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ORIGINAL ARTICLE

Effect of Zinc Supplementation on Weight and Food Intake in Patients under Hemodialysis

Seyyedeh Maryam Sadeghi[1], Fatemeh Sadeghi[1], Masoumeh Akhlaghi[2*]

1. Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
2. Nutrition Research Center, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran

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**Corresponding author:*
Masoumeh Akhlaghi,
Associate Professor of Nutrition,
Nutrition Research Center,
School of Nutrition and Food
Sciences, Shiraz University of
Medical Sciences, Shiraz, Iran.
Tel: +98-71-37251001
Fax: +98-71-37257288
Email: akhlaghi_m@sums.ac.ir;
msm.akhlaghi@gmail.com
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ABSTRACT

Background: Poor appetite is one of the nutritional problems of hemodialysis patients. We examined the effect of zinc supplementation on weight and dietary intakes in hemodialysis patients.

Methods: In a single-blind randomized clinical trial, 61 hemodialysis patients were recruited and randomly divided into two groups of zinc supplements (capsules containing 50 mg elemental zinc) and control (placebo capsules containing cornstarch). The intervention lasted for 60 days. Thirty-eight patients (17 in zinc supplements and 21 in the placebo group) completed the study. Weight, blood pressure, biochemical parameters including serum calcium, phosphorus, potassium, sodium, blood urine nitrogen, and creatinine were measured and 24-hour food recalls were obtained before and after the intervention.

Results: Weight of the subjects in the zinc group increased (2.4, 95% CI: -1.6 to 6.5 kg) and that of the control decreased (-0.85, 95% CI: -2.9 to 1.2 kg) during the intervention. Although none of these alterations was significant, the difference between the two groups was statistically significant. Changes in biochemical parameters and blood pressure were not significantly different between the two groups. The intake of protein (12.7% vs. 8.6% for zinc vs. control), carbohydrate (13.8% vs. 3.0% for zinc vs. control), and energy (8.9% vs. 4.7% for zinc vs. control) increased in both groups, although there was no significant difference between the groups.

Conclusion: It was shown that zinc supplementation may increase weight gain and food intake in hemodialysis patients.

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Introduction

Chronic renal failure is one of the major public health problems in the world (1, 2), which affects 8-16 percent of the population worldwide (1). Growing prevalence of end stage renal disease (ESRD) imposes an extensive financial burden on health care system in both industrialized and industrializing countries. (2-7). In Iran, the prevalence of ESRD has increased by 14.9% and 5.3%, annually in periods of 1995–2004 and 2005–2014, respectively (8). Hemodialysis, which is the most common method for treating ESRD, reduces uremic toxins by equilibration of plasma and dialysate across a semipermeable membrane (9,

10). Substances which have higher concentrations in blood than in dialysate tend to be cleared by dialysis (7).

Although this can exert beneficial effects on the clearance of the uremic toxins, it may cause a diminution of essential elements. Due to continuous removal of trace elements by dialysis and low dietary intake that results from uremic-related anorexia as well as dietary restrictions, hemodialysis patients are at increased risk of trace element deficiency (7). Poor nutritional status could result from dietary restrictions, anorexia, nutrient losses during dialysis, increased inflammatory cytokines which enhance protein catabolism, proteinuria, and consequently protein-bound element losses (7).

Zinc is essential for many biochemical reactions in the body (10, 12). Zinc deficiency is associated with a number of clinical manifestations such as anemia, impaired immune function, hypogeusia and subsequently anorexia, delayed wound healing, alopecia, skin lesions, hypogonadism, growth retardation, and weight loss. Zinc deficiency has been reported in hemodialysis patients (13-15). In long-term dialysis patients, the serum level of zinc is the predictor of infectious diseases, hospitalization, and overall mortality (16). Also, serum zine levels and protein catabolic rate improve following zinc supplementation in hemodialysis patients (17). Due to the lack of data on the effect of zinc supplementation on weight and dietary intakes, the present study aimed to investigate the effect of zinc supplementation on dietary intakes, weight gain, and some of biochemical parameters of hemodialysis patients.

