Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 4, July 2024
Manuscript ID ZUMJ-2310-2988 (R2)
DOI 10.21608/ZUMJ.2023.244431.2988

Original Article

Oral Zinc Supplementations as Adjuvant Therapy in the Treatment of Anemia in Maintenance Hemodialysis Patients with Hypozencemia

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Submit Date 15-11-2023
Revise Date 20-11-2023
Accept Date 20-11-2023

ABSTRACT:

Background: Regular hemodialysis patients are at an increased risk of developing anemia due to multiple causes. Some research has suggested that hypozencemia may contribute to anemia in regular hemodialysis patients. Objective: Evaluation of the effect of zinc supplementation in the treatment of anemia in regular hemodialysis patients with hypozencemia. **Methods:** An intervention study(open labeled) that was conducted on 54 anemic regular hemodialysis patients with hypozencemia was divided into 2 groups: group I (zinc supplementation group), which included 27 cases, and group II (control group), which included 27 controls. All patients were followed up for 6 months. **Results:** post-zinc treatment, group 1 showed a statistically significant increase in serum zinc level, whereas group 2 showed no statistically significant difference in serum zinc level *($p<0.05$*). Serum iron and transferrin saturation showed no statistically significant difference before and after follow-up in both groups*($p>0.05$*).. haemoglobin level showed a statistically significant increase between baseline and six months. meanwhile, after 3 to 6 months, there was a statistically significant increase in haemoglobin in group 1 compared to group 2*($p<0.05$*). There was no statistically significant difference between the two groups regarding haemoglobin, serum zinc, C-reactive protein, ferritin, and erythropoietin resistance index before the start of the study*($p>0.05$*). Erythropiotine dosage showed a statistically significant decrease from baseline to 6 months in group I*($p<0.05$*). Logistic regression analysis revealed that the age of the patients, change in zinc, and EPO change are the best determinants affecting the responsiveness of the patient's Hb to treatment **CI 95%:5.8,** highly significant p<0.01. **Conclusions**: Oral zinc supplementation, when used as adjuvant therapy, may have a positive impact on haemoglobin levels and erythropiotine, utilization in hemodialysis patients with hypozencemia.

Keywords: hypozencemia; hemolysis patients; anemia; zinc supplementation

INTRODUCTION:

Renal anemia is a severe complication in patients treated with hemodialysis. Anemia is a common complication among maintenance hemodialysis patients and is associated with poor quality of life and increased morbidity and mortality. One potential contributing factor to anemia in this

population is zinc deficiency, as zinc is essential for erythrocyte production and maturation [1].

Initial treatment for renal anemia consisted only of blood transfusions and massive dosages of iron until recombinant human erythropoietin (rhEPO) was clinically introduced in 1990. The rhEPO has changed renal anemia therapy for hemodialysis patients significantly [2].

Erythropoietin Resistance Index (ERI) is defined as the average weekly erythropoietin (EPO) dose per kg body weight (wt) per average haemoglobin (Hgb) over 3 months (ERI = (EPO/wt)/Hgb). It is an important evaluation index to evaluate the EPO's responsiveness [3].

EPO-hyperresponsiveness is defined as the inability to maintain a desired haemoglobin (Hgb) level despite a dose of 450 U/kg/week of intravenous (IV) EPO [4].

Zinc is an essential micronutrient that is necessary for the proper functioning of the body's systems. It plays a vital role in various physiological processes, including erythropoiesis, which is the process of producing red blood cells (RBCs) [5].

Regular hemodialysis patients, who undergo regular dialysis to remove waste and excess fluids from the body, are at an increased risk of developing anaemia due to multiple causes, like loss of blood during the procedure and the reduced ability of the kidneys to produce erythropoietin, a hormone that stimulates the production of RBCs. Some research has suggested that zinc deficiency may contribute to anemia in maintenance hemodialysis (MHD) patients [6].

