| Original | Article |

Vitamin D status in Pulmonary Tuberculosis : a case control study

Shailesh Sah, Sunil Kumar Biswas, Tonmoy Biswas, Rajashish Chakrabortty, Shishir Sikto Sarker, Md Nazmul Hasan, ABM Abdullah

Article Info

Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka (SS, SKB, MNH); Department of Medicine, Green Life Medical College, Dhaka (TB); Department of Respiratory Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka (RC); Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka (SSS); University Grants Commission, Bangabandhu Sheikh Mujib Medical University, Dhaka (ABMA)

For Correspondence:
Sunil Kumar Biswas
Email: sunilbsmmu@gmail.com

Received: 19 February 2021
Accepted: 15 April 2021
Available Online: 30 November 2021

ISSN: 2224-7750 (Online)
2074-2908 (Print)

DOI: https://doi.org/10.3329/bsmmuj.v14i3.56604

Keywords: Pulmonary tuberculosis, vitamin D status, mycobacterium

Cite this article:
JSah S, Biswas SK, Biswas T, Chakrabortty R, Sarker SS, Hasan MN, Abdullah ABM. Vitamin D status in Pulmonary Tuberculosis: a case control study Bangabandhu Sheikh Mujib Med Univ J. 2021; 14(3): 85-91.

Available at:
www.banglajol.info

A Journal of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Abstract

Pulmonary tuberculosis is the major cause of morbidity and mortality in the developing world. In South Asia, 80% of the apparently healthy population have vitamin D deficiency (<20 ng/mL). An association between vitamin D levels with tuberculosis has been described in several studies. But there are scarcities of studies carried out in Bangladesh to determine the association. This study, a case-control study with 2 years duration, determined and compared vitamin D concentration between pulmonary tuberculosis patients and healthy controls. Patients were recruited from the department of internal medicine, Bangabandhu Sheikh Mujib Medical University. All newly diagnosed patients of pulmonary tuberculosis who fulfiled the inclusion and exclusion criteria were selected as case; equal number of healthy subjects without pulmonary TB as control. Vitamin D level less than 20 ng/ml was considered deficiency; 21 to 29ng/ml as relative insufficiency and >30ng/ml as normal. Thirty participants in each group were enrolled, from whom serum vitamin D concentration was measured, analyzed and interpreted. Mean serum vitamin D level was significantly low in case group than control group (p <0.05). The odds ratio corresponding to vitamin D deficiency in case group compared to control was 5.21 [95% CI (1.12 –27.53), (p= 0.015)]. Result indicates patients having vitamin D level <20 ng/ml has 5.21 times more risk to develop pulmonary tuberculosis. In conclusion, Vitamin D deficiency was significantly low in pulmonary tuberculosis patients and supplementation is required for them.

Introduction

Tuberculosis is a major global health problem. The number of tuberculosis death is unacceptably high.[1] Tuberculosis is a major public health problem in Bangladesh also since long and is ranked sixth among the 22 high tuberculosis burden countries. Pulmonary tuberculosis is the major cause of morbidity and mortality which is prevalent in the developing world. Khanum et al[2] study revealed that pulmonary tuberculosis (74.51%) was more prevalent than extra-pulmonary tuberculosis (25.49%). If left untreated, a person with active tuberculosis infect an average of 10-15 other people every year.[3]

Vitamin D deficiency is a global public health concern. In South Asia, 80% of the apparently healthy population is deficient in vitamin D (<20 ng/mL) and up to 40% of the population is severely deficient (<9 ng/mL).[4] Vitamin D was used for treatment of tuberculosis in the pre-antibiotic era and before then cod liver oil, which is rich in vitamin D, was used along with sun exposure.[5]

