Original Article

Status of zinc in pulmonary tuberculosis

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Abstract

Background: To study the status of zinc as a micronutrient in pulmonary tuberculosis, in our population, with the aim to see the effectiveness of therapy.

Methodology: This prospective study includes 50 patients with pulmonary tuberculosis and 30 subjects as the control group. The patients were placed into three stages (1 to 3) on the basis of chest radiographic findings. Serum zinc levels were estimated before, during, and after completion of antitiberculosis therapy.

Results: Statistically significant fall in serum zinc levels was seen with advanced age and disease, and the levels improved after initiation of antituberculosis therapy.

Conclusion: Estimation of serum zinc levels is an important tool in diagnosis and monitoring of response to treatment in pulmonary tuberculosis, and even a booster of the immunological mechanisms if instituted during the course of treatment.

Keywords: Pulmonary tuberculosis, zing, antituberculosis therapy

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Introduction

Tuberculosis (TB) is as old as mankind. In 1993, the World Health Organization (WHO) declared the reemerging menace of TB a global emergency. Nearly one third of the world's population is infected with *Mycobacterium tuberculosis*, the causative organism of TB [1-4]. The American Thoracic Society has estimated that currently tuberculosis morbidity and mortality range from a prevalence of 10 to 30 million cases of active disease, an incidence of 3.7 to 10 million new cases and 1 to 2 million deaths annually [2-5]. The Centers for Disease Control and Prevention (CDC) predicts that tuberculosis will claim 30 million lives in the current decade [6]. It is also estimated that between 2002 and 2020, approximately one billion people will be newly infected, over 150 million will get sick, and 36 million will die of TB if proper control measures are not instituted [7]. In India, approximately 4.8 million people are suffering from TB infection of which 2.2 million are smear positive; the annual risk of infection is 1 to 2% and the case fatality rate is 24% [3].

Malnutrition is frequently observed in patients with pulmonary tuberculosis, but their nutritional status, especially of micro nutrients, is still poorly documented [8]. Among the micro nutrients, zinc is essential for human growth, development and immune function; deficiency of this micro nutrient impairs overall immune function and resistance to infection [9]. Several studies have demonstrated that the serum levels of zinc decrease significantly during active tuberculosis and increase following recovery after institution of antitubercular therapy and improvement of nutritional status [10-16]. In fact, vitamin A and zinc supplementation improves the effect of tuberculosis medication after two months of antitubercular therapy and results in earlier sputum smear conversion. Estimation of serum zinc levels during the course of tuberculosis could be used as a valuable tool for clinicians to assess response to therapy or effectiveness of the ongoing antitubercular therapy [12-15]. Zinc has been documented to increase the PPD induration size in children irrespective of nutritional status [17].

Materials and Methods

The study was conducted in the department of Government Medical College, Srinagar, Kashmir, India. It included 50 patients with pulmonary tuberculosis and a control group comprised of 30 age- and sex-matched healthy individuals. Tuberculosis was diagnosed on the basis of history, clinical examination, chest radiography, sputum examination, Montoux test, and related laboratory parameters.

Exclusion Criteria

Since serum zinc levels are affected by many physiological and pathological states and drugs, subjects with the following conditions were excluded from the study:

1. Pregnancy
2. Women on oral contraceptives
3. Chronic liver disease
4. Non-tuberculous pulmonary infections
5. Extra pulmonary tuberculosis
6. Indolent ulcers
7. Chronic renal failure
8. Myocardial infarction
9. Metastatic carcinoma
10. Nephrotic syndrome
11. Malabsorption Syndrome
12. Cystic fibrosis
13. Patients taking zinc as medication

Parameters such as age, sex, body weight, height, body mass index, and nutrition details were recorded in the pro forma of every subject of the study. Patients were placed in three stages on the basis of chest radiography according to the guidelines of the National Tuberculosis Association of USA [18-19] as follows:

Stage 1 (Minimal): Lesions which are of slight to moderate density but do not contain demonstrable cavitation. They may involve a small part of one or both lungs, but total extent, regardless of distribution, should not exceed the volume of lung on one side which is present above the second chondrosternal junction and spine of the fourth or the body of the fifth thoracic vertebra.

Stage 2 (Moderately advanced): Lesions may be present in one or both lungs, but the total extent should not exceed the following limits:

Disseminated lesions of slight to moderate density which may extend throughout the total volume of one lung or equivalent in both the lungs; dense and confluent lesions which are limited in extent to one third the volume of one lung; total diameter of cavitation, if present must be less than 4 cms.

Stage 3 (Far advanced): Lesions more extensive than "moderately advanced." The serum zinc levels of the selected patients were estimated before, during, and after the completion of antitubercular therapy (ATT). Blood samples from the cases and controls were collected in fasting state via venipuncture to determine total white blood cell count, haematocrit, ESR, and various other biochemical parameters. All biochemical tests were carried out on the same day, in accordance with the study of Karyadi *et al*. [8].

Patients were treated with drugs including isoniazid, rifampicin, ethambutol, pyrazinamide per the guidelines of National Tuberculosis Control Programme and dosage was adjusted per the body weight of the patients. The samples for serum zinc estimation were collected in zinc-free plastic syringes and the blood was allowed to clot in acid-cleaned glass test tubes and stored at 16°C until collection was completed. The estimation of zinc level was done, using the atomic absorption spectrophotometery method and the readings were recorded in the pro forma.

Statistical Analysis

The data were analyzed by using paired student's *t* test (95 percent confidence limits) and chi square tests where appropriate. P value of less than 0.05 was considered significant.

