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Original Article

Effect of zinc supplementation on insulin resistance, lipid profile, and body composition in non-diabetic hemodialysis patients

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ABSTRACT

Background and Objectives: Recent studies have shown the high prevalence of insulin resistance and zinc deficiency among hemodialysis patients. Zinc deficiency can be related to insulin resistance, as zinc is involved in the synthesis, secretion, action, and storage of insulin. This study aimed at evaluating the effect of zinc supplementation on lipid profile, insulin resistance, and as well as body composition in non-diabetic hemodialysis patients. **Methods**: In this placebo-controlled, double-blind, and randomized trial, 61 non-diabetic HD patients were randomly divided into Zinc gluconate (30 mg/d, n = 30) and placebo (control, n = 31) groups for 60 days. Fasting pre-dialysis blood samples were collected from all the participants in both groups for the determination of zinc, glucose, insulin, and lipid profile concentrations, respectively before and after the intervention. The body composition of the patients was measured with by BIA device. **Results:** At baseline, the mean level of serum zinc in patients was at the lower limit of the normal range for serum zinc standards. A significant increase was observed in the mean zinc level of serum in the experimental group while changes in the placebo group were not significant. Administration of zinc improved Glycemic status (FBS, HOMA-IR, and insulin) in the experimental group compared to the placebo group. Zinc supplementation led to a significant reduction in the mean serum triglyceride and LDL-c. Mean BMI, body composition, and body weight of patients in both groups did not significantly change before and after the intervention. **Conclusion:** Consumption of 30mg zinc gluconate daily for 60 days may have beneficial effects on glycemic status and lipid profile in hemodialysis patients, but further investigations are necessary.

Keywords: zinc, insulin, lipid, hemodialysis.

Introduction

The prevalence of chronic kidney disease (CKD) is a health problem worldwide that affects approximately 9% of the adult population [1-3]. End-stage renal disease (ESRD) and chronic kidney disease have become one of the world's major problems that increase morbidity and mortality in the world and putting pressure on health systems [4-6]. Patients with chronic renal failure undergo dialysis to ensure their health [7].

Various trace element abnormalities have been reported in patients undergoing hemodialysis for a long time [8-10]. Among these elements is zinc, which is involved in the synthesis, secretion, action, and storage of insulin [11, 12]. The prevalence of zinc deficiency in hemodialysis patients is reported to be 40-78% [13, 14]. Previous studies have confirmed that zinc deficiency may be a predisposing factor for insulin resistance, impaired glucose tolerance, increased lipid profile, atherosclerosis, and cardiovascular diseases [15, 16].

Insulin resistance (IR) is a known complication of end-stage renal disease (ESRD) and is prevalent in HD patients [17]. Metabolic and nutritional problems in kidney failure are the result of abnormal

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insulin function [18-20], and dyslipidemia is also associated with IR [19]. Another important factor highlighting the importance of IR in ESRD its effect on skeletal muscle protein turnover [21]. In a study of HD patients, a direct relationship was found between the IR index (HOMA-IR) and increased protein catabolism in the skeletal muscle. These changes were reported in a group of non-obese and non-diabetic patients who had undergone hemodialysis for a long time with no signs of chronic inflammation (normal CRP levels), suggesting sarcopenia developed in HD patients related to IR [22]. Numerous studies have reported that IR predicts death not only in the general population but also in patients with ESRD [23, 24].

Considering the prevalence of IR and zinc deficiency in patients undergoing hemodialysis and the importance of zinc in these patients through its possible association with IR prompted us to design a clinical trial. To date and based on our search in various scientific databases, no study is available in the literature that examined the effect of zinc supplementation on IR in non-diabetic HD patients. Therefore, this study was designed to investigate the impact of zinc supplementation on IR, lipid profile, and body composition in non-diabetic HD patients.

Materials and Methods

Participants

This study was a placebo-controlled, double-blind, and randomized clinical trial that was performed from May 2019 to August 2019 among 61 non-diabetic HD patients referred to the hemodialysis center of Ayatollah Taleghani Hospital, Urmia, Iran. Inclusion criteria were age equal to or greater than 18 years old, undergoing hemodialysis 3 times per week and HD treatment for at least six months. Exclusion criteria were consumption of contraceptives, estrogens, antibiotics, and glucocorticoids; pregnancy; lactation; being a candidate for kidney transplantation; any sign of gastrointestinal disorders; and diabetes mellitus. The protocol of the study complied with the Declaration of Helsinki and was approved by the ethics committee of Urmia University of Medical Sciences (IR.UMSU.REC.1397.248), and also, informed written consent was obtained from all participants. The trial was registered on the Iranian website for registration of clinical trials (www.irct.ir) (IRCT code: IRCT20191223045862N1).

