Original Article

# The Efficacy of Zinc Gluconate Supplementation in the Improvement of Malnutrition Indices and Skin Abnormalities in Hemodialysis Patients: A Randomized Clinical Trial


## Abstract

**Background:** Hemodialysis patients often suffer from several complications such as malnutrition and skin abnormalities. We hypothesized that zinc supplementation may improve these complications. The aim of the present study was to examine the effects of zinc gluconate supplementation on malnutrition and skin abnormalities. **Methods:** In this parallel randomized, double-blind, clinical trial, patients in the zinc group received 210 mg zinc gluconate (equivalent to 30 mg elemental zinc) per day. Skin abnormalities (i.e. xerosis and pruritus), body composition, anthropometric variables, handgrip strength, and appetite (including hunger, fullness, desire to eat, and prospective food consumption) were measured at the beginning and end of the study. **Results:** Eighty-seven hemodialysis patients were randomly assigned to the zinc ($n$ = 44) or placebo ($n$ = 43) group for 12 weeks, After this period, 75 patients ($N$ = 38 in the zinc group and 37 in the placebo group) remained in the study. In this study, no specific side effects of zinc supplementation were observed and twelve participants were lost to follow-up ($n$ = 6 in each group) because of migration, kidney transplantation, death, dialysis access infection, and personal reasons. Zinc supplementation had beneficial effects on hunger) 95% CI: 9/55 (3/67-15/42)), desire to eat) 95% CI: 7/03 (1/82-12/24)), and prospective food consumption) 95% CI: 3/46 (0/3-14/1)) compared with placebo. Also, zinc improved pruritus) 95% CI: −0/52 (−0/82 to − 0/22)). We observed no changes in body composition, anthropometric variables, handgrip strength, and xerosis in the zinc group compared with the placebo. **Conclusions:** This randomized clinical trial showed that zinc supplementation yielded beneficial effects on appetite and pruritus in hemodialysis patients.


**Keywords:** *Appetite, body composition, handgrip strength, hemodialysis, randomized clinical trial, zinc*


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## Introduction

Chronic kidney disease (CKD) is a global public health burden.[1] It affects more than 10% of the general population worldwide.[2] Community Verified iconThere is an impairment in renal function (e.g. excretion of nitrogenous compounds and regulation of electrolytes and blood pressure) in patients with CKD.[3] The main causes of CKD are diabetes, high blood pressure, and kidney stones.[3] The process of eliminating nitrogenous wastes and removing excess fluid in end-stage renal disease (ESRD) is called dialysis, including hemodialysis (HD) and peritoneal dialysis.[4] HD is the most common form of renal replacement therapy, accounting for approximately 69% of all renal replacement therapies and 89% of all types of dialysis.[5] Nevertheless, HD is not as efficient as normal kidney function and HD patients suffer from several complications, such as malnutrition and skin abnormalities.[4]

Malnutrition is one of the most common complications in patients with ESRD and 30-70% of HD patients have some degree of malnutrition.[6,7] Body composition and handgrip strength (HGS) are two useful markers of malnutrition in HD patients.[8,9] Changes in body composition, including muscle wasting, reduced lean body mass, and increased fat mass, were observed in patients undergoing HD.[10] Evidence showed that body composition monitoring was an independent predictor of quality of life and survival in patients with ESRD.[10,11] In addition to the body composition, HGS is an indicator of some adverse outcomes



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such as malnutrition and mortality in HD patients.[12,13] It can be used as a functional and nutritional test and The 2020 'KDOQI (Kidney Disease Outcomes Quality Initiative) Clinical Practice Guideline for Nutrition in CKD' recommends that muscle function should be assessed by HGS in adults with CKD 1-5D to detect protein-energy wasting.[14] Nutritional intervention may have beneficial effects on body composition and HGS.[15]

Lack of appetite in patients with ESRD is suggested as a cause of malnutrition.[16] Evidence showed that loss of appetite was related to symptoms of behavioral disorders, increased levels of pro-inflammatory mediators, hospitalization, low quality of life, and decreased survival.[17] Lack of appetite should be managed by appetite-stimulating medications and/or nutritional supplementation.[18] Since several medications are not safe in patients with ESRD,[19] nutritional supplementation may be a choice in managing loss of appetite in HD patients.[19]

