The efficacy and safety of zinc gluconate supplementation on quality of life, sleep quality, and serum albumin in hemodialysis patients: A randomized clinical trial

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The efficacy of zinc gluconate supplementation on quality of life, sleep quality, and serum albumin in hemodialysis patients: A randomized clinical trial

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This randomized clinical trial was registered at IRCT.ir on 19-10-2020 (Registration number: IRCT20130903014551N10).

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Declarations

- **Ethics approval and consent to participate:** This randomized clinical trial was registered at IRCT.ir on 19-10-2020 (Registration number: IRCT20130903014551N10). Also, all participants completed an informed consent

form.

- **Consent for publication:** Not applicable
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Abstract:

Background: Hemodialysis patients suffer from several complications, including low quality of life, poor sleep quality, and decreased serum albumin. We hypothesized that zinc supplementation may improve these complications.

Objective: To examine the effects of zinc gluconate supplementation on quality of life, sleep quality, and serum albumin.

Methods: In this parallel randomized clinical trial, 87 hemodialysis patients were randomly assigned in the zinc (n=44) or placebo group (n=43) for 12 weeks. Patients in the zinc group received one 30 mg zinc gluconate tablet per day. Quality of life was assessed The Kidney Disease Quality of Life (KDQOL) instrument, and sleep quality was evaluated by The Pittsburgh Sleep Questionnaire. Also, serum concentrations of albumin and high sensitivity C-reactive protein (hs-CRP) were measured at baseline and end of the study. This randomized clinical trial was registered at IRCT.ir (IRCT20130903014551N10).

Results: There were beneficial effects of zinc supplementation on sleep quality ($p<0.001$) and albumin concentration ($p=0.038$), compared with placebo. However, we observed no changes in high-sensitivity C-reactive protein ($p=0.767$) and quality of life ($p=0.839$) in zinc group in comparison with placebo.

Conclusion: This randomized clinical trial showed that zinc supplementation elicited beneficial effects on sleep quality and albumin levels in hemodialysis patients

Keywords: Hemodialysis; Zinc; Sleep Quality; Quality of Life; Albumin

Introduction

Chronic kidney disease (CKD) is a condition where the removal of waste products, hemostasis of electrolytes, activation of vitamin D, and regulation of blood pressure are impaired (1). Hypertension, kidney stones, and diabetes are the main causes of CKD (1). To compensate impaired renal function, waste products and excess water are removed from the blood through dialysis, including hemodialysis and peritoneal dialysis (2). Although hemodialysis mimics some functions of the kidney, it is not as effective as normal kidney. Indeed, patients on hemodialysis have several complications, including decreased level of albumin, poor sleep quality, and low quality of life.

Hemodialysis patients usually have less albumin than healthy individuals due to increased albumin excretion during hemodialysis (3). Also, synthesis of albumin is decreased in response to high inflammation and malnutrition among hemodialysis patients. Moreover, malnutrition is a cause of albumin synthesis reduction (4); indeed, for each 1 g/dl decrease in albumin concentration results, there is a 47% increased risk of mortality (5). Studies showed that some nutrients, such as zinc, may have favorable effect on albumin level, for instance, zinc supplementation resulted in increment of albumin in sever zinc deficient subjects (6), in addition to reducing albumin loss in diabetic patients (7)

Poor sleep quality is another complication among hemodialysis patients (8); for instance, patients on hemodialysis usually display varying degrees of insomnia (9,10). Empirical evidence has showed that poor sleep quality leads to premature death (11). Hemodialysis patients usually have poor sleep quality due to side effects of medications, depression, anxiety, pain and itching (12). However, zinc may have a beneficial effect on sleep quality. For example, the results of Rondanelli

et al showed that co-supplementation of zinc, magnesium, and melatonin could improve insomnia and sleep quality in patients with primary insomnia **(**13). Also, the results of another study reported that zinc supplementation improved sleep disorders and treated main problems of falling asleep (14).

