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**Research Article**

# CALCIUM AND PHOSPHORUS AS MARKERS OF OUTCOME IN PATIENTS WITHPULMONARY TUBERCULOSIS

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**ABSTRACT**

The aim of the present study is to determine the prevalence of hypercalcemia, hypocalcemia, hypophosphatemia and hyperphosphatemia in newly diagnosed TB patients before and after six-month duration anti-TB treatment in India. Patients were required to attend the treatment facility daily during the first intensive phase (first 8 weeks) of chemotherapy and then 3 times weekly during the continuation phase. These suspected patient Blood samples were collected from seven groups. Blood samples were collected from the subjects of tuberculosis Hospital at Chennai for before treatment and after treatment variations, fasting blood samples were collected from 8 AM - 9 AM. Experiments were carried out as soon as possible. Serum was analyzed for calcium and phosphorus. Phosphorus TB incidence of the patients before treatment and after the end of six-month treatment was found to be low at levels 1.08 to 1.25 mg/dL, medium levels 2.0 to 4.0 mg/dL and high levels 7.5 to 12.84 mg/dL. Calcium TB incidence of the patients for before treatment and after the end of six-month treatment was found to be low at levels 2.0 to 4.0 mg/dL, medium levels 11.0 to 13.0 mg/dL and high levels 7.5 to 12.84 mg/dL. In the present study, mean serum calcium level is much in newly diagnosed patients as compared to after treatment group which became normal after completion of therapy. However, mean serum phosphorous level was much decreased and increased in newly diagnosed patients as compared to the control which came to normal levels after the anti-tubercular therapy. Our findings propose the probability that early intervention will help achieve calcium and phosphorus conversion and ultimately a successful treatment outcome.



## INTRODUCTION

Tuberculosis is one of the most significant public health problems all over the world and responsible for about 3 million deaths annually. There are various causes which increase the susceptivity to Mycobacterium tuberculosis infection; these include impaired immune system which occurs throughout various diseases and medications like human immunodeficiency virus (HIV), type II diabetes, end-stage kidney disease, alcoholism and intravenous drug use, certain cancers, cancer treatment such as chemotherapy, malnutrition, and very young or difficult age. While treatment success rates of 40% to 80% have been observed in the intensive phase and continuation phase of the tuberculosis patients. Before effective chemotherapy was available, many studies on the biochemistry of tuberculosis were carried out for the purpose of finding some metabolic anomaly or defect whose rectification would lead to a cure. Hence, we conducted a population-based cohort study of Calcium and phosphorus on tuberculosis patient. Calcium and phosphorus are two of the most important macrominerals required for the body's growth, bones and function. Calcium abnormalities have been reported in studies related to tuberculosis, with some studies reporting hypercalcemia and a few others reporting hypocalcemia as a major biochemical finding. (Lind L, Ljunghall S. (1990)). Found hypercalcemia in 25 % of the pulmonary TB patients in their study. Tuberculosis is an infrequent cause of hypercalcemia (Chan TY (1997). While the association is well recognized, calcium levels are seldom severely elevated and rarely result in symptoms. Through this case, we highlight tuberculosis as a potential cause of severe hypercalcemia, particularly in the elderly, as well as discuss several competing

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diagnoses specific to this susceptible group of patients. Hypercalcemia in TB associated with acute kidney injury (AKI) is more rarely reported, (Roussos A, Lagogianni I (2001)) although a few cases of hypercalcemia in TB patients have been described (Soofi A, Malik A, Khan J (2004)). Elevated serum phosphorus levels are individually associated with increased mortality and morbidity. For example, serum phosphorus levels greater than the 5.5-mg/dl level recommended by practice guidelines are independently associated with a 20% to 40% increase in mortality risk among patients with end-stage renal disease (ESRD) (Bailey DG (1996), National Kidney Foundation (2009), Gutie´ rrez OM (2008), Block GA (1998), Ganesh SK (2001), Kalantar-Zadeh K (2006), Rodriguez-Benot A (2005), Tentori F (2008), Wald R (2008)). Similarly, remodelings in serum phosphorus levels have been variedly reported in tuberculosis. Wells *et al*. (Wells HG, Dewitt LM (1923)) referred to a few early reports of phosphorus retention and reduced excretion and also to a few reports of increased urinary levels of lipid-bound phosphorus in patients with tuberculosis. Calcium and phosphorus in pulmonary tuberculosis patient have not been studied in before and after treatment for the six-month duration. A study was made for planning to prepare a preliminary report about the spectrum of calcium and phosphorus abnormal based on the routine biochemical laboratory investigation. The aim of the present study is to determine the incidence of hypercalcemia, hypocalcemia, hypophosphatemia and hyperphosphatemia in newly diagnosed TB patients before and after six-month duration anti-TB treatment in India.