Vitamin D is known to have an important role in macrophage activation and the subsequent restriction of Mycobacterium tuberculosis growth and it has been implicated as a risk factor for tuberculosis. An association between vitamin D levels and tuberculosis has been described in several case-control studies.[6] Vitamin D may enhance the production of LL-37, an antimicrobial peptide of the cathelicidin family. Cathelicidins are involved as a first line of defense in the prevention of infections, including tuberculosis.[7] A recent study in Pakistan showed that there was significant deficiency

of vitamin D in patient with tuberculosis as compared to controls and was more pronounced in females, individuals with low BMI, extra pulmonary and MDR tuberculosis.[8] Several recent studies in different population have associated vitamin D deficiency with increased risk of tuberculosis.[5] Talat et al from Karachi, assessed vitamin D levels in a cohort of tuberculosis patients and their contacts in Pakistan where most (79%) persons showed deficiency.[9] Low vitamin D levels were associated with a 5-fold increased risk for progression to tuberculosis. These data were backed up by studies of Davies et al in the UK , as well as Thai, Chinese, Indian and Indonesian cohorts.[10] Despite high burden of tuberculosis, scarcity of study was found in Bangladesh to determine association of vitamin D deficiency and tuberculosis. In this context, we prompted to assess the status of vitamin D in pulmonary tuberculosis. Vitamin D deficiency is widespread in South Asian populations and is contributing to burden of disease in this region. Several studies havesuggested that vitamin D is a potent immunomodulator of innate immune responses by acting as a cofactor for induction of antimycobacterial activity. Tuberculosis patients frequently had lower vitamin D levels than the general population. Low vitamin D levels are associated with progression to active tuberculosis disease in healthy household contacts. Because of the high prevalence of pulmonary tuberculosis in South Asia particularly in Bangladesh, it is important to compare the status of serum vitamin D level in pulmonary tuberculosis patients with that of healthy peoples.

Methods

This study was a case control study and total duration of the study was two years (Sept. 2015 to August 2017). Ethical clearance for the study was taken from the Institutional Review Board (IRB), BSMMU. Patients were recruited from Outpatient, Inpatient Department of Internal Medicine and DOTS Centre of Bangabandhu Sheikh Mujib Medical University (BSMMU). All patients, aged 18 to 60 years, who were newly diagnosed with pulmonary tuberculosis by smear test or gene expert were included as case. Controls were the apparently healthy participants of similar age groups and gender matched without tuberculosis suggested by medical history, physical examination and lab reports. However exclusion criteria were past history of tuberculosis, smoking, diabetes, hypertension, pregnancy, women on oral contraceptives, chronic liver disease, chronic kidney disease and myocardial infarction. After enrolment, data were carefully recorded by interviewing the patient. Other necessary investigations were done to avoid any confounding factors. Preferred range of vitamin D was 30 to 60 ng/ml. Vitamin D level less than 20 ng/ml was considered deficiency; 21 to 29ng/ml relative insufficiency.[11]

For measurement of vitamin D concentration, 5 ml of venous blood samples from participants were collected in a test tube protected from sunlight. Centrifugation was done immediately. Centrifuged serum sample was stored at -20°c for analysis of all the samples from the study population at a time later. Serum vitamin D concentration was measured with Siemens ADVIA Centaur XP Immunoassay system by Chemiluminescent Immunoassay (CLIA) method in the microbiology department of BSMMU. Thirty (30) participants in each group was thus enrolled, investigated and recorded for this study. Then corresponding serum vitamin D concentration of each group was compared. Thereafter, collected data was summarized, processed, analyzed, presented and interpreted.

Results

The present study was intended to compare vitamin D status between pulmonary tuberculosis patients and healthy controls that included 30 newly diagnosed pulmonary tuberculosis patients as cases and 30 apparently healthy adult individuals as controls. The findings of the study obtained from data analysis are documented below:

No significant difference was observed between the groups in terms of residence (p = 0.602), illiteracy (p = 0.809). Students were predominant in both group (p = 0.376). Most of the subjects were from low-income and lower-middle-income in both groups (P = 0.184). No significant difference was observed between the groups in terms of socioeconomic status. In case group, majority (93%) had fever & cough, anorexia 26 (86.7%) and weight loss 20 (66.7%). Regarding physical examination, 43%, 70% and 23% had fever, anemia and features of consolidation respectively.

In case group, the mean hemoglobin was 11.1±1.1 gm/dl, mean white blood cell count (per cu-mL) was 9503.55±1331.3 and mean ESR was 81.5±23.6 mm in 1st hour. Cavitary lesion, consolidation and patchy opacity on CXR was observed in 2(6.6%), 17(56.7%) and 11(36.7%) respectively. 27(90.0%) were positive for sputum for AFB. In 26 (86.7%) Gene x-pert/RIF was detected. Both sputum for AFB positive and Gene x-pert/RIF detected in 23 (76.7%) study subjects.