Another common problem in hemodialysis patients is low quality of life, which tends to be lower than healthy counterparts (15). The results of a previous study showed that there is an inverse relationship between duration of hemodialysis and quality of life (16). Additionally, hemodialysis patients with low quality of life usually present with symptoms of depression (17), whilst a study showed that zinc sulfate supplementation significantly improved quality of life in women with premenstrual syndrome (18). Finally, treatment of zinc deficiency reportedly resulted in an improvement in quality of life among patients with cancer (19).

Although zinc supplementation could putatively improve albumin level, sleep quality, and quality of life in previous studies, there is limited evidence regarding hemodialysis patients. Additionally, most previous studies used zinc supplement in the form of zinc sulfate, whilst the effect of zinc gluconate, a more digestible with less side effects form of zinc supplement, has not been examined. Therefore, the aim of this clinical trial was to examine the effect of zinc gluconate supplementation on albumin level, quality of life, and sleep quality in hemodialysis patients.

Method

Subjects and Intervention: This study was a parallel double-blind randomized clinical trial that lasted 12 weeks. The intervention was conducted in Isfahan, Iran from October 2020 to October 2021. 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.REC1399.407). This randomized clinical trial was registered at IRCT.ir on 19-10-2020 (Registration number: IRCT20130903014551N10).

Based on the inclusion and exclusion criteria, patients were selected from two dialysis centers. The subjects were included in the study if they: 1) were on hemodialysis for at least three months; 2) had two dialysis sessions per week, at least; 3) were not a smoker; 4) were not pregnant or lactating; 5) were not on parenteral or enteral feeding; 6) had no history of cancer or sever liver diseases; 7) consumed usual diet prescribed to hemodialysis patients; and 9) were over 18 years old. Following exclusion criteria were defined; 1) kidney transplant or death, 2) low compliance with the intervention (consuming 85% of supplements/placebo); and 3) switching to peritoneal dialysis.

We used following equation to estimate required sample size: $n = 2\,[(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times S^2] / \Delta^2$. In this equation, α=0.05, and β=0.20 (the power of the study was 80%). Score of sleep quality was considered as the main variable. According to previous studies conducted on Iranian hemodialysis patients, Δ=0.37 and S^2=0.57 (20). The required sample size was 36 subjects in each group. To overcome the possibility of subject withdrawal, we enrolled 80 subjects (n=40 in each group). We randomly assigned hemodialysis patients to one of the zinc or placebo groups using a computer-generated randomization sequence, with no blocking procedure. Only one staff member generated the randomization list and assigned patients. Both investigators and participants were blinded, and the randomization sequence could not be revealed by sequentially numbered. All participants received information regarding the protocols and procedures and signed a written consent form prior to participation.

Subjects in the intervention group were prescribed one 30 mg zinc gluconate tablet per day, produced by Dineh Company, Tehran, Iran, for 12 weeks. In the placebo group, tablets contained

30 mg starch, where its color, appearance, smell, and taste were similar to the zinc gluconate, and were administered to the patients. In both groups, participants were advised to take the supplements after breakfast, in non-dialysis days, and after the first post-dialysis meal in dialysis days. Also, a list of nutritional recommendations were provided for both groups including: 1) Avoid fried foods, solid oils, salty foods, high-fat dairy products, processed foods, and junk foods; 2) Avoid eating foods with added sugar and fat; 3) Eat food with low fat and sodium content; 2) Limit the consumption of sugar sweetened beverages; 3) Limit the consumption of legumes, nuts and dairy products; 4) Limit the consumption of potassium-rich foods, such as banana, spinach, orange, dates, tomato, and potato. A questionnaire including demographic information, medical history, and medications was completed for each subjects. In addition to monitoring patients every two weeks during dialysis sessions to assess compliance with intervention, supplements and placebo were given to the patients every 14 days for the proceeding two weeks, and empty packages were returned by patients.