Therefore, this study aimed to assess the effect of zinc supplementation on haemoglobin levels in regular hemodialysis patients with anemia on Epo. To evaluate the effect of zinc supplementation on the erythropoietin resistance index in regular hemodialysis patients with anemia. Also, to assess the safety and tolerability of zinc supplementation in regular hemodialysis patients with anemia,

METHODS

This intervention study(open labeled) study was conducted in the internal medicine department (Dialysis Unit) of Zagazig University Hospital. It was done from January 2023 to October 2023. Patients were followed up for 6 months.

Sample size: Assuming the mean HB level was 9.17 ± 1.43 vs 8.16 ± 1.16 in zinc treated group vs control group. At 80% power and 95% Cl, the estimated sample will be 54 cases, 27 cases in each group at Open Epi.

The included 54 regular hemodialysis patients, divided into two groups:

Group 1: (zinc group): 19 males and 8 females with an age of 65 ± 12 years.

Group 2: (control group): 22 males and 5 females with an age of 67 ± 9 years.

Inclusion criteria:

Male or female regular hemodialysis patients aged 18 years or older. Diagnosis of anemia as defined by haemoglobin levels below 11 g/dl. Stable regular hemodialysis regimen with an average of three dialysis sessions per week. Serum zinc level below 70 ug/dl. They were divided into two groups: group one (the zinc supplementation group) and group two (the control group).

Exclusion criteria:

- Known hypersensitivity or intolerance to zinc or any ingredients in the zinc supplement.
- Pregnancy or breastfeeding.
- Use of any medications known to interfere with zinc metabolism or absorption (e.g. penicillamine, tetracycline).
- Patients undergoing surgical treatment, are considered to possibly affect anemia during the study period.
- Recent blood transfusion within one month before the start of the study.
- Hemorrhagic events detected by bleeding per orifice.
- Infection and inflammation.
- Proved malignancy.

Criteria for patients' withdrawal from the study :

- Patients developed allergy or hypersensitivity to zinc supplementations.
- Patients developed zinc side effect during zinc supplementations.

Clinical Assessment:

All patients were subjected to detailed history-taking, including personal history, present history of the disease, and family history of previous medication. Demographics such as age, gender, duration of diabetes, and co-morbidities were noted in a self-structured questionnaire. A complete general examination was performed. Zinc sulphate at a dosage of 50 mg/day was administered to patients after breakfast as the adjuvant zinc therapy in the zinc group. Zinc concentration was measured before the start of the study and at the end. A complete blood count was measured regularly every month for 6 months. The iron profile (serum iron, serum ferritin, TIBC, and transferrin saturation) was measured at the start and after 3 months. C-reactive protein and PTH levels were measured at the start of the study. Routine investigations (serum creatinine, urea, calcium, and phosphorus) before the start of the study. During the treatment period, the rhEPO dosage was reduced when the haemoglobin (Hb) level exceeded 11 g/dl.In addition, patients with decreased iron or ferritin levels were started on IV iron supplements (serum ferritin<100 ng/ml or tsat< 20%).

Laboratory measurements:

A complete blood picture (CBC) was assessed by Sysmex XN-2000 (Siemens, Germany). Serum creatinine, blood urea nitrogen, serum calcium, serum phosphorus, C-reactive protein (CRP), and serum ferritin were measured by Cobas 8000 (Roche Diagnostics, Japan). Iron profile: serum iron and total iron binding capacity (TIBC) were determined by Cobas 6000 (Roche Diagnostics, Japan). Determination of serum intact PTH (iPTH) was performed by electrochemiluminescence immunoassay (ECLIA) using Cobas 6000 (Roche Diagnostics, Japan). Serum zinc concentration was determined by a colorimetric method using the 5BromPAPS reagent.

