

## Pharmacokinetics interaction of calcium on the treatment of sputum positive pulmonary tuberculosis patients

R. Saravana Kumar<sup>1</sup>, R. Arbind Kumar Choudhary<sup>2,\*</sup>, N. Arivazhagan<sup>3</sup>, R. Abirami<sup>4</sup>

<sup>1</sup>Professor & HOD of Pulmonology, <sup>2</sup>Assistant Professor, <sup>3</sup>Associate Professor, <sup>4</sup>Staff Nurse, Dept. of Pharmacology, <sup>1,2</sup>IRT-Perundurai Medical College Hospital, Sanatorium Perundurai, Tamil Nadu, <sup>3</sup>Sri Sathya Sai Medical College and Research Institute, Nellikuppam, Tamil Nadu, <sup>4</sup>PHC Ramnad, Government of Tamil Nadu, India

**\*Corresponding Author:**

Email: arbindkch@gmail.com

### Abstract

**Introduction:** Tuberculosis (TB) in children is a neglected aspect of the TB epidemic despite it constituting 20% or more of all TB cases in many countries with high TB incidence. Tuberculosis constitutes a serious global health problem with nearly 10 million new cases of tuberculosis (2011) and 1.4 million deaths every year. There were no studies done about the interaction of levels of calcium in patients suffering from pulmonary tuberculosis before and after treatment for six-month duration.

**Materials and Methods:** The study was conducted in Chennai tuberculosis hospital from January 2012 through July 2015 in seven target groups, with consecutive recruitment. Patients with newly diagnosed smear-positive pulmonary tuberculosis who had provided written information consent were randomly assigned to receive either a test or control regimen. Blood samples thus collected using standard sampling techniques were centrifuged to get the serum that was analysed for calcium by photometric test using Arsenazo III endpoint method.

**Results and Discussion:** Results were expressed as Mean  $\pm$  S.D for each measure. There were significant differences between treatment months Six months Treatment: 2.5 to 8.5 level bars are hypocalcaemia (26 patients), 9 to 10.5 level bars are normal values (31 patients), and 11 to 12.5 level bars are hypocalcaemia (4 patients). The statistically significant difference in the serum calcium concentration was found among culture-positive patients.

**Conclusion:** Studies can be carried out on the prospects of use early markers of hypocalcaemia and hypercalcemia, as for before and after TB treatment. Our findings offer the possibility that early intervention will help achieve calcium conversion and ultimately a successful treatment outcome

**Keyword:** Photometric Test, Serum Calcium, Smear-Positive Pulmonary TB.

### Introduction

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*, which is transmitted through aerosolized droplets. Tuberculosis constitutes a serious global health issue with nearly 10 million new cases of tuberculosis (2011) and 1.4 million deaths every year.<sup>1, 2</sup> TB infection can either be acute and short-lived or chronic and long term. The identification and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis pose a serious threat to the worldwide.<sup>3, 5</sup> Several studies have been proven the bioavailability, acceptability, or microbiological efficacy of rifampicin and isoniazid with or without Pyrazinamide administered in a fixed combination for daily or intermittent use. 2-5 these studies have shown that 2- and 3-drug FDCs are generally well tolerated, with proportions of adverse effects similar to those for separate formulations and no difference in acquiring drug resistance. Efforts in the past decade to control tuberculosis by the consistent application of existing strategies have met with only limited success, slowing the rate of increase but failing to make substantial progress toward the goal of tuberculosis eradication. Shortened therapy and most importantly biomarker discovery regimens will be needed to realize the goal of global tuberculosis elimination or control.<sup>6,7</sup> Before the advent of effective chemotherapy, some studies on the biomolecular of tuberculosis were carried out in the

hope of finding some metabolic anomaly or defect whose rectification would lead to a cure.<sup>8,9</sup>

Calcium most important macro minerals required for the body's growth of bones and its function.<sup>10</sup> Calcium abnormality has been variably reported in studies carried out on the infected patient. Calcium is required for vascular contraction and vasodilation, muscle function, nerve transmission, intracellular signalling and hormonal secretion.<sup>11, 14</sup> However, less than 1% of total body calcium pool is needed to support these critical metabolic functions. The most widely known granulomatous diseases causing hypercalcemia are tuberculosis, sarcoidosis, and systemic fungal infections.<sup>15, 16</sup> Hypercalcemia in these condition is mostly attributed to increase in serum calcitriol levels, due to higher 1 $\alpha$ -hydroxylase activity in activated macrophages.<sup>17, 18</sup> Although, in most of the patients, hypercalcemia has been associated with PTHrP.

