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# Investigation of Zinc Supplement Impact on the Serum Biochemical Parameters in Pulmonary Tuberculosis: A Double Blinded Placebo Control Trial

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## Abstract

***Background:*** Zinc (Zn) is nutritionally essential trace element, and thus deficiency may severely affect human health. The results of cross-sectional studies indicate that micronutrient deficiencies are common in patients with tuberculosis. Our goal is to investigate whether Zn supplementation can increase the effects of anti-TB treatment or not.

***Methods:*** Patients with newly diagnosed tuberculosis were divided in to 2 groups. One group (n= 37) received capsule contains 50 mg of elemental zinc (as zinc sulfate) for 6 months every other day (micronutrient group) and Group II (n= 37) received placebo. Both groups received the same anti-tuberculosis treatment recommended by the WHO. Clinical examination, BMI, chest X-ray, direct sputum examination, assessment of serum zinc levels (by atomic absorption spectrophotometry), and biochemical markers serum concentration (by using an RA1000 AutoAnalyzer) were carried out before and after 2- and 6-months anti-tuberculosis treatment.

***Results:*** Plasma zinc concentrations in the micronutrient group was higher than placebo group After treatment. In the placebo group increasing in SGOT and SGPT concentrations were significantly higher than micronutrient group after 2 months of treatment ($p< 0.05$). The significant changes ($p< 0.05$) were observed on the serum levels of total protein, albumin. Alkaline phosphatase (ALP) levels, serum creatinine, uric acid and urea in groups were not significantly different.

***Conclusions:*** Zinc supplementation results in earlier sputum smear conversion in the micronutrient group during the first 6 weeks. Increased body weight and serum zinc and serum albumin and decrease in total protein was observed in the micronutrient group.

**Keywords:** Anti-tuberculosis treatment, Pulmonary tuberculosis, Zinc.

## Introduction

Tuberculosis (TB) defined as an illness that occur via Mycobacterium tuberculosis in which different organs are involved such as lungs, kidneys, and bones. In order to the treatment to be effective several medications are used for instance, Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, and Streptomycin. These drugs have several side effects on the liver, skin, and nerves (1). Researchers have known for long years the link between malnutrition and TB; TB provides the basis for malnutrition and then malnutrition can lead to other serious illnesses (2). Also, people who suffer from malnutrition are exposed to new infections due to weakened

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immune systems (3). Zinc (Zn) is a micronutrient that is critical for the proper functioning of the immune system and plays an important role in the fight against TB (4). In addition, Zn as an essential trace element have numerous physiologic and metabolic roles such as antioxidant activity. Since Zn is not widely stored in the body, Zn supplements are needed to maintain steady-state (5). Zinc deficiency in developing countries is one of the major factors to exposing other diseases (6-9).

The acute and chronic infections lead to changes in serum proteins concentration; albumin is main serum protein and along with other serum proteins such as globulins have normal range 6-8 g/dl. (10). It has been shown that in the TB infection concentration of albumin is reduced and total protein is decreased (11, 12). Thus, TB infection with decreased proteins lead to decrease Body Mass Index (BMI) that is an efficient and economical measurement to describe nutritional status (13). Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) are main enzymes that used for assessment of liver function. Science, hepatotoxicity is a side effects of TB therapy and during TB liver involved, reported that the level of SGOT and SGPT elevated (14). As well as TB infectionand its therapy lead to kidney damage and nephrotoxicity that can be effects on the kidney tests function such as creatinine and uric acid (15). The negative effects of anti-TB therapy on the liver and kidneys can be balanced by concomitant administration of supplements that boost the antioxidant levels of the body (15).

In the present study in order to evaluation of Zn supplementation in increasing the effect of anti-TB drugs, we measured serum concentrations of Zn, SGOT, SGPT, albumin, and total protein in patients with TB infection that intake Zn supplement compared to placebo after 2 and 6 months.