Skin abnormalities are common complications in HD patients.[20] About 50-85% of patients undergoing HD suffer from skin abnormalities, such as xerosis cutis and pruritus.[21,22] Also, skin discoloration has been observed in about 40% of HD patients.[21,23] It seems that dietary intervention may improve skin abnormalities.[24]

Zinc is an essential dietary trace element that acts as a coenzyme of several biochemical reactions and regulates gene expression, protein synthesis, immune function, and behavioral responses.[25] Approximately 40-78% of patients undergoing HD suffer from zinc deficiency.[26] Owing to the high prevalence of zinc deficiency among these patients, it seems that zinc supplementation may improve some complications, such as malnutrition and skin abnormalities, in patients with ESRD. A clinical trial showed that zinc supplementation could improve appetite in children with CKD.[27] Also, it may increase food intake in adults with CKD.[28] Zinc has favorable effects on body composition. It can stimulate myogenesis and muscle regeneration.[29] There is an increment of muscle mass in growing children resulting from zinc supplementation.[30] Zinc deficiency is considered an independent predictor of sarcopenia and muscle mass loss.[31] Also, it is associated with reduced lean body mass and fat deposition.[32] In addition to malnutrition, zinc may have a role in the management of skin abnormalities.[33] It has been used in the treatment of skin infections (leishmaniasis, warts), inflammatory dermatosis (acne vulgaris, rosacea), pigment disorders (melasma), and neoplasms (basal cell carcinoma).[33]

Although previous studies have examined the effect of zinc supplementation on malnutrition and skin abnormalities, there is little data regarding HD patients. Also, zinc has been predominantly used in the form of zinc sulfate in previous clinical trials and the effect of the more absorbable forms of zinc (i.e. zinc gluconate), with fewer gastrointestinal side effects, has not been widely assessed.[34,35] Therefore, the aim of the present study was to examine the effects of zinc supplementation, in the form of zinc gluconate, on appetite, body composition, HGS, and skin abnormalities in HD patients.

## Methods

This study was designed as a parallel, double-blind, randomized clinical trial. The duration of the study was 12 weeks and the study was carried out from October 2020 to October 2021, in Isfahan, Iran. This study was ethically approved by The Research Council and Ethical Committee of Isfahan University of Medical Sciences, Isfahan, Iran, and Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran (Code: IR.MUI.RESEARCH.REC.1399.405). This randomized clinical trial was registered at IRCT.ir on October 05, 2020 (Registration number: IRCT20130903014551N7).

Patients were selected from two dialysis centers according to the inclusion and exclusion criteria. patients were included in the study if they were 1) on HD for at least 3 months; 2) dialyzed at least twice a week; and 3) >18 years old. Patients were excluded from the research if they were 1) smokers; 2) pregnant or lactating; 3) on enteral or parenteral feeding; 4) had a history of cancer or advanced liver disease; 5) took any drugs that could affect dependent variables of the study; and 6) were not on a specific diet, except for usual diets prescribed to the HD patients. The following reasons were considered for withdrawal: 1) kidney transplant or death; 2) low compliance with intervention (consuming <85% of supplements/placebo); and 3) undergoing peritoneal dialysis.

The following equation was used to estimate the required sample size: $n = 2\ [(Z_{1-\alpha/2}+Z_{1-\beta})^2 \times S^2]/\Delta^2$. In this study, $\alpha$ (the probability of a Type I error) was 0.05, and $\beta$ (the probability of a Type 2 error) was 0.20. Therefore, $Z_{1-\alpha/2}$ was 1.96 and $Z_{1-\beta}$ was 0.85. Lean body mass (LBM) was considered the main variable in this study. According to previous studies, $S^2$ for LBM in HD patients was 0.8 kg.[36] The minimum detectable difference in LBM between the two groups ($\Delta$) was 0.53 kg.[37] Therefore, the required sample size in each group was 35 (70 in total). We referred to two dialysis centers to select eligible participants. At first, medical records of all patients in each center were assessed based on the inclusion and exclusion criteria, and potential eligible participants were identified. Then, the aim, design, and other details of the study were explained to the identified patients. Some patients did not agree to participate in the present study. Therefore, 87 patients completed a written informed consent form and were included in the study. Also, a code number was assigned to each individual. Then, all codes were entered into the SPSS software version 20. We selected 50% of patients by using "Random sample of cases" command in the SPSS. Therefore, participants were randomly

