

Hypercalcemia In Pulmonary Tuberculosis

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ABSTRACT

BACKGROUND: Pulmonary Tuberculosis is a granulomatous disease with high prevalence of mortality and morbidity in developing countries like India. Various electrolyte disturbances have been reported in pulmonary tuberculosis and calcium abnormalities are one of them. **AIM:** To evaluate and compare frequency of calcium abnormalities in patients with inactive previously treated and active Pulmonary Tuberculosis. **METHODS:** The study was done between October 2015 and January 2016 and 100 pulmonary tuberculosis patients were evaluated. Serum calcium levels were analyzed by COBAS 400/400 plus auto analyzer. **RESULTS:** Hypercalcaemia was reported in 6% of pulmonary tuberculosis patients. Hypercalcaemia reported was mild in all patients and asymptomatic. The detection rate of hypercalcaemia was higher in radiologically far advanced active disease (3 out of 4) and was statistically highly significant (p=0.000).

Key words: Pulmonary Tuberculosis, Hypercalcaemia

INTRODUCTION

Hypercalcaemia is known to occur in granulomatous diseases among which sarcoidosis is the most common and others are tuberculosis, fungal infections, berylliosis and lymphoma. Though infrequent but it is a recognized complication of active tuberculosis. Results of various studies from different countries reporting hypercalcaemia incidence in tuberculosis did not match, probably because of ethnic and racial disturbances, the amount of sun exposure, difference in vitamin D and calcium intake. In United States hypercalcaemia is reported in 16% to 28% of pulmonary tuberculosis¹, whereas low percentage of hypercalcaemia(5.2%) was found in another study from Pakistan.² Pulmonary Tuberculosis is a very common Disease in India associated with increased morbidity and mortality. Therefore a study was planned to illicit prevalence of hypercalcaemia in pulmonary tuberculosis patients in India.

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MATERIALS AND METHODS

The present study was conducted at a teaching institute in Rajasthan on consecutive 100 hospitalized pulmonary tuberculosis patients. The study population reflected tribal population of Rajasthan. Out of 100 patients,73 were active pulmonary tuberculosis patients confirmed by sputum AFB detection by Zeihl Nelson staining method and 27 were inactive previously treated Pulmonary tuberculosis patients who were sputum AFB smear negative.

Patients with hyperparathyroidism, hypoalbuminemia as low albumin levels masks hypercalcaemia, other known calcium metabolism diseases and calcium containing drugs or vitamin supplements were not included in the study.

10 ml of venous blood collected from antecubital vein in fasting state before any prescription of intravenous fluids was collected at the time of admission and was sent for analysis . Serum calcium estimation was done by using Cobas 400/400plus integra autoanalyzer based on method according to Schwarzenbach with O-cresolphthalein complexone. Calcium ion react with O-cresolphthalein complexone (O-CPC) under alkaline conditions to form a violet coloured complex and colour intensity is determined

by measuring the increase in absorbance at 552 nm. Hypercalcaemia was considered when serum calcium levels were >10.2mg/dl. The plain chest radiographs taken at the time of presentation, before commencement of anti-TB treatment, were graded as minimal, moderately advanced and far advanced to assess the extent of active pulmonary disease.³

Statistical Analysis: Data collected was analyzed by using SPSS software (17th edition) and P value less than 0.05 is considered significant. The significance of distribution of number was tested by using chi square test.

RESULTS

Out of 100 admitted male patients ,73 patients were confirmed bacteriologically to be active and 27 were sputum negative .Mean age of patients was 40.95±12.97(range 20 -70 yrs).The distribution of hypercalcaemic patients according to age is given in table no.1.

Table 1: Distribution of hypercalcaemic patients according to age groups..

Age group (years)	No. of patients	%	Hypercalcaemia
	N=100		
20-30	29	29.0	4
31-40	27	27.0	1
41-50	26	26.0	0
51-60	15	15.0	1
61-70	3	3.0	0
P value			0.221

The mean serum calcium concentration was 8.96±0.84 mg/dl .Out of 100 patients, hypercalcaemia was reported in 6(6%) patients, among which 4 were active pulmonary tuberculosis patients (mean serum calcium=10.6) and 2 (mean serum calcium=10.5) were inactive previously treated pulmonary tuberculosis patients but difference was not statistically significant (p=0.420).All 6 patients were asymptomatic and mild hypercalcaemia (10.3-12.0mg/dl)was detected. The extent of lung involvement, as shown by radiography, in patients with pulmonary TB was minimal in 21 out of 73 patients, moderately advanced in 27 of 73 patients, far advanced in 25 of 73 patients. Out of 4 hypercalcaemic active tuberculosis patients, 3 were having far advanced disease (p=0.000 H.S.) (Table 2)

