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Serum zinc level and its association with pulmonary tuberculosis

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[†] Passed away on March 15, 2021.

Abstract

Introduction: Tuberculosis (TB), a global health problem, affects millions of people annually and has significant mortality rates. Zinc (Zn) plays a crucial role in immune function and may impact the outcomes of TB. Studies have shown that TB patients often have lower serum Zn levels, which improve with treatment and improved nutrition. Combining Zn supplements with anti-TB therapy has shown promise in reducing mortality, especially in those who are co-infected.

Objectives: This study aimed to assess serum Zn levels in healthy individuals and those with pulmonary TB, considering various parameters.

Patients and Methods: This case-control study focused on individuals aged 16 and older who were diagnosed with active pulmonary TB and referred to the TB clinic laboratory in Arak, Iran. The case group consisted of 32 individuals, and an equal number formed the control group. Diagnosis of active pulmonary TB was based on specific parameters, and patients received treatment with isoniazid, rifampin, ethambutol, and pyrazinamide drugs, with the dosage adjusted according to their weight.

Results: Regardless of age and gender, pulmonary TB patients with normal and high body mass index (BMI), as well as those with low to moderate income, exhibited lower serum Zn levels in compared to the control group. No significant correlation was observed between the disease stage and serum Zn levels. However, in individuals older than 65 years, particularly women and men with low-BMI, moderate income, and those in the initial disease stage, anti-TB treatment led to a significant increase in serum Zn levels. The findings of the study highlight the decrease in serum Zn levels in patients with pulmonary TB.

Conclusion: The present study indicates that, individuals with pulmonary TB, especially those with specific demographic and health characteristics, may have lower serum Zn levels. Treatment for TB may lead to increased Zn levels in specific groups of patients.

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Introduction

Tuberculosis (TB), an ancient human ailment, causes over a million deaths each year as declared by the World Health Organization. *Mycobacterium tuberculosis*, infects approximately one-third of the world's population (1-4). The American Thoracic Society estimates that TB currently affects 10-30 million individuals, with an incidence of 3.7-10 million new cases and 1-2 million deaths annually (2-5). The Centers for Disease Control and Prevention (CDC) projects a potential impact on 30 million people in the current decade. Without proper control measures, it is anticipated that by 2020, one billion people will be infected, over 150 million will fall ill, and 36 million will succumb to TB (6,7).

Key point

This study aimed to identify serum Zn levels in healthy individuals and patients with pulmonary TB, based on various parameters. The study included individuals aged 16 and older who were diagnosed with active pulmonary TB and referred to the TB clinic laboratory in Arak, Iran. Our study results indicated a decrease in serum Zn levels in patients suffering from pulmonary TB. We also found, in individuals older than 65 years old, women and men with a low BMI, moderate income, and in the initial disease stage, serum Zn levels significantly increased with anti-TB treatment.

Zinc (Zn) plays critical roles in catalysis, structure, and regulation. It significantly influences homeostasis, mental development, and the innate and cellular immune systems. Zinc also reduces inflammation, oxidative

stress, and apoptosis (8-10). When administered alongside serum therapy, Zn supplements effectively reduce the duration and severity of severe acute diarrhea (11-14). In severe pneumonia among children, combining Zn supplements with antibiotic therapy may not notably impact normalization parameters, but it significantly reduces mortality, particularly in those co-infected with human immunodeficiency virus (15). Malnutrition is prevalent in pulmonary TB patients due to reduced food intake and increased metabolism. Despite this fact, limited information exists regarding the nutritional status and micronutrient serum levels of these individuals, including Zn and selenium (16). TB patients often show elevated copper and cobalt levels, lower levels of Zn and selenium, and increased copper, which is associated with a worse prognosis (17). Given Zn's pivotal role in immune function and its deficiency leading to the spread of immune disorders and infection, it becomes crucial to evaluate serum Zn levels in TB patients (9). Recent studies indicate a significant decrease in serum Zn levels during the active phase of TB and multi-drug-resistant TB. However, serum Zn levels increase after improving nutritional status and undergoing anti-TB treatment (18-26). Patients with pulmonary TB and HIV exhibit lower body mass index (BMI), albumin, and serum Zn levels compared to healthy individuals and those with isolated pulmonary TB (27). Combining vitamin A and Zn supplements with anti-TB treatment after six months has demonstrated enhanced efficacy (20-23). This enhancement may be attributed to Zn deficiency affecting vitamin A metabolism by reducing circulating protein levels (28). In children, Zn administration increases purified protein derivative induration, irrespective of their nutritional status (29).

Objectives

This study aimed to assess serum Zn levels in healthy individuals and those with pulmonary TB, considering factors such as age, gender identity, BMI, and income levels. Furthermore, we sought to evaluate Zn levels at different stages of the disease, including before, during, and after anti-TB treatment.