allocated in a ratio of 1:1 to either the zinc or placebo group. No blocking was applied in the present study. The staff who ran random allocation had no role in outcome assessment. All investigators who evaluated HGS, body composition, and skin abnormalities, and the staff who ran the statistical analysis were blinded to the codes and zinc groups. Therefore, except for a staff who generated a randomization list and allocated patients, other staff, investigators, and participants were blinded. Patients in the zinc group received one tablet containing 210 mg zinc gluconate (equivalent to 30 mg elemental zinc) per day, produced by Dineh Company, Tehran, Iran, for 12 weeks. Patients in the placebo group received a tablet that contained 30 mg starch, and its color, appearance, smell, and taste were comparable to the zinc tablet. The placebo used in our study was prepared in the School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran. Starch and lactose, the main ingredients of the mentioned placebo, were mixed to produce granules. Granules were passed through a sieve and mixed with lubricant to reduce the friction. Then they were injected into a tablet press machine. Participants in both groups were recommended to take the tablets after breakfast on non-dialysis days. In dialysis days, supplements should be used after the first post-dialysis meal. A list of following dietary recommendations for dialysis patients was provided for participants in both groups: 1) avoid consuming solid oils, fried foods, salty foods, high-fat dairy products, processed foods, and junk foods; 2) limit consuming sugar-sweetened beverages; 3) limit consuming high phosphorus food such as legumes, nuts, dairy products, and meats; and 4) limit high potassium foods such as banana, spinach, orange, dates, tomato, and potato.

A questionnaire including demographic information, medical history, and medications was completed for each patient. Demographic information was obtained by oral questions. Data regarding medical history, medications, and supplements used currently were collected by reviewing clinical records. Patients were monitored 2-3 times per week because they had scheduled dialysis sessions. In each visit, patients gave completed food records. A trained dietician asked several questions regarding dietary recommendations and checked patients' responses by food records. Also, we asked about the number of used supplements/placebo and retained empty packages of supplements/placebo. Therefore, they were visited and monitored weekly during dialysis sessions to assess compliance with the intervention. Patients received supplements (zinc or placebo) every 2 weeks and the empty packages were retained.

### Measurement of indices of appetite

Appetite was evaluated in a fasted state in the morning at the beginning and end of the study using a visual analog scale (VAS) questionnaire. VAS is a measurement tool and a method used to assess variables that cannot be directly measured (e.g., pain and appetite).[38] This questionnaire had four domains including hunger, fullness, desire to eat, and prospective food consumption.[39] A 100-mm horizontal line was determined for each domain. The lowest feeling was scored zero and the highest was marked as 100. The validity and reliability of this questionnaire in Iranian populations were deemed acceptable.[40]

### Assessment of body composition

In our study, body composition was measured by using the bioimpedance analysis method based on the principle that electrical conductivity is not the same through different tissues, including muscle mass and adipose tissue.[41] Accordingly, we measured muscle mass, body fat (BF), and visceral fat (VF) by this method. For accurate results, body composition was measured after dialysis sessions,[14] and patients were asked to not consume alcohol, caffeine, or diuretics.[42,43]

### Assessment of anthropometric variables

We measured dry weight, to the nearest 100 g, with participants minimally clothed and unshod (Seca, CA, USA). Dry weight was defined as the minimum tolerable post-dialysis weight when there were no signs or symptoms of hypovolemia or hypervolemia.[34] Height was measured based on the standard protocol using a standard stadiometer. Body mass index (BMI) was calculated as dry weight in kilograms divided by the square of height in meters.[44]

### Assessment of handgrip strength

HGS was measured according to the Southampton method.[45,46] We assessed HGS with the patients seated, and elbows held in a 90-degree position. The opposite hand of the dialysis access was used to measure HGS. Measurements were repeated three times, and the mean of all three measurements was used in statistical analysis. We used the SH5002 SAEHAN Spring Hand Dynamometer.