Gender, residence, education, occupation, socioeconomic status and BMI were not associated significantly with vitamin D level in case group and control group. However, in both case and control group, age group were significantly associated with vitamin D status (p= 0.032, p = 0.026).

According to the results, younger age groups were recruited more in both case and control group, who were almost in their third decade. Majority of patients were male in both case and control group. Case group showed more frequency of underweight patients, where majority of patients of control group had normal BMI (Table I). The mean serum vitamin D was significantly lower in case group than that in control group (p <0.05) (Table II). The odds ratio corresponding to vitamin D concentration <20 ng/ml compared to control group was 5.21 which indicates subjects with vitamin D concentration <20 ng/ml had 5.21 times more risk to develop pulmonary tuberculosis with 95% CI 1.12 –27.53. The difference was statistically significant (p= 0.015) (Table III).

Female had low mean vitamin D (11.6±1.8) compared to male (14.7±4) in the case group. Similarly, in the control group, Female had low mean vitamin D (19.3±5.2) in compared to male (21.4±5.7).

Table-I

Demographic characteristics of case and control (n=60)

Demographic variable	Case (n=30)		Control (n=30)		p-value
	N	%	N	%	
Age (in years)					
18 – 30	16	53.4	18	60.0	
31 – 40	6	20.0	5	16.7	
41 – 50	4	13.3	3	10.0	
51 – 60	4	13.3	4	13.3	
Mean ± SD	32.83±14.37		33.23±14.07		0.913
Range (Min, max)	18 ,60		18 ,60		
Gender					
Male	17	56.7	17	56.7	1.000
Female	13	43.3	13	43.3	
BMI (kg/m2)*					
<18.5 (underweight)	17	56.6	8	26.7	
18.5-24.9 (normal)	11	36.7	19	63.3	
≥25 (overweight)		2	6.7	3	10.0
Mean ± SD	18.96±3.16	20.01±2.97	0.190		
Range (Min, max)	12.84, 24.77	15.58 ,32.41			

*BMI classification according to WHO.
P value reached from unpaired t-test and chi-square test.

Table-II

Comparison of mean vitamin D concentration between case and control (n=60)

	Case (n=30) Mean±SD	Control (n=30) Mean±SD	p-value
Serum vitamin D (ng/ml)	13.4±4.5	20.5±5.5	0.001
Range (min, max)	8.2,25.9	8.1,32.6	

P value reached from unpaired t-test.

Table-III

Comparison of serum vitamin D between case and control (n=60)

Serum Vitamin D (ng/mL)	Case (n =30)	Control (n=30)	OR with 95% CI	p-value
≤ 20	27	19	5.21 (1.12 – 27.53)	0.015
> 20	3	11		

P value reached from chi-square test.

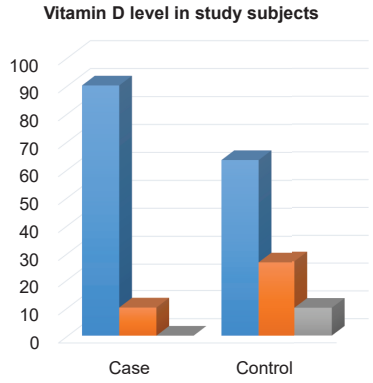

Figure 1: Bar diagram shows vitamin D level of the study subjects

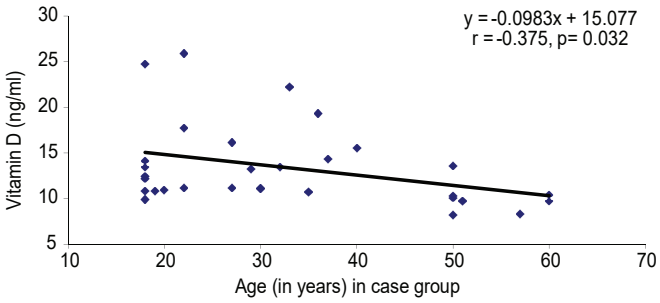

Figure 2: Scatter diagram showing significant negative correlation (r= -0.375; p=0.032) between age and vitamin D level in case group.