Patients and Methods

Study setting and participants

This case-control study was conducted in Arak, Markazi province, Iran. In order to reduce bias and increase transparency, we utilized two key approaches in our retrospective study; sensitivity analysis and transparent reporting. Around 32 patients were included in the study, and 32 individuals were randomly selected for the control group. The target patient population for this study consisted of individuals aged 16 and older with active pulmonary TB who were referred to the Arak TB Clinic laboratory in Arak, Iran, from June 2017 to June 2018. This clinic serves as the primary referral center for the majority of TB patients in the Markazi province. The control group was selected from a population at risk and closely matched the case group in terms of age, gender, and health status. The study involved evaluating serum Zn levels before, during, and after anti-TB treatment.

Statistical population and sample size

The statistical population comprised patients aged 16 years and older with active pulmonary TB in Markazi province, Iran. With a confidence level of confidence = 99%, P=93%, d=0.116, $z_{\alpha/2}$ = 2.58, $N_1 = N_2 = (z_{\alpha/2})^2 \times p \times (1-P)/d^2 \approx 32$, the calculated sample size was 32 people. The sampling method employed was simple random allocation. To ensure homogeneity among the study groups, participants were matched based on age, gender, and other relevant characteristics.

Data collection

Medical records provided inpatient treatment protocols, laboratory results, and demographic information for participants. The study's methodology involved randomly selecting cases and controls from the Arak TB clinic database. It included patients with complete data on treatment outcomes recorded from June 1, 2017, to June 1, 2018. Individuals ≥16 years old, diagnosed and treated for TB during 2017-2018, were eligible for selection. This approach ensured a representative sample for analysis.

Inclusion criteria and study definition

The study included patients aged 16 and older with active pulmonary TB who were referred to the Arak TB clinic laboratory in Arak, Markazi province, Iran. Diagnosis was determined using past-medical history, clinical examination, chest radiography, smear, sputum culture, Mantoux test, and other relevant laboratory parameters from the Arak TB clinic database. A total of 32 patients and 32 controls were included in the study, and all participants signed informed consent forms.

Exclusion criteria

Subjects who had conditions that affected their serum Zn levels were excluded from the study. This included pregnant women, individuals taking oral contraceptive pills, those with chronic liver disease, pulmonary infections other than TB, extrapulmonary TB, deep painless injuries, chronic renal failure, myocardial infarction, metastatic carcinoma, nephrotic syndrome, malabsorption syndromes, cystic fibrosis, individuals on Zn supplement treatment, and those concurrently using iron supplements. The inclusion criteria for selecting participants were clearly defined to ensure that individuals with similar baseline characteristics were included in both the case and control groups.

Outcome

Serum Zn levels were obtained from the Arak TB clinic database for the case group at three time points;

before treatment initiation, at the fourth month of treatment, and three months after treatment completion. In the control group, measurements were taken only once. Patients were classified into stages I, II, and III based on chest radiography following the guidelines of the American National Tuberculosis Association. Blood samples from both groups were used to measure serum Zn, white blood count (WBC), hemoglobin (Hb), and erythrocyte sedimentation rate (ESR). Patients were treated with isoniazid, rifampin, ethambutol, and pyrazinamide, with doses adjusted based on patient weight. Zn content was evaluated using a BT3500 device and measured in microgram per deciliter (µg/dL).

Statistical analysis

Descriptive statistical methods were employed to organize and summarize information, generate tables, and describe the collected data. Additionally, inferential statistics were conducted to test research hypotheses. The statistical analysis was conducted using SPSS software. One-way ANOVA, student *t* tests, and repeated measure test were conducted for group comparisons. Results were presented as mean ± SD, and significance was set at P value<0.05.

Table 1. Demographic characteristics of participants

Variable	Range	Case		Control	
		N	%	N	%
Gender	Male	16	50	16	50
	Female	16	50	16	50
Age (y)	<50	10	31.3	9	28.1
	51-65	9	28.1	13	40.6
	>65	13	40.6	10	31.3
Income	Low	13	40.6	9	28.1
	Middle	12	37.5	15	46.9
	High	7	21.9	8	25
BMI (kg/m²)	Low	8	25	3	9.4
	Normal	20	62.5	15	46.9
	High	4	12.5	14	43.8
Variable		**Mean**	**SD**	**Mean**	**SD**
Weight		58.66	11.21	70.59	10.97
Height		1.68	0.08	1.71	0.06
ESR		73.50	23.94	16.06	6.61
Hb		12.15	1.98	13.31	1.98
WBC		6559	2299	6784	2062
Variable	**Range**	**N**		**%**	
Disease stage	I	14		43.75	
	II	12		37.5	
	III	6		18.75	

BMI, Body mass index; ESR, Erythrocyte sedimentation rate; Hb, Hemoglobin; WBC, White blood count.

