Journal of Clinical Orthopaedics and Trauma 7S (2016) 147–149

Contents lists available at ScienceDirect

Journal of Clinical Orthopaedics and Trauma

journal homepage: www.elsevier.com/locate/jcot

Original article

Vitamin D deficiency among pediatric osteoarticular tuberculosis patients

Pradeep Kumar Dabla [a], Anil Agarwal [b,*], Madhusudan Mishra [b], Shikha Sharma [c]

[a] Department of Biochemistry, GB Pant Hospital, Delhi, India
[b] Department of Pediatric Orthopaedics, Chacha Nehru Bal Chikitsalaya, Geeta Colony, Delhi 110031, India
[c] Department of Biochemistry, Chacha Nehru Bal Chikitsalaya, Geeta Colony, Delhi 110031, India

ARTICLE INFO

Article history:
Received 18 January 2016
Received in revised form 15 September 2016
Accepted 10 October 2016
Available online 20 October 2016

Keywords:
Tuberculosis
Osteoarticular
Bone and joint
Pediatric
Child
Vitamin D

ABSTRACT

Objectives: We prospectively investigated serum 25 hydroxy vitamin D concentrations in children suffering from osteoarticular tuberculosis. The age or sex correlation to vitamin D levels in affected subjects was also calculated.
Methods: Twenty five untreated children with osteoarticular tuberculosis were taken as cases along with equal number of age and sex matched 'healthy' controls. 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). The cases were further grouped based on gender differences and age (<5 or >5 years).
Results: Out of 25 cases, there were 14 (56%) with deficiency of vitamin D. In 'apparently' healthy subjects, all 25 controls (100%) had hypovitaminosis D. The osteoarticular tuberculosis patients had significant lower levels of vitamin D when compared with their healthy peers irrespective of gender or age differences.
Conclusions: The osteoarticular tuberculosis cases had low serum vitamin D levels compared to healthy controls. The low vitamin D levels were persistent irrespective of gender and age in osteoarticular tuberculosis children. There was widespread vitamin D insufficiency in apparently healthy controls.

1. Introduction

Over the past twenty years, a renewed interest has emerged between vitamin D and its role in tuberculosis (TB). Published studies on the subject have demonstrated increased severity and/or susceptibility to TB infection in presence of decreased vitamin D concentrations.[1] Nnoaham and Clarke in their meta-analysis of 7 prospective or case control studies concluded that patients with TB have lower serum levels of vitamin D than healthy subjects irrespective of age, gender, ethnicity, diet and geographical locations.[1] The information analyzed in the meta-analysis was based largely on adult population and pulmonary TB infections. Studies related to pediatric age group are still scanty and vitamin D associations with osteoarticular TB have not yet being reported.[2–4]

Williams et al. reported 86% pediatric patients with deficient or insufficient vitamin D levels in their study involving 64 patients with active or latent TB infection. Most of their patients belonged to African or South Asian ethnic origin.[2] Their study however lacked an age and ethnic matched control group. Another study by Gray et al. in children inferred similar low levels of vitamin D in children with latent (64.4% vitamin D deficient) or active TB (81.8% vitamin D deficient) infection.[3] The non-tubercular group in their study was also vitamin D deficient (55.9%). The children in their study group were largely child refugees from countries in Africa, Asia, and Middle East. A recent multicentre study screening 996 children concluded that the risk of vitamin D deficiency is statistically correlated with TB infection and higher in active TB compared to latent TB and controls.[4] A correlation was found between age and seasonality to low vitamin D levels but not to gender, ethnicity and immigration.[4] Hypovitaminosis D was found respectively in 354 (43.5%) of controls, 80 (58%) latent TB and 33 (75%) active TB.

This study was performed to investigate (1) serum vitamin D concentrations in children suffering from osteoarticular tuberculosis with reference to age and sex matched healthy controls and (2) the age or sex differences, if any, in vitamin D levels in affected subjects.

* Corresponding author at: Department of Paediatric Orthopaedics, Chacha Nehru Bal Chikitsalaya, Geeta Colony, Delhi-110031 India.
E-mail addresses: pradeep_dabla@yahoo.com (P.K. Dabla), anilrachna@gmail.com (A. Agarwal), msm.cnbc@gmail.com (M. Mishra), drshikhacnbc@gmail.com (S. Sharma).

http://dx.doi.org/10.1016/j.jcot.2016.10.006
0976-5662/

Table 1
Cases data.