Study design

Sixty-six patients undergoing HD agreed to participate in the study. Five patients were excluded from the study due to having gastrointestinal disturbances, hospitalization, and/or death **(Fig. 1)**. Patients were randomly divided to receive a tablet daily containing 30 mg zinc gluconate (n = 30) or methylcellulose tablet as a placebo (n = 31) to be taken without food or other medications for 60 days. Zinc supplements and its placebos were manufactured by Dineh Iranian Pharmaceutical Company (Qazvin, Iran). Supplements and placebos were in the same package form and the researchers and patients were not aware of the content of the packs until the end of the analysis. Individuals were randomized in a ratio of 1:1. Random assignment was done using a biased coin method. Allocation and randomization were hidden by the patients and researchers until the main analyzes were completed.

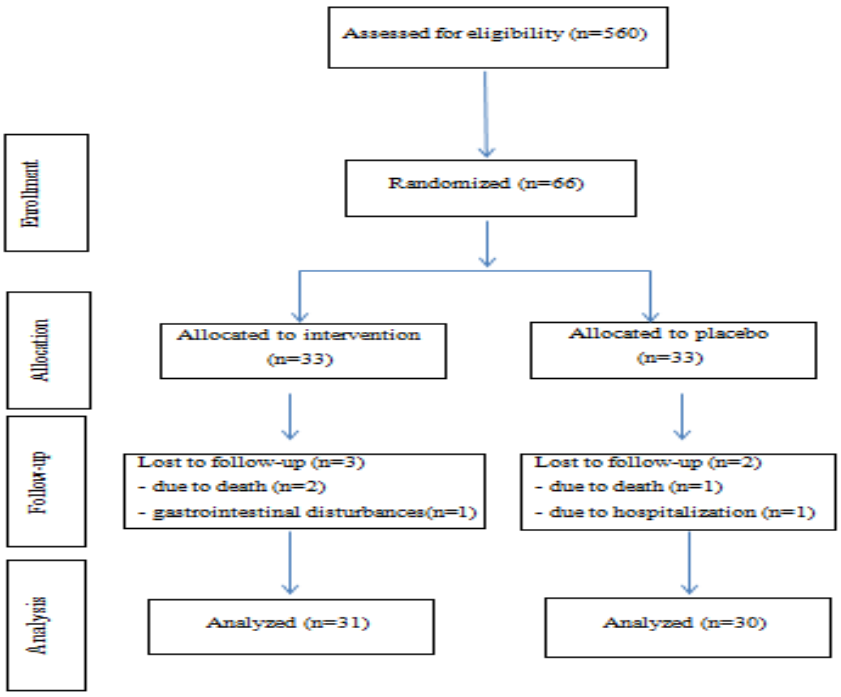

Figure 1. Summary of the patient flow diagram.

Anthropometric measures

Weight, BMI, and body composition of patients were measured with light clothing and barefoot by BIA (In body 770, Korea) at the onset and the end of study half an hour after hemodialysis. Patients' height was measured barefoot, using an amounted tape and was recorded to the nearest 0.5cm.

Dietary intake

Food intake information was collected using a 24-h recall method for 3 days (1 day dialysis, 1 day non-dialysis, and weekend), a week before supplementation, and at the end. The dietary intake of the participants was analyzed using the Nutritionist IV software.

Laboratory measurements

At the beginning and the end of the study, pre-dialysis blood samples were collected following overnight fasting then centrifuged at 3,000 rpm for 10 min and frozen at -80 °C until analyzed. The serum zinc level was determined by the autoanalyzer using the Dialab kit. Biochemical parameters (levels of serum glucose, albumin, and lipid profile) were assessed with a conventional autoanalyzer. The insulin level was measured by the ELISA method using the Dialab kit. Insulin resistance was characterized using the Homeostasis Model Assessment Method (HOMA-IR) and calculated as [fasting glucose (mg/dl) × fasting insulin (μU/ml)]/405.

Statistical analysis

Statistical analysis was performed with SPSS v.6.0 and included means and SDs. The normality of variables' distribution was evaluated using the Kolmogorov-Smirnov test. The analysis was done based on the per-protocol approach. The independent t-test was used for comparisons between-group at baseline. The differences between variables before and after intervention were compared using paired t-test. At the end of the study, ANCOVA adjusted for baseline values was used for between-group comparison. P-values <0.05 were considered statistically significant.

Results

The mean age of the subjects in the treatment group was 55.13 ± 7.51 and in the placebo group was 53.83 ± 6.89. At the beginning of the study, the mean serum zinc level in the intervention group was significantly ($p = 0.04$) lower than the placebo group and the mean serum triglyceride level in the intervention group was significantly ($p = 0.003$) higher than the placebo group, while there was not any significant difference in other study parameters between the 2 groups (all $p > 0.05$).

