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Research Article

A study of vitamin D status in children with tuberculosis in Peterborough, United Kingdom

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ABSTRACT

Background: We aimed to compare the prevalence of vitamin D deficiency and insufficiency in children with active or latent tuberculosis with the control population.
Methods: This was a retrospective case control study and included 34 patients with evidence of exposure to tuberculosis and 34 controls reviewed at Peterborough city hospital from October 2011 to September 2013, who were matched with regards to age, gender and ethnicity. All patients had blood investigations, chest X-ray, Quantiferon Gold and Mantoux done at the time of review along with serum 25-hydroxyvitamin D concentrations in serum.
Results: 73.6% of patients with Childhood Tuberculosis and 47.1 % of controls had low Vitamin D levels (deficiency and insufficiency). The median vitamin D level in children with tuberculosis was 34.75 nmol/l and in controls was 52.8 nmol/l. Patients older than 12 years of age had significantly lower serum 25-hydroxyvitamin D concentrations than those patients younger than 5 year of age. Gender, ethnicity, BMI, BCG status, serum calcium, serum phosphate and alkaline phosphatase had no significant correlation with vitamin D concentration in patients and controls.
Conclusions: The present study demonstrated that children with evidence of exposure to Tuberculosis were more likely to be associated with lower levels of vitamin D than control population. Larger multi-centric randomized controlled trials are needed to prove the association between vitamin D and Tuberculosis. The association between low levels of vitamin D and tuberculosis suggests investigation for vitamin D deficiency in all children diagnosed with Tuberculosis and supplementation of these children with vitamin D.

Keywords: Tuberculosis, Vitamin D deficiency and insufficiency

INTRODUCTION

Tuberculosis (TB) is an important public health problem in the United Kingdom and the recent data suggest that the incidence of TB in the UK remains high compared to most other Western European countries, with 8751 cases reported in 2012, an incidence of 13.9 per 100000 population. The majority of TB cases occurred in large urban centres, amongst young adults, those from countries with high TB burdens, and those with social risk factors for TB. 73% of TB cases were born outside the UK and the rate of TB among the non UK-born population is almost 20 times the rate in the UK-born.[1]

The treatment of tuberculosis has been based on anti-tuberculosis chemotherapy for the last few decades and there has been an ongoing research in newer treatment modalities. Vitamin D has been used in the treatment of TB in pre-antibiotic times. The emergence of TB sanatoriums in the 19th century and popularity of heliotherapy and cod liver oil as treatments strategies indicate the possible role of vitamin D in management of

Tuberculosis.[2,3] Recent studies have shown that vitamin D is a modulator of macrophage function and can activate host anti-mycobacterial activity.[4,5] It is henceforth likely that children can become more susceptible to TB if they are deficient in vitamin D. A lack of sunlight for most months in a year, application of suntan lotion, pigmented skin and vegetarian diet are all implicated in deficiency of vitamin D noted in UK population.[6]

There is paucity of data regarding vitamin D deficiency in paediatric tuberculosis. We performed an age, gender and ethnicity matched case control study to determine whether vitamin D deficiency was common among children in our clinic with active or latent tuberculosis.

METHODS

Study design and patient population

This study was a case controlled study conducted at the paediatric out patients department at Peterborough city hospital (a moderately large sized District general hospital). We conducted a retrospective review of all patients attending the paediatric Tuberculosis clinic with a diagnosis of either active TB or latent TB infection, at Peterborough city hospital between October 2011 and September 2013. The control population included children who did not have a diagnosis of Tuberculosis and had vitamin D levels done between October 2011 and September 2013. Children with documented previous vitamin D deficiency and on vitamin D supplementation were excluded from the control population. Patients with Tuberculosis were matched to children in the control population with regards to age, sex and ethnicity.

All patients had investigations including full blood count, calcium, phosphate, chest X-ray, Quantiferon Gold and Mantoux done at the time of review along with serum 25-hydroxyvitamin D concentrations in serum, which were measured at the time of diagnosis and before commencing TB treatment. The inclusion criteria for patients were 1)A diagnosis of active tuberculosis based on clinical findings in combination with either a positive Mycobacterium tuberculosis culture, characteristic X-ray abnormalities together with either a positive tuberculin skin test by the Mantoux method and a positive Quantiferon Gold test or a characteristic histology or 2) A diagnosis of latent tuberculosis by a positive Mantoux test and/or reactive Quantiferon Gold. Mycobacterial analyses were done at the microbiology department at Peterborough City Hospital.

Patients diagnosed with active or latent tuberculosis following clinic review at Peterborough City Hospital from October 2011 to September 2013 were included in this study. Children with previous vitamin D deficiency and children under follow up in tuberculosis clinic with diagnosis before August 2011 or already on anti-tuberculosis therapy were excluded in this study.

Analysis of serum 25-hydroxyvitamin D was by high performance liquid chromatography with pre extraction. Statistical analysis was completed with the Mann-Whitney tests using Graph Pad Prism v 4.0 and ANOVA.

