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Vitamin D Supplementation in Tuberculosis Patients: A Cross Sectional Study

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Abstract. Previous studies have not been able to show with certainty the effect of vitamin D supplementation in tuberculosis patients. The objective of this study is to determine whether vitamin D supplementation to patients with tuberculosis could influence 25-hydroxyvitamin D (25(OH)D) and calcium serum levels. The results, after 28 days, the vitamin D supplementation showed significant increase of 25(OH)D serum level at the end point (p=0.001), but not for the calcium serum level (p=0.3). The Conclusions is supplementation with 1,000 IU vitamin D per day increased the 25(OH)D serum level but there was no association with the calcium serum level.

Keyword: Calcium, Tuberculosis, Vitamin D

Abstrak. *Penelitian sebelumnya belum dapat menunjukkan dengan pasti efek suplementasi vitamin D pada pasien tuberkulosis. Tujuan dari penelitian ini adalah untuk menentukan apakah suplementasi vitamin D pada pasien dengan TB dapat mempengaruhi 25-hydroxyvitamin D (25 (OH) D) dan tingkat serum kalsium. Hasilnya, setelah 28 hari, suplementasi vitamin D menunjukkan peningkatan yang signifikan dari level serum 25 (OH) D pada titik akhir (p = 0,001), tetapi tidak untuk level serum kalsium (p = 0,3). Kesimpulannya adalah suplementasi dengan 1.000 IU vitamin D per hari meningkatkan kadar serum 25 (OH) D tetapi tidak ada hubungan dengan kadar serum kalsium.*

Kata Kunci: *Kalsium, Tuberkulosis, Vitamin D*

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1 Introduction

Vitamin D supports induction of pleiotropic antimicrobial responses in tuberculosis patient, resulting from an immunomodulatory effect (Coussens, 2012). Vitamin D supplementation accelerates sputum smear conversion and enhanced tuberculosis (TB) treatment (Martineau, 2011; Siempos, 2008). Vitamin D is also known to be essential to Mycobacterium tuberculosis containment and killing through activation of 25-hydroxyvitamin D receptors presents on all immune cells (Liu 2006).

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Deficiency vitamin D found in healthy people, especially women in the tropical country (Sari, 2017a; Sari, 2017b). Low sunlight exposure, vitamin D intake, physical activity, and vitamin D receptor gene polymorphism are risk factors for vitamin D deficiency (Sari, 2017c) However, low 25(OH)D serum level did not affect calcium serum level (Sari, 2017d).

Calcium signaling in tuberculosis infection plays a significant role in the pathogenesis of TB (Sharma, 2017). Calcium also is known as a ubiquitous second messenger that could control multiple processes and is included in cellular activities like division, motility, stress response, and signaling. However, Ca is thought to be a regulative molecule regarding TB infection but its binding relation with proteins which are influenced by Ca concentrations in host-pathogen (Chan, 2017). Therefore, we conducted a clinical trial to determine the effect of 1000 IU vitamin D for 28 days to 25(OH)D and calcium serum level.

2 Method

The objective of this study is to determine the effect of 1000 IU per day vitamin D supplementation for 28 days to 25(OH)D and calcium serum level in tuberculosis patients who lived in three community health center in Medan City, North Sumatera, Indonesia between June to September 2017. This is a randomized control trial including 48 patients, 24 tuberculosis patients for vitamin D supplementation and placebo group.

The subjects of this study consisted tuberculosis patients in community health centers with the higher tuberculosis prevalence in Medan, North Sumatera, Indonesia, man, and women with various occupations, and taken purposively; there were 32 subjects The inclusion criteria were tuberculosis patients within the range of 18-60 years old. Exclusion criteria were subjects with the history of diabetes mellitus, myocardial infarction, renal or liver dysfunction. In addition to those exclusion criteria, subjects who were pregnant and lactating were also excluded.

We measured 25(OH)D serum concentration by chemiluminescent immunoassay (CLIA) technology (Diasorin, Stillwater, MN), measures were between 4.0 and 150 ng/mL. The lowest value was 4.0 ng/mL which is based on an inter-assay precision 3.90% CV. Reference range were <20 ng/mL categorized deficiency, 20-30ng/mL (insufficiency), 30-100 ng/mL (sufficiency) (Hollick, 2007). To convert ng/mL to nmol/L is multiply with 2.496. Calcium serum was measured by ADVIA Bayer Assayed Chemistry Controls, with principle procedure: calcium ions form a violet complex with o-cresolphthaleincomplexone in an alkaline medium. The reaction is measured at 545/658 nm, and normal concentration of calcium was 8.3-10.6mg/dL.