Discussions

Tuberculosis is probably the oldest disease known to human.[7] Approximately, 95% of tuberculosis cases occur in developing countries with highest rates observed in sub-Saharan Africa, India, Bangladesh, China, and the islands of Southeast Asia.[12] Vitamin D plays an important role in macrophage activation to restrict growth of mycobacterium. Several biological studies to detect effects of vitamin D on immune system of the body show that vitamin D has a definitive role in suppression of proliferation of Mycobacterium tuberculosis and generalized inflammatory response produced secondary to it.[13,14] The production of microbe-killing cathelicidin is impaired in the absence of adequate serum vitamin D.[15] The possible association between vitamin D and tuberculosis was first reported 20 years ago (16). Smoking increases the risk of tuberculosis two to three-fold and impairs vitamin D absorption, as suggested by evidence. [17, 18] So to exclude the possible vitamin D lowering effect of smoking, only non-smoker cases and non-smoker controls were included in this study.

In the present study, the mean age was found 32.83±14.37 years in case and 33.23±14.07 years in control. Similarly, in Mashhadi et al. 2014(19) study, mean age of the cases and controls were 39.48±14.21 and 38.41±12 years respectively, which are comparable with the current study. This may be explained by the fact that tuberculosis is a disease of young and middle-aged adults with most cases occurring between the ages of 20 to 40 years due to increased exposure to infection in this active age group and the effect of physical and mental stress. [20]

The present study revealed that gender distribution between groups was completely identical with male predominance in either group. Memon et al found 59.8% male in case group[21] and Hassanein et al study revealed that 73.3% was male in case group.[22] Similarly, Iftikhar et al[8] reported 57.1% male with tuberculosis. This coincides with the epidemiological picture of tuberculosis where males are more exposed to infection in the community than females. Some studies showed that women may have poorer access to the diagnostic facilities.[15,23] Higher prevalence of tuberculosis was mostly associated with poor socio-economic condition.[2,24] In this study, most of the cases were from low-income and lower-middle-income groups.

In present study, mean BMI were 18.96±3.16kg/m2 and 20.01±2.97 kg/m2 in case and control group respectively. Iftikhar et al. (2013) found the mean BMI was 20.43±2.06 kg/m2 in cases and 23.62± 2.35 kg/m2 in controls, which is consistent with the current study. This study revealed that most of the study subjects had inadequate sun exposure in both groups. This may be due to changing lifestyles. Most of

the garment workers are engaged in duty from dawn to night, so they are not exposed to sunlight at all and they are unable to take balanced diet. The middle-class urban population is now increasingly living in densely populated apartment blocks with very little natural light.[4]

Vitamin D deficiency was significant in pulmonary tuberculosis patients compared to healthy control in this study. Different studies have been conducted in various parts of the world to find out the association of vitamin D deficiency with tuberculosis.[25] Studies in Pakistan, India, African immigrants in Australia, Tanzania, China, Vietnam, and Uganda have shown that tuberculosis patients had lower levels of vitamin D and higher prevalence of vitamin D deficiency than non-tuberculosis individuals.[8,26-31] In a case control study conducted on indigenous Pakistani population showed that there was significant vitamin D deficiency in tuberculosis patients as compared to the controls ($p < 0.001$) with an odd's ratio of 2.67 (CI 1.67–4.25).[8] Current study reported the Odds ratio between vitamin D deficiency and tuberculosis disease as 5.21 (1.12 –27.53). Mashhadi et al. (2014) observed vitamin D deficiency with Odd's ratio of 3.8 (CI 2.42—6.0, $p<0.05$), which is consistent with this study.

This study also showed that vitamin D level decreases with increasing age. This is in accordance with previous report (32). This may be due to less preference to expose larger fractions of the body to solar radiation and vitamin D photosynthesis in the skin, decreases in efficiency with increasing age.[33] Moreover, in this study, it was noted that vitamin D level was detected low in female subjects compared to male subjects which is similar to other two studies.[8,21] Possible reasons for this female preponderance can be predominantly homebound females, poorer nutritional status than their male counterparts, social stigma associated with tuberculosis, 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 cloths (Burqas). Present study showed no significant relationship between BMI and change in vitamin D level similar to other study.[8,21] As most of the patients with tuberculosis have low BMI, which is further associated with vitamin D deficiency, thus low BMI is important confounder for association of the low vitamin D and tuberculosis.

