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Vitamin D_3 as an anti tuberculosis supplement in spinal tuberculosis treatment

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ABSTRACT

Background: Tuberculous infection susceptibility emerges in individuals with low levels of vitamin D. C-reactive protein (CRP) and erythrocyte sediment rate (ESR) are low during the intensive phase of anti-tuberculous drug (ATD) therapy. Cathelicidin, which is induced by vitamin D, has been proven to reduce the inflammatory process.

Methods: This single-blind randomized control trial compared the efficacy of vitamin D in lowering CRP and ESR. The research was conducted at the Hasan Sadikin Hospital Outpatient Clinic and the Clinical Pathology Laboratory from March 2017 through August 2017. Tuberculous infected patients enrolled in the study were assigned to one of two groups; one received vitamin D supplementation, the other didn't received. The Willcoxon statistical test was used to examine the value of CRP in two groups, and the unpaired *t*-test was used to evaluate ESR values for both groups.

Results: The CRP and ESR values in the group receiving vitamin D were significantly lower than in the placebo group ($p < 0.05$), indicating that vitamin D is beneficial in treating tuberculous infection.

Discussion: Vitamin D can increase macrophage activation by increasing cathelicidin, Nitrogen Oxide (NO), and Reactive Oxygen Species (ROS) production.

Conclusions: Giving vitamin D_3 800 International Units (IU) supplementation increases the efficacy of ATDs in spine tuberculosis treatment.

ARTICLE HISTORY

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KEYWORDS

CRP and ESR; spine tuberculosis; vitamin D_3

Introduction

Tuberculosis (TB) remains a major health problem worldwide. The World Health Organization estimated that there were 8.6 million people living with TB in 2012 and 1.3 million deaths. The incidence rate of TB in Asia-Pacific Countries was 29%, Africa 27%, West Asia Pacific 17%, India 26%, and China 12% [1,2]. In 2011, Indonesia was in fourth position after India, China, and South Africa. In 2015 at Indonesia, the incidence rate of TB is 395 per 100,000 citizens, and the mortality rate is 27, 3 per 100,000 citizens [1,3,4]. The incidence of the musculoskeletal TB, a form of extrapulmonary TB, is around 10%. Almost 50% of the musculoskeletal TB cases attack the spine, 30% the hip joints, and 20% other joints [3,5,6].

Spinal TB is a chronic extra pulmonary TB infection. It is a granulomatosis infection caused by *Mycobacterium Tuberculosa* (MTB) attacking the spine, and can cause bone destruction, kyphosis deformity, and paraplegia. Motor and sensory neurological impairment had been found in 77.1% of spinal TB cases [7,8]. Because of the high morbidity rate with this disease, the authors are interested in research on the prevention, medication, and rehabilitation to reduce rate of the morbidity and death due to TB.

Several studies have investigated vitamin supplements in TB management, including vitamins A, C, and D. The classic function of vitamin D is to maintain hemostatic calcium and phosphate metabolism which helps maintain bone mineralization through

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osteoblast regulation. Non-classical functions of vitamin D include suppressing cancer cell growth, regulating cell apoptosis by controlling cell hyperplasia, and modulating the immune system [9,10]. Ramdan reported that a deficiency in vitamin D can increase the risk of MTB infection. People with low concentrations of vitamin D have a higher risk of TB infection. Vitamin D plays an important role in the immune system, when there is an MTB infection. Vitamin D improves macrophage MTB phagocytosis ability by activating anti-microbial peptides including cathelicidin, by improving formation of Reactive Oxygen Species (ROS) and Nitrogen Oxide (NO), as well as by improving production of IFN-γ [11–13]. The aim of our reseacrch was to determine whether vitamin D_3 800 International Units (IU) as a supplement can increase the effectivity of anti-tuberculous drugs (ATDs) through evaluating the laboratory infection markers erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Material and Methods

This research was designed as a single-blind randomized controlled trial. All spinal TB patients at the Hasan Sadikin Hospital, who were medicated with ATD and met the inclusion and exclusion criteria, were randomly divided in two groups. Group 1 was the control group, and Group 2 was the intervention group, which was given vitamin D_3 (cholecocalciferol) 800 IU for 2 months. Both groups were followed for 2 months and their vitamin D concentrations [25(OH)D] of CRP and ESR were measured at recruitment and 2 months after ATD medication. Laboratory examinations were performed in the Hasan Sadikin Bandung Hospital laboratory. The vitamin D serum concentration examinations were performed using a colorimetric reader using ELISA tests.

