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ORIGINAL: Evaluation of Zinc Supplement on Biochemical Parameters among Pulmonary Tuberculosis Patients

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ABSTRACT

Introduction: Zinc (Zn) is an essential micronutrient in humans, and its deficiency is reported in many disorders, including tuberculosis (TB). The current study's goal is to evaluate the anti-TB effect of Zn supplementation among pulmonary tuberculosis patients.

Material and Methods: In this study, 74 newly diagnosed tuberculosis patients referred to Qom Health Center were distributed into two groups of receiving 50 mg of zinc sulfate and placebo. All patients in both groups received the same antituberculosis antibiotics. Before starting treatment and after two and six months of treatment with antituberculosis drugs, the serum levels of zinc and biochemical parameters were measured by atomic absorption spectrophotometry and a RA1000 Auto Analyzer, respectively.

Results: After two months of treatment, the serum Zn concentration in the Zn receiving group was higher than the placebo group. After anti-TB treatment, body mass index (BMI) and serum albumin were significantly higher than pretreatment in both groups. The serum alkaline phosphatase changes, uric acid, creatinine, and urea were not significantly different in both groups at different times.

Conclusion: The supplementation of Zn micronutrient results in improved BMI, serum Zn, and other biochemical parameters compared to before treatment.

Introduction

Tuberculosis (TB) is one of the major causes of death worldwide, and about 1.45 million people died in 2018 due to this infectious agent, according to global reports (1). *Mycobacterium tuberculosis* bacillus-induced TB (Mtb) has been managed worldwide by the BCG vaccine, which uses Mycobacterium bovis strains (2). While the infection was treatable with antibiotics since the 1940s, drug-resistant Mtb strains have appeared. Pulmonary TB is more prevalent than other types because the main route of transmission is through inhalation, and the lung also create a suitable environment for the

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Mtb strains to grow (3). Mtb is a cylindrical aerobic bacterium that does not produce spores. Due to the staining possibility of bacterial wall, it has been determined that the cell wall of Mtb is composed of long chains of mycolic acid (4, 5). Due to this special structure, the wall's permeability is very low against most antibiotics (6). Once a bacterium is located in its host, a specific molecule, lipoarabinomannan, helps the bacterium survive against the immune system (7). Although technology, especially the pharmaceutical industry, has greatly advanced globally, TB is still a threat to human health. Rifampicin, isoniazid, pyrazinamide, and ethambutol are used as the first-line therapy for pulmonary TB (8, 9). The first treatment stage should include isoniazid, rifampicin, and pyrazinamide for two months, and ethambutol might be prescribed if bacterial resistance is suspected (10, 11). The main problem in treating the infection occurs when isoniazid or rifampicin is unusable due to the side effects (12). Most anti-TB drugs interfere with liver function and might lead to serious liver dysfunction (13). Also, some anti-TB drugs might cause renal injury, which in this case, nephrotoxic drugs should be removed from the patient's treatment process, and the dose of anti-TB drugs should be changed based on the kidney damage severity (14-16). Therefore, liver and renal function monitoring is recommended during TB treatment. Due to various tissue toxicity in patients undergoing anti-TB treatment, much research has been performed on herbal and dietary supplements as adjunct treatments (17).

Zinc (Zn) is found in all organisms and participates in DNA replication. Because there is no Zn storage in the human body, it must be obtained through food or dietary supplements (18, 19). Zn's effect on the immune system's function matters; a decrease in this essential micronutrient can suppress thymus function, T lymphocyte development, and T cell function (20). Zn deficiency is involved in several disorders, including diarrhea, pneumonia, malaria, skin ulcers, and TB (21, 22). In all these diseases, dietary supplements can improve the disease's healing process related to increased immune responses in the patient's body (23, 24).

Therefore, considering the prevalence and importance of pulmonary TB and considering the treatment process and the severe side effects of anti-TB drugs on various organs such as kidney and liver, novel treatment strategies are required. Due to Zn's effect on the immune system and its requirements in the human diet, it was decided to use Zn supplements in patients with TB in Qom Health Center to assess the treatment process. Therefore, this study proposed to evaluate the effect of Zn supplementation on serum liver enzymes, renal parameters, and some other biochemical parameters in TB patients within 2 and 6 months after starting anti-TB treatment.