Measurement of Sleep quality: The Pittsburgh Sleep Questionnaire was used to assess sleep quality. Seven subclasses of sleep quality were assessed by this questionnaire including: 1) subjective sleep quality; 2) sleep latency; 3) sleep duration; 4) habitual sleep efficiency; 5) sleep disturbances; 6) use of sleeping medication; and 7) daytime dysfunction. Each subclass was scored on a 4-point Likert scale, from 0 (no problem) to 3 (very serious problem). Therefore, total score ranged from 0 to 21, in which higher score indicated poor sleep quality. The validity and reliability of this questionnaire have been reviewed and confirmed previously (21, 22).

Measurement of Biochemical variables: Albumin was measured by bromocresol green method, in which serum albumin formed as a green-blue color complex. The amount of colored products

was an indicator of albumin level. Imuno turbid method (Audit kit, Delta treatment, Ireland-Iran) was applied to measure high sensitivity C-reactive protein (hs-CRP).

Measurement of life quality: The Kidney Disease Quality of Life Instrument (KDQOL) was used to measure the health-related quality of life. This questionnaire has 2 subclasses, including specific health and general health. The validity and reliability of this questionnaire has been confirmed in previous work (23).

Assessment of Dietary Intakes: During the intervention, hemodialysis patients were asked to complete two 3-day food records (two non-dialysis days and one dialysis day). Nutritionist IV and the USDA food composition database were used to analyze food diaries.

Statistical Analysis: Q-Q diagrams and the Kolmogrov-Smirnov test were used to check the normality of quantitative variables. A chi-square test was used to compare the distribution of qualitative variables between the two groups. Qualitative variables were reported as a percentage, and quantitative variables were reported as means and standard deviations. A paired t-test was used for intra-group analysis and an independent t-test and analysis was used for intergroup analysis. An analysis of covariance (ANCOVA) was applied to adjust for confounding variables (energy intake and baseline values). SPSS software version 20 was used to analyze the data, with an *a priori* significance level of $P < 0.05$. Data were analyzed according to Per-protocol analysis method.

Result

The flow diagram of study procedure is shown in **Figure 1**. Initially, we screened 101 participants for eligibility. Fourteen subjects were excluded because they did not meet inclusion criteria or declined to participant. Therefore, 87 patients were randomly allocated in zinc (n=44) or placebo

(n=43) groups. In the zinc group, 6 subjects were lost to follow-up because of kidney transplantation (n=2), death (n=1), dialysis access infection (n=1), or personal reasons (n=2). Similarly, 6 patients were lost to follow-up in the placebo group due to migration (n=1), kidney transplantation (n=2), death (n=1), or personal reasons (n=2). Therefore, data of 75 subjects (n=38 in zinc and n=37 in placebo groups) were analyzed.

Baseline characteristics

Baseline general characteristics of participants are displayed in **Table 1**. The distribution of participants diagnosed with hypertension (P=0.463), diabetes (P=0.234), and autosomal dominant polycystic kidney disease (P=0.996) were not different between two groups. There was no significant difference in age (P=0.552), sex (P=0.808), marital status (P=0.385), dialysis vintage (P=0.270), dialysis frequency (P=0.333), and serum zinc (P=0.989) between two groups at baseline.

Comparison of dietary intake during the study between zinc and placebo groups is shown in **Table 2**. Results revealed that the intakes of energy (1439.48 vs. 1304.99 Kcal/day, P=0.185), carbohydrate (P=0.076), protein (P=0.273), fat (P=0.684), sodium (P=0.273), vitamin E (P=0.106), vitamin C (P=0.289), vitamin B1 (P=0.054), vitamin B2 (P=0.118), potassium (P=0.392), calcium (P=0.104), selenium (P=0.631), zinc (P=0.643), and dietary fiber (P=0.906) were not different significantly between two groups.

The effects of zinc supplementation on quality of life and sleep quality are shown in **Table 3.** Sleep quality was increased in both groups after the intervention (P=0.020 for zinc and P<0.001 for zinc). In comparison to the placebo, zinc supplementation elicited an improvement in sleep quality, which remained unchanged after adjusting for baseline measurements. We observed no significant

difference between zinc and placebo regarding sleep quality, before and after adjusting for confounder variables.