Statistical analysis:

The statistical analysis of the collected data was performed using the SPSS program (Statistical Package for Social Science), version 23.0. The Chi-square ($\chi 2$) test or the Monte Carlo test was used to compare qualitative data, which were reported as frequencies and relative percentages. Categorical variables were interpreted as the number (percentage), while quantitative variables were presented as mean ± SD (Standard deviation). All normally distributed data were expressed as mean and SD, and were analyzed using the Independent Student T (t) test to differentiate between two groups' quantitative variables, While data that was not normally distributed was shown as a median and range. Data found to be non-normally distributed were analyzed using the Mann-Whitney U (MW) test to calculate the difference between quantitative variables in 2 groups. One-way ANOVA F-test was used to calculate the difference between quantitative variables in the four studied groups in normally distributed data. Post-hoc Highst Significant Difference test (HSD) tests were used according to homogeneity of variances. The Spearman's rank correlation coefficient (for not normally distributed data) and Pearson correlation coefficient (for normally distributed data) were used to determine the strength and direction of correlations various study parameters. The significance level for all above mentioned statistical tests was done. The threshold of significance is fixed at 5% level (P-value). P value of ≥ 0.05 was considered non-statistically significant (NS). P value of <0.05 indicates statistically significant results (S). P value of < 0.001 was considered highly statistically significant (HS).

RESULTS:

The present study showed no statistically significant difference between the two groups as regards the demographic data or comorbidities (Table 1). There was no statistically significant difference between the two groups regarding baseline lab investigations (Table 2). There is a statistically significant higher zinc level in group I than group II; moreover, serum ferritin was found to be significantly higher in group II than group I after follow-up (Table 3).The Hb level showed a statistically significant increase in group I than group II $p<0.05$. (Figure 1). Epo dosage showed a statistically significant decrease in group I than in group II $p<0.05$. (Figure 2). Logistic regression analysis revealed that age of the patients, change in zinc, and EPO change are the best determinants affecting the responsiveness of the patient's Hb to treatment CI 95% were (4.8, 6.3, and 4.3)

respectively and p values were (0.0466, 0.0001 and 0.023) respectively (Table 4).

Table (1): Demographic data and comorbidities of the study patients

Variables	Zinc group(Group1) N=27	Control group(Group2) N=27	Test	P-value
Age: Mean ± SD	65 ± 12	67 ± 9	t=0.988	0.797
Sex				
Male	19 (70.4%)	22 (81.5%)	X^2=1.188	0.811
Female	8 (29.6%)	5 (18.5%)		
Body mass index (kg/m^2): Mean ± SD	21.5 ± 3.5	21.8 ± 3.2	t=1.398	0.715

***Significant p<0.05. *** highly Significant p<0.01**

Table (2): Comparison between Group I and Group II regarding baseline lab investigations

Variables	Zinc group(Group1) N=27	Control group(Group2) N=27	Test	P-value
Hemoglobin (g/dL) Mean ± SD	9.67 ± 1.27	9.8 ± 1.08	t=0.876	0.171
Erythropoietin responsiveness index:Mean ± SD	10.5 ± 5.2	10.2 ±8.0	t=0.976	0.851
Serum zinc (µg/dL): Mean ± SD	53 ± 6	55 ± 5	t=1.734	0.427
Serum creatinine (mg/dL): Mean ± SD	8.2 ± 1.3	8.3 ± 1.2	t=0.723	0.831
Serum urea nitrogen (mg/dL): Mean ± SD	67 ± 9	78 ± 9	t=0.867	0.376
CRP (mg/dL): Mean ± SD	19 ± 16	21 ± 17	t=1.321	0.561
Corrected Calcium(mg/dL): Mean ± SD	8.7 ± 0.5	8.6 ± 0.4	t=0.712	0.362
Phosphate (mg/dL): Mean ± SD	5.7 ±0.5	5.6 ± 0.5	t=0.821	0.860
Intact PTH (pg/mL): Mean ± SD	195±113	214 ±98	t=0.912	0.241
Serum ferritin (ng/mL): Mean ± SD	142 ± 74	145 ± 85	t=0.732	0.210

CRP : C-reactive protein I pth : intact parathormone

Table (3): comparison of serum Zinc, iron, TSAT, and ferritin after the end of the study in both groups.

Variables	Zinc group(Group1) N=27	Control group(Group2) N=27	Test	P-value
Serum zinc (µg/dl)	83 ± 27	54 ± 4.5	13.95	<0.001**
Serum iron (µg/dl)	72 ± 13	69.9 ± 15	0.765	0.114
TSAT (%)	28.13 ± 7	27.24 ± 5.7	0.897	0.610
Serum ferritin (ng/ml)	115 ± 32	169.9 ± 56	3.215	0.031*

Table (4): Logistic regression analysis including all determinants affecting change in Hb in the zinc group.