The research subjects were all spinal TB outpatients or inpatients at Hasan Sadikin Hospital. The inclusion criteria were age: 15–50 years; body mass index (BMI): 15–25 kg/m^2; and vitamin D concentration <30 ng/ml. Exclusion criteria were a history of TB, diabetes mellitus, hypertension, autoimmune disease, or thyroid disease; long-term steroid medication; lung or kidney function disorder; pregnant or breastfeeding woman; and an alergy to vitamin D. Research subjects were dropped from the study if they received surgery within research period.

We used a consecutive sampling method with 17 people in each group. The intervention group received vitamin D_3 800 IU + ATD. The control group only received ATD. The independent variable in this research was vitamin D serum, and the dependent variables were CRP and LED. The confounding variables include age, sex, occupation, ethnicity, and BMI.

The Wilcoxon rank-sum test was used to analyze the relationship between vitamin D medication and changes in the CRP concentration. For the relationship between vitamin D and changes in ESR concentration, we used the independent *t*-test. To analyze the relationship between baseline vitamin D concentrations and CRP and ESR, we used the Spearman and the Pearson correlation tests.

Results

Characteristics of each group are shown in Table 1 (sex, age, BMI, location of lesion, and severity of lesion by Frankle classification). The average age in intervention group was 33.6 years [standard deviation (SD) ± 12.4] and in the control group was 25.7 years (SD ± 13.9). The average BMI was 21.3 kg/m^2 (SD ± 1.7) in the vitamin D group and 19.8 (SD ± 2.6) in the control group. The differences in characteristics between the groups were not statistically significant.

The vitamin D concentration in the intervention group before supplementation was 15.2 ng/ml, and after supplementation, it was 28.4 ng/ml. Differences were analyzed with the paired *t*-test and were found to be statistically significant ($p < 0.001$) (Table 2).

Table 1. Table characteristics.

	Without vitamin D_3	With vitamin D_3
	(*n* = 17)	(*n* = 17)
Sex (frequency)		
Male	8	8
Female	9	9
Age (years), average (SD)	35.7 (±13.9)	33.6 (±12.4)
Body Mass Index (IMT) (kg/m^2), average (SD)	19.8 (±2.6)	21.3 (±1.7)
25(OH)D ng/mL	8.1	15.2
Spine level (frequency)		
Thoracic	12	8
Lumbar	5	9
Frankle (frequency)		
B	1	1
C	6	5
D	7	8
E	3	3

Table 2. Vitamin D concentration in the intervention group before and after vitamin D supplementation.

	Before	After	P value
Vitamin D (ng/ml) Mean (SD)	15.2 (±7.7)	28.8 (±4.4)	<0.001#

: t-paired test

Table 3. Correlation between CRP and ESR concentration in spine TB groups with and without vitamin D supplementation.

	ATD	ATD+ Vit. D_3	*p* value
	(*n* = 17)	(*n* = 17)	
CRP (mg/dl)			
Median			<0.001#
Before (Min; Max)	27.1 (5.4; 35.4)	27.5 (6.7; 39.5)	
After (Min; Max)	11.3 (2.7; 27.7)	1.6 (0.2; 8.1)	
Difference (SD)	5.7 (±6.2)	21.3 (±10.2)	
ESR (mm/hour) (SD)			
Before	50.1 (±21.6)	61.1 (±22.4)	0.033*
After	31.9 (±16.3)	31.6 (±22.4)	
Difference	18.2 (±11.2)	29.5 (±17.4)	

= Wilcoxon rank-sum; * = unpaired *t*-test; normal value CRP: <5 mg/dl; LED < 20 mm/hour.