### Assessment of skin abnormalities

Xerosis is the medical term for dry skin.[47] It was assessed using an overall dry skin score.[48] Scoring was performed by following scale method[48]: zero (without xerosis), 1 (mild: faint roughness with dull appearance), 2 (moderate: slight roughness, and whitish appearance), and 3 (severe: advanced roughness, redness present, eczematous changes, and cracks). This method was valid and reliable.[47] Pruritus, defined as itchy skin, was evaluated by assessing 16 body regions.[49] Scoring was performed by following scale method[49]: zero (without pruritus), ≤2 regions (mild: 1 point), 3–5 regions (moderate: 2 points), 6–10 regions (moderate to severe: 3 points), 11–13 regions (severe: 4 points), and 14–16 regions (very severe: 5 points). The validity of this method among patients with renal diseases was acceptable.[50] Xerosis and pruritus were assessed by a trained staff and we did not use a dermatologist.

### Assessment of dietary intake

HD patients were asked to complete two 3-day food records (two non-dialysis and one dialysis day) from the 1st to 12th week of the intervention. Food diaries were analyzed using Nutritionist IV software (First Databank, San Bruno, CA, USA) based on the USDA food composition database and extra data regarding Iranian foods.

### Statistical analysis

To test the normal distribution of variables, kurtosis between −2 and +2 and skewness between −7 to +7 were considered acceptable.[51,52] In this study, quantitative variables were reported as a mean and standard deviation; and qualitative variables were reported as percentages. Intragroup analysis was performed using paired *t*-tests, and intergroup analysis was performed using independent samples *t*-test and analysis of variance (ANOVA). To adjust for confounding variables (energy intake and baseline values), analysis of covariance (ANCOVA) was applied. The distribution of qualitative variables was compared between the two groups using the Chi-square test. For all statistical analyses, SPSS software version 20 was used to analyze the data, with a significance level of $P < 0.05$. Data were analyzed using a per-protocol method.

## Result

Results of the normality test revealed that the kurtosis was between −2 and +2 and skewness was between −7 and +7 for all variables. Figure 1 depicts the CONSORT flow diagram. One hundred one patients were screened for eligibility. Fourteen patients did not meet inclusion and exclusion criteria or declined to participate. Therefore, a total of 87 patients were randomly assigned to the zinc ($n$ = 44) or placebo ($n$ = 43) groups. Twelve participants were lost to follow-up ($n$ = 6 in each group) because of migration, kidney transplantation, death, dialysis access infection, and personal reasons. Therefore, the data of 75 patients ($n$ = 38 in zinc and $n$ = 37 in placebo groups) were analyzed.

General characteristics of HD patients enrolled in the present study are reported in Table 1. There were no significant differences in the leading causes of ESRD including hypertension ($P$ = 0.46), diabetes ($P$ = 0.23), and autosomal dominant polycystic kidney disease ($P$ = 0.99) between the two groups. Also, age ($P$ = 0.55), sex ($P$ = 0.80), marital status ($P$ = 0.38), dialysis vintage ($P$ = 0.29), dialysis frequency ($P$ = 0.73), and serum zinc level ($P$ = 0.92) was not different between the two groups.

Table 2 shows the comparison of energy-adjusted dietary intake between the zinc and placebo groups during the study. Results revealed that the intakes of carbohydrates ($P$ = 0.07), protein ($P$ = 0.27), fat ($P$ = 0.68), sodium ($P$ = 0.27), vitamin E ($P$ = 0.10), vitamin C ($P$ = 0.28), vitamin B1 ($P$ = 0.05), vitamin B2 ($P$ = 0.11), potassium ($P$ = 0.39), calcium ($P$ = 0.10), selenium ($P$ = 0.63), zinc ($P$ = 0.64), dietary fiber ($P$ = 0.90), and phosphor ($P$ = 0.26) were not different between two groups.

