to ESA hypo-responsiveness, however this is not evident in patients' hemoglobin levels.[6]

Very few investigations have looked at the role of extraneous variables in hypo-responsiveness. Due to zinc elimination during hemodialysis (HD), decreased serum albumin levels, insufficient nutritional intake, and poor gastrointestinal absorption of zinc, patients on HD have been observed to have low blood concentrations of zinc. Increased production of intracellular metallothionein after oxidative stress or up-regulation of zinc importing proteins by pro-inflammatory cytokines may also lead to decreased serum zinc levels.[5,6]

We evaluated shifts in hemoglobin, zinc, iron, ferritin, and ESA dosing to learn how serum zinc is related to erythropoietin responsiveness in commonly seen HD patients.

2. Patients and methods

This cross-aectional study recruited 50 patients with CKD who attended outpatient department of Nephrology in National Institute of Nephrology & Urology. Inclusion Criteria was Patient's age of more than 18 and less than 65 years old, Patients with CKD undergoing regular HD for at least 6 months and Anuretic patients. Patient's age of less than 18 and more 65 years old, Patients on other conservative treatment and Patients with other chronic illness mainly patients with chronic liver disease and congestive heart failure and malignancy were excluded from the study.

A complete patient evaluation including a thorough history, physical exam, medication list, and laboratory tests were performed on all patients (Complete Blood Count-Serum Zinc − Serum Iron − Serum Ferritin). The results reported here were collected from individuals with arteriovenous fistula who were receiving HD for maintenance purposes three times per week for a total of around 4 h each session. The information was gathered throughout the course of three HD sessions, each lasting one week, with three, two, and two days, respectively, between dialysis treatments. To eliminate the potential confounding impact of BV changes, the researchers chose a session in which the patients did not receive any additional fluid infusions or eat or drink throughout the experiment. Before each dialysis session, the extracorporeal circuit was filled with the patients' blood, at which point the priming saline was administered into the patients.

All session parameters, including dialyzer blood flow rate, ultrafiltration rate, and dialysis fluid composition, were maintained at their previous values. The dialysate flow rate was maintained at 500 ml/min, while the temperature was held constant at 36 °C. Dialysis was performed using low flux dialyzers. Each patient stayed in the same posture during each dialysis treatment.

At the start and finish of each dialysis session, blood samples were taken from the arterial HD line. Advia 2120, an automated hematology analyzer, was used to determine blood type and other hematological characteristics (Siemens Healthcare, Erlangen, Germany). With the cyanide-free hemoglobin technique and colorimetric optical measurements, we were able to determine the hemoglobin concentration in blood (after erythrocyte lysis). Advia 2120 system technical specifications state that for RBC, MCV, and hemoglobin concentration measures, the coefficient of variation is 1.2, 0.78, and 0.93%, respectively. Dynamic Reaction Cell II Inductively Coupled Plasma Mass Spectrometry was used to determine zinc concentration.

Using Roche kits and a Hitachi 912 clinical analyzer, Ferritin concentrations were determined by immunoturbidimetry. Anti-Ferritin antibodies immobilized on latex beads react with sample antigen to create an antigen–antibody complex. The turbidity was measured once the agglutination process was complete.

Unless otherwise specified, all data will be reported as mean SD, and statistical significance will be established at a p value 0.05. A t-test will be used to compare the different variables. Spearman's correlation coefficient (R) was used to examine the degree of statistical reliance between variables.

3. Results

The mean age 52.16 ± 11.91 years, 66% of the patients were females and 34% of the males with 25.45 ± 3.61 kg/m^2 (Table 1).

The mean ferritin was 521.49 ± 143.05 ng/ml, mean TIBC was 308.56 ± 44.35 μg/dl, and mean T-sat was 36.05 ± 8.98% (Table 2).

Table 3 The mean hemoglobin was 9.95 ± 1.25 g/dl, mean CRP was 8.21 ± 2.14 U/l, The mean TC was

Table 1. Demographic distribution among the studied patients.

Variable	Studied patients ($n = 50$)
Age (years)	
Mean ± SD	52.16 ± 11.91
Range	32–85
Sex	
Female	33 (66%)
Male	17 (34%)
BMI (kg/m^2)	
Mean ± SD	25.45 ± 3.61

Table 2. Iron panel distribution among the studied patients.