## MATERIALS AND METHODS

### *Study patients and settings*

The study was conducted in Chennai tuberculosis hospital, general government hospital and Institute of Thoracic Medicine from January 2012 through July 2015 in seven target groups, with logical recruitment. Inclusion in this group required the presence of one or more representative symptoms (fever, weight loss, night sweats, and sputum positive) or risk factor for tuberculosis with chemotherapy treatment. The study group consisted of 120 patients (before treatment-120, after one month treatment-113, after two month treatment-107, after three month treatment-96, after four month treatment-85, after five month treatment-78, after six month treatment-61).

### *Eligibility criteria*

For enrollment, age of 18 years or older, history of TB or family history of TB, symptoms of the respiratory tract and other body parts for TB. The examination such as X-ray chest radiography and Sputum positive TB established Physical shape: No obvious heart, liver, kidney, gastrointestinal tract, nervous system, mental disorder and metabolic abnormalities and other medical histories, smoking and nonsmoking, alcoholism and non-alcoholics for drinking beverages during the study.

Patients who began antituberculous treatment in the first day after recruitment as a result of a positive test, then studied were calcium and phosphorus analyzed.

### *Sample collection and laboratory methods*

Patients with newly diagnosed smear-positive pulmonary tuberculosis who had contributed written informed consent were randomly selected to receive either a test or control regimen. The test Fixed-dose combinations (FDC) regimen consisted of a first intensive phase of 8 weeks of daily rifampicin, isoniazid, pyrazinamide, and ethambutol in FDC tablets followed by 18 weeks of rifampicin and isoniazid FDC tablets 3 times weekly, Patients were expected to attend the treatment facility daily during the first intensive phase (first 8 weeks) of chemotherapy and then 3 times weekly during the continuation phase. These patient Blood samples were collected from seven groups and those collected from pulmonary tuberculosis patients at sputum positive samples (Ziehl–Neelsen staining). Blood samples were collected from the subjects of tuberculosis Hospital at Chennai for before treatment and after treatment differences, fasting blood samples were collected from 8 AM - 9 AM. Experiments were carried out as soon as possible. Whenever there was the delay in experiments, samples were stored at - 10 to —15°C for at most of 1 day. Blood samples thus collected using standard sampling techniques were centrifuged to get the serum that was analyzed for calcium by photometric test using Arsenazo III endpoint (Endres DB, Rude RK (2001) and phosphorus levels by phosphomolybdate method (Endres DB, Rude RK (2001). The study protocol was approved by the Institutional Ethics Committee and was carried out in accordance with the principle of the declaration of Helsinki. The investigator who performed the calcium and phosphorus were blinded to the group status of all participants. Analyzes were done by using SPSS version 20.

## RESULTS

Enrollment started in June 2012 and was completed in March 2015, after inclusion of 120 patients. Results were expressed as Mean ± S. D for each measure. 120 newly diagnosed pulmonary TB patients were included during in the study. One twenty had positive sputum smears without negative smears. Treatment of pulmonary TB included a combination of 2 of the following: The test Fixed-dose combinations (FDC) regimen consisted of a first intensive phase of 8 weeks of daily rifampicin, isoniazid, pyrazinamide, and ethambutol in FDC tablets followed by 18 weeks of rifampicin and isoniazid FDC tablets 3 times weekly; Patients were required to attend the treatment facility daily during the first intensive phase (first 8 weeks) of chemotherapy and then 3 times weekly during the continuation phase. Study enrollment, Proportion of providers who Valid and Missing examinations for standardized tuberculosis patients (n=120 interactions). Resistance results were missing for before treatment in 0 patients,

**Table 1** Clinical outcomes of tuberculosis treatment.

| Phosphorus and Calcium | Before Treatment | One Month Treatment | Two Month Treatment | Three Month Treatment | Four Month Treatment | Five Month Treatment | Six Month Treatment |
|---|---|---|---|---|---|---|---|
| Valid Patient | 120 | 113 | 107 | 96 | 85 | 78 | 61 |
| Missing Patient | 0 | 7 | 13 | 24 | 35 | 42 | 59 |

One-month treatment in 7, Two-month Treatment in 6, Three-month Treatment in 11, Four month Treatment in 11, Five-month Treatment in 7, and for Six-months in 17 patients and follow-up are shown in the table (1).