## Materials and Methods

### *Subjects*

The current study was exerted in the central hospital in Qom, Iran from March 2013 to March 2014 (IRCT201112178429N1). patients suffering from the active pulmonary tuberculosis base on last diagnosis were selected for this study. Regardless of sex and age, cases included to study in accordance with three microscopically positive sputum smears stained by acid fast dye and culture, and also diagnosed by radiological and clinical manifestations of the pulmonary tuberculosis without a prior history of administration of anti-tuberculosis agents. The presence of drug resistance at early stage or even in the period of follow up, pregnancy, breastfeeding, usage of any zinc supplement in recent months, and the presence of chronic renal failures, hepatic disorders neoplasms led to excluding of the patients from the study.

### *Receiving supplement and anti-tuberculosis agents*

This study was a double blinded, placebo control micronutrient supplementation trial. Finally, one hundred subjects were randomly categorized into two groups administering either the real supplement (test group) or placebo (placebo group). To prepare the Zinc supplement capsule, lactose matrix was used. Each supplement capsule consists of 50 mg Zinc (as a zinc sulfate form). Cases in placebo group administered only lactose capsule. The internal and external appearance of both capsules was the same and indistinguishable. All capsules stored at 4-6° C in dark containers. The administration dosage of capsules and anti-tuberculosis agents were determined in accordance with the WHO's regimen. A health staff and at least a person in the family of patients controlled the patient compliance. The therapy was done for 6 months. A case, who administered the drug irregularly, even one dose, or patients being resistant to anti-tuberculosis agents during follow up and someone showed the severe side effects to treatment were dropped from the study.

### Microbial analysis

During the first 2 months, three morning sputum specimens were collected from each patient with two-week intervals. Furthermore, after 2 months and 6 months, the sputum smears were surveyed and followed up as the presence of tuberculosis bacilli. All specimens were stained using the

Ziehl-Nelson along with cultured on the specific media such as Lowenstein-Jensen. The tested smears were categorized as Bronkhorst scale including, grade +1, ≥ 3 AFB found in 10 fields; grade +2, 1–20 AFB in 10 fields; grade +3, 20–60 AFB in 10 fields; grade +4, 60–120 AFB in 10 fields; and grade +5, > 120 AFB in 10 fields (19). Additionally, in order to diagnosis of chest abnormalities, all subjects were monitored radiographically.

**Biochemical analysis**

To monitor the impact of zinc supplementation and anti-tuberculosis regimen on biochemical parameters, approximately 10 mL of fasting blood without any anticoagulant was drawn before the beginning of the therapy, after 2 and 6 months during the treatment. The plasma was isolated by centrifugation at 500 G for 15 min and stored at -20 °C for further examinations.

The quantity of urea, uric acid, creatinine, ALP, SGOT, SGPT< serum albumin and total protein was assessed by Pars Azmon kit (Tehran, Iran) using autoanalyzer. The flame atomic absorption spectroscopy was utilized to evaluate the zinc concentration as the Kirgbrit et al., protocol (16). Briefly, the plasma samples were diluted with deionized water and the absorbance at 213.9 nm was recorded for each sample and the standard solution, simultaneously. Discrepant zinc solutions with the known concentration were tested for drawing a standard curve.

***Statistical analysis***

To compute the normal distribution of variables, one – sample Kolmogorov-Smirnov analysis was exerted. To compare the correlation of quantities between the test group and the placebo group, independent t-test and Chi-square test were applied. SPSS 19 (Chicago, III., USA) was utilized for statistical assessments. P value lower than 0.05 was considered as a significant finding.

## Results

In this study, 74 (74%) out of 100 patients were divided into two groups of zinc supplement users and non-zinc supplementation. The mean age of the participants in this study was 33.04±14.583 years of age for those taking zinc supplements and 33.03±16.652 years for the placebo group. Table 1 outlines the reasons leading to exclude the cases from the study during the 6 months. A total of 37 subjects remained in each group.