Only nutritional aspects are not likely the basis of the high frequency of low vitamin D in tuberculosis patients as 90% vitamin D is produced in the skin under direct sunlight.[7] Sun-exposure was inadequate in most of the subjects in both group in this study. A study from India concluded that sunlight exposure was adequate in tuberculosis patients with vitamin D deficiency but reduced dietary intake.[34] Another study revealed that patients with active tuberculosis with comparable vitamin D intake and sun exposure have lower serum vitamin D concentrations than their healthy counterparts.[35] This indicates that other factors contribute to vitamin D deficiency in tuberculosis group. An alternative explanation could be that, the low concentrations of vitamin D could be the result of tuberculosis induced nutritional deficiencies rather than low vitamin D resulting in activation of tuberculosis.

Conclusions

Vitamin D deficiency was found both in pulmonary tuberculosis patients and healthy controls but it was significantly low in tuberculosis patients and supplementation is required for them. The study subjects were selected from one hospital with small sample size, further large scale study is required to validate this observation and to determine if vitamin D supplementation have a role in the prevention and treatment of tuberculosis in our country

Acknowledgement

All faculties of department of internal medicine, BSMMU

Conflict of interest disclosure: None

Source of funding or sponsor

Partially Self-funding and partially from research authority of BSMMU.

References

1. World Health Organization: Guide to Monitoring and Evaluation for Collaborative TB/HIV Activities- Update. 2015; World Health Organization.
2. Khanum H, Sultana R, Dhar R. Diagnosis of tuberculosis and risk factors involved. Bangladesh J. Zool. 2012; 40(2):213-20.
3. Dye C, Watt C, Bleed D, Hosseini S, Raviglione M. Evolution of Tuberculosis Control and Prospects for Reducing Tuberculosis Incidence, Prevalence, and Deaths Globally. JAMA.2005; 293(22): 2767-75.
4. Ahsan HAM, Das A. 2013. Vitamin D Deficiency in South Asian Populations: A Serious Emerging Problem. Journal of Enam Medical College. 2013; 3(2):63-66.

5. Alauddin M, Hussain A, Kamal S, Khan M, Rahman M, Hoque M, et al. Effect of Supplemental Vitamin D3 in the Treatment of Smear Positive Pulmonary Tuberculosis. Chest & Heart Journal.2013; 37(2):88-94.

6. Gibney KB, MacGregor L, Leder K, Torresi J, Marshall C, Ebeling PR, et al. Vimin D deficiency is associated with tuberculosis and latent tuberculosis infection in immigrants from sub-Saharan Africa. Clinical Infectious Diseases.2008; 46(3):443-46.

7. Chocano-Bedoya P, Ronnenberg AG. Vitamin D and tuberculosis. Nutrition Reviews.2009; 67(5): 289-93.

8. Iftikhar R, Kamran SM, Qadir A, HaiderE, Bin Usman H.Vitamin D deficiency in patients with tuberculosis. J Coll Physicians Surg Pak.2013; 23(10):780-83.

9. Talat N, Perry S, Parsonnet J, Dawood G, Hussain R. Vitamin D Deficiency and Tuberculosis Progression. Emerging Infectious Diseases.2010; 16(5):853-55

10. Davies PD, Brown RC, Woodhead J S, 1985. Serum concentrations of vitamin D metabolites in untreated tuberculosis. Thorax.1985; 40(3); 187-90.

11. Holick MF. Vitamin D deficiency. N Eng J Med.2007; 357:226-81.

12. World Health Organization. Centre for Health Development, 2010. Hidden Cities: unmasking overcoming health inequities in urban settings. 2010; WHO.

13. 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. The Journal of Immunology. 2007;179(4):2060-63.

14. Martineau AR, Wilkinson KA, Newton SM, Floto RA, Norman AW, Skolimowsk K, et al. IFN-γ-and TNF-independent vitamin D-inducible human suppression of mycobacteria: the role of cathelicidin LL-37. The Journal of Immunology.2007; 178(11):7190-98.

15. Liu PT, Stenge S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a Vitamin D: mediated human antimicrobial response.Science.2006;311:1770-73.