Methods

Subjects

Participants in this study were selected among suspected people with pulmonary TB referred to Qom Central Hospital. TB was confirmed by sputum culture, radiographs of the lungs, and the regional health organization. Firstly, 100 recently developed pulmonary tuberculosis people were randomly divided into two groups after completing the consent form. The first group included patients who received Zn supplements with anti-TB medications for six months. Standard Zn solution (1000 mg) was provided in the form of zinc chloride in 6% hydrochloric acid (HCl) (Titrisol, Merck Company). The second group included patients who received a placebo for six months. Before starting the investigation (day 0), patients were evaluated for clinical signs, body mass index (BMI), and serum biochemical parameters. This process was repeated at the end of the second month and the sixth month. Each supplement capsule contained 0.5 mg of Zn, and each placebo capsule carried lactose. The placebo and supplement capsules were not distinguishable in appearance and were kept in the dark bottles. The dose of anti-TB drugs used in the

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current study was based on the World Health Organization recommendations (WHO). Anti-TB treatment for patients weighing 33 to 50 kg included 300 mg of isoniazid, 450 mg of rifampicin, 1500 mg of pyrazinamide, and 750 mg of ethambutol two months every day. This treatment course with 600 mg of isoniazid and 450 mg of rifampin continued for another four months (three times a week). The medication of patients weighing more than 50 kg included 300 mg of isoniazid, 600 mg of rifampicin, 2000 mg of pyrazinamide, and 1000 mg of ethambutol daily for two months. The administration of 600 mg of isoniazid and 600 mg of rifampicin continued for another four months (three times a week). During the first two months of the study, patients were asked to refer to the clinic every week to receiving anti-TB drugs and supplement capsules or placebo. Patients who did not consume drugs regularly (even for one day) were excluded from the study. Also, patients with severe side effects of anti-TB drugs and patients with Mtb strains resistant to one or more anti-TB drugs were excluded after two months of medication treatment. From the second to the sixth month, health operators visited patients every week at home to provide anti-TB treatment and follow up the patient's symptoms. At the end of the treatment, all patients were asked to refer to the clinic. Finally, 74 patients with pulmonary TB who completed the treatment period were examined for subsequent analyses.

In patients undergoing anti-TB treatment, assessing biochemical factors and serum zinc concentration were conducted periodically and regularly due to the medications' side effects. To evaluate the concentrations of serum parameters, including Zn, creatinine (Cr), albumin (Alb), total protein, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), urea, and uric acid, 15 mL fasting blood was taken from all patients at day 0, the end of the second month, and the end of the sixth month. The obtained serum was stored at -25 °C. The serum level of the mentioned items was measured by a RA1000 auto-analyzer, and the serum Zn concentration was examined by an atomic absorption spectrophotometry device. In this project, laboratory kits were prepared from Pars Azmoun Company for measuring biochemical factors. People with pulmonary tuberculosis usually have poor nutrition, so BMI was estimated in both groups and compared after day 0, the second month, and the sixth month.

Statistical analysis

All statistical evaluations were conducted by SPSS 19 (Chicago, III., USA). The variables' normal distribution was estimated using a one-sample Kolmogorov-Smirnov analysis. All variables were presented as mean ± standard deviation (SD), and independent t-test and Chi-square were employed to compare the Zn and placebo receiving groups. P-value less than 0.05 was set as a significant difference.

Results

Briefly, 74 subjects (29.7% male and 70.3% female), including 37 TB patients receiving Zn supplements and 37 TB patients receiving placebo, were enrolled in the current study. The mean age of Zn and placebo receiving patients was 33.04±14 and 33.03±16.65, respectively. Pulmonary TB patients were studied in two groups of Zn supplement or placebo at the end of 0, 2, and 6 months.

Effect of Zn supplement on biochemical variables

Table 1 represents the serum concentrations of biochemical parameters in the Zn supplement group. Paired t-test was used to compare the variables at different times in the Zn consumption patients. As presented in ***Table 1***, there was no statistically significant difference in serum Cr, ALP, AST, and ALT levels after two and six months of Zn supplement administration ($P > 0.05$).