**Table 1.** The reasons for the removal of patients during the 6-month study.

| Initial number of supplements (n= 50) | Initial placebo group (n= 50) |
|---|---|
| Patients were dropped during 0- 2 months: 10 cases<br>• Drug resistance (2)<br>• The diagnosis of non-tuberculous mycobacteria (1)<br>• Smear negative pulmonary tuberculosis (2)<br>• Patients who did not complete treatment (2)<br>• Pleural tuberculosis (1)<br>• Category II (2) | Patients were dropped during 0- 2 month: 7 cases<br>• Drug resistance (2)<br>• The diagnosis of non-tuberculous mycobacteria (1)<br>• Patients who did not complete treatment (3)<br>• Pleural tuberculosis (1) |
| Patients were dropped during 2 to 6 months: 3 cases<br>• Drug Resistance (1)<br>• Lack of follow-up (2) | Patients were dropped during 2- 6 months: 6 cases<br>• Drug Resistance (2)<br>• Lack of follow-up (3)<br>• The patient died (1) |
| **Patients completing the study (6 months): 37 patients** | **Patients completing the study (6 months): 37 patients** |

As summarized in table 2, and Figure 1, there was no statistically significant discrepancy BMI distribution between the tested group and the placebo group. In contrast after 2 months, and 6 months the BMI significantly gives rise among the tested group in comparison to the placebo group ($p< 0.05$).

**Table 2.** Baseline properties of the tested population.

| Properties | | Tested group (n= 37) | Placebo group (n= 37) | p |
|---|---|---|---|---|
| BMI Kg/m$^2$ | M0 | 19.45±4.61 | 18.98±3.91 | 0.07 |
| | M2 | 20.95±4.55 | 19.42±3.67 | 0.04 |
| | M6 | 22.21±4.54 | 20.45±4.61 | 0.04 |

***Biochemical parameters***

The plasma biochemical parameters of subjects belonged to both groups was evaluated in three times. As depicted in table 3, the administration of zinc supplement induced no alteration in the concentration of plasma creatinine (a), uric acid (b) and urea (c) in different times and between two groups.

According to Table 3, in contrast to the similar value of SGOT and SGPT enzyme of plasma in the tested and placebo group, the levels of SGOT, and SGPT significantly attenuated after two months administration of Zinc supplement in the tested group compared with the placebo group ($p< 0.05$) (Fig. 2). However, no significant difference was seen in an alkaline phosphatase value between two groups at any time.

As shown in Table 3, the use of zinc supplementation had a significant effect on increasing plasma albumin concentration after 2 months and decreasing total protein after 6 months ($p< 0.05$) compared to the placebo group (Fig. 3).

Our findings viewed the increase plasma zinc value after administration of zinc supplement after two months and 6 months, but only after 6 months, this elevation was statistically significant in the tested group compared to the placebo group (Table 3, and Fig. 1) ($p< 0.05$).

***Microbial data***

After 2 weeks, the number of negative sputum smears was significantly higher in the tested group (24.3%) compared to the placebo group (13.5%) ($p< 0.05$). Moreover, after 4 weeks and 6 weeks, 56.8% and 70.3% of patients belonging to the tested group showed the negative smear whereas the rate of negative smears was 32.4% and 45.9% were after 4 weeks and 6 weeks, respectively ($p< 0.05$). However, we showed no significant differences between two groups after 2, 4 and 6 months.