**Table 1: General characteristics of hemodialysis patients enrolled in the present study**

| Variable | Zinc ($n$=38) | Placebo ($n$=37) | $P$ |
|---|---|---|---|
| Sex | | | |
| Male (%) | 26 (%68.4) | 24 (%64.9) | 0.80[c] |
| Female (%) | 12 (%31.6) | 13 (%35.1) | |
| Age (year) | 49.23 (±15.35)[a] | 51.21 (±13.76) | 0.55[b] |
| Marital status | | | |
| Married (%) | 29 (%76.3) | 26 (%70.3) | 0.38[c] |
| Single)%) | 9 (%23.7) | 11 (%29.7) | |
| Hypertension (%) | 23 (%60.5) | 26 (%70.3) | 0.46[c] |
| Diabetes (%) | 11 (%28.9) | 16 (%43.2) | 0.23[c] |
| Autosomal dominant polycystic kidney disease (%) | 2.6 | 2.7 | 0.99[c] |
| Dialysis vintage (month) | 32.39 (±27.94)[a] | 40.5 ±37.97 | 0.29[b] |
| Dialysis frequency (session/week) | 2.86 (±0.41)[a] | 2.83 ±0.37 | 0.73[b] |
| Serum zinc (mg/dl) | 81.94 (±16.82)[a] | 82.32±18.28 | 0.92[b] |

[a]Continuous variables are expressed as mean ) SD(.[b]*P* values resulted from independent samples *t*-test for quantitative variables. [c]*P* values resulted from Chi-square for qualitative variables: *n* (%).

**Table 2: Energy-adjusted dietary intake of the study participants during the study[a]**

| Variable | Zinc group ($n$=38) | Placebo group ($n$=37) | $P$[b] |
|---|---|---|---|
| Carbohydrate (g/day) | 200.62 (±59.67) | 171.36 (±73.70) | 0.07 |
| Protein (g/day) | 62.1 (±18.37) | 59.35 (±26.58) | 0.27 |
| Fat (g/day) | 49.59 (±13.51) | 46.59 (±15.49) | 0.68 |
| Sodium (mg/day) | 1909.46 (±1625.69) | 1632.21 (±984.66) | 0.70 |
| Vitamin E (mg/day) | 9.28 (±4.41) | 10 (±4.20) | 0.10 |
| Vitamin C (mg/day) | 107.41 (±61.94) | 82.73 (±67.05) | 0.28 |
| Vitamin B1 (mg/day) | 1.26 (±0.32) | 1.08 (±0.41) | 0.05 |
| Vitamin B2 (mg/day) | 1.47 (±0.63) | 1.16 (±0.63) | 0.11 |
| Potassium (mg/day) | 3057.01 (±1434.78) | 2513.76 (±1565.33) | 0.39 |
| Calcium (mg/day) | 1068.48 (±581.83) | 777.73 (±593.86) | 0.10 |
| Selenium (mg/day) | 78.09 (±27.98) | 73.59 (±31.62) | 0.63 |
| Zinc (mg/day) | 9.27 (±3.55) | 8.13 (±3.47) | 0.64 |
| Dietary fiber (g/day) | 23.4 (±10.83) | 20.7 (±14.10) | 0.90 |
| Phosphor (mg/day) | 1067.07 (±322.49) | 921.47 (±398.68) | 0.26 |

[a]Variables are expressed as mean ) SD(.[b]*P* value was adjusted for total energy intake. [b]*P* values resulted from independent samples *t*-test.

