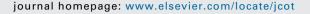
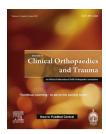


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Original Article

Vitamin D status in pediatric osteoarticular tuberculosis



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ABSTRACT

Background: Tubercular patients, in general, have been demonstrated with lower serum levels of vitamin D, but the levels in osteoarticular tuberculosis (TB) in children are largely unknown. We aimed to determine serum vitamin D status in pediatric cases with osteoarticular TB. Methods: The values of serum vitamin D were estimated in 100 children with osteoarticular TB. The patients were divided into three groups based on gender, age, and site to assess variations of vitamin D levels in pediatric osteoarticular TB.

Results: Hypovitaminosis D was associated with active osteoarticular TB in children. The mean vitamin D levels were 42.165 nmol/L. There were no statistical difference between mean vitamin D levels in boys and girls (p value = 0.6143); age groups <5 and 5–12 years (p value = 0.3857); or spinal and non-spinal osteoarticular groups (p value = 0.8350).

Conclusions: Active osteoarticular TB in children was also associated with hypovitaminosis D. The correlation between hypovitaminosis D and osteoarticular TB appears to be more disease specific rather than host specific.

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1. Introduction

The association between vitamin D concentrations and susceptibility/severity of tuberculosis (TB) is a pertinent issue throughout the world. Tubercular patients have been demonstrated to have lower serum levels of vitamin D even in children. However such data are not established for pediatric patients with osteoarticular tubercular disease. The present

study aimed to determine status of serum vitamin D levels in pediatric cases with osteoarticular TB in a developing country, and whether this was affected by gender, age, or site of TB.

2. Materials and methods

The study was conducted at a tertiary care pediatric center during February 2012–September 2014. The values of serum

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vitamin D (25-hydroxy vitamin D) were estimated in 100 immunocompetent children with an established diagnosis of osteoarticular TB before the initiation of multidrug antitubercular treatment. The vitamin D estimation was performed using the vitamin D enzyme-linked immunoassay (Competitive ELISA). We utilized the following laboratory references for defining the vitamin D status: <30 nmol/L = deficiency; 30–75 nmol/L = insufficiency; and >75 nmol/L = sufficiency.⁴ The patients were further divided into three groups to assess variations of vitamin D levels, if any. The three groups were gender based (male and female) to compare any gender predisposition in children, age related (children aged <5 and 5–12 years), and site specific (spinal and non-spinal group). The preschool children (<5 years) are generally cared for by their parents and live in a close home environment. This group generally indicates economic, educational, and cultural characteristics of the family, including the adverse health hazards (e.g., malnutrition, poor hygiene, infections, and accidents).⁵ Older children (>5 years) have much wider community and peer exposure as well as food independency. Typically, spinal TB has been believed to have higher bacterial load and severity than other forms of extrapulmonary osteoarticular TB.6 The incidence of spinal TB is also much higher than other varieties of osteoarticular TB even in pediatric age group. Approximately, 10% of patients with extrapulmonary TB have skeletal involvement. The spine is thus the most common skeletal site affected (40–60%), followed by the hip and knee. According to previous WHO guidelines, the spinal involvement was placed in Category 1 with serious, ill patients, and provided with more intensive treatment than other osteoarticular varieties would get.^{8,9} No differentiation was made among other types of osteoarticular involvements in our study. Student's t-test was done for intragroup comparisons and calculation of significance (p).

3. Observations

There were a total of 100 patients which included 46 boys and 54 girls (Tables 1-3). The mean age was 7.8, 7.64, and 7.9 years, respectively, in deficiency, insufficiency, and sufficiency groups. The mean vitamin D level in all osteoarticular tubercular patients was 42.165 nmol/L (SD \pm 50.280). Overall vitamin D deficiency (<30 nmol/L) was found in 51 and insufficiency (30-75 nmol/L) in 35 children. Thus, 86% children had deficient or insufficient levels of vitamin D. Just 14 children had sufficient vitamin D levels (>75 nmol/L). There were no statistical difference between mean vitamin D levels in boys and girls (p value = 0.6143), suffering from osteoarticular TB (Table 1). Our study did not reveal any discernable difference between age groups <5 and 5-12 years (p value = 0.3857) (Table 2). There were 28 patients with spinal involvement in current series (n = 100). No statistical difference was evidenced in spinal and non-spinal osteoarticular groups (p value = 0.8350) (Table 3).