Results

Of the 50 cases of pulmonary tuberculosis studied, 23 (46%) cases were in the age group of 30 to 39 years, 12 (24%) cases in the age group of 40 to 49 years, 8 (16%) cases in the age group of 50 to 65 years, and 7 (14%) in the age group of 20 to 29 years. The mean age was 38.4 ± 15.38 (mean ± SD). Among the controls, the age ranged from 20 to 55 years with mean of 36 ± 4.2 years. Twenty-one (42%) patients of pulmonary tuberculosis and 13 (43.3%) control subjects were females aged 23 to 51 years (mean 31 ± 2.3). The serum zinc levels revealed an inverse relationship with age in both the groups; *i.e.*, on average, the observed levels were lower with the advancement in age (Table 1). Such a discrepancy in either of the groups was statistically of high significant nature. Moreover, when the groups were

Table 1. Serum Zinc Levels in cases and controls before institution of antitubercular therapy in the study group, as per the age distribution

Age in Years	Serum Zinc, mcg/dl mean ±SD		t value	p value	Significance
	Study group n=50	Control group n=30			
20-29	73.56 ± 6.9	95.82 ± 3.12	2.62	< 0.025	S
30-39	68.22 ± 5.33	94.78 ± 5.02	17.03	< 0.001	HS
40-49	58.26 ± 7.48	88.00 ± 5.68	6.71	< 0.005	HS
50-65	53.46 ± 2.96	85.23 ± 2.16	3.18	< 0.001	HS

S- Significant , HS- Highly significant.

compared to each other, the pulmonary tuberculosis group revealed a significant fall in zinc levels in contrast to the control group. Overall, the pulmonary tuberculosis group prior to therapy showed a significant fall (p value less than 0.05) in average serum zinc levels in contrast to the control group. In the study group of pulmonary TB patients, there was a progressive fall in the serum zinc level with the highest decrease seen in stage 3, which was statistically highly significant. After the second month of antitubercular therapy and within two months after completion of treatment, there was again significant increase in the serum zinc levels (Table #2). However, no statistical significance was observed with the serum zinc levels with relation to the sex, body weight, and body mass index in either cases or controls.

Discussion

The study demonstrated diminished serum zinc levels in advanced age and progressed pulmonary tuberculosis. Although the literature regarding this observation is sparse, similar results have been documented in previous studies [8,10,16]. In India, Ray and co-workers [16] studied the plasma zinc status of 50 children with tuberculosis and compared the observations with 10 healthy and 10 malnourished children without tuberculosis at 0, 1, 2, 3 and 6 months of antitubercular therapy. The children with tuberculosis had significantly lower plasma zinc levels than those without the disease, irrespective of the nutritional status. Our results are in agreement with another study from India by Taneja [20], who found significantly low zinc levels in cases of pulmonary tuberculosis. Similarly, Karyadi and co-authors from Indonesia studied the nutritional status of patients with active pulmonary tuberculosis and compared the values with those of healthy controls. The authors found poor nutritional status and significantly low serum zinc levels in tuberculosis patients compared to controls. Contrary to previous studies and the present one, Ciftci *et al*. [21] from Turkey studied 22 pulmonary TB patients and 18 healthy subjects and found an increase in the levels of zinc; however, the mechanism of this increase was not explained. The possible mechanisms for the lowered zinc levels in cases of pulmonary TB include redistribution of zinc from plasma to other tissues [22]; reduction of hepatic production of zinc carrier protein X_2 macroglobulin; and a rise in the production of metallothionein, a protein that

Table .2 Serum Zinc Levels in relation to stage of pulmonary tuberculosis prior to, during and after the antitubercular therapy.

Stage	No. of cases (%)	Serum zinc , mcg/dl Mean ± SD			t value	p value	Significance
		Before Therapy	During Therapy	After Therapy			
1	12 (24.0)	74.14 ± 6.14	78.22 ± 2.3	76.48 ± 1.9	1.65	< 0.05	S
2	24 (48.0)	70.22 ± 6.98	73.68 ± 1.1	70.34 ± 9.0	3.83*	< 0.005	HS
3	14 (28.0)	60.7.9 ± 7.88	83.19 ± 3.4	79.68 ± 1.7	2.96	< 0.001	HS

S- Significant, HS- Highly significant.*Comparison between stages 1 and stage 3

transports zinc to liver [23]. Rankovic and Drdevic [24] studied zinc levels in serum and pleural effusion in 104 patients and found higher zinc levels in effusion due to tuberculosis compared to that in the serum, and concluded that zinc concentration in the effusion and serum higher than 1.0 reliably indicates the presence of tuberculous pleurisy, signifying the diagnostic value of zinc in tuberculosis. Cuevas [17] and co-workers in the United Kingdom studied the effect of zinc on the tuberculin response of 98 children exposed to adults with smear positive tuberculosis. They found a higher proportion of children as PPD positive in the zinc-supplemented group (57.1%) than in the placebo group (53.1%). It is postulated that zinc supplementation could work by correcting asymptomatic or marginal zinc deficiencies or as a non-specific booster of immunity irrespective of zinc deficiency. Overall, the studies conclude that zinc supplementation improves the effect of tuberculosis medication after two months of antitubercular therapy, results in earlier sputum smear conversion, serves as a booster of immunologic process [12,17]. Estimation of the zinc levels could be used as a valuable laboratory tool to assess the effectiveness of the ongoing antitubercular therapy [16,21]. We suggest that, in view of the poor nutritional status in patients of pulmonary TB, zinc supplementation be a mandatory constituent of the treatment protocol.

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Conflict of interest: No conflict of interest is declared.