Results

Demographic characteristics of participants

Table 1 provides demographic information for study participants, including gender, age, income status, and BMI, for the case and control groups. The data is presented in terms of frequency and frequency percentage. This table also includes weight, height, WBC, Hb, and ESR information for both groups, presented as mean values and standard deviations. The patients' (case group) disease stage is outlined in Table 1 based on frequency and frequency percentage.

The results of the repeated measure test at three-time points during the treatment

Table 2 provides the results of the repeated measure test for serum Zn levels at three time points; initially at the beginning of treatment, secondly four months after treatment initiation, and finally three months after treatment completion. The analysis includes five variables; age, gender, BMI, income level, and disease stage. The table presents data regarding frequency, mean value, and standard deviation. Additionally, the P value, indicating the significance of changes in serum Zn levels during the treatment period from the start to three months after treatment completion, is reported for each variable.

As depicted in Table 2, patients aged over 65 showed an average serum Zn level of 68.57 µg/dL at the beginning of treatment, 71.08 µg/dL at four months post-treatment initiation, and 76.18 µg/dL three months after treatment completion, indicating a significant upward trend (P value = 0.022).

Women's average serum Zn level was 76.16 mcg/dl at the treatment's outset, 68.43 µg/dL at four months post-treatment initiation, and 69.71 µg/dL at three months after treatment completion, demonstrating a significant upward trend (P value = 0.005). The same significant trend was observed for men in the case group.

In our study, significant differences were observed in the case group, particularly in the low-BMI category, showing an upward trend. The case group also exhibited significance in the medium-income situation.

Independent t test results between case and control groups

Table 3 presents the results of the independent *t* test on serum Zn levels between the case and control groups for four variables of age, gender, BMI, and income levels. The table includes frequency, mean value, and standard deviation. Furthermore, the P value for each variable's range between the two groups has been calculated and reported, indicating the significance of changes in serum Zn levels between the two groups.

As indicated in Table 3, significant differences between the two groups were observed across all age groups, genders, BMI, and income levels.

The results of the one-way ANOVA test on different stages of the disease

Table 4 illustrates the results of the one-way ANOVA test concerning the serum Zn levels in individuals with pulmonary TB across different stages of the disease. The analysis reveals that the observed variations in serum Zn levels are not statistically significant based on the disease stage.

Table 2. Repeated measure test results in case group

Variable	Range	At beginning			4th month			3 months after the treatment period			*P* value
		N	Mean	SD	N	Mean	SD	N	Mean	SD	
Age (y)	<50	10	66.78	10.84	10	67.87	9.94	10	69.64	10.25	0.070
	51-65	9	67.41	9.03	9	69.72	9.51	9	71.77	8.74	0.124
	>65	13	68.57	8.54	13	71.08	7.68	13	76.18	10.13	0.022
Gender	Female	16	76.16	10.38	16	68.43	10.12	16	69.71	9.58	0.005
	Male	16	68.20	8.09	16	70.96	7.26	16	76.09	9.47	0.009
BMI (kg/m²)	Low	8	64.83	9.10	8	67.54	8.83	8	70.84	9.51	0.014
	Normal	20	69.38	9.48	20	70.77	9.44	20	73.64	10.65	0.374
	High	4	64.95	7.36	4	68.65	4.91	4	73.30	8.42	0.426
Income	Low	13	67.94	9.56	13	70.24	9.81	13	72.38	10.25	0.054
	Middle	12	65.04	9.03	12	67.73	8.54	12	72.66	11.59	0.014
	High	7	71.73	8.29	7	72.06	7.43	7	74.27	6.97	0.170
Stage	I	14	68.05	10.09	14	69.86	9.45	14	75.01	11.07	0.028
	II	12	68.02	7.78	12	70.23	8.01	12	71.14	8.61	0.083
	III	6	66.15	10.94	6	68.23	9.96	6	71.48	10.27	0.169

BMI, Body mass index.

Table 3. Independent *t* test results

Variable	Range	Case			Control			*P* value
		N	Mean	SD	N	Mean	SD	
Age (y)	<50	10	66.78	10.85	9	94.89	24.59	0.004
	51-65	9	67.41	9.03	13	89.32	22.35	0.006
	>65	13	68.57	8.54	10	87.37	22.48	0.029
Gender	Female	16	67.12	10.38	16	87.39	20.28	0.002
	Male	16	68.20	8.09	16	93.16	23.96	0.0001
BMI (kg/m²)	Low	8	64.83	9.10	3	92.67	52.32	0.454
	Normal	20	69.38	9.48	15	89.80	23.13	0.005
	High	4	64.95	7.36	14	90.28	14.37	0.004
Income	Low	13	67.94	9.56	9	84.37	18.58	0.033
	Middle	12	65.04	9.03	15	90.27	19.98	0.0001
	High	7	71.73	8.29	8	96.95	30.82	0.056

BMI, Body mass index.