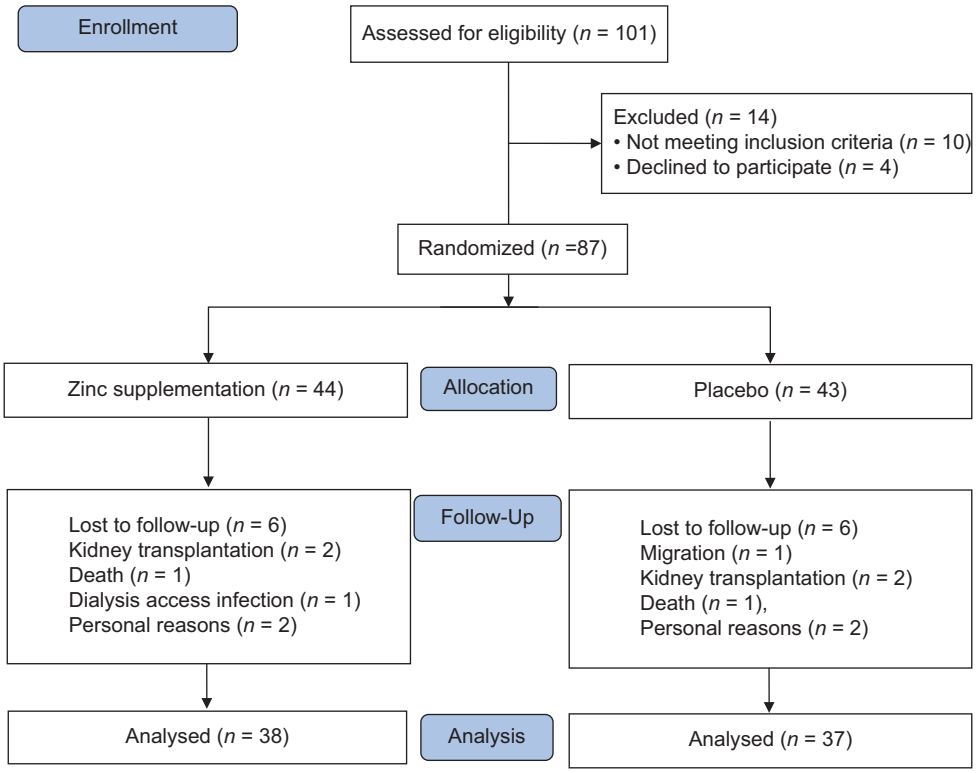


**Figure 1: CONSORT flow diagram**

The effects of zinc supplementation on hunger, prospective food consumption, fullness, and desire to eat in the intervention and placebo groups are shown in Figure 2. An improvement in hunger and desire to eat was observed after zinc supplementation compared with placebo. After adjusting for the baseline values, there were beneficial effects of zinc supplementation on hunger) 95% CI: 9/55 (3/67-15/42)), desire to eat) 95% CI: 7/03 (1/82-12/24)), and prospective food consumption (95% CI: 3/46 (0/3-14/1)) compared with a placebo. In contrast, zinc supplementation had no significant effect on fullness) 95% CI = −1/64 (−10/49 to 7/21)). The effects of zinc supplementation on dry weight) 95% CI = −0/7 (−3/22 to 1/81)), BMI) 95% CI: 0/27 (−0/14 to − 0/69)), BF, muscle mass) 95% CI: 0/8 (−0/6 to − 2/21)), VF, and HGS) 95% CI: 1/73 (−0/67 to 4/14)) are displayed in Table 3. After 12 weeks of intervention, results showed that dry weight, BMI, BF, VF, muscle mass, and HGS had no significant changes in zinc and placebo groups. Adjusting for baseline values did not change the results.

The effects of zinc supplementation on pruritus) 95% CI: −0/52 (−0/82 to − 0/22)) and xerosis score) 95% CI: −0/08 (−0/33 _0/16)) in the intervention and placebo group are shown in Table 4. In comparison with placebo, zinc supplementation elicited an improvement in pruritus. This finding was unchanged after adjusting for baseline measurements. There were no significant differences in xerosis between zinc and placebo groups before and after adjusting for baseline values.

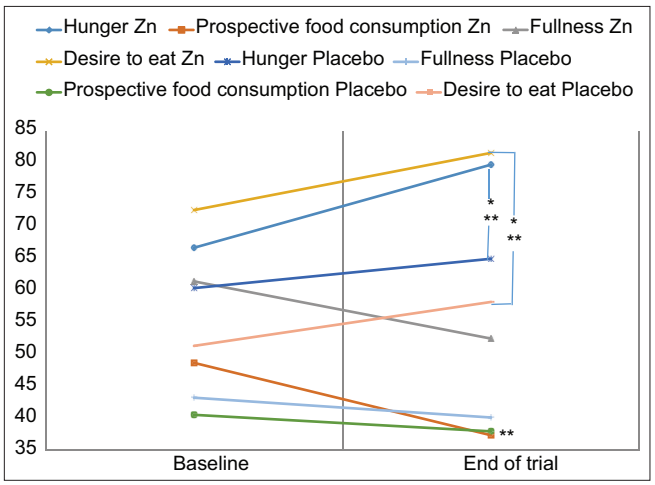


**Figure 2: The effects of zinc supplementation on appetite indicators. *It shows significance (*P* < 0.05) in endpoint values between two groups obtained from independent t-test comparing endpoint measurements. **It shows significant (*P* < 0.05) final values between the two groups after adjusting for baseline measurements obtained from ANCOVA, adjusted for baseline value**

