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Association between serum vitamin D level and tuberculosis in children

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Abstract

Background A possible association between vitamin D and tuberculosis has been described. In adult, vitamin D is considered to have a role in protecting tuberculosis. On the other hand, tuberculosis infection can decrease serum vitamin D level.

Objective To find out the difference between serum vitamin D level in children with and without tuberculosis, and to find the association of serum vitamin D level with tuberculosis.

Methods A cross sectional study was conducted in Cibabat Hospital, Bandung from July to October 2007. We selected children ≤14 years, diagnosed as tuberculosis, and had positive response after two month treatment; for control we selected randomly siblings or neighbors who didn't have tuberculosis. We excluded children with liver abnormalities and immunocompromized children. Mann-Whitney test and OR method with 95% confidence interval was used to analyze the data.

Results Thirty-nine children with tuberculosis (21 boys, 18 girls) and 39 children without tuberculosis (19 boys, 20 girls) as were enrolled. Mean serum vitamin D level of children with and without TB were 47 (SD 25) pmol/L and 125 (SD 37) pmol/L, respectively (P=0.001). All children without tuberculosis had normal vitamin D level while of those with tuberculosis, 14 children had normal level and 25 children were deficient (corrected OR: 139, 95%CI 8 to 238).

Conclusion Serum vitamin D level is low in children with tuberculosis. **[Paediatr Indones. 2008;48:350-3]**.

Keywords: *tuberculosis, vitamin D, children*

Until now, tuberculosis (TB) remains one of the infectious diseases which has the highest morbidity and mortality worldwide, and it is the second cause of death after HIV/AIDS.[1-3] Indonesia contributes 10% of total TB patients in the world, ranks the third position after India (30%) and China (15%).[2] Such magnitude of the problem invites many researchers to find out preventive, curative, and rehabilitative measures to decrease its morbidity and mortality. One of the focuses of attention is to determine risk factors for the development of *Mycobacterium tuberculosis* infection. The causative agent is not the only factor, but it has to be accompanied by other factor which is the low host immunity against tuberculosis infection.[3-5]

A possible association between vitamin D and TB has been noted since 1770 when cod liver oil, known as being rich of vitamin D, was used for TB therapy.[6] Researchers have found an association between low level of vitamin D and less immunity of

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the host against tuberculosis infection.[6-8] Vitamin D consists of two forms, i.e., cholecalsiferol (vitamin D_3) and ergocalsiferol (vitamin D_2). Precursor of vitamin D_3 is 7-dehydrocholesterol which is transformed into pre-vitamin D_3 in the skin, and with ultraviolet exposure is changed to vitamin D_3.[9] The active form of vitamin D [$1,25(OH)_2D_3$] has been known to influence the ability of mononuclear phagocyte to suppress intracellular growth of *M. tuberculosis*. This compound is mediated by vitamin D receptor (VDR) which has been proven to induce monocyte differentiation, to inhibit lymphocyte proliferation and cytokines production, including IL-1 and IL-2, as well as to suppress immunoglobulin secretion by B lymphocyte. In vitro study has shown that vitamin D may enhance macrophage activity and inhibit *M. tuberculosis* growth.[10-14]

Tuberculosis incidence tends to rise during winter due to less exposure of sunlight which causes a decrease in serum vitamin D level.[6-8] On the other hand, TB incidence among children in Indonesia is still high despite high sunlight exposure of tropical region. This fact draws our attention to carry out a study concerning the difference between serum vitamin D level of children with and without TB; and to find out an association between serum vitamin D level and TB in children.

Methods

A study was performed on children who were selected consecutively from outpatient and inpatient clinics in Child Health Department, Cibabat Hospital, Bandung, July to October 2007. We included children aged ≤14 years diagnosed as having TB based on scoring system of Respirology Working Unit, Indonesia Pediatric Society,[15] positive tuberculin test; and showed positive response after two months of appropriate anti-TB treatment. Children with liver abnormality or those with immunosuppressed condition were excluded. Control group consisted of siblings or neighbors of the case group who did not have TB with negative tuberculin test. After obtaining written consent, all subjects had their blood specimens drawn to measure serum active vitamin D [$1,25(OH)_2D_3$] level using competitive protein binding assay method.

Using 5% significance test, 80% power, tuberculosis Odds Ratio (OR) of 3.1 in patients with vitamin D deficiency from previous study, and 10% proportion of vitamin D deficiency in control group, a minimum sample size of 38 children for each group was needed.