Similarly, there was a statistically significant decrease in CRP and ESR concentrations after supplementation with vitamin D_3 for 2 months ($p < 0.001$ and $p < 0.03$, respectively) (Table 3).

There was no significant correlation between the level of either CRP or ESR before and after vitamin D_3 supplemention ($p = 0.328$ and $p = 0.895$, respectively) (Table 4).

Discussion

After randomization, the potentially confounding variables were found to be distributed evenly between the intervention group and control group.

In this research, Gibbus deformity was typically located in the thoracic vertebrae. It caused by the Adamkiewicz artery, a segmental blood vessel located in the thoracolumbar vertebral region. This artery supplies the body of the vertebrae and might carry MTB bacteria to the vertebrae [4,14,15].

The mean for 25(OH)D concentration in the control group was 8.1 ng/ml while in intervention group was 15.2 ng/ml. The mean 25(OH)D concentration in both groups showed a 11.6 ng/ml vitamin D deficiency. Holick categorizes 25(OH)D concentration deficit as: normal = 30–60 ng/ml, insufficient = 20–29 ng/ml, and deficient ≤ 20 ng/ml [16].

Karmila and Kibiringer reported that a person with vitamin D deficiency has increased vulnerability to TB infection compared to a person without vitamin D deficiency. Research performed by Ramdan on spine TB patients also suggests that most spinal TB patients suffer from vitamin D deficiency [14–16].

This research found that the intervention group had improved the mean concentration of 25(OH) D, but the concentration was still categorized as insufficient. The mean concentration of 25(OH)D before intervention of 15.2 ng/ml (±7.7) indicated a deficiency, but after vitamin D_3 800 IU administration for 2 months, the 25(OH)D concentration showed improvement: 28.8 ng/ml (±4.4). Holick states that giving vitamin D_3 700–800 IU per day can improve 25(OH)D concentration from less than 17 ng/ml to about 40 ng/ml [17]. Previous research suggests that an insufficient 25(OH)D concentration can cause inhibition of monocyte initiation and macrophage activation in the innate immune response to infections [17,18].

Table 4. Correlation between CRP and ESR concentration before and after vitamin D_3 supplementation.

	Before	After	*p* value
	(*n* = 17)	(*n* = 17)	
CRP (mg/dl)	0.17	0.32	0.328*
ESR (mm/hour)	0.02	0.09	0.895#

* = Pearson test; # = Spearman test.

The increase of CRP and ESR concentrations in both groups was caused by an increase in acute phase protein synthesis in the liver due to the inflammation process. MTB that enters the human body stimulates antigen presenting cell, increasing Th1 and Th2. Th1 secretes cytokine Interleukin (IL)-2, IL-12, and Interferron (IFN)-γ, while Th2 secretes IL-4, IL-5, IL-6, IL-9, IL-10, and Tumor Necrotizing Factor (TNF)-α. This process increases macrofage activation to eradicate MTB. CRP is an acute phase protein which is influced by IL-6, IL-1, and TNF-α. Thus, CRP is a sign of inflammation in an MTB infection [19,20]. After receiving vitamin D_3 supplementation for 2 months, CRP and ESR concentrations decreased in the intervention group (Table 3). The main functions of vitamin D include not only regulating calcium homeostasis for bone mineralization but also its immunity function [21,22]. Vitamin D can increase immune system efficacy through an antimicrobial peptide activity called cathelicidin. Cathelicidin activity improves macrophage activity by increasing the phagocytosis function to *M. tuberculosis* [22]. In addition to that activity, vitamin D can also improve the function of NO and ROS in eliminating MTB. A decrease of MTB colonies in the body causes a reduction of the inflammation process by decreasing pro-inflammation mediator synthesis, which is IL-6 and TNF-α [23]. IL-6 and TNF-α are cytokines that stimulate liver hepatocyte cells to produce CRP, i.e., IL-6 and TNF-α, which are cytokines that stimulate liver hepatocyte cells to produce CRP. CRP is an acute phase protein produced when the body suffers