## Discussion

After 12 weeks of zinc gluconate supplementation, we observed that hunger, prospective food consumption, desire to eat, and pruritus were significantly improved compared with placebo. Malnutrition is one of the predominant predictors of a high rate of mortality in HD patients.[53] Lack of appetite in patients with CKD is a potential cause of malnutrition and consequent mortality in

**Table 3: The effects of zinc supplementation on body mass index, body composition, and handgrip strength**

| Variable | Zinc group (*n*=38) | | | | Placebo group (*n*=37) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | End of trial | Change | *P*[b] | Baseline | End of trial | Change | *P*[b] | *P*[c] | *P*[d] |
| Weight (kg) | 68.31 (±16.65)[a] | 67.41 (±19.42) | -0.90 (±7.23) | 0.44 | 70.64 (±18.07) | 70.53 (±18.22) | −0.10 (±2.6) | 0.80 | 0.47 | 0.58 |
| BMI (kg/m$^2$) | 24.38 (±5.61) | 24.41 (±5.57) | 0.03 (±0.63) | 0.73 | 25.38 (±5.98) | 25.13 (±6.03) | −0.25 (±1.11) | 0.18 | 0.59 | 0.19 |
| BF (%) | 26.27 (±11.08) | 25.80 (±11.20) | -0.47 (±4.87) | 0.55 | 25.02 (±13.44) | 25.32 (±13.42) | 0.29 (±2.89) | 0.53 | 0.86 | 0.44 |
| Muscle mass (%) | 32.25 (±6.76) | 32.86 (±6.71) | 0.60 (±4.05) | 0.36 | 33.7 (±6.32) | 33.32 (±6.28) | −0.37 (±1.72) | 0.19 | 0.75 | 0.26 |
| VF (%) | 8.23 (±6.01) | 8.36 (±5.77) | 0.13 (±1.25) | 0.52 | 9.27 (±6.66) | 9.18 (±6.59) | −0.08 (±1.18) | 0.68 | 0.56 | 0.54 |
| Handgrip Strength (kg) | 20.16 (±8.47) | 22.05 (±9.21) | 1.88 (±6.36) | 0.07 | 23.16 (±9.04) | 22.91 (±9.08) | −0.24 (±3.78) | 0.69 | 0.68 | 0.15 |

BMI: body mass index; BF: body fat; VF: visceral fat. [a] Variables are expressed as mean (SD). [b] Obtained from paired *t*-test comparing baseline and endpoint values. [c] Obtained from independent samples *t*-test comparing endpoint measurements. [d] Obtained from ANCOVA, adjusted for baseline value, and comparing endpoint values.

**Table 4: The effects of zinc supplementation on skin abnormalities**

| | Zinc group (*n*=38) | | | | Placebo group (*n*=37) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | End of trial | Change | *P*[b] | Baseline | End of trial | Change | *P*[b] | *P*[c] | *P*[d] |
| Pruritus score | 1.21 (±1.23)[a] | 0.39 (±0.71) | −0.81 (±1.00) | 0.001 | 1.32 (±1.15) | 0.97 (±0.98) | −0.35 (±0.78) | 0.010 | 0.005 | 0.001 |
| Xerosis score | 0.78 (±0.84) | 0.26 (±0.55) | −0.52 (±0.82) | 0.001 | 0.56 (±0.92) | 0.27 (±0.69) | −0.29 (±0.74) | 0.020 | 0.960 | 0.502 |

[a] Variables are expressed as mean (SD). [b] Obtained from paired *t*-test comparing baseline and endpoint values. [c] Obtained from independent samples *t*-test comparing endpoint measurements. [d] Obtained from ANCOVA, adjusted for baseline value, and comparing endpoint values.

HD patients.[16] Therefore, increased appetite following zinc supplementation may have beneficial effects on survival rates in these patients.