S no.	Age (years)	Sex	Diagnosis	Vitamin D levels	Status
1	11	F	TB right wrist joint	20	D
2	2	F	Pott's spine C3–C4	16	D
3	12	M	Pott's spine C7 to D1	25	D
4	4	F	TB left ulna	35	I
5	7	M	Pott's spine L1–L3	7	D
6	8	M	TB right knee	28	D
7	7	M	TB right fourth metacarpal	40	I
8	4	M	TB left ulna	30	I
9	6	F	Pott's spine D12 to L3	32	I
10	9	M	Pott's spine D12 to L1	16	D
11	2	M	TB right first metatarsal	45	I
12	4	M	TB right calcaneum	30	I
13	4	M	TB left talus foot	22	D
14	3	M	Pott's spine C1–C2	19	D
15	10	F	TB sternum	45	I
16	12	F	TB left hip joint	30	I
17	7	F	TB cuboid right foot	37.5	I
18	11	F	TB left distal humerus	3	D
19	8	M	TB left first metatarsal foot	20	D
20	10	F	TB left calcaneum foot	50	I
21	3	F	TB right talus	8	D
22	4	M	Pott's spine T12-L1	62.5	I
23	4	M	TB left talus foot	22	D
24	2	F	TB left olecranon	25	D
25	9	M	Pott's spine D4	22.5	D

2. Material and methods

The prospective study was conducted at a tertiary care Pediatric hospital in a developing country during April 2013–December 2014. Institution's Scientific Committee approval was obtained for the study. Informed consent was obtained from participating subjects. A total of 50 children enrolled for the study. Twenty five untreated immunocompetent children with an established diagnosis of osteoarticular TB before initiation of multidrug antitubercular treatment were taken as cases. Age and sex matched 25 children undergoing elective surgery in the department of orthopedics with following exclusion criteria (TB/any other infection; rickets/other metabolic dystrophies; prolonged immobilization; malnutrition) were taken as controls. The vitamin D estimation (25 hydroxy vitamin D) was done 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; >75 n nmol/L = sufficiency.[5] The cases were grouped based on gender differences (male and female) and age (<5 years or >5 years). 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 health characteristics of the family (e.g. malnutrition, poor hygiene, infections).[6] Older children (>5 years) have much wider community and peer exposure and food independency.

Mean values of vitamin D were calculated in each group and compared using Student's *t* test. Calculations were done using SPSS software, version 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

Out of 25 cases, there were 14 (56%) with deficiency (<30 nmol/L) of vitamin D (Table 1). The mean levels of vitamin D in these patients were 18.11 ± 7.41. In 11 (44%) cases, vitamin D levels were insufficient (30–75 nmol/L) and were in the range 39.72 ± 10.25 (Table 1).

In 'apparently' healthy subjects, 23 controls (92%) had vitamin D levels (mean 45.87 nmol/L) in insufficiency group and 2 patients had deficient vitamin D levels (mean 28 nmol/L). The comparison of overall mean values of vitamin D in patients and healthy subjects are given in Table 2. The TB patients had significant lower levels of vitamin D when compared with their healthy peers. Even when gender based comparisons were made (Tables 3 and 4), mean levels of vitamin D were significantly lower in TB patients compared to healthy counterparts. The vitamin D levels in age matched groups (<5 years and >5 years) similar demonstrated significant differences irrespective of age (Table 5).

Table 2
Comparison of vitamin D levels in TB patients and controls.

	TB patients ($n=25$)	Controls ($n=25$)	*p*-Value
Mean vitamin D levels (nmol/L)	27.62 ± 13.90	43.56 ± 12.62	$p<0.0001$

Table 3
Comparison of vitamin D levels in TB male patients and controls.

	TB male patients ($n=14$)	Male controls ($n=14$)	*p*-Value
Mean vitamin D levels (nmol/L)	27.79 ± 13.79	45.43 ± 13.93	$p<0.01$

Table 4
Comparison of vitamin D levels in TB female patients and controls.

	TB female patients ($n=11$)	Female controls ($n=11$)	*p*-Value
Mean vitamin D levels (nmol/L)	27.41 ± 14.73	41.18 ± 10.90	$p<0.05$

Table 5
Comparison of vitamin D levels between TB patients and controls in different age groups.