Table 1 shows the mean±SDs of dietary intake (macronutrients and zinc intakes) in both groups before and after the intervention. After 60-day follow-up, energy intake in the control group ($p = 0.011$) and fat intake in both groups significantly decreased compared to the baseline (all $p < 0.05$).

The mean body weight, body composition, and BMI of patients at the beginning and the end of the study are shown in Table 2. BMI, mean body weight, and body composition of patients in both groups did not significantly change before and after the intervention (all $p > 0.05$).

The means ± SDs of serum albumin and zinc levels in the supplemented and control groups are shown in Table 3. The initial mean concentration of serum zinc in both control and supplemented groups (83.25±17.1 g/dl and 78.6±10.4 g/dl, respectively) were at the lower limit of the normal range (70–110 g/dl) for serum zinc standards. in the experimental group, a significant increase was observed in the mean level of serum zinc while changes in the placebo group were not significant. At the beginning of the study, the mean serum albumin level in both groups was lower than the normal range (3.5-5.2 g/dL). In the experimental group, the mean serum albumin increased significantly ($p < 0.05$) compared to the baseline level.

Changes in glycemic status (FBS, HOMA-IR, and insulin) and lipid profile before and after intervention are shown in Table 3. After 60 days of intervention, in the experimental group, FBS, insulin, and HOMA-IR significantly (all $p < 0.05$) decreased compared with the placebo group, while a significant increase was observed in the mean serum HOMA-IR and insulin in the placebo group at the end of the study compared with the baseline level. Additionally, there was a significant reduction in serum triglycerides ($P < 0.001$) and LDL-c concentrations ($P < 0.001$) after the administration of zinc supplements compared to placebo. No significant effect of zinc supplementation on other lipid profiles was observed.

Discussion

zinc deficiency is now known in various diseases such as ESRD patients undertaking HD [25]. In this large group of patients, there are numerous reasons for zinc deficiency such as protein-energy malnutrition, losses by dialysate, low dietary intake, absorption and transport disorders, and increased excretion [26-28]. According to the results of this study, after zinc supplementation, the concentration of serum zinc increased from 70.02 ± 9.35 μg/dl to 98.84 ± 12.71μg/dl within the normal range. This is in line with the results of previous investigations, which showed subnormal zinc concentration of serum in the hemodialysis population with improvements following zinc supplementation [29-31].

Our results showed the prevalence of insulin resistance among non-diabetic HD patients. This is in line with the findings of other studies, which reported there was a high prevalence of insulin resistance in non-diabetic HD patients [22, 32, 33]. The causes of IR in kidney patients have not yet been fully understood, but IR is associated with increased triglyceride and LDL-c, and decreased HDL-c levels [34]. To the best of our knowledge, this is the first study that evaluated the effect of zinc supplementation on IR in non-diabetic HD patients but their relationship was reported in previous investigations.

According to the results of this study, zinc supplementation improved glycemic status (FBS, HOMA-IR, and insulin) in the experimental group. Several mechanisms may be explained for the association between zinc intake and decreased FBG and insulin resistance. Previous studies have shown that zinc has an important role in stabilizing insulin hexamers and the pancreatic storage of insulin as it can increase insulin binding to hepatocyte membranes [35].

Findings of our study revealed that zinc supplementation in non-diabetic HD patients led to a significant reduction in serum triglycerides and LDL-c levels compared with placebo, but had no effect other lipid profiles. Khan et al. [36] in their study demonstrated that 50mg of elemental zinc as zinc sulphate supplementation for 12 weeks in type-2 diabetes with microalbuminuria patients has resulted in a significant decrease in triglycerides, VLDL- c and a significant rise in HDL-c levels, whereas there was no significant decrease in LDL-c and total cholesterol concentrations. In addition, Payahoo et al. [37] observed that receiving 30 mg zinc gluconate per day among healthy obese adults did not significantly change lipid profile biomarkers but triglyceride levels were significantly decreased. The absence of the significant effect of taking zinc supplements on other lipid profiles in the current study compared to other studies may be due to different dosages of zinc supplementation, different study designs, and participants of the study.

Conclusions

Zinc supplementation for 60 days among non-diabetic HD patients had beneficial effects on glycemic status parameters, triglycerides and LDL-c levels; however, it did not affect other lipid profiles and body composition.

