Comparison of Serum Vitamin D Status Between Tuberculous Lymphadenitis Patients and Healthy Controls

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Abstract

Background: Extra pulmonary tuberculosis accounts for 20% of all tuberculosis cases, among them 35% are tuberculous lymphadenitis. Persistent and/or paradoxically enlarged lymph node, newly developed lymph node as well as suppuration of the lymph node give rise to controversies about duration of therapy, mode of treatment and further evaluation. Various outcomes not only affect the patients psycho-socially and economically but also burdened the country's Tuberculosis Control Program me. So it is wise to search the possible links to prevent these situations. Vitamin D has a significant role in stimulating macrophage and the subsequent limitation of Mycobacterium tuberculosis growth as well as acceleration of resolution of inflammatory responses secondary to it which is mainly responsible for these various outcomes. The present study was attempted to determine the status of serum vitamin D concentration in patient with tuberculous lymphadenitis and to compare it with apparently healthy controls.

Materials and methods: This case-control study was conducted in the Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU) between May 2016 and March 2017.Thirty-one (31) newly diagnosed patients of tuberculous lymphadenitis were selected as cases and equal numbers of age-sex matched apparently healthy individuals were taken as controls for the study. Different diagnostic modalities (FNAC, Histopathology and PCR) were employed to diagnose the cases. Blood samples were collected and estimated for serum vitamin D [25(OH) D] by Chemiluminescent Immunoassay (CLIA) method. Serum vitamin D <20 ng/ml was considered as vitamin D deficiency. The exposure and outcome variables were level of serum vitamin D and tubercular lymphadenitis. The results were analyzed on SPSS version 20.

Results: Mean (±SD) serum vitamin D levels were 13.08±6.32 ng/ml in cases and 21.08±4.5 ng/ml in controls ($p<0.001$). Over 80% of the cases had low serum vitamin D as compared to 35.5% of the controls. More than 70% of the cases exhibited severe deficiency (≤15ng/mL), 9.7% deficiency (<20 ng/ml) and16.2% insufficiency (20 – 30 ng/mL) of serum vitamin D, whereas in the control group 6.5% were severely deficient, 29.1% deficient and 61.3% were insufficient. The odds ratio corresponding to serum vitamin D level <20 ng/ml in case group were 7.5 (95% CI = 2.3 – 24.1, $p<0.001$).

Conclusion: Tubercular lymphadenitis patients had significantly lower serum vitamin D level in comparison to control.This association of low serum vitamin D level in tuberculous lymphadenitis patients may be bidirectional, either low serum vitamin D level increases the risk of tuberculous lymphadenitis or tuberculous lymphadenitis may be a risk factor for low serum vitamin D concentration.

Key words: Tuberculosis; Tuberculous lymphadenitis; Vitamin D.

Introduction

Nearing one-third of the planetary population, i.e. over two billion people, is infected with Mycobacterium tuberculosis and in consequence at threat of developing the disease.[1] It is the 2nd leading cause of death from an infectious disease. In 2014 an estimated 9.6 million new TB cases were detected worldwide and 1.5 million died of the disease. Among 9.6 million new cases 58% were in South Asia (Including Bangladesh) and Western Pacific regions. According to WHO Global Tuberculosis Report 2015 Bangladesh ranks sixth among 22 high TB- load countries in the world.[1]

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In spite of adequate treatment regimen for Tuberculosis (TB) it remains a leading cause of morbidity and mortality in developing countries. In Bangladesh, the prevalence of TB in 2014 was 404 (Range: 211-659) per 100,000 populations with a mortality of 51(Range: 37-68) per 100,000 populations and with an incidence of 227 (Range: 200-256).[1] Among the total 1, 96,797 cases, extra pulmonary cases were 37,717 (New + Relapse = 37,406 + 309) in 2014.[1]

Pulmonary tuberculosis is the prevailing form of TB and occurs in about 80% of cases whereas rests 20% are Extra Pulmonary Tuberculosis (EPTB).[2] Among EPTBs, TB lymphadenitis is the most common accounting for up to 35% of extra pulmonary TBs in India, whereas in Bangladesh it is 68-75%.[3-5]