Discussion

In this study, an equal number of men and women (16 each) participated in the case and control groups. The affected patients in the case group showed lower average height and weight compared to the control group. Additionally, the average ESR rate was significantly higher in affected patients, and their Hb levels were lower, indicating anemia of chronic disease.

Ramakrishnan et al, discovered a lower BMI, serum albumin, and Zn levels in patients with pulmonary TB and HIV compared to healthy individuals and those with pulmonary TB. They attributed these changes to nutritional factors, enteropathy, and acute phase reactive proteins (27). Another study examined the relationship between serum Zn and vitamin A levels in 208 patients with active pulmonary TB. Their study suggested that Zn deficiency in these patients may indirectly affect vitamin A metabolism by reducing circulating protein levels (28). Moreover, Choi et al reported elevated copper and cobalt levels and reduced Zn and selenium levels in patients with pulmonary TB. These findings potentially have prognostic implications (17). Additionally, Ciftci et al conducted a study to investigate changes in serum levels of selenium, copper, Zn, and the cupper/Zn ratio in patients with pulmonary TB during therapy. The researchers used atomic absorption spectrometry to measure cupper, Zn, and selenium levels in the serum at the start of therapy and two months later. Their study also showed that selenium and cupper levels remained unchanged throughout the treatment, but there was a significant increase in Zn levels and a decrease in the cupper/Zn ratio (30). In a separate study, Ray et al examined plasma Zn levels in Indian children with TB and found significantly lower levels regardless of nutritional status (24). Meanwhile, Barman et al conducted a study on Bangladeshi adults with multidrug-resistant TB and found no correlation between serum Zn levels and age or gender. They attributed the lower Zn levels to immune system disorders (26). In another study,

Table 4. One-way ANOVA test results

		N	Mean	SD	*P* value
Disease stage	I	14	68.05	10.09	0.907
	II	12	68.02	7.78	
	III	6	66.15	10.94	

Mohan et al assessed Zn and copper levels in Indian adults with TB and noted higher copper levels and lower Zn levels. These levels normalized after treatment (25).

The study results presented here align with findings from other research, such as the works of Ramakrishnan et al (27), Ali et al (28), Choi and colleagues (17), Ray et al (24), Barman et al (26), and Mohan et al (25). These studies collectively indicate a decrease in serum Zn levels in patients with pulmonary TB. Additionally, the study by Ray et al revealed that children with TB have significantly lower serum Zn levels than others, regardless of nutritional status. After six months of anti-TB treatment, serum Zn levels notably increased. Therefore, serum Zn levels are a valuable objective marker for assessing disease severity and treatment response.

While there are similarities between our research and the studies conducted by Ray et al and Mohan et al (25), one significant difference is our analysis of the impact of anti-TB treatment on elevated serum Zn levels. We considered variables such as age, gender, BMI, income, and disease stage. In contrast, Barman et al found no correlation between serum Zn levels and the age and gender of subjects in their study. In our investigation, both women and men with pulmonary TB exhibited significantly lower serum Zn levels than the control group, regardless of age. However, in the age group above 65 years, a significant increase in serum Zn levels was observed with anti-TB treatment. These variations in results among studies may stem from differences in sample sizes, geographic and epidemiological factors, and notably, variations in the age groups studied.

Conclusion

In conclusion, individuals with pulmonary TB and average to high BMI, as well as low to medium income, regardless of age and gender, exhibited lower serum Zn levels compared to the control group. There was no significant correlation found between the disease stage and serum Zn levels. It is worth noting that women and men above 65 years of age, in stage one of the disease, with low BMI and medium income, experienced a significant increase in serum Zn levels with anti-TB treatment. This suggests that evaluating serum Zn levels in these specific patient groups can indicate the effectiveness of anti- TB treatment. However, due to the limited evidence in this area, further comprehensive studies are necessary to provide more conclusive clinical recommendations.

Limitations of the study

A significant limitation was the decrease in pulmonary TB cases in recent years in Arak, leading to an extended sample collection period.

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Authors' contribution

Conceptualization: Farzaneh Kianifar, Mohammad Eslami, Aliasghar Farazi.
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Writing–original draft: Khadijeh bagtash, Reza fardyar, Mohammad Yassin Zamanian.
Writing–review & editing: Amir Reza Vahid Dastjerdi, Mohammad Eslami.

Conflicts of interest

The authors declare no conflicts of interest regarding the publication of this article.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Arak University of Medical Sciences approved this study (Ethical code#IR.ARAKMU.REC.1395.221). In addition, written informed consent was obtained from all participants before any intervention. This study was extracted from a specialized degree in medicine thesis of Farzaneh Kianifar at the Arak University of Medical Sciences (Thesis #1214B/2803). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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