In pharmacokinetic studies, co-administration of various inhibitors of this enzyme (eg, erythromycin, antifungal substances, protease inhibitors, and grapefruit juice) raised plasma calcium channel blocker concentrations by up to 500%. Earlier, there were no studies done about the interaction of levels of calcium in patients suffering from pulmonary tuberculosis before and after treatment for six-month duration.<sup>19, 22</sup>

This study here is to prepare a preliminary report about abnormal spectrum of calcium presentation on the routine biochemical laboratory investigation.

## Materials and Methods

### Study Patients and Setting

The study was conducted in Chennai tuberculosis hospital from January 2012 through July 2015 in seven target groups, with consecutive recruitment. The first group consisted of otherwise deselected patients who are presented with suspected tuberculosis to the tuberculosis hospital in Chennai. The second to seventh group consisted of patients who are presented with suspected tuberculosis to the tuberculosis hospital and who were at high risk for tuberculosis with chemotherapy. Inclusion in this group required the presence of one or more constitutional symptoms (fever, weight loss, night sweats, and sputum positive), or patients with risk factor for tuberculosis with chemotherapy treatment

### Sample Collection and Laboratory Methods

Patients with newly diagnosed smear-positive pulmonary tuberculosis who had provided written information consent were randomly assigned to receive either a test or control regimen. The test Fixed-dose combinations (FDC) regimen consisted of a first intensive chemotherapy phase of 8 weeks of continue daily rifampicin, isoniazid, pyrazinamide, and ethambutol in 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 after 3 times week during the continuation phase. Every treatment dose was taken under supervision of a member of the medical staff (i.e., as directly observed therapy). The blood samples of these suspected patients were collected from seven groups and those collected from sputum positive

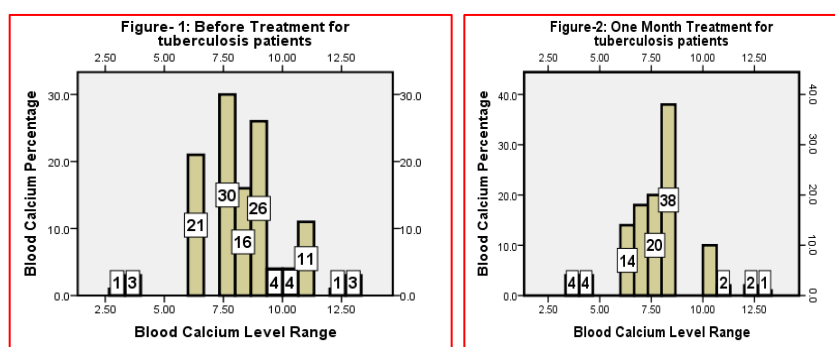
pulmonary tuberculosis patients were stained for mycobacterium visualization (Ziehl–Neelsen staining). Blood samples were collected from the subjects of tuberculosis Hospital at Chennai. To non-treatment and treatment variations, fasting blood samples were collected from 8 AM - 9 AM. Experiments were carried out as soon as possible. Whenever there is a delay in experiments, samples were stored at  $-10^{\circ}$  to  $-15^{\circ}\text{C}$  for a maximum of 1 day. Blood samples were collected using standard sampling techniques were centrifuged to get the serum that was analysed for calcium by photometric test using Arsenazo III endpoint.<sup>32</sup> The research proposal was approved by the Institutional ethics committee and was carried out in accordance with the principle of the declaration of Helsinki.