As demonstrated in ***Table 1***, there is a significant increase in serum urea at the end of the second and sixth months of treatment compared to pretreatment ($P < 0.05$), but no

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Table 1. Paired t-test results to compare variables at different times in the zinc consumption group

Variable	Month	Tested group(n=37) (Mean±SD)	*p-value*
ALP (U/L)	M0	213.16±59.41	0.062
	M2	218.5±58.59	
	M0	213.16±59.41	0.380
	M6	218.90±61.07	
	M2	218.5±58.59	0.455
	M6	218.90±61.07	
ALT (U/L)	M0	8.11±5.57	0.537
	M2	8.66±5.27	
	M0	8.11±5.57	0.525
	M6	8.89±5.82	
	M2	8.66±5.27	0.848
	M6	8.89±5.82	
AST (U/L)	M0	17.93±9.39	0.273
	M2	18.89±7.72	
	M0	17.93±9.39	0.490
	M6	19.12±8.44	
	M2	18.89±7.72	0.890
	M6	19.12±8.44	
Alb (g/dL)	M0	4.05±0.42	0.000
	M2	4.31±0.37	
	M0	4.05±0.42	0.000
	M6	4.47 ±0.36	
	M2	4.31±0.37	0.004
	M6	4.47 ±0.36	
Total Protein (g/dl)	M0	8.24±0.62	0.005
	M2	7.97±0.68	
	M0	8.24±0.62	0.000
	M6	7.11±0.67	
	M2	7.97±0.68	0.000
	M6	7.11±0.67	
Zn (ppm)	M0	0.93±0.47	0.000
	M2	1.22±0.45	
	M0	0.93±0.47	0.000
	M6	1.36±0.39	
	M2	1.22±0.45	0.000
	M6	1.36±0.39	
Cr (mg/dL)	M0	0.73±0.20	0.34
	M2	0.76±0.21	
	M0	0.73±0.20	0.18
	M6	0.80±0.20	
	M2	0.76±0.21	0.45
	M6	0.80±0.20	
Uric acid (mg/dL)	M0	4.75±1.99	0.004
	M2	6.67±2.07	
	M0	4.75±1.99	0.731
	M6	5.58±1.93	
	M2	6.67±2.07	0.940
	M6	5.58±1.93	
Urea (mg/dL)	M0	27.29±10.59	0.025
	M2	28.93±12.49	
	M0	27.29±10.59	0.019
	M6	30.67±12.14	
	M2	28.93±12.49	0.244
	M6	30.67±12.14	
BMI (Kg/m^2)	M0	19.45 ± 4.60	0.000
	M2	20.95 ± 4.55	
	M0	19.45 ± 4.60	0.000
	M6	22.21 ± 4.54	
	M2	20.95 ± 4.55	0.000
	M6	22.21 ± 4.54	

All variables were demonstrated as mean ± SD. Paired t-test was employed to compare variables. P-value < 0.05 was set as significant difference. Abbreviations: ALP= Alkaline phosphatase; AST= Aspartate transaminase; ALT= Alanine transaminase; Alb=Albumin; Cr= Creatinine; Zn = Zinc; M= Month; SD= Standard deviation.

significant difference was observed between the second and sixth months (P *>0.05*).

Compared to starting treatment time, serum uric acid was increased significantly in the second month after Zn treatment (P <0.05), but no significant difference was seen after six months of Zn supplementation compared to the second month or before Zn supplementation (P *>0.05*).

Before Zn or anti-TB supplementation, the total serum protein was significantly higher than 2 and 6 months after supplementation (P <0.05). The total protein was higher in the second month than the sixth month after Zn treatment (P <0.05).

Two and six months after Zn or anti-TB treatment, BMI, serum Alb, and Zn were significantly increased compared to starting treatment (P <0.05). These parameters were markedly elevated in the sixth month compared to the second month after Zn supplementation (P <0.05).

Comparing BMI and serum biochemical variables in placebo receiving patients

Table 2 shows that in the placebo receiving patients, serum Cr and ALP levels were not significantly different at different times. Serum uric acid two months after treatment was significantly enhanced than month 0, but there is no significant difference between

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Table 2. Paired t-test results to compare variables at different times in the placebo consumption group