Materials and Methods

In this single-blind randomized clinical trial, hemodialysis patients were recruited from hemodialysis departments of two hospitals (Razi and Golestan Hospitals in Ahvaz, Iran). Participants aged between 20 and 80 years and had been on hemodialysis for a minimum of 6 months. Patients with malignancy, organ failure, thyroid abnormality, and applicants of chemotherapy and immunosuppressive medications were not included. Also, hospitalization and loss of inclusion criteria during the intervention period led to exclusion from the study. Weight and energy intake were considered as the primary outcome and blood urea nitrogen (BUN), creatinine, sodium, potassium, phosphorous, and calcium concentrations were considered as secondary outcomes. Written informed consent was obtained from all participants. The trial was approved by the Ethics Committee of Shiraz University of Medical Sciences (approval no. IR.SUMS.REC.1395-143) and registered with the Iranian Registry of Clinical Trials (IRCT 20180621040177N1).

The patients were randomly allocated to either intervention (receiving one capsule containing 220 mg zinc sulfate with 50 mg elemental zinc per day) or control group (receiving one placebo capsule containing 220 mg cornstarch per day). Zinc and placebo capsules were identical in shape, size, and color. The patients were blinded to the allocations. To minimize gastrointestinal side effects of supplements, subjects were asked to take supplements after lunch. During the study, each patient was under supervision and care of a nephrologist and medical care team. No extra dietary advice was given to the participants other than their usual renal diet which had been prescribed by a dietitian. Thus, the patients were free to adjust their eating according to their appetite.

Fasting blood samples were collected at baseline and the end of the study after a 12-h overnight fast. Serum was separated by centrifugation at 3000 rpm for 15 min and serum samples were frozen and kept at -70°C until the time of the experiments. Serum blood urea nitrogen (BUN), creatinine, sodium, potassium, phosphorus, and calcium were measured using commercially available kits (Pars Azmoon, Tehran, Iran). Weight and blood pressure were measured as previously described (18). Dietary assessments were performed by a well-trained dietitian using 2-day 24-h diet recall. Nutrient composition of the consumed foods was determined by Nutritionist IV version 3.5.2 (Hearst Corp., San Bruno, CA) with modifications and additions for Iranian foods.

Statistical analyses were performed with SPSS version 19 (SPSS Inc., Chicago, IL, USA). Normality of data distribution was examined by Kolmogorov-Smirnov test and non-parametric tests were used in case of abnormality. Changes in assessed parameters from baseline to the end of the intervention were assessed by paired t-test except for diastolic blood pressure and creatinine that had abnormal distribution and were examined with Wilcoxon test. Between-groups, alterations were evaluated by ANCOVA with baseline values as the covariate. $P<0.05$ was considered as the significant level.

Results

At the beginning of the study, 61 subjects participated and 23 were excluded because of stomach ache, nausea, heart burn, and hospitalization. Therefore, the statistical analysis was performed on 38 individuals who completed the study. Of these, 17 individuals were in the zinc and 21 were in the control group. The flow chart of the trial is demonstrated in Figure 1. Selected demographic characteristics of the study population were presented in Table 1. There was no

Table 1: Demographic characteristics of the subjects.[1]

Variable	Zinc (n=17)	Control (n=21)	P value
Age, year	55.9±11.2	53.7±11.1	0.5
Sex, n (%)			
Male	12 (70.6%)	13 (61.9%)	0.5
Female	5 (29.4%)	8 (38.1%)	
Education, n (%)			
School	15 (88.2%)	19 (90.5%)	0.5
College	2 (11.8%)	2 (9.5%)	
Duration of dialysis, y	1.6±0.94	3.1±1.8	0.002

[1]Data were expressed as either mean±standard deviation or number and percentage

significant difference in sex and educational level between the two groups, but participants in the control group were longer on dialysis treatment. To evaluate the nutritional status of the patients, the ratio of baseline micronutrient intakes to recommended dietary allowances were assessed (Table 2).

