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Effect of Zinc Supplementation on Blood Pressure and Complete Blood Count in Hemodialysis Patients

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MM, HA, NR and BKA designed the study, performed the statistical analysis, and wrote the protocol. Author SB corrected the manuscript, and approved the final submission. Author LR managed the analyses of the study, managed the literature searches, and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: Zinc is an important trace element in human nutrition and its deficiency is a worldwide problem. Zinc deficiency incidence is predominantly high in many diseases such as ESRD (End Stage Renal Disease) patients undertaking hemodialysis (HD). Beside, hypertension and cardiac output, is a predictor of cardiovascular mortality in HD patients. This study investigated the effects of zinc supplementation on blood pressure (BP) and complete blood count (CBC) in HD patients.
Materials and Methods: In a randomized, double-blind, and placebo-controlled trial, Sixty-five HD patients were randomly divided into two groups. Patients in group I and group II received placebo and Zn supplementation (100 mg/day) respectively for two months. After withdrawing for the

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duration of the next two months, the study was continued as a crossover design for another two months (group I and II received zinc supplementation and placebo, respectively). Systolic and diastolic BP, cardiac ejection fraction (EF), and CBC were measured at the 0^{th}, 60^{th}, 120^{th}, and 180^{th} days. Statistical analyses were performed using SPSS software.

Results: Zinc supplementation resulted in a significant increase in the mean red blood cell (RBC), Hematocrit (Hct), whereas a significant decrease was seen in systolic and diastolic BP. Changes observed in the placebo group were not significant.

Conclusion: Zinc supplementation for two months improved the systolic and diastolic BP, RBC, and Hct in HD patients.

Keywords: Zinc supplementation; hemodialysis; blood pressure; complete blood count.

1. INTRODUCTION

End Stage Renal Disease (ESRD), a complete and irreversible kidney failure, is the advanced form of chronic kidney disease (CKD). There are more than one million ESRD sufferers worldwide and many of them die from causes related to kidney failure each year. Hypertension is the second leading cause of chronic kidney disease (CKD) after diabetes. Furthermore, renal failure is the most common form of secondary hypertension and available evidence proposes that, it is an important risk factor for cardiovascular mortality and morbidity [1,2]. Therefore, hypertension is both a cause and result of kidney disease. Hypertension can be a risk factor for CKD in two general ways. In the first pathway, chronic hypertension causes glomerular ischemia and arterial injury and glomerulopathy. As a result, it reduces glomerular blood flow and causes nephropathy. In the second pathway, chronic hypertension causes the loss of auto-regulation of afferent arterioles and glomerular systemic hypertension. Therefore, this process leads to glomerulosclerosis and renal failure [3]. In patients with CKD, sodium misbalance leads to an increase in blood pressure. Initially, the extracellular fluid and peripheral resistance are increased, which these cause an increase in blood pressure. In addition, the activation of the renin-angiotensin system may stimulate the sympathetic nervous system and cause hypertension [2].

The prevalence of hypertension in patients on hemodialysis is as high as 90%. Controls of hypertension in the ESRD patients are recommended [3]. Therefore, the necessity to search for appropriate preventive and management strategies should be the concern of health care providers. Pathogenesis of hypertension is wide-spread, for this reason, many strategies such as, decreased oxidative stress, and increased antioxidant activities proposed for management of this abnormality in ESRD patients [4,5].

Several studies have demonstrated that essential trace elements play important roles in states of cardiovascular diseases such as hypertension [6]. Zinc, one of the essential trace element and intracellular ion and the second most abundant transition metal in organisms after iron, is the only metal which appears in all enzymes [7]. Zinc is complicated in numerous biochemical functions. More than 300 enzymes to function and approximately 2000 transcription factors for gene expression require this element [8].

Although essentiality of zinc for humans and its deficiency was identified during the past 50 years, it has become seeming that insufficiency of zinc in humans is a prevalent nutritional deficiency of zinc may affect approximately 2 billion of global population [9,8]. The current work was designed with the aim of investigating the potentials of zinc supplementation in the ameliorating of hypertension and CBC indices in HD patients.