Variable	Month	Tested group(n=37) (Mean±SD)	*p-value*
ALP (U/L)	M0	205.12±58.92	0.533
	M2	212.86±53.18	
	M0	205.12±58.92	0.777
	M6	210.44±79.40	
	M2	212.86±53.18	0.782
	M6	210.44±79.40	
AST (U/L)	M0	6.77±4.96	0.001
	M2	12.29±7.96	
	M0	6.77±4.96	0.108
	M6	9.14±5.92	
	M2	12.29±7.96	0.007
	M6	9.14±5.92	
ALT (U/L)	M0	17.09±10.34	0.000
	M2	28.78±12.13	
	M0	17.09±10.34	0.524
	M6	18.22±8.97	
	M2	28.78±12.13	0.000
	M6	18.22±8.97	
Alb (g/dL)	M0	3.94±0.39	0.007
	M2	4.11±0.34	
	M0	3.94±0.39	0.000
	M6	4.4 ±0.4	
	M2	4.11±0.34	0.004
	M6	4.4 ±0.4	
Total Protein (g/dl)	M0	8.02±0.81	0.752
	M2	8.07±0.63	
	M0	8.02±0.81	0.000
	M6	7.11±0.82	
	M2	8.07±0.63	0.000
	M6	7.11±0.82	
Zn ppm	M0	1.25±0.52	0.561
	M2	1.21±0.39	
	M0	1.25±0.52	0.001
	M6	1.6±0.32	
	M2	1.21±0.39	0.000
	M6	1.6±0.32	
Cr (mg/dL)	M0	0.77±0.20	0.108
	M2	0.81±0.19	
	M0	0.77±0.20	0.720
	M6	0.82±0.29	
	M2	0.81±0.19	0.845
	M6	0.82±0.29	
Uric acid (mg/dL)	M0	4.81±1.9	0.035
	M2	6.81±1.8	
	M0	4.81±1.9	0.486
	M6	5.63±1.95	
	M2	6.81±1.8	0.043
	M6	5.63±1.95	
Urea (mg/dL)	M0	29±11.29	0.025
	M2	31.08±12.87	
	M0	29±11.29	0.009
	M6	32.15±12.77	
	M2	31.08±12.87	0.477
	M6	32.15±12.77	
BMI (Kg/m^2)	M0	18.98 ± 3.91	0.075
	M2	19.42 ± 3.67	
	M0	18.98 ± 3.91	0.000
	M6	20.24 ± 3.72	
	M2	19.42 ± 3.67	0.000
	M6	20.24 ± 3.72	

All results were presented as mean ± SD. Paired t-test was utilized to compare values. P-value < 0.05 was considered as significant difference. Abbreviations: ALP= Alkaline phosphatase; AST= Aspartate transaminase; ALT= Alanine transaminase; Alb=Albumin; Cr= Creatinine; Zn = Zinc; M= Month; SD= Standard deviation.

months 0 and 6 and between months 2 and 6 (P >0.05).

The urea levels were significantly elevated after two and six months of administering placebo supplements than starting treatment (month 0). However, no significant difference was observed between the second and sixth months (P >0.05).

Serum AST and ALT levels were not significantly different after six months of receiving placebo supplement compared to starting treatment period (P >0.05).

The serum concentrations of both AST and ALT were dramatically increased at the end of the second month after receiving the placebo supplement compared to starting treatment period, while their levels were attenuated at the end of the sixth month receiving placebo compared to the second month (P <0.05).

As shown in ***Table 2***, serum Alb was significantly higher than starting the study after the second and sixth months (P <0.05). After receiving a placebo supplement at the end of the sixth month, the serum Alb was significantly higher than the end of the second month (P <0.05).

BMI and the serum Zn and total protein were not significantly different after two months of placebo treatment (P >0.05), but after six months, the Zn and BMI were significantly

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higher than the second month and starting time of the study (before treatment). After six months, the total protein was significantly lower than the second months and starting the study.

Discussion

In the current project, the effect of Zn supplementation was evaluated on BMI, serum liver enzymes (ALP, AST, and ALT), renal parameters (urea, uric acid, and Cr), Alb, total protein, and serum Zn concentration in TB patients before treatment and two and six months after starting treatment.

Zn is required as a cofactor for many enzymes (about 300 enzymes), and also, the Zn-binding motifs make this element able to regulate many cellular mechanisms. Zn's effect on immune function is very important, and its deficiency suppresses thymus function, T lymphocyte development, lymphatic production, and T cell function, involving in some diseases such as pneumonia, malaria, skin ulcers, and TB (23, 25, 26).