Our findings showed that zinc gluconate supplementation improved hunger, prospective food consumption, and desire to eat. Although previous studies did not assess the effect of zinc supplementation on appetite among HD patients, changes in appetite after zinc supplementation have been examined in other patients. For instance, a clinical trial that enrolled 80 preschool children showed that using 10 mg/day of zinc for 12 weeks had positive effects on energy intake and improved anorexia nervosa.[28,54] Also, 24 weeks of zinc supplementation in children aged 2-10 years resulted in an improvement in appetite and growth compared with placebo.[55]

In our study, zinc supplementation had a beneficial effect on pruritus. This finding was corroborated by previous studies. For instance, a clinical trial that enrolled 19 HD patients with persistent pruritus showed that using 445 mg/day of zinc sulfate resulted in pruritus improvement among 53% of the participants.[33] Also, there is a direct and significant relationship between zinc levels and the occurrence of skin disorders such as pruritus.[56]

There are several mechanisms that might explain the improvement of hunger, prospective food consumption, and desire to eat after zinc supplementation. Zinc has a role in the regulation of hormones involved in appetite control, such as leptin. Leptin is an appetite-controlling hormone secreted by adipose tissue responsible for inhibiting food consumption and increasing energy expenditure.[57,58] The levels of leptin are increased in patients with CKD as a result of diminished renal clearance rate. Previous studies showed that zinc supplementation decreased serum leptin levels in HD children.[59] Additionally, low zinc serum concentration is negatively associated with high leptin levels in HD patients,[59] where elevated leptin levels may cause, or contribute to, a loss of appetite and malnutrition in patients with renal failure.[59] On the other hand, zinc may regulate the production of appetite-related peptides including neuropeptide Y (NPY) and ghrelin.[60] NPY is a transporter and modulator of catecholamines in peripheral, sympathetic, and cardiovascular control.[61]

The beneficial effect of zinc on pruritus may be explained by the antihistamine properties of zinc. HD patients have high levels of serum histamine, which may be a cause of pruritus in these patients.[62] Topical use of zinc is common to relieve symptoms of pruritus.[62] Moreover, zinc prevents mast cell degranulation and subsequent histamine secretion.[63] Therefore, pruritus may be improved resulting in decreased levels of histamine.

We found that zinc supplementation had no significant effect on anthropometric variables and body composition. It should be noted that BMI and BF were in the normal range at baseline in our study. The mean BMI was 24.38 kg/m$^2$ in the zinc group. However, the global mean BMI among adults aged 18-81 years was 25.8 kg/m$^2$.[64] The patients in our study were not underweight or cachectic. Also, the mean BF of the patients was 26.27% in the zinc group, where the average BF in adults aged 18-70 years is 10-15% in men and 20-30% in women.[65] Therefore, the BF among participants of our study was in the normal range. Also, zinc had no effect on anthropometric variables and body composition because baseline measurements were in the normal range and participants had no complications in this regard.

We did not use serum zinc concentration as a biomarker of compliance with zinc supplementation because of controversies regarding the effect of zinc supplementation on

serum zinc concentration in patients with ESRD. Although serum/plasma zinc is the most commonly used biomarker of zinc status in healthy populations, it is considered a flawed biomarker.[66] Indeed, it is commonly used because there is no better biomarker.[66] In patients with CKD, zinc supplementation is not effective in patients with high creatinine serum (>5.0 mg/dl) such as HD patients.[67] Also, zinc supplementation could not increase serum zinc in children with CKD.[27] Therefore, serum zinc may be not a good biomarker for evaluating compliance with zinc supplementation in studies that recruited patients with ESRD such as HD patients.

Limitations of the present study must be considered: 1) We used a simple randomization method supposed to lead to selection bias. The blocked randomization method is preferable and future studies should use this method rather than a simple randomization. 2) Although we employed validated tools to measure outcomes, some outcomes were self-reported such as indices of appetite. The validity of self-reported data is limited by a type of measurement error called responsible bias.[68] Indeed, individuals may over-/underestimate outcomes or have a misunderstanding of what an outcome is.[69] In this study, we measured appetite indices by self-reported data. Therefore, findings should be compared with other similar studies.

## Conclusions

This randomized clinical trial showed that zinc supplementation had beneficial effects on prospective food consumption, desire to eat, and pruritus in HD patients. However, it had no significant effect on anthropometric variables in non-cachectic patients.

### Ethics approval and consent to participate

This randomized clinical trial was registered at IRCT.ir on October 05, 2020 (Registration number: IRCT20130903014551N7). Also, all participants completed an informed consent form.

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### Author contribution statement

S.S and N.T designed the study. M.H.R and M.T collected data. M.H.R analyzed data. M.H.R and M.T interpreted results. C.C.T.C and M.T wrote the manuscript.

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### Conflicts of interest

There are no conflicts of interest.

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