The diagnosis of tuberculosis was established if a score ≥ 6 (from 14 maximum) was obtained based on scoring system of Respirology Working Unit, with positive tuberculin test, and showed positive response after two months of appropriate anti-TB treatment. Positive response after treatment was shown by no or decreased symptoms of fever and cough, increased appetite, and significant increase in body weight. Deficiency of serum [$1,25(OH)_2D_3$] was defined as a level of vitamin D was <50 pmol/L.

The difference between vitamin D level of children with and without TB was analyzed using Mann-Whitney test. Association between serum vitamin D level and TB was determined by calculating the OR and 95% confidence interval (95%CI). This study was approved by the Ethics Committee of Health Research, Faculty of Medicine Padjadjaran University/Hasan Sadikin General Hospital, Bandung.

Results

During the study period, 39 children with TB (21 boys, 18 girls) and 39 children without TB (19 boys, 20 girls) were enrolled. The characteristics of the subjects are shown in **Table 1**.

Table 1. Characteristics of the subject

Characteristics	Children with TB	Children without TB
Age (year)		
Mean (SD)	4.5 (3.1)	4.9 (1.7)
Gender		
Boy	21	19
Girl	18	20
Total	39	39

SD : standard deviation

The mean serum vitamin D level of children with TB was 47 (SD 25) pmol/L whereas of those without TB was 125 (SD 37) pmol/L (**Table 2**); this mean difference of 78 pmol/L was statistically significant, P = 0.001.

Table 2. Difference of serum vitamin D level of children with and without TB

Vitamin D level (pmol/L)	Children with TB	Children without TB
Mean (SD)	47 (25)	125 (37)
Median	41	120
Range	9.5- 88	66- 213

Z_{M-W} = -7.22, P = 0.001 SD: standard deviation

All children without TB had normal serum vitamin D level, where as the majority of children with TB had serum vitamin D below normal level (**Table 3**). Only 14 children with TB had normal level of serum vitamin D and 25 children were deficient. Statistical analysis showed a significant association between serum vitamin D level and TB in children, with corrected OR: 139, 95%CI 8 to 238.

Table 3. Number of children with TB and without TB according to normal and deficient level of serum vitamin D

Serum Vitamin D Level	Children With TB	Children without TB	Total
Low	25	0	25
Normal	14	39	53
Total	39	39	78

*Corrected OR: 139, 95%CI 8; 238

Discussion

The mean age of children with TB in this study was 4.5 years, in accordance with that represented in the literature that children aged <5 years had a higher incidence than other age groups, due to incomplete immune system.[3,16]

This study showed that serum vitamin D level of children with TB was lower than of those without TB. A study in adults by Ormerod reported that immigrants from Asia who lived in England, known as Indian Sub Continental (ISC) immigrants, had lower vitamin D status than the natives. It was known that TB incidence in ISC immigrants was very much higher than that in white population. In 1993, TB incidence among ISC immigrants was as high as 128.2, where as among white people was only 4.8 per 100,000 population per year.[11]

We found an association between serum vitamin D level and TB in children with significant high Odds Ratio value, which was 139 (95% CI 8 to 238), which is higher than the finding of a study among adults by Wilkinson, reported by Davies and Grange, which was 3.1 OR.[17]

The factors that cause children had higher probability to develop TB compared to adults with low vitamin D level, besides from the incomplete immune system, is that vitamin D level in children is generally lower than that in adults. This was due to the high vitamin D requirement in children to provide their growth.[3,17] All children without TB in this study had normal vitamin D level, which meant that children with dark colored skin were still able to produce vitamin D, discordance with statement from previous studies that melanin level influences vitamin D metabolism.[18,19]

Low vitamin D level of children may be caused by several factors, such as decrease of appetite, a common symptom in children with TB which causes low intake of dietary vitamin D.[15] Other factor was probably high utilization of vitamin D which served as a host defense mechanism towards *M. tuberculosis*, starting from incubation period until the development of disease.[9] Genetic factor still could not be excluded in influencing vitamin D metabolism. A study by Lanphear in New York, reported by Haynes, discovered that genetic factor, other than environment, social, and nutrition, has also influence on the level of serum vitamin D. A gene polymorphism was found to influence vitamin D metabolism which in turn causes a low level of serum vitamin D.[20]

We conclude that serum vitamin D level in children with TB is lower than in those without TB and that there is an association between serum vitamin D level and TB in children. All children in the control group had normal vitamin D level, while most of the case group had low level.

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