Rankovic et al. investigated serum and pleural Zn levels in 104 patients and then analyzed them; In that study, higher pleural Zn related to TB indicates Zn's diagnostic value in TB (27). In 2021, Kabir et al. evaluated Zn's serum concentration in 25 TB lymphadenitis patients and 25 healthy subjects by atomic absorption spectrophotometry. They showed that patients with TB lymphadenitis had a lower Zn concentration (28). In another cross-sectional study, Mohamed and his co-workers indicated that Zn's serum level in the patients with TB was markedly reduced compared to healthy individuals (29). A study in India also found that chemotherapy with anti-TB drugs for six months increased plasma Zn concentrations in TB patients. Therefore, it has been suggested that plasma Zn may be a marker for monitoring the severity of infection and response to treatment (30). Zn as a dietary supplement can improve the immune system during anti-TB treatment (31). Thus, in patients who have used Zn, the two-month course of initial anti-TB therapy is more efficient than other patients, which indicates an increase in immunological processes of patients receiving Zn (32). Several studies have reported that patients with pulmonary TB suffer from malnutrition, indicating decreased anthropometric indices and micronutrient status (33, 34). Ramakrishnan conducted a study indicating that serum concentrations of Zn, Alb, and BMI were reduced in patients with pulmonary TB (35). Various causes such as nutritional factors, enteropathy, and acute-phase proteins can contribute to this reduction. Studies in pulmonary TB patients have shown that micronutrient supplementation such as Zn improves health by increasing the number of CD4, increasing patients' weight, improving medication treatment effectiveness, and reducing opportunistic infections (36, 37).

A decrease in plasma Zn concentration was observed in the placebo group after two treatment months in our study. This phenomenon may be due to the length of the severe phase of anti-TB treatment at the first two months. Another suggested mechanism is the effect of anti-TB medications on Zn absorption. It has been observed that Zn's urinary excretion is increased as a result of ethambutol consumption in mice (38). In our study, Zn's plasma concentration was increased in both Zn and placebo groups six months after anti-TB treatment, which was significant in the Zn receiving group. Based on the results, an increase in ALT and AST concentrations was seen in both groups two and six months after anti-TB treatment, which can be due to the severe phase and the hepatic side effects of drugs. There was a significant increase in the placebo group than the supplement receiving group two months after treatment, which was similar to a study of Zn supplementation effect on liver enzymes in hepatitis and cirrhosis (39, 40).

Serum ALP was not significantly different after two or six months of Zn and placebo treatment; ALP is located in the cell membrane and is not easily released. AST isoenzymes are located in the mitochondria and cytoplasm, and ALT is present in the

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cytoplasm, so an increase in these enzymes' level is observed in the early stages of liver damage (41). In this study, ALT and AST levels were increased after TB treatment compared to pretreatment, although this increase was not significant. Many studies have reported increased bilirubin, ALT, AST, and ALP after TB treatment (42, 43). Creatinine test was used to measure nephrotoxicity. In this study, serum Cr levels were normal before and after treatment, which may be due to the patients' drug treatment lack of streptomycin. One of the side effects of streptomycin is nephrotoxicity (44). In our study, uric acid and urea were increased significantly two months after treatment than pretreatment. This increase may be due to pyrazinamide's therapy because six months after treatment, the serum uric acid was within the normal range in all patients. In one study, the concentrations of Alb, pre-Alb, and transferrin transport proteins were measured in a severely Zn deficiency state. It was observed that the concentration of all proteins was normalized only by taking supplements. According to the present study results, serum Alb levels were elevated after two and six months of treatment compared to pretreatment in both Zn and non-Zn groups. Zinc plays an important role in protein metabolism in humans and is essential for maintaining normal levels of transport proteins, and Zn deficiency leads to a decrease in the serum proteins.

One of the limitations of this study was the small number of patient samples. Zn is a cofactor for many enzymes; in this investigation, we measured routine factors related to liver and kidney dysfunction, and the effects of Zn deficiency and Zn supplementation on other organs are not investigated in patients with TB.

Conclusion

Due to the wide prevalence of Zn deficiency and its essential biological function, nutrition correction affects various aspects of human health. Over the years, several studies have been conducted on Zn consumption and its effects on various diseases, including TB. In the present study, Zn supplementation on serum Zn levels and reducing the pharmacological side effects of anti-TB treatment were considered in TB patients. It seems that dietary or pharmacological Zn supplementation is useful. Also, more studies with larger sample sizes are recommended to evaluate patients' other clinical outcomes.

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Conflicts of interest

The authors have stated that no conflict of interest occurs.

Ethical standards statement

The current study was exerted in the central hospital in Qom, Iran from March 2013 to March 2014 (IRCT201112178429N1).

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to governmental policy and privacy.

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