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Calcium abnormalities in pulmonary tuberculosis

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SUMMARY

Objective: To study the disorders of calcium metabolism in patients with untreated pulmonary tuberculosis.
Design: A cross-sectional comparative study.
Places and Duration of Study: Department of Pathology Army Medical College and Department of Pulmonology MH Rawalpindi, Department of Chemical Pathology and Endocrinology AFIP Rawalpindi from Jan 2002 to Jan 2003.
Subjects & Methods: One hundred and fifty two patients of untreated pulmonary tuberculosis and forty four age and sex- matched disease free controls were included in the study. Blood ionized calcium (Ca^{++}), pH, sodium (Na) and potassium (K) were analyzed by ion selective electrode method on Easylyte® auto analyzer. Other related parameters were measured by colorimetric methods.
Results: Blood Ca^{++} levels in patients of pulmonary tuberculosis were found (mean ± SD: 1.15±014 mmol/L) significantly low as compared to control subjects (mean ± SD: 1.23±0.03 mmol/L) (p<0.001). Fifty two (38%) subjects had hypocalcaemia while seven (5%) subjects were found to be falling in hypercalcaemic range. Serum phosphate levels were also low corresponding to Ca^{++} levels control (mean ± SD: 0.97±0.19 mmol/L vs 1.17±0.21 mmol/L; p<0.001). There was no statistically significant difference in other parameters e.g. albumin, urea, creatinine, pH, Na and K levels in study subjects and controls.
Conclusion: Hypocalcaemia and hypphosphataemia are more prevalent in our population of untreated pulmonary tuberculosis.

Key Words: Pulmonary tuberculosis, Hypocalcaemia, Hypercalcaemia

INTRODUCTION

Pulmonary tuberculosis (Pulm TB) is still a very common cause of morbidity & morbidity in our country[1]. Keeping in mind its high prevalence all aspects of the disease need to be thoroughly studied. Disturbance in calcium metabolism leading to variations in blood calcium concentration can cause a spectrum of clinical features[2]. Such patients may be asymptomatic or may have signs and symptoms, which can easily be attributed to primary disease if calcium abnormalities are not suspected.

Calcium abnormalities have been variedly reported in studies carried out on the subject. In a Swedish study hypercalcaemia was found in 25% of 67 patients of Pulm TB[3]. In United States 16% to 28% patients of Pulm TB have been found to be suffering from hypercalcaemia[4] though lower incidence of hypercalcaemia has also been reported from US[5]. Hypercalcaemia was detected in 25% Greek patients[6] and in 27.5% of the Malaysian patients[7] with pulmonary tuberculosis, with symptoms of hypercalcaemia present in only 5% and 12% of these patients, respectively. Hypercalcaemia and hyperphosphataemia in Pulm TB has also been reported from Germany[8]. Albumin Corrected Calcium (ACC) was also found significantly higher in Pulm TB patients from Hong Kong despite a lower calcium intake[9]. However, comparatively low percentage of hypercalcaemia was found in another study from Hong Kongs (6%) [10]. Pulm TB has also been found associated with hypocalcaemia in some studies. In a Japanese study 38% patient showed Ca level lower than reference range[11]. Serum Ca and Parathyroid hormone (PTH) levels were found significantly reduced in an Egyptian group of Pulm TB patients[12.13]. Similar results were also found in a Nigerian study[14].

Calcium abnormalities in pulmonary TB patients have not been studied in any Pakistani population in spite of the fact that this is still a very common disease in our country. A study was, therefore, planned to prepare a preliminary report about spectrum of calcium abnormalities based on the routine biochemical laboratory investigations.

MATERIALS AND METHODS

This cross-sectional comparative study was carried out in the Department of Pathology Army Medical

College Rawalpindi, Department of Pulmonology Military Hospital Rawalpindi and Dept of Chemical Pathology and Endocrinology AFIP Rawalpindi from Jan 2002 to Jan 2003. One hundred and fifty two patients of Pulm TB were selected by convenience sampling diagnosed on the basis of clinical features, X-Ray chest, blood complete picture, sputum Acid Fast Bacilli detection and Montoux Test (in various combinations). Only those patients were included in the study who were not yet started with the anti-tuberculosis treatment. Forty-four disease-free persons were also included in the study after exclusion of the disease on clinical history and examination. The major limitation in restricting the number of control subjects was proper exclusion of a common disease (Pulm TB) in age, sex and socioeconomic group matched individuals. None of the patients or control subjects was on calcium supplements. Blood ionized calcium (Ca^{++}), pH, Na^{+} and K^{+} were analyzed by Ion Selective Electrode (direct method)[15] on Easylyte® auto analyzer on whole blood samples collected in a lithium heparin tube from each subject and control. A second sample (5ml) was also collected from the subjects and controls in a plain tube for the analyses of total calcium (TCa), serum inorganic phosphate, (iP), albumin (Alb), urea and creatinine, these analyses were carried out by routine colorimetric methods on clinical chemistry analyzer Selectra-II (Vita-Lab, Germany). Investigations like pH, Na^{+} and K^{+}, urea, and creatinine were carried out to rule out other causes of calcium abnormalities e.g. renal dysfunction, acid base and electrolyte disorders. Whole blood analyses was done within four hour of collection (transported on ice) while colourimetric tests were carried out in larger batches after thawing the samples frozen at -20°C. Appropriate quality control materials were used for ensuring quality assurance.