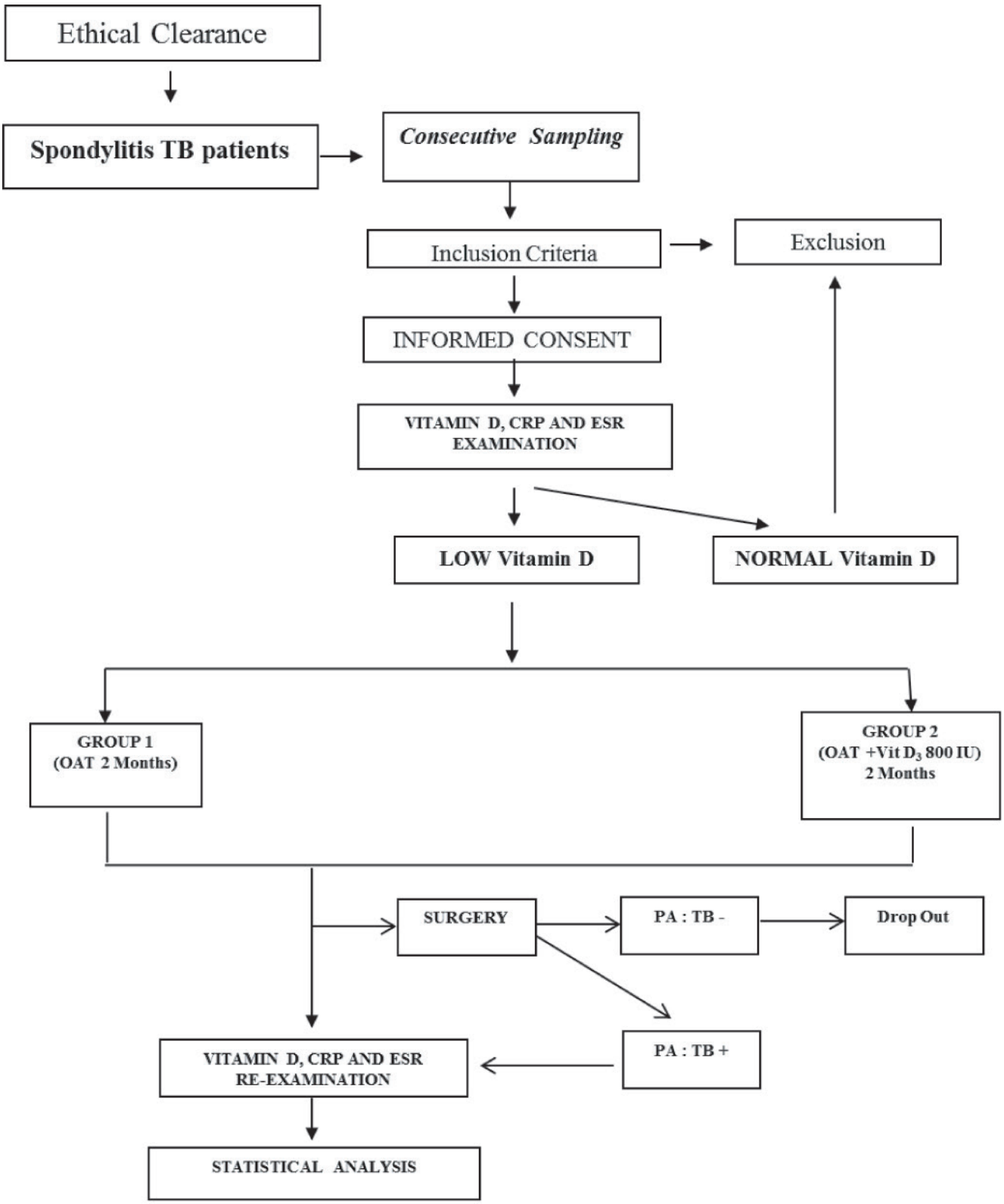

Figure 1. Research flowchart diagram.