**Inclusion Criteria:** In order to enrolled the patient were an age of 18 years or older, history of TB or family history of TB, symptoms of respiratory tract and other body parts for TB The examination such as X-ray chest radiograph and Sputum positive TB confirmed, Physical condition: No obvious heart, liver, kidney, gastrointestinal tract, nervous system, mental disorder and metabolic abnormalities and other medical history, Smoking and non-smoking, alcoholic and non-alcoholic for drinking beverages during the study, Negative HIV infection and no previous receipt of chemotherapy treatment patients.

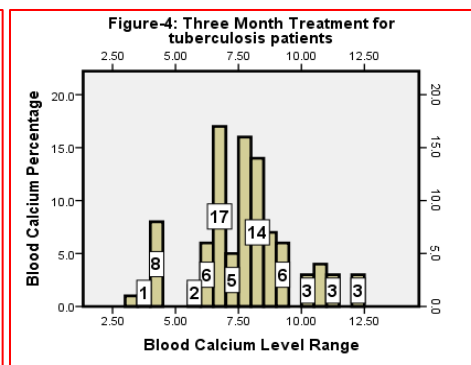
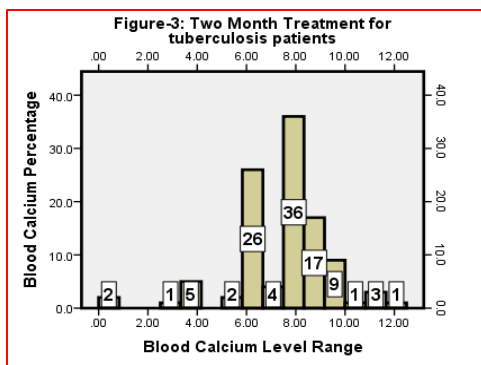
## Results and Discussion

Enrolment started in June 2012 and was completed in December 2015, after inclusion of 162 patients. Results were expressed as Mean  $\pm$  S.D for each measure. There was significant differences between treatment months.

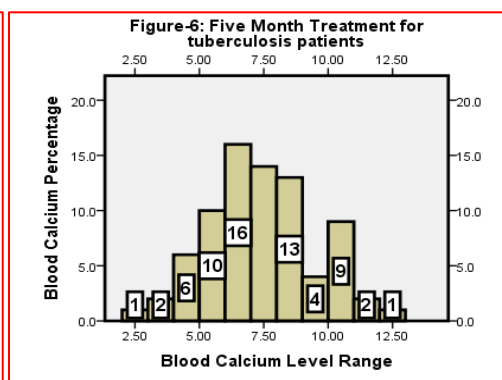
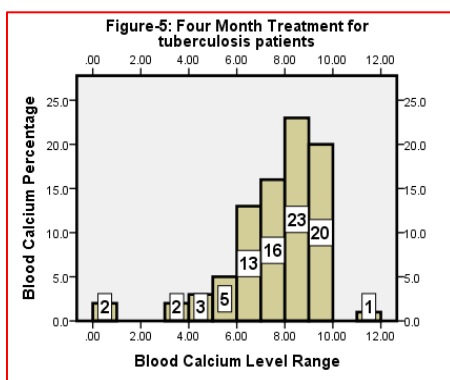
### Calcium level for Tuberculosis



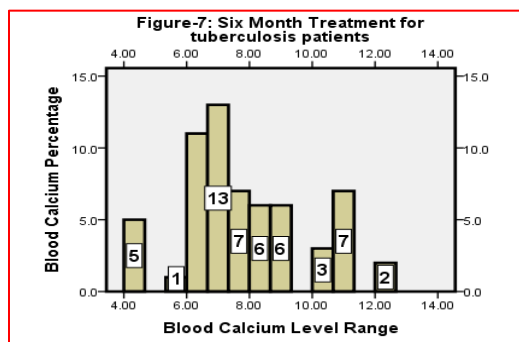
Before Treatment: 2.5 to 8.5 level bars are hypocalcaemia (71 patients), 9 to 10.5 level bars are normal values (34 patients), and 11 to 12.5 level bars are hypercalcaemia (15 patients). One month Treatment: 2.50 to 8.50 level bars are hypocalcaemia (80 patients), 9 to 10.5 level bars are normal values (30 patients), and 11 to 12.5 level bars are hypercalcaemia (3 patients).