Variables	95% CI			P value
	Lower	Upper	Odds (CI 95%)	
Age	−0.0398	0.0546	4.8	0.0466 ***
Hemodialysis duration	−0.0238	0.0259	0.6	0.9327
Male sex	−0.4542	0.3637	0.30	0.8188
Diabetes	−0.4268	1.0657	0.9	0.3842
Kt/V average	−2.4126	9.1190	0.8	0.2375
Change in serum zinc	−0.0740	−0.0219	6.3	0.0001 ***
EPO dose change	−1.332	−0.0352	4.3	0.023***

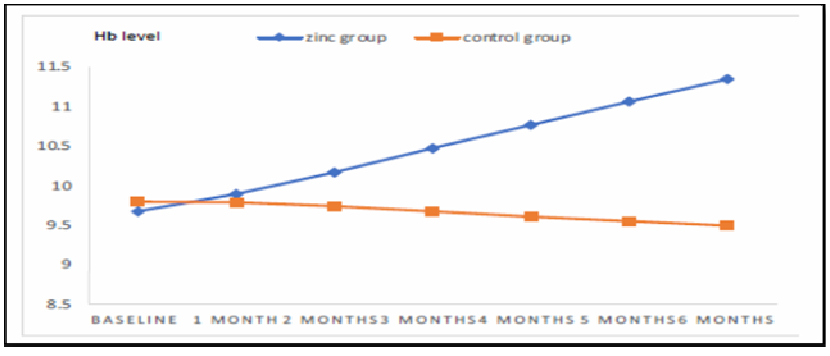

Figure 1: Changes in hemoglobin (Hb) during the study period. Data are expressed as mean (*p<0.05*).

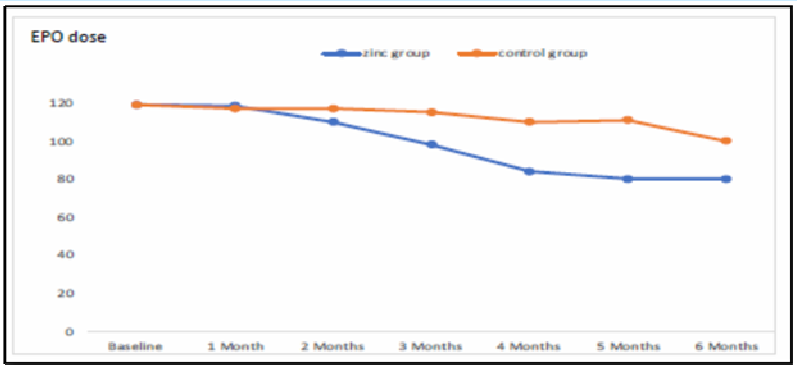

Figure 2: Changes in the required monthly recombinant human erythropoietin dosage during the study period. EPO, erythropoiesis-stimulating agent, *(p<0.05).*

DISCUSSION:

Anemia is a common complication among maintenance hemodialysis patients and is associated with poor quality of life and increased morbidity and mortality. One potential contributing factor to anemia in this population is zinc deficiency, as zinc is essential for erythrocyte production and maturation **[1]**.Patients undergoing hemodialysis (HD) have been found to have low serum concentrations of zinc due to zinc removal during HD and decreased serum albumin levels, as well as inadequate dietary intake and reduced gastrointestinal absorption of zinc. Serum zinc levels can also be reduced by increased expression of intracellular metallothioneins following oxidative stress or up-regulation of zinc-importing proteins by pro-inflammatory cytokines **[7].**

Zinc is a component necessary for the activation of more than 300 types of enzymes. It also plays an important role in cell division and nucleic acid metabolism. Over-the-counter supplements are also available. Zinc has various physiological effects, including an increase in height (in children), skin metabolism, reproductive function, skeletal development, taste, maintenance of sensation, mental or behavioral effects, and immune function **[8].**

On the other hand, treatments for zinc deficiency have not progressed sufficiently. Zinc supplementation from dietary intake is possible but is not appropriate for patients with chronic kidney disease (CKD) because it requires a high-protein diet, such as oysters, which causes hypernitrogenemia. Since some gastric drugs contain zinc, they have long been administered for zinc supplementation **[8]**.