2. METHODS AND MATERIALS

In this study 78 chronic hemodialysis patients were selected to double-blind randomized controlled trial (RCT) at Tabriz Imam Khomeini Hospital. This experiment was performed according to the Declaration of Helsinki as well as the International Medical Research and was approved by the ethics committee of Tabriz University of Medical Sciences. An informed agreement was obtained from each volunteer. Inclusion and exclusion criteria for participation in the study was shown in the Table 1. Five patients were excluded from the study, 3 died because of cardiac arrest, 2 were receiving antibiotics, and 3 were excluded because of zinc intolerance (nausea).

Table 1. Inclusion and exclusion criteria for participation in the study

Inclusion	Chronic hemodialysis patients
Exclusion	Hemodialysis for less than 6 months;
	Hospitalization apart from chronic renal failure;
	Any sign of gastrointestinal disorders;
	Smoking;
	Being a candidate for kidney transplantation; Pregnancy or lactation;
	Consumption of glucocorticoids, antibiotics, estrogens, and contraceptives (in females).

Sixty-five patients [41 males (63.1%) and 24 females (36.9%)] with a mean age of 52.77 ± 12.68 years (26-80 ages) completed the study. The etiology of ESRD was chronic glomerulonephritis (n=16), diabetic nephropathy (n=9), polycystic kidney disease (n =5), chronic interstitial nephropathy (n=5), urological problems (n=4), Hypertension (n=7), vascular disease (n=6), Urinary tract obstruction or dysfunction (n=2), Hereditary nephropathy (n=5), and unconfirmed etiology of HD (n=6). All of the patients were on HD 3 times per week (each time for 4 hours) by using a cellulosic membrane to maintain a minimum Kt/V urea index of 1.2 per session.

Patients were randomly divided into two groups: Group I included 35 patients (22 males and 13 females) with a mean age of 50.97 ± 11.50 years. The duration of dialysis was 42.03 ± 27.75 months. This group received 100 mg cornstarch capsules (two-per-day) as placebo for 2 months. Group II included 30 patients (19 males and 11 females) with a mean age of 54.87 ± 13.74 years. The duration of dialysis was 47.31 ± 22.78 months. This group received 100 mg/day of elemental zinc sulfate (as two 220 mg zinc heptahydrate, ALHAVI Co., Tehran, Iran) for 2 month at the same time with group I.

The placebo and zinc were withdrawn for the duration of the next 2 months, and then the study was continued as a crossover design for another 2 months (group I and II received zinc and placebo, respectively). In this study, none of the groups were aware of being in the supplementation or placebo group. Also, the experimenter was not aware of the samples. For the placebo group, capsules similar to zinc supplementation were used, but the capsules were filled with corn starch. Our study, with little difference, is similar to Finckh et al. In this study, a double-blind and crossover study, randomly, there were two groups that administered the methotrexate and placebo for three months. Then, they washed out for two months, and again for three months, the study was as Crossover. As, before the wash out, the group receiving methotrexate administered the placebo in the second trimester and the group receiving placebo administered methotrexate in the second trimester [10].

Overnight fast (12-h) blood samples were obtained before the start of zinc and placebo, at the 0^{th}, 60^{th}, 120^{th}, and 180^{th} days in fasting. These Pre-dialysis blood samples were divided into a heparinized tube and a microtube containing EDTA (1.5 mg/mL) and then used for complete blood count (CBC) or centrifuged and stored at −18°C until other analyzed.

Serum zinc level was determined by an atomic absorption spectrophotometry after a 1:5 dilution in double deionized water at 213.9 nm (ChemTech Analytical Co., Bedford, UK) using external standard calibration curve.

Measurement of hemoglobin, hematocrit, white blood cells (WBC), and red blood cells (RBC) was performed with Sysmex KX-21N Automated Hematology Analyzer. Systolic and diastolic blood pressure was measured by cardiologists using a mercury sphygmomanometer with subjects in a supine position after five minutes of relaxing.

All statistical analyses were performed using IBM SPSS statistics software (version 20; SPSS). Results are presented as mean ± SD. Between-group comparisons were made using independent *t*-test. The differences between variables before and after intervention were compared using paired *t*-test. *P*-value <0.05 was considered statistically significant.

