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Original article

Vitamin D levels among pediatric tuberculosis patients – Does it alter following antitubercular treatment? A prospective study in 19 children

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ABSTRACT

Objectives: It is still unknown whether altered vitamin D levels observed with osteoarticular tuberculosis change during treatment in a child or modify the disease course. To find a possible answer to the above query, we investigated serial serum 25 hydroxy vitamin D concentrations in children suffering from osteoarticular tuberculosis treated with multidrug antitubercular drugs.

Methods: The prospective study enrolled 19 untreated immunocompetent children with an established diagnosis of osteoarticular tuberculosis. None of the patients were offered any therapeutic vitamin D supplementation at initiation or during the treatment. The patients were followed for response to multidrug antitubercular therapy (DOTS) at 2 months interval. Mean values of vitamin D were calculated at 0, 2, and 6 months and statistically compared. The following laboratory references for defining the vitamin D status were used: <30 nmol/L = deficiency; 30–75 nmol/L = insufficiency; >75 nmol/L = sufficiency.

Results: All the patients responded to antitubercular therapy. Out of the enrolled children, 73.67% had low vitamin D levels at initial presentation. There was no statistically significant difference in vitamin D levels in affected children at either 0–2 ($p = 0.452$), 2–6 ($p = 0.240$), or 0–6 months ($p = 0.854$) following antitubercular treatment. Although the mean vitamin D levels were higher in male patients when compared to female patients at all times, there was no statistically significant difference in vitamin D levels during treatment stages in either sex.

Conclusions: Vitamin D levels were low at initiation of treatment and did not significantly improve during multidrug antitubercular treatment. Further, tuberculosis healed well with antitubercular therapy despite persistence of low serum levels of vitamin D.

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1. Introduction

The presence of serum low vitamin D levels in tuberculosis (TB) is established in several pediatric and adult studies.¹⁻⁴ This correlation is found irrespective of age, gender, ethnicity, diet, and geographical locations.¹ The pertinent query raised following these reports is whether altered vitamin D levels observed with TB change during treatment or modify the disease course.

To find a possible answer to this question, the present study investigated serum 25 hydroxy vitamin D concentrations at 0, 2, and 6 months of multidrug antitubercular therapy in children suffering from osteoarticular TB.

2. Materials and methods

The prospective study was conducted at a tertiary care pediatric hospital in a developing country between April 2013 and December 2014. The institution's Scientific Committee approval was obtained for the study. Prior informed consent was obtained from the parents/guardians of the enrolled children. A total of 19 untreated immunocompetent children with an established diagnosis of osteoarticular TB agreed for the study. The immunocompetency of the patients was decided on the basis of clinical examination and laboratory investigations – hemogram and complete blood counts, fasting blood sugar, liver function tests, kidney function tests, peripheral blood smear, and testing for HIV and HBsAg. All the patients were subsequently given multidrug antitubercular therapy according to DOTS regime as per their weight {4HREZ [Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z)] + 2HR}. The patients were followed for response to treatment clinically, hematologically, and radiologically at 2 months interval. None of the patients were offered any therapeutic vitamin D supplementation at initiation or during the treatment duration according to the study protocol.^{5,6} The serum vitamin D estimation (25 hydroxy vitamin D) was done using the vitamin D enzyme linked immunoassay (competitive Elisa) at 0 months (before initiation of multidrug antitubercular therapy), at 2 months (switch over from intensive phase to continuation phase), and at 6 months (completion of DOTS regime). The following

Table 1 – Mean vitamin D levels in children at 0, 2, and 6 months.

S. no.	Parameter	Mean vitamin D levels (nmol/L)
1.	0 months (n = 19)	40.73
2.	2 months (n = 19)	48.52
3.	6 months (n = 19)	38.81
4.	Males; 0 months (n = 11)	42.22
5.	Males; 2 months (n = 11)	51.90
6.	Males; 6 months (n = 11)	42.54
7.	Females; 0 months (n = 8)	38.68
8.	Females; 2 months (n = 8)	43.87
9.	Females; 6 months (n = 8)	33.68

laboratory references were utilized for defining vitamin D status: <30 nmol/L = deficiency; 30–75 nmol/L = insufficiency; >75 nmol/L = sufficiency.⁷ The mean values of serum vitamin D levels obtained at 0, 2, and 6 months were compared using paired t test and unpaired t test. Calculations were done using SPSS software, version 20 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

All the patients enrolled for the study responded to antitubercular therapy and showed progressive clinical, hematological, and radiological recovery. Out of the 19 enrolled children, 9 patients had vitamin D deficiency (47.36%) and 5 insufficiency (26.31%) at the time of initial presentation (0 months). Thus, 14/19 (73.67%) children with manifest osteoarticular TB infection had low vitamin D levels at the time of initial presentation. At the end of 2 months of multidrug antitubercular therapy, 8 children had vitamin D deficiency (42.1%) and 5 insufficiency (26.31%). At completion of DOTS regime at 6 months, 10 still had deficiency (52%) and 5 insufficiency (26.31%). The mean vitamin D values obtained in male and female children at 0, 2, and 6 months are tabulated in Table 1. The level of significance obtained when the mean values were compared at 0, 2, and 6 months is tabulated in Table 2. As is evident from Table 2, there was no statistically significant difference in vitamin D levels in affected children at 0, 2, and 6 months following treatment. Although the mean vitamin D levels were higher in male patients when compared to female

Table 2 – Statistical significance of vitamin D levels at 0, 2, and 6 months.