4. Discussion

Vitamin D has long been implicated to play an important role in immune system regulation in TB.⁹ Activation of vitamin D receptor by active form of vitamin D (1,25-dihydroxy vitamin D) influences cytokine secretion, suppresses effector T cell

Sex	No. of patients (mean vit. D levels)	Vit. D level		
		<30 nmol/L	30–75 nmol/L	>75 nmol/L
Male	46 patients (39.40 ± 37.92)*	26 patients	13 patients	7 patients
Female	54 patients $(44.52 \pm 59.07)^*$	25 patients	22 patients	7 patients

Table 2 - Vitamin D levels according to age distribution of children with osteoarticular tuberculosis. Age (mean age years) No. of patients (mean Vit. D levels) Vit. D level								
1-80 (and age Jears)	1.0. or passing (ineal) via B leveloy	<30 nmol/L	30–75 nmol/L	>75 nmol/L				
$<$ 5 years (2.65 \pm 0.95 years) 5–12 years (9.18 \pm 2.17 years)	24 patients (51.95 ± 52.86) [%] 76 patients (45.78 ± 18.34) [%]	9 patients 42 patients	10 patients 25 patients	5 patients 9 patients				

Table 3 – Vitamin D levels according to site: spinal and non-spinal osteoarticular tuberculosis.									
Osteoarticular tuberculosis	No. of patients (mean Vit. D levels)		Vit. D level						
		<30 nmol/L	30–75 nmol/L	>75 nmol/L					
Spinal	28 patients (40.47 \pm 29.12) $^{\$}$	12 patients	12 patients	4 patients					
Non-spinal	72 patients (42.82 \pm 56.58) $^{\$}$	39 patients	23 patients	10 patients					
\$ p-Value = 0.8350 (by Student's t-test) comparing mean vitamin D (Vit. D) in spinal and non-spinal tuberculosis.									

activation, and promotes regulatory T cells. ¹⁰ Active vitamin D can potentiate phagocytic activity of macrophages and increase the activity of natural killer cells. Active vitamin D leads to the expression of cathelicidin enzyme, a microbicidal peptide for Mycobacterium tuberculosis. Insufficiency of vitamin D may therefore impair the first-line defense mechanism of macrophage-initiated immune response against TB. ¹¹ Vitamin D, therefore, may have a role in tubercular etiopathogenesis, and that tubercular patients have lower vitamin D concentrations has been demonstrated in both adult and pediatric studies. ^{1,3}

Our study too supported the finding that hypovitaminosis D is associated with active TB in children including osteoarticular TB. Eighty-six percent patients either had deficiency or low levels of vitamin D. Our study could not prove any variation between vitamin D levels according to age, sex, or site of infection in osteoarticular infections. Thus, the correlation between hypovitaminosis D and osteoarticular TB appears to be more disease specific rather than host specific.

Two previous pediatric studies have evidenced a decreased vitamin D status and presence of tubercular infection, a similar association seen in adults patients. 1,3 Williams et al. 3 examined vitamin D prevalence in 64 patients with active TB (n=26) or latent TB infection (n=38). Eighty-six percent patients (n=55) were either vitamin D deficient or insufficient. Only one patient with active TB demonstrated sufficient vitamin D levels. Although this study was conducted mostly on Black African (38%) or South Asian children (55%), there was no demonstrated effect of gender or ethnicity on vitamin D status. Children younger than 1 year had higher serum vitamin D levels than children older than 10 years, as infants were probably supplemented with vitamin-fortified milk. 3

In another pediatric study in 328 children, 11 had active tubercular pulmonary infection (3.3%). Vitamin D deficiency was present in 9 out of 11 children (81.8%) with tubercular infection but without any gender-related differences.

Clinical evidence on vitamin D supplementation along with multidrug antitubercular treatment has still remained controversial. While a few studies credited beneficial clinical effects, others have contradicted the same. Two recent Cochrane reviews have found no reliable evidence that supports routine supplementation at or above recommended daily amounts of oral nutritional supplements (food, protein/energy supplements, or micronutrients) in active TB. 14,15

Possible limitations of our study included presence of several confounding factors, including seasonal variations in vitamin D levels, levels of nutrition and dietary intake, socioeconomic and cultural status, sunlight exposure, co-infections, host immunity status, bacterial virulence and load, host bacterial interactions, presence of tubercular relatives, BCG vaccination, etc. Further, we also acknowledge lack of an age-matched control group without tubercular infection for comparison. The strengths were the large number of patients

(n = 100) with a relatively rare disease such as osteoarticular TB, and first of its kind study to estimate the status of vitamin D in pediatric patients with osteoarticular TB. Better understanding of vitamin D and its interactions in TB may pave a way for its management, and further research investigations in larger pediatric population are warranted.

Conflicts of interest

All authors have none to declare.

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