3. RESULTS

Table 2 represents the mean values of systolic and diastolic BP, EF, and CBC with differential levels in group I during the placebo (from day 0 to day +60) and zinc supplementation (from day

+120 to day +180) periods. As shown in this table, there was a significant decrease in EF level after 60 days in the placebo group (P<0.05) whereas the other factors were not significantly changed. After the zinc supplementation period (from days +120 to +180), an increase was seen in EF (P<0.05). Blood pressure indicators including systolic and diastolic BP were decreased significantly (P<0.05). Hb (hemoglobin), Hct levels as well as erythrocyte count improved significantly (P=0.011, P=0.043, and P<0.05 respectively). White blood cell count (WBC) differential such as neutrophils, and lymphocytes were not changed considerably.

Table 3 shows the mean values of systolic and diastolic BP, EF, and CBC with differential levels in group II during the zinc supplementation (from day 0 to day +60) and placebo (from day +120 to day +180) periods. There were increases in EF, Hct, and RBC levels (P<0.05, P=0.016, and P<0.05 respectively) and significant decrease in systolic BP (P<0.05) and diastolic BP (P<0.05) after 60 days in zinc supplementation period. Whereas, there were no statistically or clinically significant change in mean hemoglobin levels in this period. After the placebo period (from days +120 to +180), a reduction was found in the mean EF. Significant changes were not shown in other factors. Comparison of significance level of study groups at different time intervals was showed in the Table 4.

4. DISCUSSION

According to the results of our study, in both group I and group II, the amount of Hb and Hct as well as erythrocyte count, indicating anemia in HD patients, was lower than normal. Administration of Zn supplements improved these factors significantly. Increasing of Hb in group II didn't signify. Erythrocytes due to intracellular enzymes such as SOD, catalase, and glutathione are important components of blood antioxidants [11]. One of the possible causes of renal anemia and reduce the life of RBCs is due to oxygen free radical attack (because of increased oxidative stress in patients) in their membranes. This effect, reduces intravascular hemolysis and RBCs half-life [12-14]. Effect of Zn in improving anemia, appear to be at least partially due to the improvement of antioxidant status and oxidative stress reduction. Improving oxidative stress and anemia can have a synergistic effect on each other [15]. Therefore, correction of renal anemia may be effective in strengthening the capacity of the antioxidant in the body. Siems et al. reported that lipid peroxidation in patients with Hb<10 g/dl is more than that in patients with Hb>10 g/dl [14]. Other study, reported that the decrease of Hb and RBCs in rats is correlated with deficiency of Zn level [16].

The systolic/diastolic blood pressure was 146/81 mmHg in our study. Blood pressure did not change significantly in the placebo period, but Zn supplementation resulted in a significant reduction in systolic and diastolic blood pressure. Hypertension is a common phenomenon in HD patients [17-19]. High blood pressure can be a cause or consequence of chronic kidney disease [20]. Mechanisms of hypertension in renal failure are complex and include neural and hormonal effects [21,22]. Galley et al. reported that the administration of Zn, vitamins C and E for eight weeks reduced systolic blood pressure [13]. Importance of peroxidation and oxidative stress on the pathogenesis of hypertension was reported by Russo et al. [23].

The EF baseline, in the range of 52% -55% of patients who are prescribed in the absence of Zn (placebo period) has decreased after 60 days, indicating the rapid effects of acute uremia conditions in the performance of the heart. Decreasing in this performance probably by reducing trace elements such as Zn, as one of the factors to be considered. Decreasing average systolic function and EF level in about 20% of HD patients was reported by Virga et al. [24]. In our study, administration of Zn not only prevents the reducing of EF in patients, but also it has been effective in improving EF, is an indication of the beneficial effects of Zn complementation. It is possible that at least the part of this effect is because of improving anemia as well as decreasing blood pressure in these patients. In the previous study, it was shown that there is a direct relationship between the level of Zn and antioxidant status in the hemodialysis patients [25]. There is growing evidence that oxidative damages and many of the complications in HD patients are related to accelerated atherosclerosis. Thus, Zinc deficiency and, consequently, oxidative stress can exacerbate atherosclerosis as a heart disease is involved in long-term HD patients [13,26,14,27]. In addition, the harmful consequence of high blood pressure in chronic kidney disease is the rapid decline in renal and heart function [20]. This suggests the relationship between blood pressure and cardiovascular disease.