Six-month outcome was defined as treatment completion or a relapse-free cure, Death, default, failure and relapse were considered unsuccessful outcomes on phosphorus levels. The analysis of prevalence at the six-month end of the study excluded phosphorus with before treatment and after six-month duration treatment results. In the study, mean serum phosphorus level in newly diagnosed patients was 13 ± 3.30 mg/dL, after one month treatment patient was 13 ± 3.60mg/dL, two month treatment patients was 11 ± 3.30 mg/dL, three-month treatment patients was 10.50 ± 3.30 mg/dL, four-month treatment patients was 11 ± 3.30 mg/dL, five month treatment patients was 11.20 ± 2.80 mg/dL and six month treatment patients was 10.20 ± 2.80 mg/dL on completion of therapy. Of the 120 patients, 46 were Normal phosphorus, 17 were hyperphosphatemia and 74 were hypophosphatemia. Patients with an adverse outcome contributed observation phosphorus to the midpoint of a 30-day interval. Phosphorus TB incidence of the patients for before treatment and to be after six-month end of treatment was found on the low levels 1.08 to 1.25 mg/dL, medium levels 2.0 to 4.0 mg/dL and then high levels 7.5 to 12.84 mg/dL and follow-up are shown in the table (2).

**Table 2** Per-protocol analysis at 0 to 6 months for phosphorus.

| Duration of treatment | N | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|---|
| Before Treatment | 120 | 1.08 | 7.50 | 2.6368 | 1.63815 |
| One Month Treatment | 113 | 1.08 | 10.00 | 4.2953 | 2.47145 |
| Two Month Treatment | 107 | 1.00 | 10.00 | 3.8517 | 2.74040 |
| Three Month Treatment | 96 | 1.25 | 12.84 | 4.2397 | 2.32131 |
| Four Month Treatment | 85 | 1.25 | 10.00 | 4.5795 | 2.51232 |
| Five Month Treatment | 78 | 1.00 | 12.84 | 5.1726 | 2.48114 |
| Six Month Treatment | 61 | 1.25 | 12.84 | 4.1538 | 2.33581 |

The analysis of prevalence at the six-month end of the study excluded phosphorus with before treatment and after six-month duration treatment results. There were significant between-group differences. In the study, mean serum phosphorus level in newly diagnosed patients was 1.08 ± 7.50 mg/ dL, after one-month treatment patient was 1.08 ± 10.0mg/dL, two month treatment patients was 1.25 ± 10.0 mg/dL, three month treatment patients was 1.25 ± 12.84 mg/dL, four-month treatment patients was 1.25 ± 10.00 mg/dL, five month treatment patients was 1.25 ± 12.84 mg/dL and six month treatment patients was 1.25 ± 12.84 mg/dL on completion of therapy. The statistically significant difference in the serum phosphorus and serum calcium concentration was found among culture-positive patients. The mean serum phosphorus concentration in the before treatment patients was 1.08 ±7.50 mg/dL (range 1.08 to 12.84 mg/dL), which was significantly higher than in the after treatment TB patients (Table 2). The mean serum calcium concentration in the before treatment patients was 3.30 ±13.0 mg/dL (range 2.0 to 12.12 mg/dL), which was significantly lower than in the after treatment TB patients. Patients with an adverse outcome contributed observation phosphorus to the midpoint of a 30-day interval. Calcium TB incidence of the patients for before treatment and after the six-month end of treatment was found on the low levels 2.0 to 4.0 mg/dL, medium levels 11.0 to 13.0 mg/dL and high levels 7.5 to 12.84 mg/dL (Table 3).

**Table 3** Per-protocol analysis at 0 to 6 months for Calcium.

| Duration of treatment | N | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|---|
| Before Treatment | 120 | 3.30 | 13.00 | 8.3111 | 1.75797 |
| One Month Treatment | 113 | 3.60 | 13.00 | 7.8019 | 1.67036 |
| Two Month Treatment | 107 | 2.00 | 12.12 | 7.4362 | 1.83691 |
| Three Month Treatment | 96 | 3.30 | 12.12 | 7.5995 | 1.94476 |
| Four Month Treatment | 85 | 2.00 | 11.00 | 7.5638 | 1.86554 |
| Five Month Treatment | 78 | 2.80 | 12.12 | 7.3958 | 2.13849 |
| Six Month Treatment | 61 | 4.00 | 12.12 | 7.8736 | 2.00095 |

