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Vitamin D Status in Patients with Pulmonary Tuberculosis: A Teaching Hospital Based Study.

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ABSTRACT

Background: To evaluate the Vitamin D status in patients with pulmonary tuberculosis and normal healthy adults. **Methods:** Total of 48 subjects 24 (14 male and 10 female) newly diagnosed pulmonary tuberculosis and 24 (16 male and 8 female) healthy controls) was selected through non-probability purposive sampling according to inclusion and exclusion criteria. **Result:** Significant differences were observed for the obesity and smoking p-value 0.032 and 0.021 respectively. Chest x ray revealed cavitary in 9 (37.5%) of cases. Hemoglobin, RBC counts and Platelet counts revealed statistically significant difference between cases and controls. **Conclusion:** Patients with tuberculosis are significantly Vitamin D deficient as compared to normal individuals.

Keywords: Vitamin-D Status and Pulmonary tuberculosis.

INTRODUCTION

Tuberculosis (TB) is a global pandemic that mainly affects the low- and middle- income countries. India, followed by Indonesia, China, Nigeria, Pakistan and South Africa account for 60% of the total TB statistics in the world. Despite advances in diagnostic technology and invention of new antituberculous drugs, TB continues to remain a major public health concern. In May 2014, the World Health Assembly at Geneva endorsed "The End TB Strategy" with an aim to end the global TB epidemic by 2035 with targets to reduce TB deaths by 95% and cut down the new cases by 90% and ensure that no family is burdened with catastrophic expenses due to TB. India contributes to one-quarter of the global TB burden. WHO statistics for 2015 gives an estimated incidence and prevalence of 2.2 and 2.5 million respectively for TB in India.[1] TB along with HIV remains as one of the leading causes of morbidity and mortality among general population.

Macrophages phagocytize the bacilli, but the normal destruction of bacilli by macrophages can be interrupted by the defense mechanisms of the mycobacteria. One of the potential pathways through which the mycobacteria prevent their own destruction involves glycosylated phosphatidylinositol lipoarabinomannan, a compound of the mycobacterial cell membrane. Lipoarabinomannan is translocated to the phagosome wall, interrupting the normal maturation of the phagosome and its further fusion with the lysosome.[2,3] Another potential mycobacterial defense mechanism involves inhibition of Ca+2 signaling events, which are also required for phagosome maturation.[4] Thus protected from host defenses, the

viable mycobacteria reproduce inside the macrophages and can also migrate to other tissues. However, a localized inflammatory response promotes the recruitment of T lymphocytes, which leads to the formation of a granuloma to wall off the spread of the infection. The TB infection is usually contained inside the granuloma, and the infection may remain dormant, or latent, for many years. However, immunodeficiency secondary to an event such as coinfection with human immunodeficiency virus (HIV) or malnutrition, can lead to activation of the disease.[5,6] Vitamin D is believed to have an important role in macrophage activation and the subsequent restriction of MTB growth.[7,8] Low levels of Vitamin D is a common finding world over, specially prevalent in developing countries and varies depending on the food fortification policies, demographic features, geographic location and season. Vitamin D deficiency has been implicated as a risk factor for tuberculosis.[9] The role of Vitamin D in preventing several malignancies is increasingly

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being recognized. Recent evidences link vitamin D deficiency to diseases like Diabetes, Hypertension, infections, autoimmune disorders and cancer.[10,11] Vitamin D modifies gene expression in the tissues where it acts by binding to specific receptors vitamin D binding receptors and has several known actions and several more hitherto unknown to us.[12-14] Only few studies on the role of vitamin D in tuberculosis have been done in Asian populations. There is paucity of literature addressing this issue in Indian population as well. Aim of this present study was to evaluate the Vitamin D status in patients with pulmonary tuberculosis.