16. Wilkinson RJ, Llewelyn M, Toossi Z, Patel P, Pasvol G, Lalvani A, et al. 2000. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. The Lancet.2000; 355:618-21.

17. World Health Organization. Immunization surveillance, assessment and monitoring. WHO-UNICEF estimates of DTP3 coverage.2008. Available at: http://www.who.int/mmunization_ monitoring/en/ globalsummary/timeseries/ tswucoveragedtp3.htm. [Accessed 19th august 2017].

18. Brotel C, Jorgensen N, Sorensen O. The influence of smoking on vitamin D status and calcium metabolism. European Journal of Clinical Nutrition.1999; 53(12): 920-26.

19. Mashhadi SF, Rahman M, Azam N, Hashim R, Khan A, Fawad A. Association of vitamin D deficiency with tuberculosis in adult patients reporting to a tertiary care hospital of Rawalpindi. Pakistan Armed Forces Medical Journal.2014; 64(3):479-83.

20. Dye C. Global epidemiology of tuberculosis. Lancet.2006; 367: 938–40.

21. Memon A, Raqeeb A, Humaira M, Khoharo HK. Vitamin D3 in Newly Diagnosed Pulmonary Tuberculosis Patients: A Comparative Case Control Study. J Liaquat Uni Med Health Sci. 2016; 15(1): 16-20.

22. Hassanein EG, Mohamed EE, Baess AI, EL-Sayed ET, Yossef AM. The role of supplementary vitamin D in treatment course of pulmonary tuberculosis. Egyptian Journal of Chest Diseases and Tuberculosis. 2016; 65(3):629-35.

23. Kanunfre K A, Leite OH, Lopes M I, Litvoc M, Ferreira AW. Enhancement of diagnostic efficiency by a gamma interferon release assay for pulmonary tuberculosis. Clin.Vaccine Immunol.2008; 15:1028-30.

24. Liestol K, Tretli S, Tverdal A, Maehlen J. Tuberculin status, socioeconomic differences and differences in all-cause mortality: experience from Norwegian cohorts born 1910–49. International Journal of Epidemiology.2009; 38(2): 427-34.

25. Nnoaham K, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. International Journal of Epidemiology. 2008; 37:113-19.

26. 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. Journal of Infection. 2005; 50(5):432-37.

27. Wejse C, Olesen R, Rabna P, Kaestel P, Gustafson P, Aaby P, et al. Serum 25- hydroxyvitamin D in a West African population of tuberculosis patients and unmatched healthy controls. The American Journal of Clinical Nutrition. 2007; 86(5):1376-83.

28. Mehta S, Mugusi FM, Bosch RJ, Aboud S, Urassa W, Villamor E, et al. Vitamin D status and TB treatment outcomes in adult patients in Tanzania: a cohort study. BMJ Open. 2013; 3(11):37-38.

29. Chan TY, Poon P, Pang J, Swaminathan R, Chan CH, Nisar M, Williams C S, Davies PD. A study of calcium and vitamin D metabolism in Chinese patients with pulmonary tuberculosis. The Journal of Tropical Medi

30. Ho-Pham LT, Nguyen ND, Nguyen TT, Nguyen D H, Bui PK, Nguyen VN, et al. Association between vitamin D insufficiency and tuberculosis in a Vietnamese population. BMC Infectious Diseases. 2010; 10(1): 306.

31. Kibirige D, Mutebi E, Ssekitoleko R, Worodria W, Mayanja-Kizza H. Vitamin D deficiency among adult patients with tuberculosis: a cross sectional study from a national referral hospital in Uganda. BMC Research Notes.2013; 6(1):293.

32. Gallagher JC. Vitamin D and Aging. Endocrinol Metab Clin North 2013; 42(2):319-32.

33. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest.1985; 76:1536-38.

34. Sashidharan PK, Rajeev, Vijayakumari V. Tuberculosis and vitamin D deficiency. J. Assoc Physicians India. 2002; 50: 554-58.

35. Lumsden S A, Lapthorn G, Swaminathan R, Milburn HJ. Reactivation of tuberculosis and vitamin D deficiency: the contribution of diet and exposure to sunlight. Thorax. 2007; 62(11):1003-07.