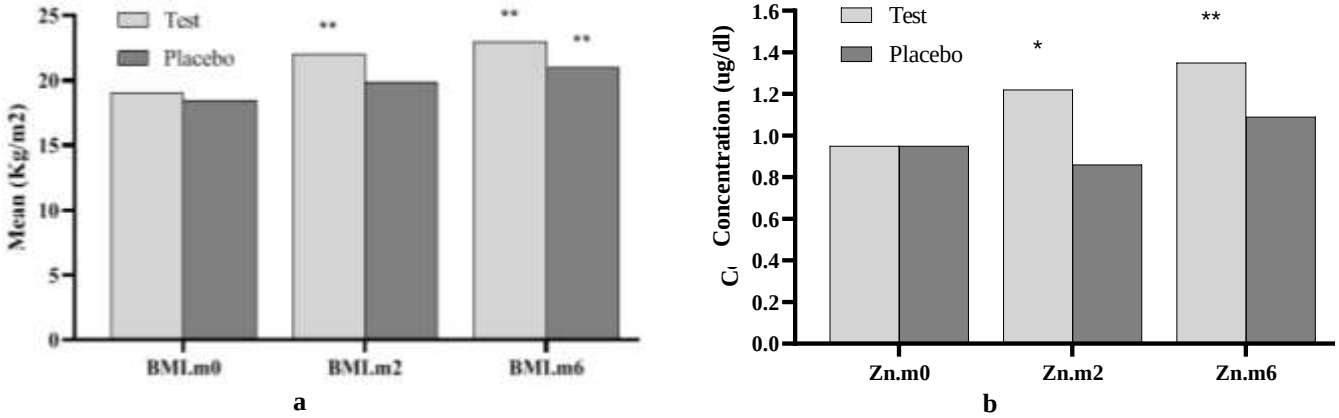


**Fig. 1**. Comparison of mean BMI (a), and serum Zn concentrations (b) in two groups.

**Table 3.** Comparison of mean serum levels of Variables between the two groups.

| Variable | Month | Tested group (n= 37) (Mean±SD) | Placebo group (n= 37) (Mean±SD) | p |
|---|---|---|---|---|
| **ALP (u/l)** | M0 | 213.16±59.41 | 205.12±58.92 | 0.38 |
| | M2 | 212.5±58.59 | 220.86±53.18 | 0.24 |
| | M6 | 224.90±61.07 | 223.44±79.40 | 0.84 |
| **SGPT u/l** | M0 | 8.11±5.57 | 6.77±4.96 | 0.27 |
| | M2 | 8.66±5.27 | 12.29±7.46 | 0.01 |
| | M6 | 8.89±5.82 | 9.15±5.92 | 0.85 |
| **SGOT u/l** | M0 | 17.85±9.39 | 17.17±10.34 | 0.71 |
| | M2 | 18.89±7.72 | 29.89±12.13 | 0.000 |
| | M6 | 19.12±8.44 | 18.22±8.97 | 0.65 |
| **ALB g/dl** | M0 | 4.05±0.42 | 3.94±0.39 | 0.22 |
| | M2 | 4.31±0.37 | 4.11±0.34 | 0.02 |
| | M6 | 4.47±0.36 | 4.40±0.41 | 0.39 |
| **Total Protein g/dl** | M0 | 8.24±0.62 | 8.02±0.81 | 0.19 |
| | M2 | 7.97±0.68 | 8.07±0.63 | 0.52 |
| | M6 | 7.11±0.67 | 7.52±0.82 | 0.02 |
| **Zn ppm** | M0 | 0.93±0.47 | 0.93±0.52 | 0.93 |
| | M2 | 1.22±0.45 | 0.89±0.39 | 0.002 |
| | M6 | 1.36±0.39 | 1.08±0.32 | 0.000 |
| **Cr** | M0 | 0.73±0.21 | 0.77±0.2 | 0.43 |
| | M2 | 0.76±0.21 | 0.81±0.2 | 0.32 |
| | M6 | 0.75±0.2 | 0.8±0.29 | 0.98 |
| **U.A** | M0 | 4.75±1.99 | 4.81±1.9 | 0.88 |
| | M2 | 6.54±2.7 | 6.81±1.82 | 0.92 |
| | M6 | 5.18±1.94 | 5.43±1.95 | 0.91 |
| **Urea** | M0 | 27.29±10.59 | 29±11.29 | 0.29 |
| | M2 | 28.93±12.49 | 31.08±12.87 | 0.69 |
| | M6 | 30.67±12.14 | 32.15±12.77 | 0.71 |