MATERIALS AND METHODS

This Present study was conducted in the Department of TB and Chest, World College of Medical Sciences Research and Hospital, Jhajjar, during the period from December 2016 to November 2018. A total of 48 subjects 24 (14 male and 10 female) newly diagnosed pulmonary tuberculosis and 24 (16 male and 8 female) healthy controls) was selected through non-probability purposive sampling according to inclusion and exclusion criteria. Informed consent was taken from all the study subjects. Newly diagnosed TB cases were included in the study with age and sex matched apparently healthy controls. Subjects who fulfilled the following criteria: i) clinical history suggestive of tuberculosis, ii) Sputa +ve for acid fast bacilli, iii) Roentgenography findings consistent with the pulmonary tuberculosis like cavity formation in lung apices. Informed written consent was taken from the participants. Patients with past and present history of anti tuberculous drugs who have discontinued the drugs because of unknown reason, chronic cases of pulmonary tuberculosis, drug defaulter, and extra pulmonary tuberculosis were excluded from the study. General physical and chest examination was performed for the presence of cavitations, consolidation, fibrosis, pneumothorax and pleural effusion.

Biochemical Analysis

An overnight fast 5 ml of venous blood samples were collected for 25 (OH) D3 levels. We collected 5 ml of venous blood in plastic serum tubes. Samples were placed in ice boxes and sent immediately to laboratory. Serum was separated by centrifugation and 25 (OH) D3 levels measured using chemiluminescence assay using Roche diagnosis Elesys. All the results were duly verified by pathologist. For the purpose of study, a patient with vitamin D level less than 25 ng/ml was considered to be Vitamin D deficient.

Statistical Analysis

All values were expressed as mean ± S.D. Data was analyzed on SPSS version 18 Continuous and categorical variables were analyzed by student's ttest and chi square test respectively. The significant p-value was taken at ≤ 0.05.

RESULTS & DISCUSSION

The clinical and demographic characteristics of study population are shown in [Table1]. There were 24 patients (14 male and 10 female) with tuberculosis and 24 patients (16 male and 8 female) as control. Mean age of cases was 38.0±6.2 years while that of controls was 35±4.02 years. The gender distribution, obesity, BMI, smoking habit and chest x ray showing cavitations are shown in [Table1].

Table 1: Clinical and Demographic characteristics of study group.

Variables	Study Group	Control
Age in Years	38.0±6.2	35±4.02*
Male	14(58.3%)	16(66.6%)*
Female	10(41.6%)	8(33.3%)*
Obesity	33.3%	42%
BMI (kg/m2)	26.02±3.01	25.0±2.7*
Smokers	48%	21%
Chest X-ray cavity	9 (37.5%)	-
Hemoglobin (gm/dl)	11±2.4	13±3.2
RBC counts (x109 µl-1)	3.7±1.2	4.2±2.0
WBC counts (µl-1)	7390±170.1	7077±155.2
Platelets (x109 µl-1)	3.5±2.0	3.9±2.7
ESR	49±19.3	6.2±3.0
Alkaline phosphatase(iu)	106.3±14.2	94.7±10.2
Vitamin D3 (ng/ml) Mean ± SD)	22.2 ± 10.2	30.47 ± 12.56
Vitamin D3 deficiency [n(%)]	15 (62.5%)	8 (33.3%)

(Statistically Significant at p value <0.05) *NS: Statistically not Significant)

Significant differences were observed for the obesity and smoking p-value 0.032 and 0.021 respectively. Chest x ray revealed cavitary in 9 (37.5%) of cases. Hemoglobin, RBC counts and Platelet counts revealed statistically significant difference between cases and controls. Low normal hemoglobin values were observed in most of study subjects in general and pulmonary tuberculosis patients in particular. Serum alkaline phosphatase showed significant differences as shown in [Table1]. [Table2] shows the clinical characteristics of patients with pulmonary tuberculosis, 15 patients were found to have Vitamin D deficient and 9 patients had normal levels.

Table 2: Clinical characteristics of patients with pulmonary tuberculosis.

Variables	Vitamin D Levels	
	Deficient < 25 ng/ml	Normal > 25 ng/ml
Number of patients	15 (57%)	9 (43%)
BMI(kg/m2)	20.01±6.52	22.6 ± 4.3
Vitamin D3(ng/ml)	17.21 ± 4.2	27.3 ± 5.12