We defined the Vitamin D status of the study participants based on recommendations by the British Paediatric and Adolescent Bone Group, and RCPCH. Vitamin D deficiency was defined as a serum 25(OH) D concentrations below 25 nmol/L and vitamin D insufficiency as blood levels between 25 and 50 nmol/L.

RESULTS

34 patients with tuberculosis and 34 controls who were matched with regards to age, gender and ethnicity were included in the study. The mean age of children was 7.7 years in children with tuberculosis and 8.2 years in control group.

Figure 1 shows the distribution of 25(OH)D in patients and control population. Vitamin D deficiency (<25 nmol/l) was observed in 32.4% of the patients and 26.5 % of the controls, whereas insufficiency (25-50 nmol/l) was found in 41.2 % of the patients and 20.6% of the controls. 73.6% of patients with Childhood Tuberculosis and 47.1 % of controls had low Vitamin D levels (deficiency and insufficiency). The median vitamin D level in children with tuberculosis was 34.75 nmol/l and in controls was 52.8 nmol/l.

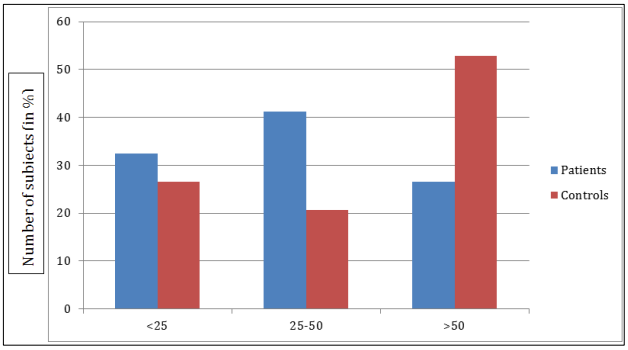

Figure 1: Serum 25 (OH)D concentrations in nmol/L.

Patients older than 12 years of age had significantly lower serum 25-hydroxyvitamin D concentrations (median,<20 nmol/L) than those patients younger than 5 year of age (median, 55.1 nmol/L; $P < 0.05$). Children with TB presenting between November and April had lower serum 25-hydroxyvitamin D concentrations (median, 25.25 nmol/L) than those presenting between May and October; (median, 35.84 nmol/L; $P > 0.05$). Gender, ethnicity and BCG status had no significant effect on Vitamin D concentration in patients and controls. There was no significant difference in Vitamin D levels in patients with active and latent tuberculosis.

There was no significant relationship between serum 25-hydroxyvitamin D concentrations and Body Mass Index (BMI) .There was no significant correlation between serum calcium, serum phosphate and alkaline phosphatase measurements in serum and serum 25-hydroxyvitamin D concentrations

Table 1 shows the distribution of patients and controls in groups of low (<50 nmol/l) and normal (>50 nmol/l) 25(OH)D concentrations together with OR and 95% CI.

Table 1: Distribution of patients and controls with relation to vitamin D status.

Vitamin D levels (nmol/l)	Patients		Controls		OR	CI	P
	n	%	n	%			
<50	25	73.5	16	47.1	3.125	1.1304 to 8.6392	0.0281
>50	9	26.5	18	52.9			

DISCUSSION

The present study demonstrated that children with TB were more likely to be associated with deficiency and insufficiency of vitamin D than control population.

Our clinic population is representative of the current paediatric population of Peterborough. The lower vitamin D levels may also be an indicator of the socioeconomic deprivation and limited provision of safe, outdoor play facilities with poor dietary intake. The lower levels of Vitamin D noted in children above the age of 12 may be explained by the department of health instituting the healthy start programme in which vitamins are available to under 5 years in lower socioeconomic groups. This may be relevant as older children who develop tuberculosis may be more likely to spread the disease due to a larger number of potential contacts. We also noted higher levels of vitamin D in infants which may be attributed to the bottle feeding with supplemented milk formula. We did not take a detailed dietary history during our study.

The association between vitamin D and Tuberculosis has been documented in various previous studies. Vitamin D contributes to protection against TB inducing antimicrobial peptides and boosting concentrations of the antimicrobial peptide LL37 (cathelicidin) in human neutrophils.[7] Vitamin D exerts its effects on innate immune responses by the promotion of autophagy and the suppression of tissue remodeling and lung matrix breakdown.[8,9] A systematic review and meta-analysis on low serum vitamin D levels and tuberculosis in 2008 had included 7 studies with 531 participants and reported that low serum vitamin D levels were associated with a higher risk of active TB.[10] However,there is paucity of relevant epidemiological data regarding vitamin D deficiency in paediatric tuberculosis.

Larger multi-centric randomized controlled trials are needed to prove the association between vitamin D and TB. The association between low levels of vitamin D and tuberculosis suggests investigation for Vitamin D deficiency in all children diagnosed with Tuberculosis and supplementation of all children with TB with vitamin D. The increased prevalence of vitamin D deficiency in the control population does suggest consideration of universal supplementation of all children with vitamin D.

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