TB lymphadenitis has both diagnostic and therapeutic confrontation, because it mimics other pathologic process and yields conflicting physical and laboratory findings. Moreover, treatment monitoring is more complex due to peculiar behavior of TB lymph nodes, which among others include paradoxical reaction, suppuration & persistence of the lymph nodes.[2] After starting or completion of Category-I anti tuberculous treatment 10% TB-lymphadenitis patient shows persistent enlargement of previous lymph nodes or development of new lymph nodes at another site which may be due to treatment failure or relapse of tuberculosis or due to paradoxical reaction, pyogenic infection, atypical mycobacterium infection or other causes.[6]

Though lymphadenopathy is found in TB-lymphadenitis patients due to a number of causes, it has been observed that patients who develop new lymph nodes enlargement or enlargement of previous ones are sometimes given further anti-TB regimen or extended anti-TB treatment beyond 6 months without adequate evidence of treatment failure or relapse of tuberculosis. This approach is creating additional economical, psychological and social burden on patients as well as burden on our TB control Programme. Both medical and surgical management is suggested but in a low socioeconomic high burdened TB country, like- Bangladesh it is wise to find the possible links to prevent the situation beforehand. One of the possible links is malnutrition and/or micronutrients deficiency including vitamin A, C, D, E, Zinc, Selenium, Iron, Copper, polyunsaturated fatty acids and cholesterol which lead to secondary immuno-deficiency that increases the host's susceptibility to infection, reinfection as well as reactivation of latent or subclinical tuberculous infection.[7]

The role of vitamin D in bone homeostasis and calcium metabolism is well established but some evidences support its immune-regulatory role as well, particularly in cases of tuberculosis. Vitamin D was used to treat tuberculosis in the preantibiotic era and vitamin D supplementation has been shown to enhance healthy tuberculosis contacts' immunity to mycobacteria.[8,9] For the intracellular pathogen Mycobacterium tuberculosis, role for Vitamin-D in the antimicrobial activity of human monocytes and macrophages was well established. Vitamin-D deficiency is more common in TB patients than in healthy individuals.[10,11,12] Vitamin D plays an important role in stimulating macrophageand restriction of mycobacterial growth. It has been observed that extra pulmonary TB is more frequently associated with vitamin D deficiency (72%) than pulmonary TB (52%).[13,14] Although TB lymphadenitis is the most common extra pulmonary manifestation of tuberculosis there is paucity of data on the relationship between serum vitamin D levels in patients with TB lymphadenitis. In this context we attempted to address the role of Vitamin-D in tuberculous lymphadenitis which may be helpful for the clinicians and policy-makers in updating their TB treatment plan.

Materials and methods

This case control study was carried out in the out patient and Inpatient Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, between 1st May 2016 and 31stMarch 2017.Ethical clearance for the study was taken from the institutional review board, BSMMU. There is a total of 62 study population. Among them 31 were considered as case (Group I) who were newly diagnosed patients of TB lymphadenitis before starting anti-TB drugs, diagnosed on the basis of typical clinical features of tuberculous lymphadenitis with histological/cytological features of caveating granuloma on lymph node biopsy/FNAC and/or who were positive for AFB staining or molecular

test (Gene X-pert/PCR) or MTB culture. Equal number of apparently healthy individuals (Selected on the basis of meticulous history, examination and minimum appropriate investigations) from family member of cases or attendants of the indoor patients or employees of the institute or post graduate students who fulfilled the eligibility criteria were considered as controls (Group II). Upon selecting the cases and controls the participants were explained the aims and implications of the study. Subjects who voluntarily consented to participate in the study were enrolled as sample. Patients with disseminated tuberculosis, past history of tuberculosis, diabetes, hypertension, pregnancy, women on oral contraceptives, chronic liver disease, renal failure/CKD, myocardial infarction, any malignancy, any infectious condition other than TB and those who were taking Vitamin D as medication were excluded from the study. The cases were enrolled after meticulous history, physical examination and appropriate necessary investigations required for confirmation of the diagnosis, like MT tests, Lymph node biopsy, PCR for MTB-DNA and investigations required for exclusion, like CBC, serum Albumin, RBS, liver function tests, renal function test, Chest X-ray and USG of whole abdomen. Equal number of apparently healthy participants without lymphadenopathy who fulfilled the eligibility criteria were selected as control. An individual with vitamin D level < 20 ng/ml (50nmol/l) was considered as vitamin D deficient. For measurement of vitamin D concentration in serum, 5 ml of venous blood samples were collected from the study subjects (Both case and controls) in a test tube protected from sunlight. Centrifugation was done immediately and serum was stored at - 20°c for analysis of all the samples at a time at a later date. Serum vitamin D concentration was measured with Siemens ADVIA Centaur XP Immunoassay system by Chemiluminescent Immunoassay* (CLIA) method in the Microbiology Department of BSMMU. Data were processed and analysed using computer software SPSS 20 (Statistical Package for Social Sciences).*Data were analysed using Chi-square (χ^2) Testand also usingUnpaired t-Test and were presented as mean ± SD.