(Statistically Significant at p value <0.05) *NS: Statistically not Significant

Even before the discovery of the etiologic cause of tuberculosis by Robert Koch in 1903, vitamin D from cod liver oil,[15] and from exposure to sun or

radiation was used to treat tuberculosis. Several recent studies in different populations have associated a deficiency in vitamin D with increased risk of tuberculosis.[16–21] Vitamin D plays an important role in macrophage activation and restriction of mycobacterial growth. Several biological studies to detect effects of Vit D on immune system of the body show that Vit D has a definitive role in suppression of proliferation of Mycobacterium TB and generalized inflammatory response produced secondary to it.[22,23] Similarly, on triggering of toll-like receptors by molecules of the tubercle bacillus, the production of microbe-killing cathelicidin is impaired in the absence of adequate serum Vitamin D.[24] However, the in-vivo association between Vitamin D status and tuberculosis is still a debatable issue. In this study, we found that Vitamin D insufficiency, as assessed by 25 (OHD) level, was high in patients with TB, both in men and women. As antituberculosis chemotherapy can lower serum Vitamin D levels, so only those of tuberculosis patients were included who were yet to commence treatment. The possible association between Vitamin D and tuberculosis was first reported more than 20 years ago,[25] but subsequent studies have yielded conflicting findings. A number of studies in Gujarati Indian,[26] African residents in London,[27] African immigrants living in Australia,[28] and people of West Africa,[29] all have shown that tuberculosis had lower levels of 25 (OH) D and higher prevalence of Vitamin D deficiency than non-TB individuals. Among African immigrants in Australia, for example, individuals with latent or active tuberculosis were observed to have substantially lower serum Vitamin D levels than those without tuberculosis. Although there is good evidence to suggest that a fall in serum Vitamin D levels compromises cell mediated immunity and leads to the activation of latent tuberculosis,[30] it is also possible that low serum Vitamin D levels result from tuberculosis itself. Smoking is a risk factor for tuberculosis disease. Although Vitamin D is important for calcium absorption (which is impaired by smoking), there is no evidence to suggest that Vitamin D absorption is impaired directly by smoking. This study also showed no significant relationship between BMI and change in Vit D level. As most of the patients with TB have low BMI, which is further associated with Vit D deficiency, thus low BMI is important confounder for association of the low Vitamin D tuberculosis. Low Vit D level in TB patients needs to be further evaluated as the prevalence of diabetes mellitus (DM) is increasing globally and people with DM are 4-5 times more likely than those without DM to have clinically significant chronic kidney disease (CKD).[31] In addition, patients with CKD or those who are dialysisdependent are more likely to have low levels of Vitamin D in comparison to those without kidney disease.[32] The incidence of tuberculosis is high in CKD patients partly as a result of impaired cell-mediated immunity but if low serum Vitamin D levels also predisposed to tuberculosis, the growing population of people with CKD from underlying causes like DM may need early attention to their body Vitamin D levels to mitigate the risk of active tuberculosis. Moreover, in this study, it was noted that Vit D deficiency was detected in approximately half of normal female population which is quite significant and does raise a healthcare concern that a sizeable majority of the healthy population is deprived of the proven benefits of Vitamin D. Possible reasons for this female preponderance can be predominantly homebound females, poorer nutritional status than their male counterparts, social stigma associated with TB, which discourages women from seeking early medical care, and Vitamin D deficiency due to poor dietary intake as well as inadequate exposure to sunlight because of poor housing and the culture of wearing hooded cloaks (Burqas). However, prevalence of Vit D deficiency was much lower than what was found in another study conducted in Karachi.[8] Similarly, in this study, prevalence of Vit D deficiency in asymptomatic females were much lower than in premenopausal women bone health survey carried out in Karachi in year 2010 by Mansoor et al. where 82.8% women were found Vit D deficient.[33] The smaller size, different cut off limit of Vit D deficiency level, darker skin pigmentation in women of Karachi and betal chewing,[34] habit may explain the disparity between results. The present study postulates that Vit D may be effective as adjuvant therapy in patients with tuberculosis. This observation is supported by the work of Martineau et al. in which a single dose of Vitamin D improved immunity to Mycobacteria in vitro in contacts to patients with TB.[35] In addition, 1,25-dihydroxyvitamin D may enhance the production of LL-37, an antimicrobial peptide of the cathelicidin family.[22,24,36]