The patients received antioxidant vitamins (vitamin A, E, and C), riboflavin, folic acid, vitamin B_6, and zinc less than their recommended dietary allowances (RDA) and thiamin, niacin, vitamin B_{12}, and iron more than RDA. Changes in body weight, BUN and creatinine, serum electrolytes, and blood pressure during the study are presented in Table 3. Subjects' weight increased in the zinc group and decreased in the control group. Although none of these alterations was significant, the difference between the two groups was statistically significant (P=0.046). Changes in BUN, serum creatinine, serum electrolytes, and blood pressure were not significantly different between the two groups. Alternation in macro- and micro-nutrient intakes

Table 2: The ratio of micronutrient intakes to RDA

Micronutrients	Ratio (n=38)
Vitamin A (RE)	0.44
Vitamin E (mg)	0.23
Vitamin C (mg)	0.64
Thiamin (mg)	1.27
Riboflavin (mg)	0.88
Niacin (mg)	1.09
Vitamin B_6 (mg)	0.54
Folic acid (µg)	0.28
Vitamin B_{12} (µg)	1.33
Iron (mg)	1.33
Zinc (mg)	0.52

RDA: recommended dietary allowances

Table 3: Alterations in weight, kidney function parameters, serum electrolytes, and blood pressure during the study.[1]

	Zinc (n=17)			P	Control (n=21)			P	P
	Baseline[1]	Week 8	Difference (95% CI)	value[2]	Baseline	Week 8	Difference (95% CI)	value[2]	value[3]
Weight (kg)	68.0±14.5	70.4±14.1	2.4 (-1.6 to 6.5)	0.2	71.7±15.4	70.9±14.7	-0.85 (-2.9 to 1.2)	0.4	0.046
BUN (mg/dl)	48.9±11.9	52.5±14.8	3.6 (-3.6 to 10.8)	0.3	56.2±13.8	66.0±19.9	9.7 (5.3 to 14.1)	<0.001	0.2
Creatinine (mg/dl)	7.7±2.3	8.9±2.6	1.2 (0.16 to 2.3)	0.02	8.6±2.2	9.3±2.6	0.70 (-0.38 to 1.8)	0.2	0.7
Calcium (mg/dl)	8.5±1.3	8.8±1.6	0.31 (-0.10 to 0.72)	0.1	8.3±0.96	8.5±1.2	0.20 (-0.20 to 0.60)	0.3	0.7
Phosphorus (mg/dl)	6.0±1.5	6.9±2.2	0.89 (-0.13 to 1.9)	0.08	6.0±1.4	7.1±2.0	1.1 (-0.33 to 1.8)	0.007	0.7
Potassium (mg/dl)	4.9±0.87	5.5±1.1	0.56 (-0.08 to 1.2)	0.08	5.9±0.58	5.9±0.54	-0.03 (-0.24 to 0.18)	0.8	0.9
Sodium (mg/dl)	138.0±3.4	136.0±4.1	-2.0 (-3.7 to -0.27)	0.03	142.1±3.7	139.1±3.1	-3.1 (-4.3 to -1.7)	<0.001	0.7
SBP (mmHg)	130.0±14.7	135.4±16.1	5.4 (-4.7 to 15.4)	0.3	126.1±17.7	127.4±20.3	1.3 (-7.8 to 10.5)	0.8	0.1
DBP (mmHg)	80.0±10.8	75.4±11.3	-4.6 (-13.4 to 4.1)	0.3	70.9±14.2	74.1±10.3	3.2 (-3.1 to 9.5)	0.3	0.8

[1]Data were either mean±standard deviation or mean difference and 95% CI. [2]P-value assessed by paired samples t-test (Wilcoxon for DBP and creatinine). [3]Between-groups alterations were evaluated by ANCOVA with baseline values as the covariates. BUN: blood urea nitrogen; DBP: diastolic blood pressure; SBP: systolic blood pressure