The effects of zinc supplementation on biochemical variables are reported in **Table4.** hs-CRP was decreased in both groups after intervention (P<0.001 for both). In comparison to the placebo, zinc supplementation yielded a marginal improvement in albumin level (P=0.056). After adjusting for baseline measurements, we observed zinc supplementation caused an increase in albumin concentration compared with placebo. (P=0.038).

Discussion

Our study showed that zinc supplementation could improve quality of sleep and ameliorate the reduction of albumin. Low sleep quality and loss of albumin are prevalent among hemodialysis patients, and thus, improved sleep quality and malnutrition may help to increase quality of life and survival rate in subjects undergoing hemodialysis (24).

An improvement in quality of sleep was observed after zinc supplementation in the present study. Previous studies have reported similar findings, for instance, an observational study revealed that dietary zinc intake was inversely associated with sleep disorders in young women (25). In children, adequate serum zinc concentration was related to the improved sleep quality (26). Also, serum and hair concentration of zinc was associated with sleep duration among women (27). Clinical trials have showed that co-supplementation of melatonin, magnesium, and zinc had a beneficial effect on sleep quality in subjects with primary insomnia (28), whilst zinc supplementation was shown to increase quality of sleep in nurses, compared with placebo (29). Therefore, zinc may be beneficial in improving sleep quality in different subjects.

Our results showed that zinc supplementation could ameliorate the reduction of albumin compared with placebo. Comparable results were reported in previous studies. Zinc deficiency has been considered as a reason of hypoalbuminemia in patients with liver dysfunction (30). Albumin levels have been associated with serum zinc concentration in subjects with liver diseases (31), including in children with CKD (32). In another study, albumin synthesis increased after zinc supplementation compared with placebo (33). Therefore, considering the extant literature, albumin synthesis may be improved following zinc supplementation.

Albumin is a negative acute phase protein influenced by inflammation (34). In the present study, we measured hs-CRP as an indicator of inflammation to ensure that changes in albumin concentration were not affected by inflammation. Accordingly, our results showed that there was no significant changes in hs-CRP in zinc and placebo groups. Therefore, changes in albumin levels were not dependent on inflammation and indicated an improvement in nutritional status.

The mechanism of action of zinc on sleep remains unclear. Most studies have focused on interaction of zinc on glutamatergic receptors. Transmission of neural messages in retrograde axons leads to accumulation of zinc nanocrystals in nerve cavity lysosomes (35). Zinc has also observed in the glycinergic terminals of the cerebellum and spinal cords, whilst glycinergic neurons have been reported to inhibit the activity of arousal related neurons in the hypothalamus (36). Thus, it seems that zinc has an effect on improving the sleep quality based on this pathway.

Zinc may effect on serum albumin through various mechanisms. Zinc is involved in the function of the hepatic urea cycle and zinc deficiency causes hyperammonemia (37), and in this regard, branched chain amino acids (BCAAs) play a role in ammonia detoxification, which results in reduced BCAAs level in muscles. Indeed, BCAA deficiency may disturb hepatic protein synthetic that leads to a decrease in albumin levels (38, 39).

This study possess the following strengths: 1) the chemical form of the zinc in current study was zinc gluconate; this type of zinc supplement has better gastrointestinal absorption and less digestive side effects; 2) we measured hs-CRP to ensure that albumin changes was not dependent on inflammation. However, the loss of the participants due to the COVID-19 pandemic represents a prominent limitation of the present study.

Conclusion

In conclusion, zinc supplementation elicited improvements in sleep quality and ameliorated albumin reduction in hemodialysis patients. Accordingly, it appears that malnutrition and poor sleep quality may be improved by zinc supplementation.