Continuous variables were expressed as continuous variables as means±SDs. Categorical variables were expressed as percentage proportions, using chi-square to expressed significant difference between two groups, and Fischer test if the data did not meet the criteria. The p

values <0.05 were considered statistically significant. We used SPSS program (version 11.5; SPSS Inc, Chicago, IL) to perform the analysis.

This study was carried out after ethical approval was obtained from the Health Research Ethics Committee of Sumatera Utara University Medical School (No. 264/TGL/KEPK FK USU-RSUP HAM/2017) and all participants were given written informed consent to the study procedures.

3 Results

3.1 Characteristics of Subjects

Table 1 shows the characteristics of the two groups, one receiving vitamin D supplementation and the other a placebo; there were no significant differences between the two groups.

Table 1 Demographic and lifestyle characteristics of subjects before intervention

Characteristic	Intervention (D) Group (n=24)	Control (C) Group (n=24)	*p*-value
Age (years)[1]	37 ±2.5	33.8±9.1	0.4
Body mass index (kg/m^2)[1]	19.8±3.9	20.3±3.1	0.2
Serum 25(OH)D (ng/mL)[1]	19.7±6.6	19.3±4.6	0.1
Serum calcium (mg/dL)[1]	9.0±0.5	9.1±0.5	0.3

Table 2 shows the difference before and after intervention in the intervention group. After supplementation, there was a significant increase in vitamin D intake, while there was no significant difference in any of the nutrient intakes in the Control Group.

Table 2 Energy and nutrient intake of subjects before and after intervention in D group

Nutrient intake	Intervention (D) group (n=24)		
	Before	After	*p*-value
Energy (kcal)	710.3	760.9	0.25
Protein (g)	25.4	28.3	0.10
Calcium (mg)	219.1	198.4	0.47
Vitamin D (µg)	**3.6**	**31.1**	**0.01**

Table 3 shows the difference between before and after intervention in both groups, after supplementation, there was significant increase in vitamin D intake, while there was no significant difference with all the nutrients intake in Control Group.

Table 3 Mean serum 25(OH)D and calcium levels before and after intervention

Variable	Baseline	Endpoint	*p* value[2]
Serum 25(OH)D (ng/mL)			
Intervention (D) group	19.7±6.6	27.3±3.1	**0.04**
Control (C) group	19.3±4.6	21.9±2.4	0.01
p value[1]		**0.01**	
Serum calcium (mg/dL)			
Intervention (D) group	9.0±0.5	8.9±0.3	0.34
Control (C) group	9.1±0.5	8.9±0.4	0.1
p value[1]		0.5	

4 Discussion

Vitamin D helps the body effectively absorb calcium; there is an interaction between vitamin and mineral. Calcium is known as a ubiquitous second messenger that could control multiple processes and have a role in tuberculosis infection and significant role in pathogenesis.

Calcitriol, the active metabolite of vitamin D, induce innate antimicrobial responses and suppresses proinflammatory cytokine responses in vitro (Martineau, 2007). This microbial activity is mediated via induction of reactive nitrogen intermediates, reactive oxygen intermediates, antimicrobial peptides, and autophagy (Hewison, 2011).

These studies have a similar report with previous studies that in tuberculosis patient found vitamin D deficiency (Martineau, 2011; Salahuddin, 2013). However, after vitamin D supplementation, patients with baseline categorized in deficiency resulting greater weight gain and more rapid radiographic clearing of disease as compared to placebo (Salahuddin, 2013; Sari, 2017d).

The previous study showed that high dose of vitamin D which is in that study was 600.000 IU vitamin D intramuscular accelerated clinical, radiographic improvement in all tuberculosis patients and increased host immune activation, but the length of the study reached 12 weeks (Salahuddin, 2013). In this study, length of the study was 28 days (4 weeks), and tuberculosis patient received 1000 IU oral vitamin D supplementation per day. However, this study also showed an increased of 25(OH)D serum level at the end point.

Hypercalcemia found in tuberculosis patient; the previous study confirmed that serum calcium is raised in tuberculosis, but the effect may be reduced by a low calcium intake and a low parathyroid hormone level. Although the calcium and vitamin D metabolism appeared to be altered in tuberculosis, no direct relationship between serum calcium and 1,25(OH)2D, was found (Chan, 2017). Our study reported normal calcium serum level and no significant different before and after vitamin d supplementation. But we found that serum

Our study had limitations; we did not assess parathyroid hormone and other clinical tuberculosis parameters such as chest X-Ray, and blood examination (C-reactive protein).

5 Conclusion

From the study results, it can be concluded that in tuberculosis patient there were the deficiency and insufficiency vitamin D, but calcium serum level in normal level. No association found between 25(OH)D and calcium serum level.

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