Variable	Studied patients ($n = 50$)
Ferritin (ng/ml)	
Mean ± SD	521.49 ± 143.05
TIBC (μg/dl)	
Mean ± SD	308.56 ± 44.35
T-saturation (%)	
Mean ± SD	36.05 ± 8.98

Table 3. Lab parameters among the studied patients.

Variable	Studied patients ($n = 50$)
Hemoglobin (g/dL)	
Mean ± SD	9.95 ± 1.25
CRP (U/l)	
Mean ± SD	8.21 ± 2.14
TC (mg/dl)	
Mean ± SD	206.41 ± 46.69
TG (mg/dl)	
Mean ± SD	196.7 ± 57.76

Table 4. Zinc distribution among the studied patients.

Variable	Studied patients ($n = 50$)
Zinc (μg/dl)	
Mean ± SD	64.88 ± 8.6
Range	48–79

206.41 ± 46.69 mg/dl and mean TG was 196.7 ± 57.76 mg/dl.

The mean Zinc was 64.88 ± 8.6 μg/dL (Table 4).

The mean HD duration was 49.3 ± 55.17 months, mean KT/V was 1.26 ± 0.245, median EPO dose was 8000 IU per week, and mean ERI was 9.42 ± 4.77 (Table 5).

Table 5. Clinical characteristics among the studied patients.

Variable	Studied patients ($n = 50$)
HD duration (months)	49.3 ± 55.17
Median (range)	30 (6–300)
KT/V	
Mean ± SD	1.26 ± 0.245
EPO dose (IU/week)	8000
Median (range)	(4000–12000)
ERI	
Mean ± SD	9.42 ± 4.77

Table 6. Correlations between zinc and other parameters among the studied patients.

Variable	Zinc	
	r	*P*
Age	0.218	0.188
Disease duration	**−0.369**	**0.013**
BMI	−0.062	0.669
EPO dose	−0.021	0.885
Hemoglobin	0.081	0.576
Ferritin	**−0.558**	**0.002**
TIBC	**−0.497**	**0.007**
CRP	**−0.431**	**0.031**
TC	0.237	0.097
TG	0.047	0.747
ERI	**−0.498**	**0.000**

There was a negative significant correlation between zinc with disease duration, ferritin, TIBC, CRP, and ERI (Table 6).

This table shows that zinc and HD duration found to be independent factors that influencing ERI in HD patients (Table 7).

4. Discussion

Using a semipermeable dialyzer membrane, HD is a blood purification treatment that mainly equilibrates the composition between the patient's sera (higher concentrations) and the dialysate (lower concentrations) to eliminate metabolic waste products ('uremic toxins').[7]

Due to zinc elimination during HD, decreased serum albumin levels, insufficient nutritional intake, and poor gastrointestinal absorption of zinc, patients on HD have been observed to have low blood concentrations of zinc. Increased production of intracellular metallothionein after oxidative stress or up-regulation of zinc-importing proteins by pro-inflammatory cytokines are two additional mechanisms by which serum zinc levels might be depleted. It is unclear how zinc deficiency contributes to renal anemia in HD patients on ESA medication.[8]

The primary objective of this research was to examine the impact of changes in hemoglobin, zinc, iron, ferritin, and ESA dose on the relationship between serum zinc and erythropoietin responsiveness in commonly treated HD patients. Fifty CKD patients who visited the outpatient department of Nephrology at the National Institute of Nephrology and Urology were included in this cross-sectional research. Six months to a year was the time frame of the research.

As regard demographic characteristics of studied cases. The mean age 52.16 ± 11.91 years, 66% of the patients were females and 34% of the males with 25.45 ± 3.61 kg/m2.

While in the study of (Kulkarni et al.),[9] There were a total of 464 patients in the trial, with men making

Table 7. Multivariate linear regression analysis of factors influencing ERI in HD patients.

Independent variables	Unstandardized B Coefficients (95% CI)	Standardized B Coefficients	Sig.
HD duration (Months)	47.056 (12.538–81.575)	0.244	**0.009**
Zinc (μg/dl)	0.089 (0.013–0.165)	0.221	**0.023**
$r^2 = 0.69$			

up 68% (317) of the sample. The mean age of the patients was 47.2 years, and the majority were between the ages of 40 and 59.