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Legend to the Figure:

Figure 1: Study CONSORT flow diagram

Table 1. Baseline characteristic of study subjects [a]

Variable	Zinc (n=38)	Placebo (n=37)	P [b]
Male (%)	68.4	64.9	0.808
Age (year)	49.23(15.35)	51.21(13.76)	0.552
Married (%)	76.3	70.3	0.385
Hypertension (%)	60.5	70.3	0.463
Diabetes (%)	28.9	43.2	0.234
Autosomal Dominant Polycystic Kidney Disease (%) (%)	2.6	2.7	0.996
Dialysis vintage (Month)	32.39(27.94)	40.5(37.97)	0.270
Dialysis Frequency (Session/week)	2.86(0.41)	2.83(0.37)	0.333
Serum Zinc(mg/dl)	81.94(16.82)	82.32(18.28)	0.989

BMI; body mass index, WC; waist circumference

[a] Continuous variables are expressed as mean ± SD.

[b] *p*-values resulted from independent t tests for quantitative and Chi-square for qualitative variables.

Table 2. Dietary intake of the study participants throughout the study [a]

Variable	Zinc (n=38)	Placebo (n=37)	*P*[b]
Energy (Kcal/day)	1439.48(399.72)	1304.99(470.66)	0.185
Carbohydrate (g/day)	200.62(59.67)	171.36(73.7)	0.076
Protein (g/day)	62.1(18.37)	59.35(36.58)	0.273
Fat (g/day)	49.59(13.51)	46.59(15.49)	0.684
Sodium (mg/day)	62.1(18.37)	59.35(36.58)	0.273
Vitamin A (re/day)	49.59(13.51)	46.59(15.49)	0.681
Vitamin E (mg/day)	9.28(4.41)	10(4.2)	0.106
Vitamin C (mg/day)	107.41(61.94)	82.73(67.05)	0.289
Vitamin B1 (mg/day)	1.26(0.32)	1.08(0.41)	0.054
Vitamin B2 (mg/day)	1.47(0.63)	1.16(0.63)	0.118
Potassium (mg/day)	3057.01(1434.78)	2513.76(1565.33)	0.392
Calcium (mg/day)	1068.48(581.83)	777.73(593.86)	0.104
Selenium (mg/day)	78.09(27.98)	73.59(31.62)	0.631
Zinc (mg/day)	9.27(3.55)	8.13(3.47)	0.643
Dietary Fiber (g/day)	23.4(10.83)	20.7(14.1)	0.906

[a] Variables are expressed as mean ± SD.
[b] All variables were adjusted for total energy intake

Table 3. The effects of zinc supplementation on quality of life, sleep quality in hemodialysis patients

Variables	Zinc (n=38)				Placebo (n=37)				P[c]	P[d]
	Baseline	End of trial	Change	P[b]	Baseline	End of trial	Change	P[b]		
Quality of life (score)	68.87 ± 4.26	69.27±3.92	0.39 ± 3.58	0.499	69.77 ± 5.04	70.00 ± 4.91	0.22 ± 3.86	0.725	0.480	0.839
Quality of sleep (score)	6.68 ± 2.73	5.23 ± 2.73	-1.44 ± 1.15	<0.001	7.29±2.45	6.89 ± 2.65	-0.40 ± 1.01	0.020	0.010	<0.001

[a] Variables are expressed as mean ± SD
[b] Obtained from Paired T test1.01268
[c] Obtained from Independent t-test comparing endpoint measurements
[d] Obtained from ANCOVA, adjusted for baseline value

Table 4. The effects of zinc supplementation on biochemical variables in hemodialysis patients

	Zinc (n=38)				Placebo (n=37)					
	Baseline	**End of trial**	**Change**	**P[b]**	**Baseline**	**End of trial**	**Change**	**P[b]**	**P[c]**	**P[d]**
C-reactive protein (mg/dl)	1.25 ± 4.80	0.07± 6.13	-9.72 ± 48.74	<0.001	0.73 ± 3.94	0.07± 6.71	-1.99± 6.09	<0.001	0.930	0.767
Albumin (g/dl)	4.02 ± 0.85	3.96± 0.65	-0.06 ± 1.27	0.765	3.91 ± 0.64	3.66± 0.66	-0.24 ± 0.91	0.106	0.056	0.038

[a] Variables are expressed as mean ± SD
[b] Obtained from Paired T test
[c] Obtained from Independent t-test comparing endpoint measurements
[d] Obtained from ANCOVA, adjusted for baseline value