Results

Table I Demographic characteristics of case and control groups (n=62)

Demographic characteristics	Group				
	Case (n = 31)		Control (n = 31)		p-value
	n	%	n	%	
Age (Years)*					
< 20	10	32.3	9	29.0	0.892
20 – 30	10	32.3	10	32.3	
30-40	8	25.8	7	22.6	
≥40	3	9.7	5	16.1	
Mean ± SD#		27.9 ± 9.3		27.9 ± 9.1	0.935
Gender*					
Male	11	35.5	11	35.5	
Female	20	64.5	20	64.5	
Occupation*					
Service	5	16.1	8	25.8	0.856
Business	2	6.5	2	6.5	
Students	9	29.0	7	22.6	
Housewife	8	25.8	9	29.0	
Others	7	22.6	5	16.1	
Income#					
5,000-10,000	7	22.6	5	16.1	
10,001 – 25,000	14	43.2	18	58.1	0.417
25,001 – 50,000	6	19.4	5	16.1	
>50,000	4	12.9	3	9.7	
BMI (kg/m^2)					
<18.5 (Underweight)	10	32.3	6	19.4	0.301
18.5-25.0 (Normal BMI)	15	48.4	21	67.7	
≥ 25 (Over weight)	6	19.4	4	12.9	

Table I shows the age distribution between case and control groups was almost identical (p = 0.935). Gender distribution between groups was completely identical with female predominance in either group. No significant difference was observed between the groups in terms of occupation with students being predominant in case group and house-wife being predominant in control group (p = 0.856). The average monthly income of case and control groups were Taka 20605 ± 8324 and 19260 ± 3643 respectively (p = 0.417). About one-third (32.5%) of the case group was underweight compared to 19.4% of the controls. However, the difference between the case and control groups in terms of BMI was not significant (p = 0.301).

Table II Distribution of study subject according to vitamin D level (n=62)

Serum Vitamin D (ng/mL)	Group				
	Case (n = 31)		Control (n = 31)		*p-value
	n	%	n	%	
Severe Deficiency (<15)	22	70.9	2	6.5	
Deficiency (15 – 20)	3	9.7	9	29.1	<0.001
Insufficiency (20 – 30)	5	16.2	19	61.2	
Sufficient (≥ 30)	1	3.2	1	3.2	
Mean±SD	13.08±6.32		21.08±4.5		<0.001

Reference values: Preferred range 30-60 ng/mL, Insufficient 20-30 ng/ml, Deficient < 20 ng/mL, severely deficient < 15 ng/mL

Table II shows Over 70% of the cases exhibited severe deficiency of serum vitamin D (< 15 ng/mL) 16.2% had insufficient (20 - 30 ng/mL) and 9.7% deficient in vitamin D (15 - 20 ng/mL) level, whereas in the control group 61.2% were insufficient, 29.1% deficient and 6.5% were severely deficient. The difference between the groups in terms of serum vitamin-D level was statistically significant (p < 0.001). The mean serum vitamin D was significantly lower in case group than that in control group (p < 0.001).

Table III Association between TB lymphadenitis and serum vitamin D

Serum Vitamin D (ng/mL)	Group						
	Case (n =31)		Control (n = 31)		OR (95% CI of OR)	χ^2 value	*p-value
	n	%	n	%			
≤ 20	25	80.6	11	35.5	7.5 (2.3 – 24.1)	12.98	< 0.001
> 20	6	19.4	20	65.4			

Reference values: Preferred range 30-60 ng/mL, Insufficient 20- 30 ng/ml, Deficient < 20 ng/mL, Severely deficient <15 ng/mL

Table III shows Over 80% of the cases had deficient serum vitamin D as compared to 35.5% of the controls. The odds ratio corresponding to vitamin D concentration < 20 ng/ml compared to control group was 7.5 which indicates subjects with vitamin D concentration < 20 ng/ml might have 7.5 times more risk to develop tuberculous lymphadenitis with 95% CI 2.3 - 24.1. The difference was statistically significant (p<0.001).