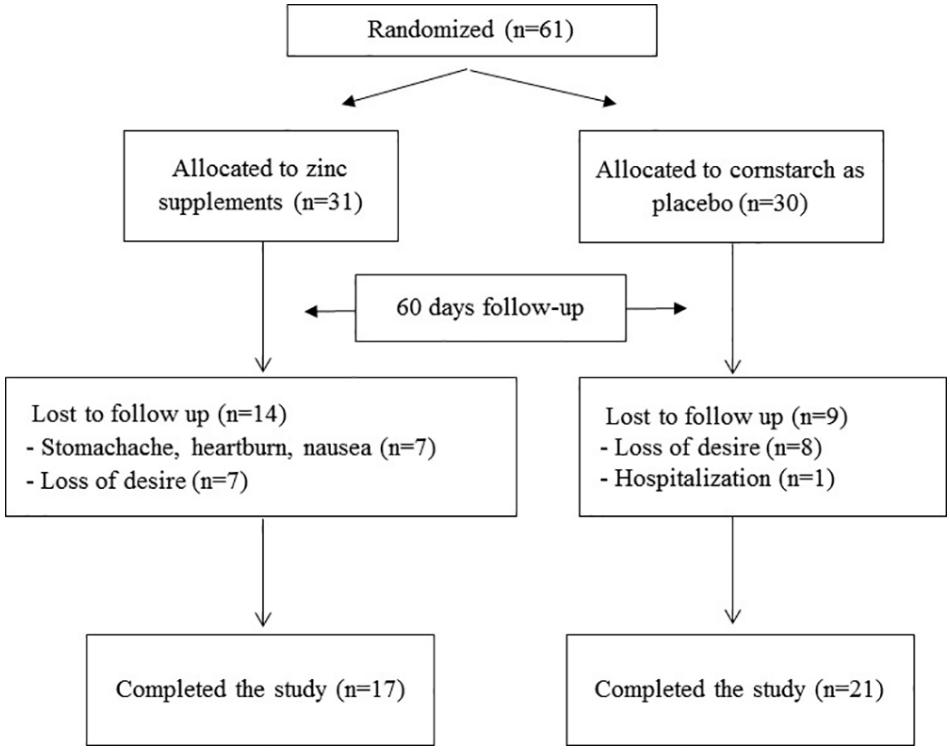

Figure 1: Flowchart of the trial

were presented in Table 4. For most of the nutrients, improvements in intakes were observed in the zinc group, but there was no significant difference between the two groups in any nutrient.

Discussion

Zinc, as an essential trace element with vital roles in human body, is reported to be deficient in hemodialysis patients. Due to the role of zinc on the sense of taste and regulation of appetite, we questioned if zinc supplementation could positively affect dietary intakes and weight of hemodialysis patients. Following two months zinc supplementation, a significant improvement was observed in the weight of the patients compared to the control group. Available evidence derived from clinical and observational studies investigating the effects of zinc supplementation on body weight are inconsistence. Several studies have reported weight gain following zinc supplementation (19, 20), while others failed to show a significant increase in body weight by zinc supplementation (17, 21).

We observed that protein, carbohydrate, and energy intake increased in both groups with a higher elevation in the zinc group, but there was no significant difference between the groups. Available data on the effect of zinc supplementation on increasing dietary intake are inconclusive, ranging from positive significant effects to no significant effect (17, 22-25). The absence of statistical difference between energy and macronutrient intake in the present study might be due to small sample size and a short period of our study that may not have been adequate to allow detection of a significant difference in dietary intakes.

It has been suggested that zinc exerts its beneficial effects on weight by improving appetite. This effect may be exerted through various mechanisms. First of all, it has been suggested that zinc supplementation could prevent taste changes which occur in hemodialysis patients because of the accumulation of uremic toxins. Second probable mechanism is the positive effects of zinc supplementation on hormones involved in appetite control. For instance, zinc supplementation decreased serum leptin levels in children under hemodialysis (26). Leptin is an appetite-controlling hormone secreted by adipose tissue responsible for inhibition of food consumption and increasing energy expenditure (27). The levels of leptin are increased in patients suffering from chronic kidney disease as a result of diminished renal clearance rate (28).