Table 2. Systolic and diastolic body pressure (BP), cardiac ejection fraction (EF), and complete blood count (CBC) indices in group I during the placebo period (at Days 0 and +60) and the supplementation period (at Days +120 and +180), Males (n=22), females (n=13)

Variables	Placebo period			Supplementation period		
	Day 0 (mean±SD)	Day +60 (mean±SD)	P-value	Day +120 (mean±SD)	Day +180 (mean±SD)	P-value
BMI	23.83±3.68	24.10±4.01	NS	23.44±3.30	23.99±3.37	NS
Male	23.68	23.86		23.49	23.90	
Female	24.08	24.50		23.35	24.13	
Dietary zinc (mg/day)	3.76±1.97	3.62±1.56	NS	3.70±1.53	3.84±1.59	NS
Male	4.17	3.89		3.97	4.07	
Female	3.07	3.27		3.24	3.44	
Serum zinc (μg/dl)	79.49±13.12	79.17±11.34	NS	80.37±10.69	111.37±20.43	<0.001*
Male	80.41	79.36		82.36	112.63	
Female	77.92	78.84		77.0	109.23	
Systolic BP (mmHg)	146.00±19.99	144.29±22.63	NS	145.71±21.04	139.86±21.37	<0.05*
Male	146.14	145.45		146.36	139.10	
female	145.77	142.31		144.61	141.15	
Diastolic BP (mmHg)	81.23±7.96	81.14±9.93	NS	82.71±8.52	80.29±8.99	<0.05*
Male	82.04	82.04		84.54	82.27	
Female	79.85	79.61		79.61	76.92	
% EF	55.37±8.72	54.14±8.44	NS	53.11±8.36	54.40±8.15	NS
Male	55.14	53.77		52.77	53.68	
Female	55.77	54.77		53.69	55.61	
Hb (g/dl)	9.57±1.95	9.59±1.74	NS	9.31±1.73	9.92±1.94	0.011*
Male	10.31	9.31		9.61	10.4	
Female	8.31	9.04		8.81	9.1	
Hct (%)	29.49±5.79	29.59±5.11	NS	29.37±5.11	30.88±5.67	0.043*
Male	31.62	30.57		30.50	32.26	
Female	25.89	27.92		27.46	28.54	
RBC ($\times 10^6/\mu l$)	3.39±0.71	3.40±0.68	NS	3.27±0.69	3.50±0.81	<0.05*
Male	3.54	3.39		3.23	3.58	
Female	3.14	3.44		3.33	3.35	

Variables	Placebo period			Supplementation period		
	Day 0 (mean±SD)	Day +60 (mean±SD)	P-value	Day +120 (mean±SD)	Day +180 (mean±SD)	P-value
WBC (/μl)	6062.86±1743.24	5722.86±1574.63	NS	5440.00±1627.38	5625.71±1803.65	NS
Male	6063.64	5900		5531.82	5586.36	
Female	6061.54	5423.08		5264.81	5692.31	
Neutrophil (%)	60.40±6.38	59.54±7.20	NS	59.46±7.75	59.91±6.61	NS
Male	61.73	60.5		60.64	60.14	
Female	58.15	57.92		57.46	59.54	
Lymphocyte (%)	35.03±6.15	35.51±6.30	NS	35.63±7.06	34.46±6.80	NS
Male	34.27	35.04		34.91	34.73	
Female	36.31	36.31		36.85	34.00	

**Statistically Significant. NS: Non-Significant. SD: Standard Deviation*

Table 3. Systolic and diastolic body pressure (BP), cardiac ejection fraction (EF), and complete blood count (CBC) indices in group II during the supplementation period (at days 0 and +60) and the placebo period (at days +120 and +180), Males (n=19), females (n=11)

Variables	Supplementation period			Placebo period		
	Day 0 (mean±SD)	Day +60 (mean±SD)	P-value	Day +120 (mean±SD)	Day +180 (mean±SD)	P-value
BMI	24.24±7.86	23.37±4.39	NS	23.33±4.36	23.40±4.31	NS
Male	24.96	23.41		23.34	23.42	
Female	23.02	23.30		23.30	23.38	
Dietary zinc (mg/day)	2.94±1.66	2.71±1.33	NS	2.86±1.07	2.77±1.24	NS
Male	3.26	2.87		3.11	3.05	
Female	2.38	2.43		2.42	2.28	
Serum zinc (μg/dl)	77.40±14.51	103.93±14.47	<0.001*	94.73±15.61	88.07±12.40	0.003*
Male	81.63	106.32		97.16	91.89	
Female	70.09	99.82		90.54	81.45	
Systolic BP (mmHg)	150.17±23.29	146.17±20.79	<0.05*	146.67±23.32	146.67±22.45	NS
Male	151.05	146.05		146.05	145.79	
Female	148.64	146.36		147.73	148.18	
Diastolic BP(mmHg)	82.33±8.88	79.67±7.87	<0.05*	81.07±8.51	80.83±8.31	NS
Male	83.16	81.32		81.58	81.56	
Female	80.91	76.82		80.18	79.54	