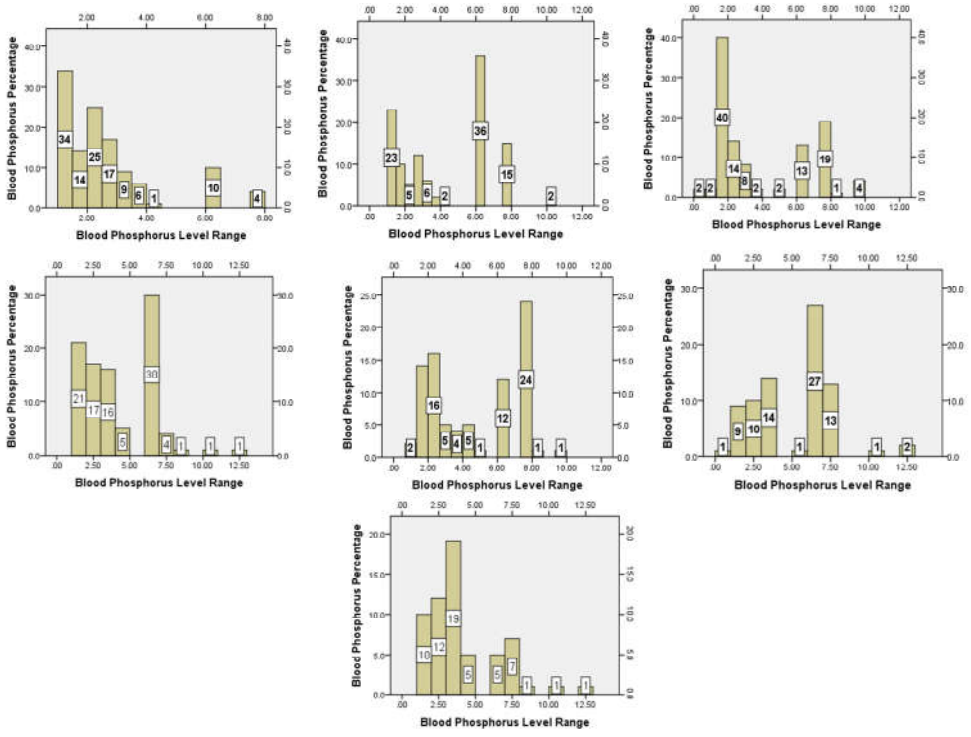


**Fig. 1** Incremental benefit of Phosphorus analysis as compared with before and after treatment.

There were significant differences between the study groups. Before Treatment and after treatment group were reported by the investigator. Tuberculosis treatment included both before and after treatment. The frequency of select before and after treatment for each of the keyword groups presented in the figure, with the following variations of the blood normal phosphorus levels. Before treatment: 0 to 2 level bars are hypophosphatemia (48 patients), 2 to 4 level bars are normal values (57 patients), and 4 to 8 level bars are hyperphosphatemia (15 patients). One month Treatment: 0 to 2 level bars are hypophosphatemia (23 patients), 2 to 4 level bars are normal values (11 patients), and 4 to 12 level bars are hyperphosphatemia (55 patients). Two months Treatment: 0 to 2 level bars are hypophosphatemia (4 patients), 2 to 4 level bars are normal values (64 patients), and 4 to 12 level bars are hyperphosphatemia (39 patients). Three-month Treatment: 0 to 2 level bars are nil hypophosphatemia (0 patients), 2 to 4 level bars are normal values (54 patients), and 4 to 12.5 level bars are hyperphosphatemia (55 patients). Four months Treatment: 0 to 2 level bars are hypophosphatemia (2 patients), 2 to 4 level bars are normal values (27 patients), and 4 to 12 level bars are hyperphosphatemia (44 patients). Five-month Treatment: 0 to 2 level bars are hypophosphatemia (1 patients), 2 to 4 level bars are normal values (33 patients), and 4 to 12.5 level bars are hyperphosphatemia (44 patients). Six-month Treatment: 0 to 2 level bars are Nil hypophosphatemia (0 patients), 2 to 4 level bars are normal values (41 patients), and 4 to 12.5 level bars are hyperphosphatemia (20 patients).

