

## HYPOCALCEMIA AND HYPERPHOSPHATEMIA IN TUBERCULOSIS

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### ABSTRACT

Tuberculosis (TB), a major public health problem, is a granulomatous infection caused by *Mycobacterium tuberculosis*. One third of world's population is infected with *M. tuberculosis*. This study was aimed to estimate serum calcium and phosphorous levels in TB patients before during and after DOTS (Directly Observed Treatment Short course). Calcium and phosphorous are essential macro-minerals required for various physiological functions; changes may cause a detrimental effect on those functions. 92 subjects (42 normal healthy controls and 50 patients with TB) were studied and their serum calcium and phosphorous levels were estimated. Serum calcium level was observed to be low and Serum phosphorous level was found to be high; both being statistically significant ( $p < 0.001$ ) at diagnosis and after two months of therapy whereas both the levels became normal on completion of therapy. This study helps in macro-minerals level changes during TB infection and may suggest need for therapy targeted at normalizing those levels for early prognosis of the disease.

### KEY WORDS

Tuberculosis (TB), serum calcium, serum phosphorous, DOTS

### INTRODUCTION

Tuberculosis (TB) is a contagious disease caused by *Mycobacterium tuberculosis* which is an aerobic non motile bacillus. The tubercle bacilli can attack any part of the body, most commonly lungs. It spreads through droplet infection. When infectious people cough, sneeze, talk or spit they propel TB germs known as bacilli into air. Inhalation of very small numbers of these bacilli will lead to *M. tuberculosis* infection. One third population of the world is infected with *M. tuberculosis*. The vast majority of these have latent infections. Annually more than 8 million people develop tuberculosis and approximately 1.8 million cases results in death.<sup>1</sup> Most of the estimated number of cases in 2010 occurred in Asia (59%) and Africa (26%). India alone accounted for an estimated one quarter (26%) of all TB cases worldwide, and China and India combined accounted for 38%.<sup>1</sup>

Calcium and phosphorous are important macro-minerals required for vital functions. Calcium is important for growth and development of bones and teeth, action of enzymes, mediation of hormonal responses, blood coagulation, muscle contractility and normal neuromuscular irritability.<sup>2</sup> Phosphorous is required for formation of bone and teeth, production of high energy phosphate compounds such as ATP, GTP, creatine phosphate etc, synthesis of nucleoside co-enzymes like NAD and NADP, DNA and RNA synthesis and formation of phosphate esters like glucose-6-phosphate and phospholipids.<sup>3</sup> Any imbalance in the serum calcium and phosphorous concentration will have a detrimental effect on the physiological functions they perform.

## MATERIALS AND METHODS

A prospective study was carried out in 92 subjects, of which 42 were normal healthy individuals and 50 suffering from tuberculosis. The subjects were selected from OPD, IPD and DOTS centre of MGM group of Hospitals, Navi Mumbai, India. The estimation of serum calcium and phosphorous was carried out. Out of 50 tuberculosis patients, 31 were assessed after two months and after six months (completion) of DOTS therapy. DOTS therapy comprises of combination of drugs – Rifampicin, Isoniazid, Pyrazinamide and Ethambutol. The regimen was administered as per the RNTCP (DOTS) guidelines<sup>4</sup>. The control group comprised of healthy subjects of both sexes. The diagnosis of TB was based on clinical, radiological, sputum Acid Fast Bacilli (AFB) smear positivity and tuberculin skin test positivity. Venous blood samples were obtained from tuberculosis patients (3 times- at the time of diagnosis, after two months and on completion of DOTS therapy) and healthy controls. Serum calcium and phosphorous levels were estimated by Trinder's Method<sup>5</sup> and Fiske Subbarow Method<sup>6</sup> respectively.

**Statistical analysis:** Comparison of serum calcium and phosphorous levels were performed between control group and study groups (newly diagnosed TB patients, patients after 2 months of therapy and patients on completion of therapy) by using MS Office Excel 2007 and the software 'GraphPad Quick Cals t-test calculator'. Results were expressed as mean (M),

standard deviation (S.D) and considered significant when  $p < 0.05$  determined by Student's t-test and Paired t-test.

## RESULTS

Results were expressed as Mean  $\pm$  S.D for each parameter

**Control group:** 42 normal healthy individuals aged between 20 to 60 years of age [27 males (64.28%) and 15 females (35.72%)] were included as controls. In this group Mean  $\pm$  S.D of serum calcium and phosphorous were found to be  $10.31 \pm 0.40$  mg/dl and  $3.53 \pm 0.37$  mg/dl respectively.