S. no.	Parameters	p-Value	Interpretation
1.	Vitamin D levels in all children at 0 and 2 months	0.452	Nonsignificant
2.	Vitamin D levels in all children at 2 and 6 months	0.240	Nonsignificant
3.	Vitamin D levels in all children at 0 and 6 months	0.854	Nonsignificant
4.	Vitamin D levels in males and females at 0 months	0.833	Nonsignificant
5.	Vitamin D levels in males and females at 2 months	0.610	Nonsignificant
6.	Vitamin D levels in males and females at 6 months	0.536	Nonsignificant
7.	Vitamin D levels in males at 0 and 2 months	0.500	Nonsignificant
8.	Vitamin D levels in males at 2 and 6 months	0.351	Nonsignificant
9.	Vitamin D levels in males at 0 and 6 months	0.985	Nonsignificant
10.	Vitamin D levels in females at 0 and 2 months	0.752	Nonsignificant
11.	Vitamin D levels in females at 2 and 6 months	0.505	Nonsignificant
12.	Vitamin D levels in females at 0 and 6 months	0.611	Nonsignificant

patients at all times, the study demonstrated no statistical significant differences in vitamin D levels following treatment in either sex.

4. Discussion

Vitamin D metabolites act as important immunomodulatory agents regulating monocytes, lymphocytes, immunoglobulin, and cytokines during the inflammatory response.⁸ Vitamin D can suppress intracellular growth of *Mycobacterium tuberculosis* in vitro. Further, vitamin D induced expression of cathelicidin may have a potential role in the first line of defense in patients with TB.⁸

Determination of vitamin D levels has emerged as a new hematological investigation in TB with evidence pointing to increased risk of active TB following low vitamin D levels.¹ The low serum levels of vitamin D had been demonstrated irrespective of age (both adults and children), sex, ethnicity, diet, and geographical locations.^{1–4} The site of tubercular infection, either pulmonary or extrapulmonary (including osteoarticular tuberculosis) has not influenced this correlation.^{2–4} However, it is still unclear whether fall in serum vitamin D levels is responsible for lowering of cell-mediated immunity and resurgence of active TB disease from a latent focus or whether the presence of TB per se lowers the serum vitamin D concentrations in an individual.¹ The current study investigated the variations in serum vitamin D levels in a subset of immunocompetent children being treated for osteoarticular TB at 0, 2, and 6 months. No significant variations in serum vitamin D levels at different points of treatment reasonably indicate that disease healing does not improve vitamin D levels in osteoarticular TB. Our study also showed that TB heals well with appropriate drug therapy despite vitamin D deficiency.

Following revelations of low vitamin D levels association with TB, several studies have been done to investigate role of vitamin D supplementation in treatment of TB. The clinical results have been variable with few studies demonstrating the adjuvant effect while some other studies have negated this view.^{5,6,9–12} The study by Morcos et al. on 24 children with tuberculous infection receiving vitamin D supplementation has demonstrated clinical and radiological improvement at 8 weeks.⁹ Contrary to this study, a Cochrane review found no effect on sputum conversion rates in adults or body weight in children following vitamin D supplementation.⁵ Another recent Cochrane review had 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.⁶ The children enrolled in our study were not provided with any therapeutic supplementation of vitamin D during treatment period.

The strengths of our study were that it was a first of its kind prospective study to determine the vitamin D levels serially in children undergoing treatment for active osteoarticular TB. Our study enrolled children with a relatively rare disease, such as pediatric osteoarticular tuberculosis, to have a similar

subset of affected children. The children hailed from the same geographical region thus minimizing the bias of seasonal variations and sunlight exposure. Possible limitations in the current study included presence of confounding factors, such as initial nutritional health of children, socioeconomic and genetic status of the children, and host bacterial interactions.^{2–4}

5. Conclusions

TB healed well with multidrug antitubercular therapy despite the presence of low serum vitamin D levels and even the absence of vitamin D supplementation during the course of treatment. The levels of vitamin D did not change significantly following treatment with multidrug antitubercular therapy.

Conflicts of interest

The authors have none to declare.

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