Two months Treatment: 2.5 to 8.5 level bars are hypocalcaemia (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 hypocalcaemia (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 hypocalcaemia (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 hypocalcaemia (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 hypocalcaemia (26 patients), 9 to 10.5 level bars are normal values (31 patients), and 11 to 12.5 level bars are hypercalcemia (4 patients).

There was statistically significant difference in the serum calcium concentration was found among culture-positive patients. According to the results of blood test at admission, levels of calcium were significantly low and increase before treatment to 6-month end of the treatment. While these results suggest some known factors associated with increasing calcium levels, we also found increased risk with anaemia, as indicated by

low haemoglobin levels, as well as an association with lower BMI, and some time it will caused by mineral and bone disorders (CKD-MBD) may result in a direct suppressive effect on erythropoiesis, resulting in anaemia, including low vitamin D, calcium and increased serum parathyroid hormone levels.<sup>23, 24</sup>

Our study indicated calcium level in the treatment patients before treatment to four month treatment low level. Hypocalcaemia, defined by serum calcium level less than 8.5 mg/dl<sup>25</sup> could be caused by HIV infection and widely known granulomatous diseases causing hypercalcemia are tuberculosis, sarcoidosis, and systemic fungal infections. But infection was common among the patient of calcium groupn little patient only high. The high serum calcium levels were strongly associated with mortality risk condition. These factors may help to identify the most reliable markers of early hypocalcemia, hypercalcemia, hyperphosphatemia, and hypophosphatemia helping to risk patients for short-stay to treatment or nutrition maintenance.<sup>26, 27</sup>

### Conclusion

In the present study, mean serum calcium level was much increased during therapy for initial four months and slowly started decreasing at fifth month onwards in

newly diagnosed patients as compared to after treatment group which became normal after completion of 6 months therapy.

However, mean serum calcium level was much decreased and increased in newly diagnosed patients as compared to the PTB 7 group which came to normal levels after the anti-tubercular therapy but here end stage 20 patients. Studies can be carried out on the prospects of use early markers of hypocalcemia and hypercalcemia, as for before and after TB treatment. Our findings indicating the possibility of early intervention will help achieve calcium conversion and ultimately a successful treatment outcome. We need to update guidelines and optimize patient care, some gaps in the evidence base need to be addressed.