Antimicrobial peptides, such as defensins and cathelicidins, are involved as a first line of defense in the prevention of infections, including tuberculosis.[36] Although cathelicidins are widely distributed in mammals, LL-37 is the only member of the cathelicidin family that has been identified in humans, where it is found in alveolar macrophages, lymphocytes, neutrophils, and epithelial cells.[15,36] In addition to having direct bactericidal activity, LL-37 also modulates the immune response by attracting monocytes, T cells, and neutrophils to the site of infection.[15] The presence of 1,25- dihydroxyvitamin D3 in neutrophils and macrophages upregulates in a dose-dependent manner the hCAP-18 gene that codes for LL-37 which suggests that 1,25-dihydroxyvitamin D induction of LL-37 may play a role in host defense against TB infection.[15,22]

CONCLUSION

These findings suggest that, the Patients with tuberculosis are significantly Vitamin D deficient as compared to normal people. In present study, compared to healthy adults, patients of pulmonary tuberculosis were found vitamin D deficient. Vitamin D supplementation is warranted for patients of pulmonary tuberculosis. Literature search shows that vitamin D deficiency is much prevalent in India. Although many studies have evaluated for the association of vitamin D deficiency with tuberculosis, there are no uniform results and hence the correlation remains doubtful. Public health education should encourage people to spend more time in sunlight and emphasise on adequate dietary intake of vitamin D. It should also give importance to address the aetiologies of vitamin D deficiency and implement effective population based strategies such as vitamin D fortified food products.