Age	Mean vitamin D levels in TB patients	Mean vitamin D levels in controls	*p*-Value
<5 years ($n=11$)	28.59 ± 15.00	41.18 ± 10.91	$p<0.05$
>5 years ($n=14$)	26.86 ± 13.55	45.43 ± 13.93	$p<0.01$

4. Discussion

Vitamin D has long been implicated to play an important role in immune system regulation in TB. There two main postulated mechanisms by which vitamin D modulates the immune system against Mycobacterium *tuberculosis*. Firstly, active form of vitamin D (1,25 dihydroxy vitamin D) promotes intracellular killing of Mycobacterium *tuberculosis* by enhancing the fusion of the phagosome and lysosome in infected macrophages. The activated vitamin D increases the activity of natural killer cells, potentiate phagocytic activity of macrophages, enhances cytokine secretion, suppresses effector T cell activation and promotes regulatory T cells.[7] In addition, active vitamin D leads to expression of cathelicidin enzyme which is involved as a first line of macrophage initiated defense in the prevention of infections, including tuberculosis.[7] Thus, vitamin D may have a role in tubercular etiopathogenesis and that tubercular patients have lower vitamin D concentrations have been demonstrated in both adult and pediatric studies.[2,3]

In the present study, 92% subjects recruited as age and sex matched apparently healthy controls were having vitamin D insufficiency as per the criteria used.[5] A study evaluating vitamin D levels in bronchial asthma cases in 44 children (Bangalore, India) revealed similar findings with majority of controls (84%) having insufficiency of vitamin D and there were neither controls nor cases with sufficient vitamin D levels.[8] A preliminary study conducted by Goswami et al. on 25-hydroxyvitamin D concentrations in *apparently* healthy subjects in Delhi (India) revealed significant hypovitaminosis D in 90% cases.[9] Since then several researchers has substantiated the finding of low vitamin D levels and widespread vitamin D deficiency in all age groups including toddlers, school children, adult males and females residing both rural and urban areas. Skin complexion, poor sun exposure, vegetarian food habits and lack of vitamin D food fortification programme in the country probably explain the high prevalence of vitamin D deficiency in India despite its tropical sunny climate.[9,10]

Having said that, studies in other countries have also shown hypovitaminosis D in non tubercular or controls patients. Studies by Gray et al. (Australia) (55.9%),[3] Venturini et al. (Italy and United kingdom) (47%),[4] Chung et al. (Korea) (97%),[11] Stagi et al. (Italy) (88.7%)[12] in pediatric groups have revealed widespread low vitamin D levels. These findings raise concerns over significance and precise standards of adequate vitamin D levels in children.

The current study and the few available pediatric studies in literature indicate that vitamin D levels are lower in pediatric age group similar to adults in TB infections.[2–4] The osteoarticular TB shares a similar profile of low serum vitamin D levels found associated with pulmonary TB. Thus, the levels of vitamin D are low irrespective of TB site-pulmonary, extrapulmonary, osteoarticular.[2–4] Another important finding of current study is low vitamin D levels irrespective of gender and age in osteoarticular TB children. Similar findings have been reported by other observers for adult and pulmonary TB.[1] The consistency of the low serum vitamin D levels irrespective of anatomical regions, age, gender, ethnic groups and geographical regions voices the question whether low vitamin D levels are responsible for TB infection or vice versa.[1]

The strengths of our study were first of its kind control study to determine the vitamin D levels in a relatively rare disease such as pediatric osteoarticular tuberculosis and inclusion of two possible cofounders gender and age. The control group hailed from same geographical region as cases thus minimizing the bias of seasonal variations and sunlight exposure. Possible limitations in current study included presence of several other confounding factors such as nutritional, socioeconomic and genetic status, host bacterial interactions, etc.[2–4] The control group patients may had a possible selection bias compared to general pediatric population as they had obtained fitness for anesthesia and elective surgery as well. Further this group too had findings of low vitamin D levels which may influence the relative significance of the observations made. Although the current study suggests that low vitamin D level were associated with osteoarticular tuberculosis, the overall interaction between TB and vitamin D levels is far from established. The study also revealed widespread vitamin D insufficiency in apparently healthy controls. Prospective randomized study in larger pediatric groups are required to determine the vitamin D levels adequacy and the exact correlation between vitamin D and tuberculosis.

Author's contributions

(1) The conception and design of the study, or acquisition of data, or analysis and interpretation of data: PKD, AA, MM, SS.
(2) Drafting the article or revising it critically for important intellectual content: PKD, AA.
(3) Final approval of the version to be submitted: PKD, AA, MM, SS.

Conflicts of interest

The authors have none to declare.

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