## References

1. EpcO Hasker, Maksad Khodjikhonov, Shakhnoz Usarova, Umid Asamidinov, Umida Yuldashova, Marieke J van der Werf, Gulnoz Uzakova, and Jaap Veen Default from tuberculosis treatment in Tashkent, Uzbekistan; who are these defaulters and why do they default? ; BMC Infect Dis. 2008;8:97.10.1186/1471-2334-8-97
2. Reid A, Scano F, Getahun H, et al. Towards universal access to HIV prevention, treatment, care and support: the role of tuberculosis and HIV c. Lancet Infect Dis 2006;6:483–95.
3. Treatment of tuberculosis. MMWR Recomm Rep 2003; 52(RR-11):1e77. 2. Jasmer RM, Seaman CB, Gonzalez LC, Kawamura LM, Osmond DH, Daley CL. Tuberculosis treatment outcomes: DOT compare with self-administered therapy. Am J Respir Crit Care Med 2004; 170(5):561e6.
4. WHO. Anti-tuberculosis drug resistance in the world: report no. 4. WHO/HTM/TB/2008.394. Geneva: World Health Organization, 2008.
5. WHO global tuberculosis control report 2010. Summary. Cent Eur J Public Health 2010;18:237.
6. McNerney R, Maeurer M, Abubakar I, et al. Tuberculosis diagnostics and biomarkers: needs, challenges, advances, and opportunities. J Infect Dis. 2012;205:S147–S158.
7. Wallis R, Pai M, Menzies D, et al. Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice. Lancet. 2010;375:1920–1937.
8. Renkema KY, Alexander RT, Bindels RJ, Hoenderop JG. Calcium and phosphate homeostasis: concerted inter-play of new regulators. Ann Med. 2008;40:82–91.
9. Sommer S, Berndt T, Craig T. The phosphatonin and the regulation of phosphate transport and vitamin D metabolism. J Steroid BiochemMol Biol. 2007;103:497–503.
10. Brown GR, Greenwood JK. Drug- and nutrition-induced hypophosphatemia: mechanisms and relevance in the critically ill. Ann Pharmacophore 28:626-632, 1994.
11. Imel EA, Econs M.J Approach to the hypophosphatemic patient. J Clin Endocrinol Metab 97:696-706, 2012.
12. Levine BS, Kleeman CR, Felsenfeld AJ. The journey from vitamin D Resistant rickets to regulation of renal phosphate transport. Clin J Am SocNephrol 2009;4:1866–1877
13. Gonzalez-Parra E, Tunon J, Egido J, Ortiz A. Phosphate: a steal killer than previously thought? Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology. 2012;21:372–81.
14. Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people affected with CKD. J Am Soc Nephrol. 2005;16:520–8.
15. Dhingra R, Sullivan LM, Fox CS, et al. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. Arch Intern Med. 2007;167:879–85.
16. Palmer SC, Hayen A, Macaskill P, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease among individuals with chronic kidney disease: a systematic review and meta-analysis. JAMA : the journal of the American Medical Association. 2011;305:1119–27.
17. Grandi NC, Brenner H, Hahmann H, et al. Calcium, phosphate and the risk of cardiovascular events and all-cause mortality among population with stable coronary heart disease. Heart. 2012;98:926–33.
18. Evans KN, Taylor H, Zehnder D, Kilby MD, Bulmer JN, Shah F, Adams JS, Hewison M. Increased expression of 25-hydroxyvitamin D-1alpha-hydroxylase in dysgerminomas: a novel method of humoral hypercalcemia of malignancy. Am J Pathol. 2004 Sep;165(3):807-13.
19. Bemnet A, Solomon M, Tomoki Y, Beyene M, Afework K: A Hypercalcemia in Patients with Tuberculosis and HIV Infections in Northwest Ethiopia. Asian Pac J Trop Dis 2012, 1–6.
20. Jacobs TP, Bilezikian JP. Clinical review: rare causes of hypercalcemia. J Clin Endocrinol Metab. 2005;90(11):6316-22.
21. Shrayyef MZ, DePapp Z, Cave WT, Wittlin SD. Hypercalcemia in patients with sarcoidosis and Mycobacterium avium intra-cellulare not mediated by elevated vitamin D metabolites. Am J Med Sci. 2011;342(4):336-40
22. Fierer J, Burton DW, Haghighi P, Deftos LJ. Hypercalcemia in disseminated coccidioidomycosis: parathyroid hormone-related peptide is characteristic of granulomatous inflammation. Clin Infect Dis. 2012;55(7):e61-63.
23. Krikorian A, Shah S, Wasman J. Parathyroid hormone-related protein: an unusual mechanism for hypercalcemia in sarcoidosis. Endocr Pract. 2011;17(4):e84.
24. Eleonora Riccio, Massimo Sabbatini, Dario Bruzzese, Ivana Capuano, Silvia Migliaccio, Michele Andreucci, Antonio Pisani Effect of Paricalcitol vs Calcitriol on Hemoglobin Levels Chronic Kidney Disease Patients: A Randomized Trial PLoS One. 2015;10(3):e0118174.
25. Emejulu AA, Onwuliri VA, Ojiako OA: Electrolyte Abnormalities and Renal Impairment in Asymptomatic HIV-infected Patients in Owerri, South Eastern Nigeria. Aust J Basic ApplSci 2011,5(3):257–260. ISSN 1991–8178.
25. GlesbyMJ, Aberg JA, KendallMA, et al; Adult AIDS Clinical Trials Group, Pharmacokinetic interactions between indinavir plus ritonavir and calcium-channel blockers. Clin Pharmacol Ther. 2005;78(2):143-153.
26. Mondy K, Yarasheski K, Powderly WG, Whyte M, Claxton S, DeMarco D, Hoffmann M, Tebas P. Longitudinal evolution of bone mineral density and bone markers in human immunodeficiency virus infected patient. Clin Infect Dis. 2003;36(4):482–490. doi: 10.1086/367569. PubMed:12567307.