REFERENCES

1. Global Tuberculosis Control 2015, WHO, Geneva, 2015.
2. Cosma CL, Sherman DR, Ramakrishnan L. The secret lives of the pathogenic mycobacteria. Annu Rev Microbiol. 2003;57: 641–676.
3. Hmama Z, Sendide K, Talal A, Garcia R, Dobos K, Reiner NE. Quantitative analysis of phagolysosome fusion in intact cells: inhibition by mycobacterial lipoarabinomannan and rescue by an 1alpha,25-dihydroxyvitamin D3-phosphoinositide 3-kinase pathway. J Cell Sci. 2004;117:2131–2140.
4. Houben EN, Nguyen L, Pieters J. Interaction of pathogenic mycobacteria with the host immune system. CurrOpinMicrobiol. 2006;9:76–85.
5. Russell DG. Mycobacterium tuberculosis: here today, and here tomorrow. Nat Rev Mol Cell Biol. 2001;2:569–577.
6. Martineau AR, Honecker FU, Wilkinson RJ, Griffiths CJ. Vitamin D in the treatment of pulmonary tuberculosis. J Steroid BiochemMol Biol. 2007;103:793–798.
7. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B. Global Vitamin D status and determinants of hypovitaminosis D. Osteoporosis Int 20; 2009:1807-20.
8. Chandra G, Selvaraj P, Jawahar M, Banurekha V, Narayanan P. Effect of Vitamin D3 on phagocytic potential of macrophages with live Mycobacterium tuberculosis and lymphoproliferative response in pulmonary tuberculosis. J ClinImmunol 2004; 24: 249-57.
9. Chan T. Vitamin D deficiency and susceptibility to tuberculosis. Calcif Tissue Int 2000; 66:476-8.
10. Stechschulte SA, Kirsner RS, Federman DG. Vitamin D: Bone and Beyond, Rationale and Recommendations for Supplementation. Am J Med 2009; 122(9):793-802.
11. Garland CF, Gorham ED, Mohr SB, Garland FC. Vitamin D for Cancer Prevention: Global Perspective" Ann Epidemiol 2009;19(7):468-83.
12. Denis M. Killing of Mycobacterium Tuberculosis within human monocytes, Activation by cytokines and Calcitriol. ClinExpImmunol 1991;84:200-6.
13. Abu-Amer Y, Bar-Shavit Z. Impaired bone marrow derived macrophage differentiation in vitamin D deficiency. Cell Immunol 1993; 151(2):356-68.
14. Kreutz M, Anderson R. Induction of human monocyte to macrophage maturation in vitro by 1, 25- dihydroxyvitamin D3. Blood 1990;76(12):2457-61.
15. Martineau AR, Honecker FU, Wilkinson RJ, Griffiths CJ. Vitamin D in the treatment of pulmonary tuberculosis. J Steroid BiochemMol Biol. 2007;103:793–798.
16. Gibney KB, MacGregor L, Leder K, et al. Vitamin D deficiency is associatedwith tuberculosis and latent tuberculosis infection in immigrants from sub-Saharan Africa. Clin Infect Dis. 2008;46:443–446.
17. Williams B, Williams AJ, Anderson ST. Vitamin D deficiency and insufficiency in children with tuberculosis. Pediatr Infect Dis J. 2008;27:941–942.
18. Wejse C, Olesen R, Rabna P, et al. Serum 25-hydroxyvitamin D in a west African population of tuberculosis patients and unmatched healthy controls. Am J ClinNutr. 2007;86:1376–1383.
19. Ustianowski A, Shaffer R, Collin S, Wilkinson RJ, Davidson RN. Prevalence and associations of vitamin D deficiency in foreign-born persons with tuberculosis in London. J Infect. 2005;50:432–437.
20. Sasidharan PK, Rajeev E, Vijayakumari V. Tuberculosis and vitamin D deficiency. J Assoc Physicians India. 2002;50:554–558.
21. Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. Int J Epidemiol. 2008;37:113–119.
22. Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: Vitamin D mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol 2007; 179:2060-3.
23. Martineau AR, Wilkinson KA, Newton SM, Floto RA, Norman AW, Skolimowska K, et al. IFN-gamma- and TNF-independent Vitamin D-inducible human suppression of mycobacteria: the role of cathelicidin LL-37. J Immunol 2007; 178:7190-98.
24. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. 2 Toll-like receptor triggering of a Vitamin D: mediated human antimicrobial response. Science 2006; 311:1770-3.
25. Davies PD, Brown RC, Woodhead JS. Serum concentrations of vitamin D metabolites in untreated tuberculosis. Thorax 1985; 40:187-90.
26. Wilkinson RJ, Llewelyn M, Toossi Z, Patel P, Pasvol G, Lalvani A, et al. Influence of Vitamin D deficiency and Vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. Lancet 2000; 355:618-21.
27. Ustianowski A, Shaffer R, Collin S, Wilkinson RJ, Davidson RN. Prevalence and associations of Vitamin D deficiency in foreign-born persons with tuberculosis in London. J Infect 2005; 50:432-7.
28. Gibney KB, MacGregor L, Leder K, Torresi J, Marshall C, Ebeling PR, et al. Vitamin D deficiency is associated with tuberculosis and latent tuberculosis infection in immigrants from sub-Saharan Africa. Clin Infect Dis 2008; 46:443-6.
29. Wejse C, Olesen R, Rabna P, Kaestel P, Gustafson P, Aaby P, et al. Serum 25-hydroxy Vitamin D in a West African population of tuberculosis patients and unmatched healthy controls. Am J ClinNutr 2007; 86:1376-83.
30. Rook GAW. The role of Vitamin D in tuberculosis. Am Rev Respir Dis 1988; 138:768-70.
31. New JP, Middleton RJ, Klebe B, Farmer CK, de Lusignan S, Stevens PE, et al. Assessing the prevalence, monitoring and management of chronic kidney disease in patients with diabetes compared with those without diabetes in general practice. Diabet Med 2007; 24:364-9.
32. Khan S. Vitamin D deficiency and secondary hyperparathyroidism among patients with chronic kidney disease. Am J Med Sci 2007; 333:201-07.
33. Mansoor S, Habib A, Ghani F, Fatmi Z, Badruddin S, Mansoor S, et al. Prevalence and significance of Vitamin D deficiency and insufficiency among apparently healthy adults. ClinBiochem 43; 2010:1431-5.

34. Ogunkolade WB, Boucher BJ, Bustin SA, Burrin JM, Noonan K. Vitamin D metabolism in peripheral blood mononuclear cells is influenced by chewing "betel nut" (Areca catechu) and Vitamin D status. J ClinEndocrinolMetab 2006; 91: 2612-7.
35. Martineau AR, Wilkinson RJ, Wilkinson KA, Newton SM, Kampmann B, Hall BM, et al. A single dose of Vitamin D enhances immunity to mycobacteria. Am J RespirCrit Care Med 2007; 176:208-13.
36. Rivas-Santiago B, Hernandez-Pando R, Carranza C, et al. Expression of cathelicidin LL-37 during Mycobacterium tuberculosis infection in human alveolar macrophages,monocytes, neutrophils, and epithelial cells. Infect Immun. 2008;76:935–941.

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