Severity of hypercalcaemia v/s radiological severity of active disease

Table 2: Hypercalcaemia grading in relation to radiological severity of disease

	Calcium (mg/dl)	CX-Ray		
		Minimal	Moderate Advanced	Far Advanced
Active	Hypercalcaemia			
	Mild (10.3-12.0)	0	1	3
	Moderate (12.1-14.0)	0	0	0
	Severe (>14.1)	0	0	0
Pvalue				0.000**

DISCUSSION

Hypercalcaemia has been variedly reported in pulmonary tuberculosis , but is often mild and asymptomatic in most cases. In the present study, 6% of patients had hypercalcaemia. This is comparable with the 5.2 % noted by Aamir Ijaz et al²¹ in Pakistan and 6% in a study from Hong Kong⁴ and the 16% reported from previous study done in India⁵, 27.5% from Nigeria⁶, 48% reported from Greece⁷ and the 51% from Australia⁸.

This difference with previous study from India could be due to dissimilar study populations from two different hospitals in different regions. However similar to our study none of the hypercalcaemic patients with pulmonary TB had symptoms related to hypercalcaemia in the previous study from India⁵. In a study from Hong Kong⁹, only two of 318 patients with active TB had hypercalcaemia severe enough to warrant specific treatments such as hydration and a course of steroids. In a study done from Malaysia¹⁰ Tan TT observed hypercalcaemia in only one of 43 patients (2.3%).

Dissimilarity in our findings and those from US and Europe could be explained by many factors e.g. ethnic differences, malnutrition and malabsorption associated with our patients of Pulmonary Tuberculosis

Hypercalcaemia is commonly observed during the active phase of TB¹⁰.The occurrence of hypercalcaemia in TB patients may be related to the extent of disease, dietary intake of vitamin D and calcium, and the amount of sun exposure.^{11,12,13,14,15,16}

Several studies^{17,18,19,20} have shown that extrarenal conversion of 25-hydroxycholecalciferol (25[OH]D3) to

metabolically active 1,25-dihydroxycholecalciferol (1,25[OH]2D3), is important in causing hypercalcaemia in tuberculosis patients. High circulating levels of 1,25(OH)2D3 reported in anephric patients with TB^{18,19}, supports the idea of extrarenal production of 1,25(OH)2D3. A French study on bronchoalveolar lavage (BAL) cells has shown 25-hydroxycholecalciferol (Vit D3) synthesis by alveolar immune cells²¹. Another study²² showed the production of 1,25(OH)2D3 by CD8+T lymphocytes and alveolar macrophages recovered by bronchoalveolar lavage from active TB patients. High dietary intake of calcium, results in increased gut absorption of calcium. TB patients with relatively high vitamin D levels have more circulating vitamin D for extrarenal synthesis of 1,25(OH)2D3 than others. Apart from ingestion, vitamin D3 (cholecalciferol) is synthesized from 7-dehydrocholesterol in the skin by ultraviolet light. The amount of sun exposure and the circulating levels of 25(OH)D3, a product of hydroxylation of vitamin D3 in the liver, may partly explain the rare occurrence of hypercalcaemia in TB patients in countries with temperate climates.^{11,15} It has been reported¹³ that in tropical climates, where sunlight is abundant, a relatively high level of serum 25(OH) D3 may give rise to hypercalcaemia in patients with TB. But as our study was conducted in winter season so decreased sun exposure, poor nutritional status, and absorptional disturbances in tribal population of our study may be the cause of low hypercalcaemia prevalence.

The exact cause of increase serum calcium levels in far advanced cases is not known. Several possible explanations for hypercalcaemia have been considered.

Braman et al²³ suggested involvement of bone or adrenals by tuberculosis as a possible cause, while acute bone atrophy due to reduced physical activity or immobilization was suggested another possible cause by Wolf et al.²⁴

Reiner et al²⁵ suggested hypersensitivity to vitamin D as in sarcoidosis, may be possible explanation of hypercalcaemia in pulmonary tuberculosis. Lung is the major organ responsible for metabolism of prostaglandin E, since PGE are potent stimulator of bone resorption, extensive tubercular involvement of lung could theoretically reduced the rate of degradation of PGE, leading to hypercalcaemia.

Another mediator of bone resorption is osteoclast reactivating factor. Activation of leucocytes in chronic inflammation of the lung tissue has been suggested as a stimulus for secretion of osteoclast reactivating factor, resulting in bone resorption and leading to hypercalcaemia during the active phase of disease.

CONCLUSIONS

Hypercalcaemia is less common in Indian pulmonary tuberculosis patients but prevalence of hypercalcaemia increases with severity of disease and patients are usually asymptomatic. Limitations of our study was small sample size because of the stringent selection criteria. In this study, the differences noted compared to the previous studies might be because of the small sample size and difference in sun exposure. Therefore a detailed study is recommended to investigate the vitamin D and PTH metabolism in these subjects.

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