Table IV S. vitamin D level according to Age, Gender and BMI in Cases (n=31)

Demographic variables	Serum Vitamin-D (ng/mL)				*p-value
	≤ 20 (n = 25)		>20 (n = 6)		
	n	%	n	%	
Age# (Years)					
< 20	8	32.0	2	33.3	
20 – 30	7	28.0	3	50.0	0.639
30-40	7	28.0	1	16.7	
≥ 40	3	12.0	0	0.0	
Gender					
Male	9	36.0	4	66.7	0.172
Female	16	64.0	2	33.3	
BMI (kg/m^2)					
<18.5 (Underweight)	9	36.0	1	16.7	0.376
18.5-25.0 (Normal BMI)	10	40.0	5	83.3	
≥25 (Overweight or obese)	6	24.0	0	0.0	

None of the variables presented in table IV (Age, sex, BMI) was found to be associated with level of serum vitamin D (p= 0.639, p=0.172 and p=0.376 respectively).

Table V S. vitamin D level according to Age, Gender and BMI in Controls (n=31)

Demographic variables	Serum Vitamin-D (ng/mL)				p-value*
	≤ 20 (n = 11)		>20 (n = 20)		
	n	(%)	n	(%)	
Age# (Years)					
< 20	5	45.5	4	20.0	
20 – 30	1	9.1	9	45.0	0.095
30-40	4	36.4	3	15.0	
≥ 40	1	9.1	4	20.0	
Gender					
Male	3	27.3	8	40.0	0.479
Female	8	72.7	12	60.0	
BMI (kg/m^2)					
<18.5 (Underweight)	3	27.3	3	15.0	0.816
18.5-25.0 (Normal BMI)	7	63.6	14	70.0	
25 (Overweight)	1	9.1	3	15.0	

None of the variables presented in Table V (Age, gender and BMI) was found to be associated with level of serum vitamin-D (p = 0.095, p = 0.479 and p = 0.816 respectively).

Table VI Association of low S.Vitamin D with Granulomatous inflammation with or without caseation in cases (n=31)

Granulomatous Inflammation with or without caseation	Serum VitaminD (ng/mL)						
	≤ 20 (n=31)		≥20 (n=31)		OR (95% CI)	χ^2 value	*p-value
	n	%	n	%			
without caseation	5	20	1	16.7	1.250 (0.118 – 13.24)	0.034	1.000
with caseation	20	80	5	83.3			

Table VI shows cases (80%) with caseation necrosis are more vitamin D deficient as compared to without caseation necrosis (20%) but the odds ratio is non-significant as 95% of CI included 1. p-value is also statistically non-significant.

Discussion

A total number of 62 subjects were included in the present study out of which 31(50%) patients were diagnosed case of tuberculous lymphadenitis who were eligible as per case definition and inclusion criteria and 31(50%) individuals were age and gender matched eligible healthy controls.

The present study demonstrated that a substantial proportion of patients (over 80%) of tuberculous lymphadenitis had hypovitaminosis D and The odds ratio corresponding to vitamin D concentration < 20 ng/ml compared to control group was 7.5 which indicates subjects with vitamin D concentration < 20 ng/ml might have 7.5 times more risk to develop tuberculous lymphadenitis with 95% CI 2.3 – 24.1.The difference was statistically significant (p<0.001). As all the demographic variables and BMI were almost identically distributed between cases and control groups, the result obtained might be a cause or effect of tuberculous lymphadenitis. Consistent with this finding a number of studies have shown an association between tuberculosis and low serum vitamin D level. Iftikhar and associates in a study compared Vitamin D deficiency in pulmonary versus extra pulmonary TB and it was found that extrapulmonary TB is associated more frequently with Vit D deficiency (72%) than Pulmonary TB (52%).[8] Studies on African residents in London conducted by Ustianowski, on African immigrants living in Australia conducted by Gibney and associates and on people of West Africa conducted by Wejse and associates all have shown that patients of tuberculosis had lower levels of serum vitamin D than non-TB individuals.[15,8,16]