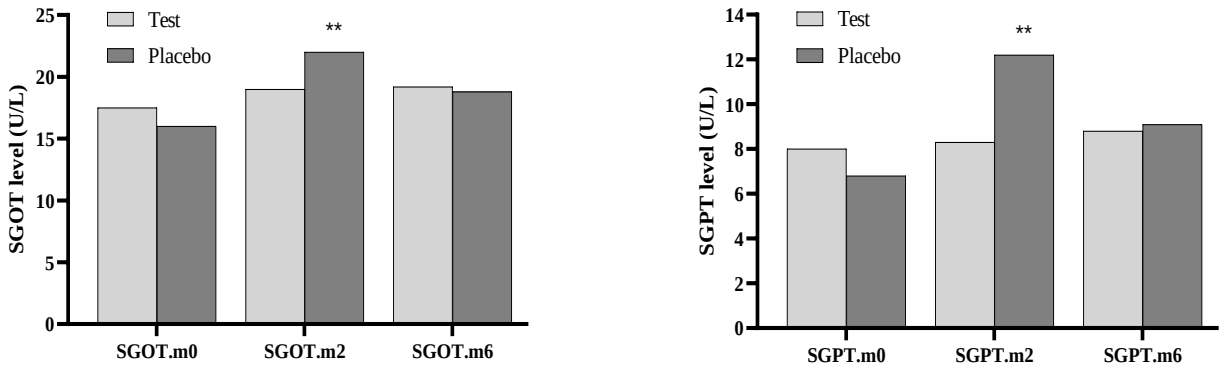


**Fig. 2**. Impact of zinc supplementation on the serum level of SGOT, and SGPT for 6 months.

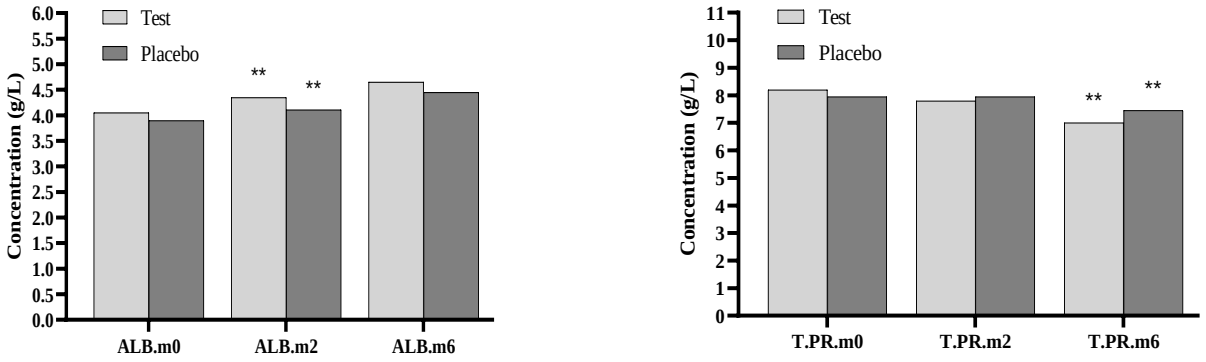


**Fig. 3**. Effect of zinc supplementation on the serum level of albumin (ALB), and total protein (T.PR.).

## Discussion

TB infection is a prevalent complication which leads to a high mortality rate in the world. In order to treatment of TB used of multi drugs therapy, these drugs have several side effects include, hepatoxicity, nephrotoxicity, harm effects on the bones, malnutrition, and etc. In the former studies it has been reported that TB infection causes a decrease in serum concentrations of Zn and albumin in men beings also experimental animals (16).

In current study, we assessed the serum concentration of Zn in patients with TB infection that intake Zn supplement compared to placebo group after 2 and 6 months. Our data showed that Zn levels in the supplement recipient group were significantly higher than that levels in placebo group in both 2nd and 6th months. Also, we measurement the levels of albumin and total protein in both groups that were recruited; we found that after 6 months of taking Zn, the albumin concentration was higher and total protein were markedly lower compared to placebo group.

Some studies declared possible reasons to the low serum Zn and albumin and total protein in patients with TB infection may be nutritional factors, enteropathy, and acute phase reactant proteins (17-19). Immune factors such as interleukin-6 and TNF-α are causes to induction of acute phase reactant proteins in the liver, which can lead to decrease of serum albumin also, reason to significant changes in the serum levels

of some essential trace elements and total protein (20). Moreover, this was probably because of the redistribution of Zn from blood to other organs, or a decrease of the hepatic zinc-carrier protein $\alpha_2$-macroglobulin production because of an increase in the metallothionine creation, a protein that carry out transport of Zn to the hepatocytes (22). Accordingly, after 6 months of starting Zn supplementation therapy, albumin level was observed to increase. Furthermore, reported that BMI is meaningfully lower in patients with TB infection compared with healthy subjects (13). The low BMI among patients with TB infection may be caused by low dietary intake, anorexia, reduced absorption of nutrients, decreased of hepatic synthesis proteins, and increased catabolism (23).