Variables	Supplementation period			Placebo period		
	Day 0 (mean±SD)	Day +60 (mean±SD)	P-value	Day +120 (mean±SD)	Day +180 (mean±SD)	P-value
% EF	52.20±11.00	54.33±9.43	NS	53.73±10.39	52.67±10.50	NS
Male	49.58	52.74		51.53	50.26	
Female	56.73	57.09		57.54	56.82	
Hb (g/dl)	9.59±1.80	9.96±1.78	NS	9.62±1.89	9.20±1.71	NS
Male	9.97	10.34		10.10	9.66	
Female	8.94	9.3		8.87	8.4	
Hct (%)	29.78±5.33	31.28±4.92	0.016*	30.13±5.64	28.98±5.10	NS
Male	30.34	32.37		31.68	29.97	
Female	27.95	29.41		27.45	27.27	
RBC ($\times 10^6/\mu l$)	3.33±0.73	3.51±0.76	<0.05*	3.27±0.79	3.14±0.69	NS
Male	3.35	3.56		3.35	3.17	
Female	3.29	3.44		3.12	3.09	
WBC (/μl)	5610.00±1262.82	5470.00±1393.37	NS	5550.00±2077.26	5576.67±2048.33	NS
Male	5636.84	5326.32		5715.79	5694.74	
Female	5563.64	5718.18		5263.64	5372.73	
Neutrophil (%)	60.90±6.67	61.77±6.39	NS	62.07±8.53	62.33±8.69	NS
Male	60.37	61.26		61.95	62.42	
Female	61.82	62.64		62.27	62.18	
Lymphocyte (%)	35.20±6.13	33.27±7.07	NS	32.90±7.08	31.83±7.09	NS
Male	36.42	35.00		34.10	32.00	
Female	33.09	30.27		30.82	31.54	

**Statistically Significant. NS: Non-Significant. SD: Standard Deviation*

Table 4. Comparison of significance level of study groups at different time intervals

Time Point	Variables	Group 1	Group 2
		P-value	P-value
Day 0 – Day +60	BMI	NS	NS
	Dietary zinc (mg/day)	NS	NS
	Serum zinc (μg/dl)	NS	<0.001*
	Systolic BP (mmHg)	NS	<0.05*
	Diastolic BP (mmHg)	NS	<0.05*
	% EF	NS	NS
	Hb (g/dl)	NS	NS
	Hct (%)	NS	0.016*
	RBC ($\times 10^6/\mu l$)	NS	<0.05*
	WBC (/μl)	NS	NS
	Neutrophil (%)	NS	NS
	Lymphocyte (%)	NS	NS
Day +120 - Day +180	BMI	NS	NS
	Dietary zinc (mg/day)	NS	NS
	Serum zinc (μg/dl)	<0.001*	0.003*
	Systolic BP (mmHg)	<0.05*	NS
	Diastolic BP (mmHg)	<0.05*	NS
	% EF	NS	NS
	Hb (g/dl)	0.011*	NS
	Hct (%)	0.043*	NS
	RBC (×106/μl)	<0.05*	NS
	WBC (/μl)	NS	NS
	Neutrophil (%)	NS	NS
	Lymphocyte (%)	NS	NS

**Statistically Significant. NS: Non-Significant*

5. CONCLUSION

In conclusion, zinc supplementation improved blood pressure (BP), cardiac ejection fraction (EF), and erythrocyte count in HD patients. Increasing cardiac ejection fraction and the number of red blood cells as well as improving blood pressure can increase life expectancy in patients undergoing hemodialysis. One of the limitations of this study is the lack of measurement of albumin and some other ions, including cupper which were not measured due to insufficient serum. Further Studies on the mechanisms by which heart and blood indices are influenced as a result of zinc supplementation in HD patients should be undertaken.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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