Additionally, it has been observed that zinc deficiency reduces ghrelin-stimulated feeding and weight gain (29), although the exact mechanism of the effect of zinc on ghrelin and malnutrition in hemodialysis patients has not been fully characterized. Furthermore, results of an animal study indicated that different zinc levels affect gene expression of appetite-related peptides, including neuropeptide-Y, melanin-concentrating hormone,

Table 4: Changes in daily nutrient intake during the study.[1]

Variable	Zinc (n=17)	Control (n=21)	P value[2]
Energy (kcal)	173 (-1211 to 2086)	83.6 (-1428 to 900)	0.7
Carbohydrate (g)	31.3 (-157 to 323)	6.5 (-157 to 135)	0.4
Protein (g)	7.9 (-28.9 to 60.4)	3.7 (-30.1 to 34.8)	0.5
Fat (g)	2.1 (-68.6 to 115.7)	4.4 (-85.8 to 53.4)	0.9
Saturated fats (g)	1.5 (-18.3 to 20.0)	0.54 (-12.1 to 12.6)	0.7
Cholesterol (g)	38.8 (-313 to 600)	18.0 (-171 to 228)	0.7
Dietary fiber (g)	1.8 (-6.1 to 14.2)	1.2 (-15.4 to 14.6)	0.8
Vitamin A (RE)	166 (-322 to 1600)	88.1 (-497 to 1373)	0.6
Vitamin E (mg)	-0.99 (-11.7 to 1.9)	-0.49 (-12.0 to 4.0)	0.7
Vitamin C (mg)	6.2 (-70.6 to 95.4)	-0.78 (-72.7 to 87.7)	0.7
Thiamin (mg)	0.21 (-1.0 to -1.8)	0.14 (-0.76 to 0.75)	0.7
Riboflavin (mg)	0.19 (-0.54 to 1.0)	0.05 (-0.82 to 0.68)	0.3
Niacin (mg)	2.6 (-13.5 to 13.0)	0.83 (-9.3 to 11.3)	0.4
Vitamin B_6 (mg)	0.25 (-1.4 to 2.5)	-0.05 (-0.5 to 0.4)	0.2
Folic acid (µg)	35.9 (-109 to 300)	24.2 (-142 to 293)	0.7
Vitamin B_{12}	0.05 (-8.4 to 12.0)	0.61 (-5.6 to 11.2)	0.7
Calcium (mg)	118 (-323 to 500)	-11.5 (-506 to 261)	0.07
Phosphorus (mg)	117 (-392 to 500)	81.0 (-400 to 507)	0.6
Sodium (mg)	-42.0 (-1611 to 999)	-108 (-892 to 654)	0.7
Potassium (mg)	273 (-1127 to 1888)	-32.2 (-2157 to 1623)	0.4
Iron (mg)	3.5 (-8.6 to 15.0)	0.29 (-8.8 to 11.7)	0.1
Zinc (mg)	1.9 (-2.7 to 10.1)	0.57 (-4.1 to 5.6)	0.2

[1]Values were expressed as the mean (95% CI)

ghrelin, calcitonin gene-related product, and serotonin (30). Zinc can also reduce anxiety and stress and this may be another potential mechanism of zinc in improving appetite in hemodialysis patients (31, 32).

The exact daily dose that prevents zinc deficiency in hemodialysis patients and guarantees its optimal effect on appetite is not well defined. Dietary requirements depend on the frequency of dialysis, the type of dialysis membrane, the amount of urine excretion, and dietary habits of the patients. Protein-rich foods mainly from animal-base have the most bioavailability for zinc, although additional factors, such as body size, dietary levels of zinc, the patient's zinc storage, and the existence of other potential interfering materials in the diet, can also affect zinc absorption (33).

This study had limitations. Zinc supplements caused gastrointestinal side effects, such as nusea and heartborn, that led to considerable dropouts and substantial decrease of the sample size. In addition, short intervention time did not allow to see long-term consequences of zinc supplementation in this group of patients. Also, it is not clear from the results herein whether discontinuance of zinc supplements will reverse the weight benefits. Furthermore, we did not assess plasma zinc levels to see how zinc status changes following zinc supplementation. Future studies are needed to consider these points and focus on the underlying mechanisms.

Conclusion

The results of the present study indicated that zinc supplementation can improve weight of hemodialysis patients. Future studies with larger sample sizes and longer intervention periods are needed to re-examine these results. It would also be beneficial to evaluate appetite-related hormones and to investigate possible mechanisms involved.

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Conflict of Interest

None declared.

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