Thus, treatment for zinc deficiency has remained problematic. The recent launch of zinc acetate hydrate and its subsequent administration to several patients have been the latest developments in the treatment of zinc deficiency. The use of zinc acetate hydrate, a drug for the treatment of Wilson's disease, has been extended to treat hypozencemia**[9].**

This is An intervention study(open labeled) study that was conducted in the internal medicine department (dialysis unit) at Zagazig University Hospital on 54 subjects: 27 cases and 27 controls. The study aimed to evaluate the effect of zinc supplementation on anemia treatment in hemodialysis patients with hypozencemia.

The distribution of comorbidities in hemodialysis patients was comparable to our results. Thus, in a study by **Kobayashi et al. [7],** who reported that diabetes mellitus was 16 (45.7) in the zinc group, 15 (42.8) in the control group, and cardiovascular comorbidity 6 (17.1) in Polaprezinc Group 5 (14.2) in the Control Group

In this study, we reported that the group I (Zinc Group) mean hemodialysis duration was 66 months and for group II (control group) ,it was found 64 .There was no significant difference between the two groups. Also, **Kobayashi et al. [7]** found a hemolysis duration (mo) of 66 ± 45 in the zinc group and 64 ± 43 in the control group.

In this study, the serum zinc (µg/dL) in the hemodialysis patients was 53 ± 6 in the group receiving zinc and 55 ± 5 in the control group.

In clinical practice, **Maruyama et al. [10]** found that, out of 816 patients with conservative renal failure, 52.3% had a marginal serum zinc deficiency (60–80 µg/dL), whereas 30.6% had an absolute deficiency (<60 µg/dL), indicating that hypozencemia may already be present during the renal failure stage before dialysis.

In line with us, **Fukushima et al. [11]** found no significant differences were seen between the two groups for total protein or albumin level or in the dialysis efficiency measured by Kt/V.

In our study, there was no statistically significant difference between the two groups (Zinc and control) regarding baseline lab investigations.

Similarly, **Kobayashi et al. [7]** found that there were no significant changes in red blood cell (RBC) counts or Hb levels within groups or between the control and polaprezinc groups during the 12-month study period.

The main result of our study revealed that after follow-up, it was found that the level of serum zinc was statistically significantly higher than before. On the other hand, there is a statistically significant higher zinc level in group I (the zinc group) than group II (the control group).

Similar to our results, **Fukushima et al. [11]** reported that, compared to the baseline, zinc concentration increased significantly at 1 month at the latest and was maintained within the normal range (80 to 120 mg/dL) on average for a period of one year.

In our results, Epo dosage showed a statistically significant decrease from baseline to three months, four months, five months, and six months. This finding is considered to be the consequence of reducing EPO dosage with the improvement of anemia. Still, despite the reduced EPO, Hb levels were found to continue rising significantly. The Hb level showed a statistically significant increase from baseline to two months, three months, four months, five months, and six months. Moreover, serum ferritin was found to be significantly higher in group II than group I after follow-up.

A study supported our results by **Kobayashi et al. [7],** who reported the dose of ESA (recombinant human erythropoietin) was significantly decreased at 10 months after polaprezinc treatment compared to the baseline values; this was continued to the end of the study. However, there was no significant difference in the ESA (recombinant human erythropoietin) dose between the two groups. ERI (erythropoietin responsiveness index) was significantly decreased at nine months compared with the baseline value in the polaprezinc group; the decrease persisted until the end of the study. Furthermore, a significant difference in ERI (erythropoietin responsiveness index) was observed between the groups from 10 to 12 months.

Also, **Fukushima et al. [11] treated** the patients with polaprezinc. Significantly decreased erythropoietin dosage (7125± 1196 units/week vs. 5427± 2860 units/week, P < 0.001) was also confirmed in the treatment group. They also reported that in patients with zinc and iron deficiency and ESA-hypo responsive anemia, zinc supplementation leads to improvement of anemia in a shorter duration.