Statistical Analysis

Data was stored and analyzed using SPSS (version 11.0). Since most of the data was parameteric, independent `t` test was applied for inferential statistics between study group and control subjects. Frequencies of occurrence of Ca abnormalities by various modalities were compared by Chi square test. Pearson`s correlation test was applied for correlation studies between various diagnostic modalities

RESULTS

There were 137 males and 58 females in the patients and control groups (combined) with the median age of 35 y and range of 13 to 80 y. Blood Ca^{++} levels were significantly low in cases of Pulm TB (mean ± SD: 1.15±014 mmol/L) as compared to control population (mean ± SD: 1.23±0.03 mmol/L) (p<0.001) (Fig1). Comparison of blood Ca^{++} levels in male and female patients of Pulm TB yielded no significant results (p> 0.5) (Table 1). Mean serum iP levels were also significantly less in patients(mean ± SD: 0.97±0.19 mmol/L) with Pulm TB as compared to disease free controls (mean ± SD:1.17±0.21 mmol/L) (p<0.001) (Fig 1) but there was no significant difference in iP in male and female patients of Pulm TB (Table I). TC and ACC were also significantly low in pulmonary TB group as compared to controls (p< 0.05). (Fig I). Hypocalcaemia defined as Ca^{++} levels < 1.15 mmol/L was found in 59 (39%) subjects. However, number of hypocalcaemic Pulm TB patients detected by Ca^{++} was significantly higher as compared to those detected by TC (33 or 22%) & ACC (21 or 19%) (p< 0.05) (Fig 2). Only 9 (5.9 %) patients were found hypercalcaemic (Ca^{++} levels > 1.27 mmol/L) among Pulm TB group. The detection rate of hypercalcaemia was also higher by Ca^{++} as compared to that for TC (4%) or ACC (4%) (Fig 2).

Table 1: Comparison of Calcium and Phosphorus between males and female patients of Pulm TB patients and control subjects.

Parameter	Sex	n	Mean	SD	Significance
Ionized ca (mmol/L)	Male	137	1.17	0.13	$p = 0.39$
	Female	58	1.16	0.10	
Total Ca (mmol/L)	Male	137	2.23	0.25	$p = 0.57$
	Female	58	2.26	0.20	
Albumin corrected ca (mmol/L)	Male	136	2.27	0.25	$p = 0.38$
	Female	58	2.30	0.20	
Phosphorus (mmol/L)	Male	133	1.01	0.22	$p = 0.73$
	Female	56	1.02	0.18	

Table 2: Comparison of related parameters in Pulm TB patients and control subjects.

Parameter	Group	n	Mean	SD	Significance
Potassium (mmol/L)	Subjects	151	3.87	0.61	$p = 0.011$ (NS)
	Controls	44	3.72	0.51	
Sodium (mmol/L)	Subjects	151	133	4.72	$p = 0.89$ (NS)
	Controls	44	133	3.05	
PH	Subjects	150	7.33	0.07	$p = 0.31$ (NS)
	Controls	44	7.348409	0.10	
Creatinine (µmol/L)	Subjects	141	86	13.9	$p = 0.21$ (NS)
	Controls	44	83	15.3	
Urea (mmol/L)	Subjects	144	4.35	1.19	$p = 0.634$ (NS)
	Controls	44	4.42	0.86	

There was no statistically significant difference in concentrations of other biochemical parameters in study and control groups (Table 2).

Figure 1: Mean levels of ICa, TCa, ACC and iP in Pulm TB patients (n=151) and control subjects (n=44)

Figure 2: Comparison of various modalities of Ca estimations for the diagnosis of Ca abnormalities in Patients of Pulm TB (n=151)

DISCUSSION

Abnormalities in calcium, metabolism have not been studied in our population of Pulm TB. The most striking

finding of the present study was presence of hypocalcaemia in these patients. This finding is consistent with earlier studies from Japan[11], Egypt[12,13] and Nigeria[14]. Surprisingly the percentage of hypocalcaemic patients found in our study (35%) is also quite close to that reported in Japanese study (38%)[11]. The number of pulmonary TB patients with hyperlcaemia was found to be very low (5.2 %). This is in contrast to the reports from Sweden[3], US[4] and Greece[6] while closer to that reported from Hong Kong[10]. The discrepancy 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 Pulm TB. Presence of nutritional and absorptional problems as evident form concomitant finding of hypophophataemia could be a part of the same disease process or could be due to coexisting gastrointestinal disease. Although utmost care was exercised to select control subjects from the same socioeconomic groups, factors leading to hypocalcaemia and hypophosphataemia because of vitamin D deficiency cannot be ruled out. A detailed study is recommended to investigate the vitamin D and PTH metabolism in these subjects.

The mechanism of hypercalcaemia in pulmonary TB is not known. Macrophage activation and dysregulated vitamin D production has been implicated[16,17] with decreased PTH[18]. A French study carried out on bronchoalveolar lavage (BAL) cells has shown that major contribution is from 25 - hydroxycholecalciferol (Vit D_3) synthesis by alveolar immune cells[19]. However, no direct relationship between serum Ca and Vit D_3 has been found[6]. Ability of Ca^{++} estimation to pick more cases of Ca abnormalities in pulmonary TB is in agreement with studies carried on other diseases[20].

CONCLUSION

It is concluded that calcium abnormalities especially hypocalcaemia is quite common in our patients of pulmonary TB and physicians must maintain a high index of suspicion for diagnosis and correction of these abnormalities.

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