an inflammation. CRP concentration will begin to increase within 4–6 hours after inflammation occurs and will reach its peak after 48–72 hours, after which CRP concentration will decrease as the inflammation process decreases [20,24]. This research used CRP as a measuring instrument to estimate the prognosis. This research found that administration of vitamin D decreased CRP concentration within the first

2 months of ATD consumption ($p < 0.05$). This result is consistent with previous research that reported decreased CRP concentrations may provide a good overview of the healing process in spinal TB [25]. The present research results are consistent with previous research conducted on patients with pulmonary TB, which reports that vitamin D in cases of pulmonary TB accelerates the repair of the inflammatory processes as characterized by decreased CRP values [17,26,27]. ESR is another laboratory parameter for assessing the inflammatory processes in spinal TB infections. Although ESR is a non-specific marker of the inflammatory process, it is a simple measurement that can be checked in laboratories in rural areas where equipment for more precise measurements is not available. It is a non-specific parameter for assessing the therapeutic and prognosis response [25].

Table 4 shows the increase in vitamin D serum concentration in the group receiving vitamin D_3 800 IU: 15.2 rose to 28.8 ($p < 0.001$). Increase of vitamin D concentration within the body can be accomplished by administering vitamin D supplementation orally. Vitamin D is a vitamin that can be produced by the human body. Production is influenced by geography, skin tone, food consumption, and amount of sun exposure (which is often correlated with the occupation of the individual) [28]. In this research, those factors are among the uncontrollable factors, so the samples that are not homogenic becomes potentially making the two groups less homogeneous, a limitation of this research.

Another limitation of this study is the inability to control the location of participant activities and their food consumption which might affect the concentration of vitamin D. Other limitations are that CRP and ESR laboratory examination results can be affected by some clinical conditions and the lack of proof of patient adherence to the regime of consuming vitamin D every day.

Conclusions

Supplementation of vitamin D_3 800 IU increases the efficacy of ATD in spinal TB management. Vitamin D_3 is an appropriate supplement in a spine TB treatment regimen.

References

[1] Millet J, Moreno A, Fina L, Del Baño L, Orcau A, De Olalla PG, et al. Factors that inluence current tuberculosis epidemiology. Euro Spine J 2013; 22:539–48.

[2] World Health Organization. Global tuberculosis report 2013. 2013.

[3] Bastomi I, Utoyo G, Tiksnadi B. Surveillance epidemiology penatalaksanaan spondilitis tuberkulosis dengan metoda total treatment di rs hasan sadikin bandung, periode 1999–2006. Proceeding pertemuan ilmiah Perhimpunan Tulang Belakang Indonesia, Jogjakarta, Indonesia, 2007.

[4] Pellise F. Tuberculosis and pott's disease, still very relevant health problem. Euro J Spine 2013; 22:527–8.

[5] Kesehatan KR. Pedoman nasional pelayanan kedokteran tata laksana tuberkulosis 2013. 2013.

[6] Tiksnadi B., Pengaruh polimorfisme gen nrampi terhadap kerentanan terjadinya spondilitis tuberkulosa. Universitas Padjadjaran, Bandung, Indonesia, 2008.

[7] Salter R. Infection. In: Textbook of disorders and injuries of the muskuloskletal system. 8th edition, Lippincot Williams and Wilkins, Philadelpia, PA, p 17, 1997.

[8] Tandiyo D. Pott disease. Available via http:// desy.tandiyo.staff.uns.ac.id/files/2010/07/potts-disease.pdf (Accessed 14 February 2015).

[9] Karyadi E, West CE, Schultink W, Nelwan RH, Gross R, Amin Z, et al. A double-blind, placebo-controlled study of vitamin A and zinc supplementation in persons with tuberculosis in Indonesia: effects on clinical response and nutritional status. Am J Clin Nutr 2002; 75:720–7.