A study by **Sato et al. (9)** demonstrated that the ESA dose significantly decreased, from 0–12,000 IU/week (5630 ± 3351 IU/week) to 0–9000 IU/week (4428± 2779; p = 0.04); and ERI significantly decreased, from 0.0–18.2 (8.1 ± 5.1) to 0.0–
16.0 (6.3 ± 4.3; p = 0.04) that was agreeable with us.

This study revealed that the age of the patients, changes in serum zinc, and EPO dose change are the best determinants affecting the responsiveness of the patients Hb to treatment.

Similar to our findings, **Fukushima et al. [11]** reported that all the parameters showed a significant positive correlation: red blood cell (RBC) count (r = 0.210, r2 = 0.044, P = 0.028), haemoglobin (Hb) level (r = 0.6899, r2 = 0.4759, P < 0.001),
hematocrit (Ht) level (r = 0.2147, r2 = 0.044, P = 0.024), and reticulocyte (Ret) (r = 0.2559, r2 = 0.0654, P = 0.007). Particularly, a very high correlation was confirmed in the Hb parameter. These findings indicate that anemia improves in patients with high serum zinc values.

In contrast to our study, **Matson et al. [12] reported that** the differences in serum zinc

levels were not statistically significant between the treatment and placebo groups.

A cause of excess loss of zinc is removal by hemodialysis. A total of 80% of zinc in the blood is found in RBCs, most of which is carbonic anhydrase (a zinc-requiring enzyme). The remaining zinc (approximately 20%) is present in serum, 60%–80% of which is bound to albumin and is not removed by hemodialysis. Other zinc in serum is bound to alpha-2 macroglobulin, but a small amount of this is bound to amino acids, such as cysteine, which are removed by hemodialysis **[13].**

Another study by **Fukushima et al. [11]** reported that the serum zinc concentration during the screening was 63.29 ± 9.91 µg/dL for the polaprezinc treatment group and 68.08 ± 12.57 µg/dL for the nont-reatment group, in contrast to our study, as the serum zinc level showed a statistically significant increase in group 1 compared to group 2.

On the other hand, **Sato et al. [9]** reported that blood Hb did not change significantly, from 10.0–13.6 g/dL (11.5 ± 1.0 g/dL) to 10.2–12.4 g/dL (11.4 ± 0.7 g/dL), which was in contrast to our results.

Another study by **Kobayashi et al. [7]** reported that the change in serum zinc levels was an independent predictor of the reduction in ERI, in contrast to our study.

The point of strength of the study: we were able to show that better-quality hematopoiesis can be performed from the viewpoint of zinc supplementation. Additionally, that zinc sulphate is a zinc preparation with high zinc content. Therefore, it has become possible to provide appropriate zinc supplementation to more hypozencemia patients. Furthermore, we were able to consider the merits and demerits of zinc preparations. However, further large-scale clinical studies are needed to confirm these findings.

Study limitations: The study was limited by the small sample size and short treatment duration. Additional long-term randomized controlled trials are needed to accurately assess the effects of zinc supplementation and evaluate the optimal dose of zinc in dialysis patients. Moreover, the relationship between zinc levels and erythrocyte maturation needs to be clarified in detail.

CONCLUSIONS:

Zinc supplementation increased the serum zinc concentration and significantly reduced the ESA dose and ERI, suggesting that a correction of hypozencemia contributes to lessening renal anemia in these patients.

Conflicts Of Interest

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

Ethical Consideration:

Oral and written consent was obtained from each patient, an approval of the study was obtained from the Zagazig University Academic and Ethical Committee Written informed consent from all the participants was obtained. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans(number : 10565-14-3-2023) .

FUNDING INFORMATION

None declared

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Citation:
AL Nahal, A. S., Shehata, M., Fikry, A., Mahmoud, M. Oral Zinc Supplementations as Adjuvant Therapy in Treatment of Anemia in Maintenance Hemodialysis Patients with Hypozencemia. *Zagazig University Medical Journal*, 2024; (2185-2193): -. doi: 10.21608/zumj.2023.244431.2988