However, in the study of (Dashti-Khavidaki et al.),[10] The research included 94 participants: 60 men and 34 females (mean age: 52.90 18.28 years), and 47 age-matched controls: 26 males and 21 females (mean age: 46.70 18.28 years).

The current study showed that as regard iron panel distribution among the studied patients: the mean ferritin was 521.49 ± 143.05 ng/ml, mean TIBC was 308.56 ± 44.35 μg/dl, and mean T-sat was 36.05 ± 8.98%.

Our results were supported by the study of (Kaneko et al.),[11] as they reported the mean transferrin saturation was 31%. While the mean ferritin was 125.2 ng/ml.

However (Kulkarni et al.),[9] revealed that patients had a mean hemoglobin of 9.4 g/dL, with 14% (n = 65) having a hemoglobin value of 7 g/dL. The iron levels of around 15% of the patients were checked. Ferritin levels averaged 828.65 ng/dL.

In the study in our hands, the mean TC was 206.41 ± 46.69 mg/dl, **mean TG was 196.7 ± 57.76 mg/dl,** mean HDL was 36.65 ± 17.37 mg/dl, and mean LDL was 115.39 ± 53.37 mg/dL.

While, in the study of (Kobayashi et al.),[12] the mean TC was 150 ± 28 mg/dl, mean **TG was 110 ± 52 mg/dl.**

In the study of (Kaneko et al.),[11] the mean TC was 190.9 ± 45.2 mg/dl, **mean TG was 113 mg/dl,** mean HDL was 91.8 ± 36 mg/dl, and mean LDL was 46.7 ± 14.2 mg/dL.

The current study showed that mean HD duration was 49.3 ± 55.17 months, mean KT/V was 1.26 ± 0.245, median EPO dose was 8000 IU per week, and mean ERI was 9.42 ± 4.77.

Our results were in line with study of (Kobayashi et al.),[12] as they reported that the mean ERI was 10.5 ± 5.2. However, the mean HD duration was 66 ± 45 months.

In the study of (Kaneko et al.),[11] the median dialysis period was 23.6 [20.8–25.4] months.

The present study showed that the mean Zinc was 64.88 ± 8.6 μg/dl. **There was a negative significant correlation between zinc with disease duration, ferritin, TIBC, CRP and ERI.**

(Kobayashi et al.),[12] found that serum ferritin and copper levels were decreased by zinc supplementation.

Furthermore (Dashti-Khavidaki et al.),[10] demonstrated that 57.83% of HD patients had zinc deficiency, defined as a blood Zn value of 70 ng/dL or below. Except for total bilirubin, they found no association between serum Zn levels and any of the other lab values. The average blood zinc concentrations of patients on calcium carbonate, sevelamer, intravenous iron, calcitriol, or erythropoietin were not significantly different from those of patients taking any of the control medications. However, a positive connection was found between serum Zn content and daily dosage of EPO (erythropoietin) ($r = 0.24$, $P = 0.03$). No association was seen between serum Zn levels and HD frequency or duration of HD use.

Studies conducted by (Bozalioglu et al.),[13], (Mariak & Grzegorzewska)[14] have documented inverse correlation of serum Zn levels and age both in HD and peritoneal dialysis patients.

In meta-analysis held by (Elgenidy et al.),[15] included a total of 42 studies with 4161 individuals; 460 represented CKD patients and 2047 represented HD patients. A total of 1654 people were included as healthy comparisons. Lowered blood zinc levels were seen in CKD and HD patients as compared to HC (mean difference = −22.86 g/dl, 95% CI [−33.25, −12.46]; mean difference = −13.64 g/dl, 95% CI [−21.47, −53.80]). However, there was no statistically significant difference between CKD and HD patients' blood zinc levels (mean difference = 15.39, 95% CI [−8.91, 39.68]). Serum zinc levels were considerably lower pre-HD compared to post-HD (mean difference = −7.51 g/dl, 95% CI [−14.24, −0.78]).

4.1. Conclusion

In conclusion, there was a negative significant correlation between zinc with disease duration, ferritin, TIBC, CRP and ERI. Zinc and HD duration found to be independent factors that influencing ERI in HD patients.

Authorship

All authors have a substantial contribution to the article.

Conflicts of interest

The authors declared that there were NO conflicts of Interest.

Acknowledgements

Disclosure: The authors have no financial interest to declare in relation to the content of this article.

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