[10] Zakkiyah E, Gurnida D, Kartasasmita C. Pengaruh pemberian vitamin C terhadap perubahan kadar total antioksidan serum pada penderita tuberkulosis paru anak, in Sari pediatri, Indonesia Pediatric Society, Jakarta, Indonesia, 2014.

[11] Uitterlinden AG, Fang Y, van Meurs JB, Pols HA, van Leeuwen JP. Genetics and bioloy of vitamin D receptor polymorphisms. Gene 2004; 338:143–56.

[12] Malcolm D, Kearns B, Tangpricha V. The role of vitamin D in tuberculosis. J Clin Trans Endocrinol 2014; 1:167–9.

[13] Wesje C, Gomes VF, Rabna P, Gustafson P, Aaby P, Lisse IM, et al. Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2009; 179:843–50.

[14] Karmila A, Nazir M, Yangtjik K. Vitamin D serum levels and vitamin D receptor FokIpolymorphism on tuberculosis children in Palembang, Indonesia. Int J Pediatr Endocrinol 2013; Suppl 1:202.

[15] Kibirige D, Mutebi E, Ssekitoleko R, Worodria W, Mayanja-Kizza H. Vitamin D deficiency among adult patients with tuberculosis: a cross sectional study from a national referral hospital in Uganda. BMC Res Notes 2013; 6:293.

[16] Ramdan A. Hubungan vitamin D polimorfisme gen reseptor vitamin D dan cathelicidin LL-37 dengan kejadian tuberkulosis tulang belakang, in Orthopaedi. Padjadjaran, Bandung, Indonesia, 2017.

[17] Siswanto, Jane Y, Widayanti OA, Muktiati NS. Vitamin D as Supportive Treatment Improve The Sputum Conversion and Radiographic Finding in Tuberculosis Patients. J Ked Brawijaya 2009; XXV(3):128–30.
[18] Chun R, Adams J, Hewinson. Immunomodulation by vitamin D: implication for TB. Exp Rev Clin Pharmacol 2011; 4(5):583–91.
[19] Kaihena M. Propolis sebagai immunostimulator terhadap infeksi. J Farmakol Univ Pattimura 2013; 12:69–72.
[20] Setiyawati F. Kadar C-reactive protein dalam darah selama pengobatan dengan obat anti tuberkulosis kombinasi dosis tetap tahap intensif dan hubungannya dengan konversi kuman pada pasien tuberkulosis paru dewasa BTA positif di Yogyakarta, Universitas Gadjah Mada, Yogyakarta, 2010.
[21] Lappe J. The role of vitamin D in human health: a paradigm shift. J Evid Comp Alter Med 2011; 16(1):58–72.
[22] Whalen W, Werner E, Chakraborty N. Vitamin D: the immunologic role and its effect on human pathophysiology. Am J Immunol 2015; 11(1):10–6.
[23] Welin A. Survival strategies of mycobacterium tuberculosis inside the human macrophage. Linkoping University, Sweden, 2011.
[24] Rao S, Murthy S. High-sensitivity C-reactive protein? Is it significant in tuberculous spondylitis. Int J Sci Study 2016; 3(12):274–9.
[25] Rasaouli M, Mirkoohi M, Vaccaro AR, Yarandi KK, Rahimi-Movaghar V. Spinal tuberculosis: diagnosis and management. Asian Spine J 2012; 6(4):294–308.
[26] Abakay O, Abakay A, Sen HS, Tanrikulu AC. The relationship between inflammatory marker level and pulmonary tuberculosis severity. J Inflam 2015; 38(2):691–4.
[27] Sahiraatmaja E. Innate and adaptive host response and their genetic control in tuberculosis: studies in Indonesia, a highly tuberculosis endemic setting. The Netherland, 2007.
[28] Nimitphong N, Holick M. Vitamin D status and sun exposure in southeast Asia. Dermatoendocrinol J 2013; 5(1):34–7.