**Study group:** 50 newly diagnosed TB patients were included in the study. Out of those, in 31 patients serum calcium and phosphorous levels were also estimated during treatment and on completion of therapy.

In the study, mean serum calcium level in newly diagnosed patients was  $8.91 \pm 0.94$  mg/dl. The values were estimated to be  $9.28 \pm 0.46$  mg/dl and  $10.09 \pm 0.58$  mg/dl in patients after two months of therapy and on completion of therapy respectively.

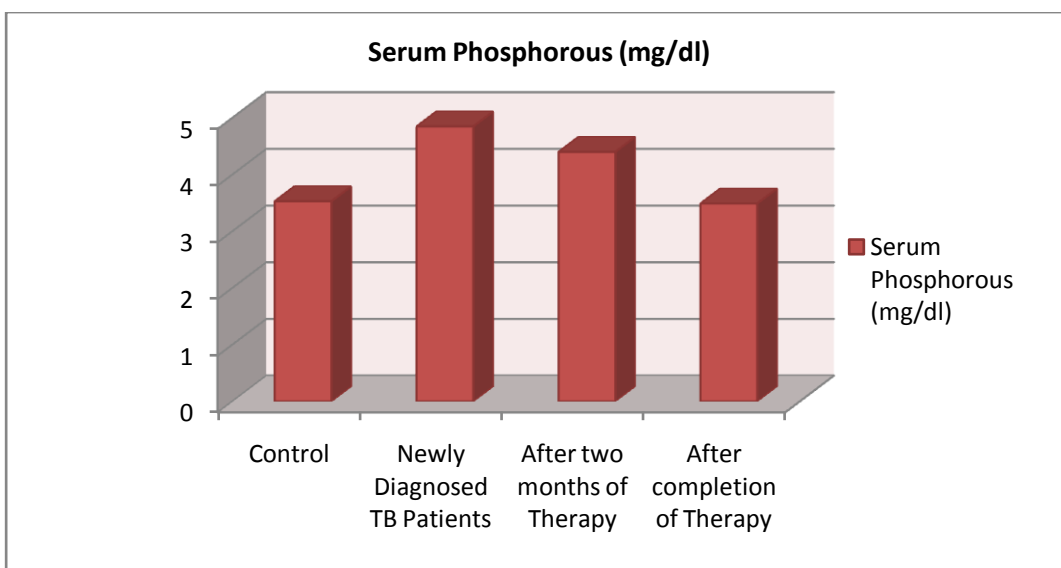
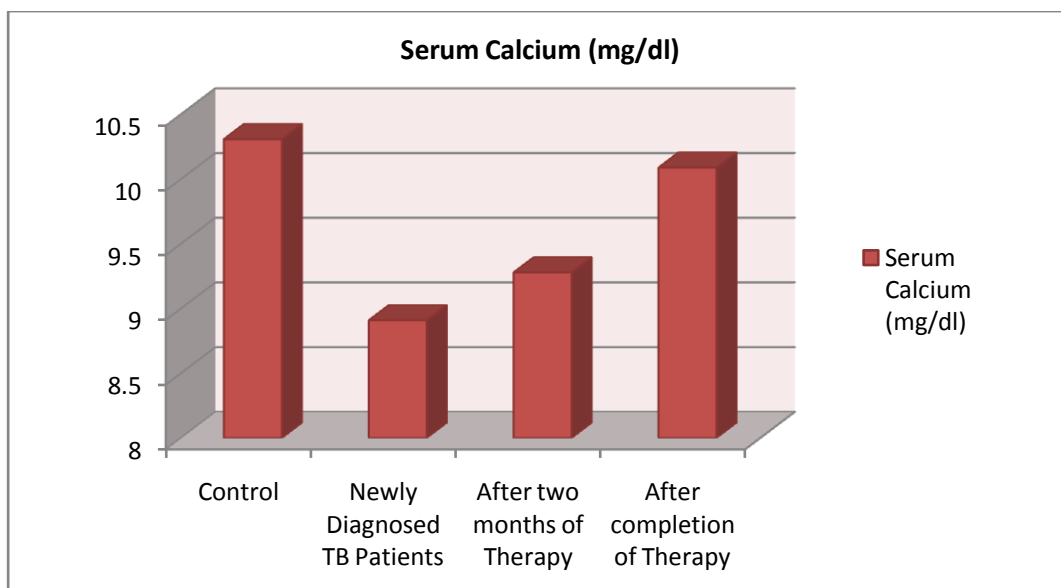
In the study, mean serum phosphorous level in newly diagnosed patients was  $4.85 \pm 0.38$  mg/dl. The values were estimated to be  $4.40 \pm 0.30$  mg/dl and  $3.49 \pm 0.62$  mg/dl in patients after two months of therapy and on completion of therapy respectively.