The frequency of select before and after treatment for each of the keyword groups presented in the figure, with the following variations of the blood normal calcium levels. Before Treatment: 2.5 to 8.5 level bars are hypocalcemia (71 patients), 9 to 10.5 level bars are normal values (34 patients), and 11to 12.5 level bars are hypercalcemia (15 patients). One month Treatment: 2.50 to 8.50 level bars are hypocalcemia (80 patients), 9 to 10.5 level bars are normal values (30 patients), and 11 to 12.5 level bars are hypercalcemia (3 patients).

Two months Treatment: 2.5 to 8.5 level bars are hypocalcemia (76 patients), 9 to 10.5 level bars are normal values (26 patients), and 11 to 12.5 level bars are hypercalcemia (5 patients). Three-month Treatment: 2.5 to 8.5 level bars are hypocalcemia (53 patients), 9 to 10.5 level bars are normal values (35 patients), and 11 to 12.5 level bars are hypercalcemia (6 patients). Four months Treatment: 2.5 to 8.5 level bars are hypocalcemia (41 patients), 9 to 10.5 level bars are normal values (43 patients), and 11 to 12.5 level bars are hypercalcemia (1 patients). Five-month Treatment: 2.5 to 8.5 level bars are hypocalcemia (45 patients), 9 to 10.5 level bars are normal values (31 patients), and 11 to 12.5 level bars are hypercalcemia (3 patients).Six months Treatment: 2.5 to 8.5 level bars are hypocalcemia (26 patients), 9 to 10.5 level bars are normal values (31 patients), and 11 to 12.5 level bars are hypercalcemia (4 patients).