We also measured the serum levels of SGOT and SGPT in three modes, before supplementation with Zn, in the Zn receiving group, and in the placebo group. Our results shown that after 2 months of supplementation therapy the levels of SGOT and SGPT were elevated in both groups; in consistent with previous studies, we also found that the serum levels of SGOT and SGPT in placebo group were significantly higher than that in group with Zn consumption. Studies have assumed that the greatest increase in liver enzyme activity is two to four weeks after starting treatment (24). Numerous drugs that are anti-TB have a prominent role in the initiation development of hepatotoxicity. Although previously reported that exist a mixed hepatocellular-cholestatic damage, typically damage is acute hepatocellular (25, 26). This liver injury caused by drugs is a common side effect of anti-TB therapy. A cause is hepatotoxicity of drugs; enzymes that have a role in drug metabolism in hepatocyte microsomes may have congenital flaw, deformity, low activity, or be repressed via drugs, so drugs or drug metabolites are very toxic to hepatocytes (27). The another evidence is hypersensitivity via drugs; The medications can act as hapten and induce allergic reactions through immune response leading to the elevation of SGOT and SGPT (28). Usually drugs that used in TB infection therapy such as isoniazid, rifampicin, pyrazinamide, ethambutol, etc., are all hepatotoxic, particularly when used some drugs as combination therapy such as used of rifampicin and pyrazinamide (14). Our results in line with previous investigations showed that Zn supplementation therapy can exert anti-inflammatory effects of Zn in the liver subsequently, reduced inflammation in hepatic cells. The high levels of liver enzymes in the placebo group compared to Zn recipient group may be due to the beneficial effects of Zn (29, 30).

We performed kidney function tests include measured creatinine, urea, and uric acid to evaluate nephrotoxicity. We observed that levels of creatinine before and after Zn therapy were in normal range also, in both groups were not statically significant. Non-use of streptomycin in the treatment of patients may be a possible reason for these results because streptomycin have nephrotoxicity affects (31). In line with previous study, we detected that levels of urea and uric acid in the both groups elevated significantly but, it seems that is due to the use of pyrazinamide because, urea and uric acid concentration returned to normal range (32, 33). Nephrotoxic medications are healing factors that have the potential to prompt harmful effects on kidney function because of direct toxicity or disruption of renal perfusion. Nephrotoxicity and nephropathy are significant microvascular disease of anti-TB treatment (34, 35). Several investigations have proved that both inflammation and oxidative stress are involved in drug-induced tissue damage (36). Rekha et al. stated that damage results in anti-TB drugs is typically revocable and could be treated properly after 90 days (37). In this regard, Mahmoud et al. recommended that the consumption of antioxidants could defend in contrast to isoniazid/rifampicin-induced oxidative stress and nephrotoxicity (38). Previously showed that used of isoniazid and rifampicin has prompted kidney damage and glomerular dysfunction demonstrated through the raised the serum creatinine, urea, and uric acid concentrations (36, 39). However, the nephrotoxicity results in isoniazid/rifampicin damage established through the documented histological changes such as degenerated of glomerular tuft, dysplastic renal

tubules and inflammatory cells infiltration (38). In conclude, since Zn deficiency is common in developing countries, correction of nutrition with this element affects various aspects of human health. In the present study we found that Zn supplementation in patients with TB infection may be helpful in some cases include, increased serum zinc concentration 2 and 6 months after treatment, decreased serum concentrations of SGOT and SGPT, 2 months after treatment, increased serum albumin concentration 2 months after treatment and total protein decrease 6 months after treatment, and increased BMI 2 and 6 months after treatment.

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