No significant difference was observed in mean serum calcium and phosphorous levels in different sex and age group among the patients.

**Table 1: Comparison of serum calcium and phosphorous in control group and different study groups**

Parameter	Control Group (Mean $\pm$ S.D)	Study Groups		
		Newly diagnosed TB patient (Mean $\pm$ S.D)	Patients after two months of therapy (Mean $\pm$ S.D)	Patients on completion of therapy (Mean $\pm$ S.D)
Calcium (mg/dl)	$10.31 \pm 0.40$	$8.91 \pm 0.94$ *	$9.28 \pm 0.46$ #	$10.09 \pm 0.58$ *
Phosphorous (mg/dl)	$3.53 \pm 0.37$	$4.85 \pm 0.38$ *	$4.40 \pm 0.30$ *	$3.49 \pm 0.62$ *

\*  $p < 0.001$  (high statistically significant) #  $P < 0.05$  (statistically significant)



## DISCUSSION

In present study, out of 50 newly diagnosed tuberculosis patients 20 were found to have a low level of serum calcium (i.e. hypocalcemia) and rest were normo-calcemic. We found that the serum calcium levels were significantly low ( $P<0.001$ ) in newly diagnosed TB patients as compared to the control group. There was a significant increase ( $P<0.05$ ) in the mean calcium level after two months of anti-tubercular treatment. The mean calcium level in patients after the completion of DOTS therapy was highly statistically significant ( $P<0.001$ ) as compared to the newly diagnosed patients. A significant

increase ( $P<0.001$ ) in the mean calcium level in patients after completion of therapy was observed as compared to the same patients after two months of anti-tubercular therapy. This finding is consistent with the earlier studies from Pakistan<sup>7</sup>, Japan<sup>8</sup>, Egypt<sup>(9, 10)</sup> and Nigeria<sup>11</sup>. Controversial reports of changes in serum calcium levels in tuberculosis patients have also been reported. L. Lind et al<sup>12</sup> reported that out of 67 patients with pulmonary tuberculosis 25% were hypercalcemic before the initiation of therapy. The mean  $\pm$ SD value for serum calcium in the newly diagnosed patients was  $2.51 \pm 0.16$  mmol/L which was significantly higher ( $P<0.001$ ) than the mean level

found in the control group ( $2.43 \pm 0.07$  mmol/L). They also found that after one year of successful treatment the serum calcium values had normalized. Similar observation was also reported by Abbasi A.A et al.<sup>13</sup>, Subash C Sharma et al.<sup>14</sup>, C.K. Liam et al.<sup>15</sup> and Kitrou MP et al.<sup>16</sup>. It could be explained by influence of many factors like ethnic differences, malabsorption and malnutrition associated with patients of pulmonary tuberculosis.

The serum phosphorous level was significantly high ( $P < 0.001$ ) in newly diagnosed TB patients as compared to the control. There was a significant decrease ( $P < 0.05$ ) in the mean phosphorous level after two months of anti-tubercular treatment. The mean phosphorous level in patients after the completion of anti-tubercular therapy (six month) was statistically significant ( $P < 0.001$ ) as compared to newly diagnosed patients. A significant decrease ( $P < 0.001$ ) in the mean phosphorous level in patients on completion of therapy (six months) was observed as compared to the same patients after two months of DOTS therapy. Similar observations were reported by Well H.G. et al.<sup>17</sup>, Sweany H.C. et al.<sup>18</sup> and Sharma et al.<sup>19</sup>. This finding could be due to the distribution of the intracellular phosphate which is liberated due to the destruction of the cells.

## CONCLUSION

In the present study, mean serum calcium level was significantly decreased in newly diagnosed patients as compared to control which became normal after completion of DOTS therapy. However, mean serum phosphorous level was significantly increased in newly diagnosed patients as compared to control which came to normal levels after the anti-tubercular therapy. This may signify the changes in different macro-minerals' levels due to TB infection. Studies can be carried out on the prospects of use of calcium based phosphate binders as adjuvant to DOTS for TB treatment.

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