A study conducted by Islam and associates found that there are multiple factors contributing to the hypovitaminosis D such as extreme of age, female sex, lack of sun exposure, covered clothing style, sunscreen use, skin pigmentation or dark skin, winter season, latitude, malabsorption, anticonvulsant drugs, chronic kidney disease, liver disease and obesity.[17]

In respect to age, study conducted by Lugunova and associates found significantly lower serum vitamin D with increasing age (More marked after the age of 50 years) in normal population whereas in present study no significant association of age with low serum vitamin D was found.[18] This may be due to only 16.1% of controls were above 40 years with no controls beyond 50 years. The age distribution between case and control groups was almost identical (p = 0.935) in the current study. Similarly, study conducted by Iftikhar and associates found no statistical significant difference in respect of age between case & control (p=0.687) though the mean age was higher than our study.[8]

This study also showed no significant relationship between BMI and change in vitamin D level in both case and control groups although overweight as well as obesity often associated with vitamin D deficiency (Studies conducted by Holick and colleagues and by Lugunova and associates).[19,18] In present study the proportion of overweight considerably higher in the case group however, the difference between the case and control groups in terms of BMI was not significant (p = 0.301). On the contrary studies conducted by Iftikhar and colleagues and Wejse and colleagues observed significant statistical difference in mean BMI in their study (p=0.02).[8,16]

In Bangladesh hypovitaminosis D was found in women regardless of age, lifestyle and clothing and was detected in 39% of young women (university students), 30% in veiled women and 38% in diabetic women, respectively.[20] Possible reasons for this female preponderance can be predominantly homebound females, poorer nutritional status than their male counterparts, pregnancy, poor dietary intake as well as inadequate exposure to sunlight because of poor housing and the culture of wearing hooded cloaks (Burqas). In another study between man versus woman conducted by Ruiter and associates revealed a significantly lower proportion of men (6.0%) were vitamin D deficient in comparison to women (21.7%; p<0.0001).[21] Whereas current study did not find such significant association with vitamin D although females were more vitamin D deficient than the males but the gender distribution between groups was completely

identical with female predominance (64.5%) in either group (p = 0.602). Similarly, studies conducted by Iftikhar and associates and by Wejse and associates also observed no significant difference (p>0.05)) in respect to gender distribution but with male predominance (57% and 61% respectively) in their study.[8,16]

In present study no significant difference was observed between the groups in terms of occupation with students being predominant in case group and house-wife being predominant in control group (p = 0.856). The average monthly income of case and control groups were Taka 20605 ± 8324 and 19260 ± 3643 respectively (p = 0.417).

Socio-demographic profiles of this study showed most of the patient (85%) came from middle class income group (Monthly income < 25,000tk BD).These socio-economic profiles were similar with study done from some other regional studies regarding vitamin D status (In India 72.5% and in Pakistan 70%) where majority of the patients belonged to middle income group.

Above observations warrant further studies to determine whether vitamin D supplementation can have a role in the prevention and treatment of the tuberculous lymphadenitis or tuberculosis as a whole.

Limitations

The present study was conducted within limited period of time. The study population was selected from one selected hospital, so that the results of the study may not be reflect the exact picture of the country. Small sample size was also a limitation of the present study. Serum parathyroid hormone and Serum calcium level might have strengthened the results of vitamin D status which couldn't be done due to budgetary restriction.

Conclusion

This study concludes that average serum vitamin D level among patients with tuberculous lymphadenitis were significantly low in comparison to controls. This association of low serum vitamin D level in tuberculous lymphadenitis patients may be bidirectional, either low serum vitamin D level increases the risk of tuberculous lymphadenitis or tuberculous lymphadenitis may be a risk factor for low serum vitamin D concentration.

Recommendations

Further large scale multi-centric prospective studies should be considered to confirm the strength and direction of association of low serum vitamin D level and TB lymphadenitis with good control of confounders.

Contribution of authors

SMMC-Data collection, data analysis, interpretation of results, manuscript preparation & final approval.

LK-Data analysis, interpretation of results, critical revision & final approval.

NH-Interpretation of data, critical revision & final approval.

MJUJ- Data analysis, drafting & final approval.

MF-Data analysis, critical revision & final approval.

MAJC- Interpretation of results, critical revision & final approval.

MKA-Data analysis, drafting & final approval.

TAA-Data analysis, drafting & final approval.

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Disclosure

The authors declare no competing interests.

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