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Table 1. Mean ± SD of energy, macronutrients, and zinc intakes before and after intervention in both groups.

		supplemented group (n=30)	P-value*	Control group (n=31)	P-value*	P-value#	P-value^
Energy (kcal)	before	1869.53 ± 211.88	0.659	1950 ± 280.96	0.011	0.213	0.443
	After	1848.53 ± 202.71		1841.34 ± 202.81			
Carbohydrate (g)	before	233.08 ± 36.28	0.26	232.34 ± 37.65	0.961	0.938	0.437
	After	240.2 ± 37.54		232.71 ± 43.61			
Protein (g)	before	68.23 ± 9.87	0.612	68.24 ± 14.33	0.732	0.999	0.847
	After	69.38 ± 11.24		68.89 ± 12.21			
Fat (g)	before	70.7 ± 16.72	0.027	75.67 ± 13.98	0.02	0.213	0.218
	After	64.07 ± 9.89		68.57 ± 11.87			
Zinc (mg)	before	10.82 ± 4.27	0.792	10.67 ± 3.26	0.491	0.876	0.556

P-value*, Calculated by paired Student's t-test
P-value#, Calculated by independent sample t-test
P-value^, Calculated by ANCOVA adjusted for baseline values

Table 2. Mean ± SD of body weight, BMI, and body composition at the onset and end of study.

		supplemented group (n=30)	P-value*	Control group (n=31)	P-value*	P-value#	P-value^
Total body water (L)	Before	35.49 ± 5.80	0.354	36.38 ± 6.25	0.503	0.565	0.264
	After	35.01 ± 6.35		36.48 ± 6.18			
Free fat mass (kg)	Before	48.01 ± 7.84	0.52	49.3 ± 8.18	0.565	0.544	0.907
	After	48.18 ± 8.03		49.42 ± 8.35			
Body fat mass (kg)	Before	32.92 ± 10.86	0.485	36.79 ± 9.77	0.357	0.148	0.316
	After	31.56 ± 11.74		36.51 ± 9.81			
Skeletal muscle mass (kg)	Before	26.48 ± 4.68	0.309	27.2 ± 5.14	0.932	0.572	0.313
	After	27.27 ± 6.37		27.21 ± 5.08			
Weight (kg)	Before	80.44 ± 11.99	0.752	85.31 ± 12.6	0.417	0.127	0.146
	After	80.13 ± 10.55		86.14 ±12.18			
BMI (kg/m2)	Before	30.96 ± 4.04	0.823	32.98 ± 5.3	0.465	0.101	0.103

P-value*, Calculated by paired Student's t-test
P-value#, Calculated by independent sample t-test
P-value^, Calculated by ANCOVA adjusted for baseline values

Table 3. Mean ± SD of serum zinc and albumin levels, glycemic status parameters, and lipid profiles before and after intervention.

		Supplemented group (n=30)	P-value*	Control group (n=31)	P-value*	P-value*	P-value*
Serum Zinc (µg/dL)	Before	70.02 ± 9.35	0.001<	75.41 ± 10.6	0.389	0.04	0.001<
	After	98.84 ± 12.71		73.06 ± 13.96			
Albumin (g/dl)	Before	3.89 ± 0.38	0.024	3.89 ± 0.31	0.134	0.996	0.381
	After	4.12 ± 0.39		4.03 ± 0.41			
FBS (mg/dL)	Before	107/93 ± 10.12	0.006	102.6 ± 10.87	0.459	0.052	0.042
	After	101.53 ± 10.16		103.68 ± 9.34			
Insulin (µIU/mL)	Before	5.25 ± 1.02	0.001<	5.11 ± 0.9	0.043	0.581	0.001<
	After	4.62 ±0.84		5.28 ± 0.91			
HOMA-IR	Before	1.4 ± 0.33	0.001<	1.3 ± 0.29	0.001<	0.192	0.001<

	After	1.16 ± 0.25		1.36 ± 0.49			
Triglycerides (mg/dL)	Before	191.6 ± 78.84	0.001<	152.26 ± 67.12	0.022	0.003	0.001<
	After	147.9 ± 62.39		137.03 ± 56.52			
Total cholesterol (mg/dL)	Before	173.6 ± 34.87	0.016	185.39 ± 43.08	0.019	0.246	0.806
	After	161.87 ± 35.08		171.19 ± 37.01			
LDL-c (mg/dL)	Before	90.47 ± 28.59	0.001<	88.68 ± 24.19	0.005	0.793	0.001<
	After	77.53 ± 20.58		97.48 ± 23.83			
HDL-c (mg/dL)	Before	42.23 ± 8.37	0.026	46.06 ± 9.03	0.097	0.093	0.218
	After	45 ± 9.36		43.64 ± 7.3			

P-value*, Calculated by paired Student's t-test
P-value#, Calculated by independent sample t-test
P-value^, Calculated by ANCOVA adjusted for baseline values