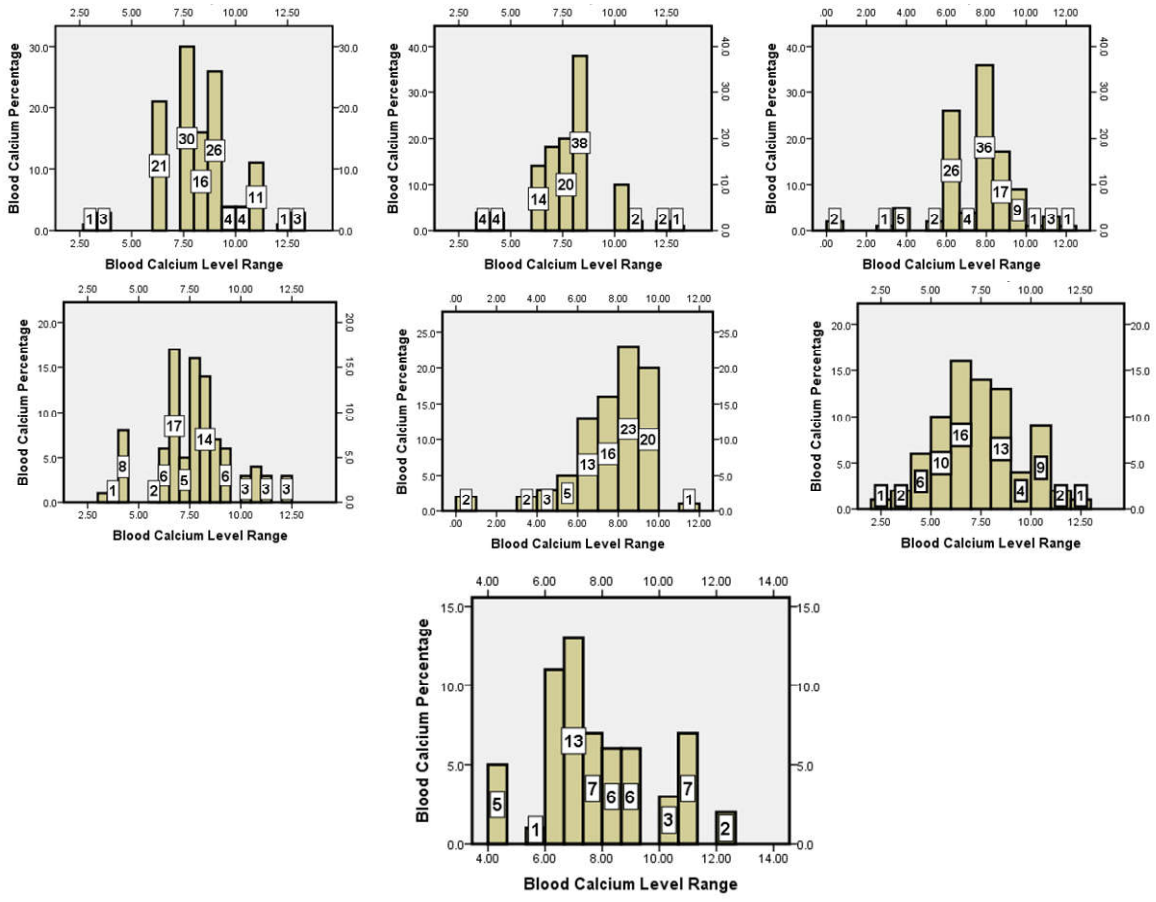


**Fig. 2** Incremental benefit of Calcium analysis as compared with before and after treatment.

## DISCUSSION

In the present study, out of 120 newly diagnosed tuberculosis patients, 20 were found to have a low-level of serum calcium (i.e. hypocalcemia) and rest were normocalcemic. We found that the serum calcium levels were much low and normal (P<0.001) in newly diagnosed TB patients as compared to the treatment group. There was a significant decrease (P<0.05) in the mean calcium level after six months of anti-tubercular treatment. it were also reported that out of 67 patients with pulmonary tuberculosis 25% were hypercalcemic before the initiation of therapy and then tuberculosis is an infrequent cause of hypercalcaemia ((Lind L, Ljunghall S. (1990), Block GA, Klassen PS (2004)). We found pulmonary tuberculosis 17% were hypercalcaemia. Tuberculosis causing hypercalcemia is an uncommon but well-recognized occurrence, particularly in the Asian subcontinent where consequent vitamin D deficiency makes the occurrence even less likely (Abal AT (2005), Howe WR (2007); Bouillon (2007). The incidence of hypercalcemia in cases of TB varies widely among countries, probably due to differences in vitamin D and calcium intake, the amount of sun exposure, the extent of disease and the criteria for hypercalcemia. But we found tuberculosis patient were in the microbes or drug resistance because of daily anti-tuberculosis antibiotic domination composed of rifampicin 450 mg, isoniazid 200 mg, ethambutol 800 mg, moxifloxacin 400 mg and other drugs(Holick MF (2007). In patients with active TB, hypercalcaemia appears to occur more often after usually recommended supplementation of vitamin D (Payne and Menson (2011). Vitamin D deficiency (VDD) is common in patients with active TB and supplementary vitamin D in usual daily doses or high dose is often started along with fixed-dose combination (Lavender TW (2012)). Our findings show that vitamin D supplementation did not reduce time taken for sputum culture conversion. Some researcher reported an unusual case of hypertension, diabetes mellitus, nephrolithiasis status-post left nephrectomy, presenting with 1 month of fever, generalised weakness and weight loss Laboratory data were significant for anaemia, hypercalcaemia and acute kidney injury, so that here fever, weakness and weight loss patient data were significant for hypercalcaemia. Several factors may be involved in the development of hypocalcemia in cancer hypoalbuminemia, hypoparathyroidism, hypomagnesemia, vitamin D deficiency, renal failure, massive cell lysis, drug effect, sepsis and osteoblastic metastases (So and Bolger (2014). Although hypocalcemia we were found for tuberculosis patients. They also found that after one year of successful treatment the serum calcium values had normalized. It could be explained by the influence of many factors like ethnic differences, malabsorption, and malnutrition associated with patients of pulmonary tuberculosis. The serum phosphorous level was much low and normal (P<0.001) in newly diagnosed TB patients as compared to the after six-month treatment. There was a significant increase (P<0.05) in the mean phosphorous level after six months of anti-tubercular treatment. The mean phosphorous level in patients after the completion of anti-tubercular therapy (six months) was statistically significant (P<0.001) as compared to newly diagnosed patients. A significant small increase (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 six months of therapy.. This finding could be due to the distribution of the intracellular phosphate which is liberated due to the destruction of the cells.

## CONCLUSIONS

In the present study, mean serum calcium level was much decreased and increased in newly diagnosed patients as compared to after treatment group which became normal after completion of therapy. However, mean serum phosphorous level was much decreased and increased in newly diagnosed patients as compared to the 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 for TB treatment. In patients with active TB, hypercalcaemia appears to occur more often after usually recommended supplementation of vitamin D. Our findings show that vitamin D supplementation did not reduce time taken for sputum culture conversion. Our findings suggest the possibility that early intervention will help achieve calcium and phosphorus conversion and ultimately a successful treatment outcome.

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**Conflict of interest statement**

We declare that we have no conflict of interest.

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