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RESEARCH ARTICLE

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Sputum Conversion is Faster with Vitamin D Supplementation in Pulmonary TB Patients

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ABSTRACT

Pulmonary tuberculosis (TB) is still a problem that must be resolved in Indonesia, especially North Sumatra. The study aims to determine the effect of vitamin D supplementation on the speed of sputum conversion in pulmonary TB patients. Randomized controlled trial study was conducted on 41 pulmonary TB patients according to inclusion criteria. Research subjects were given TB drug (DOTS program) and vitamin D treatment for 2 months. Sputum examination based on smear was carried out microscopically at 2nd week, 4nd week, 6nd week, and 8nd week after treatment. The results showed that all pulmonary TB patients who were given the intervention experienced sputum conversion. Research subjects with AFB +1 occurred the fastest conversion compared to the others. Statistical analysis using chi square obtained significant results ($p = 0.0001$). Sputum conversion evaluation based on the initial AFB status, there was a significant relationship between the time of sputum conversion with the initial AFB status with a very strong correlation level ($r = 0.767$). Vitamin D has been shown to have a significant effect on the patient's sputum conversion.

Keywords: pulmonary TB; vitamin D; sputum conversion

INTRODUCTION

Background

WHO noted that Indonesia in 2018 was still ranked third (10%) in the world after India (25%) and Nigeria (12%)⁽¹⁾. The results of the Basic Health Research (Riskesdas) in 2018, prevalence of TB based on a diagnosis of 759 per 100,000 population for ages 15 and older. Pulmonary TB is still a problem that must be resolved as written in the RPJMN of Ministry of Health Indonesia in 2015-2019. Prevalence of TB is based on a diagnosis of 0.4% of the total population in North Sumatra, which means there are 400 people diagnosed with pulmonary TB per 100,000 population.⁽²⁾ Population census data of the Central Statistics Agency of Medan as the capital of North Sumatra has an area of 261.5 km², with a population of 2,983,868 people and a population density of 8,008 people /km².⁽³⁾

Treatment of TB patients with vitamin D supplementation has been carried out in several populations in Indonesia Jakarta, Malang, and Wonosobo with the results of accelerating sputum conversion⁽⁴⁻⁶⁾. Vitamin D plays a key role in increasing the natural immunity of TB patients against TB germs. Low vitamin D levels in a person's body indicate a low body defense ability against M. tuberculosis infection in several studies. Vitamin D is one of the mediators that can inhibit the growth of M. tuberculosis in macrophages and monocytes⁽⁷⁾⁽⁸⁾.

The solution to overcome the problem of TB is mostly done with preventive measures rather than curative. This method is considered more effective, because TB germs have a risk of becoming resistant during the treatment process. Research on TB patients has also linked genetic problems of TB patients such as vitamin

D receptors. Vitamin D receptor genes (FokI, BsmI, TaqI, ApaI) are associated with a person's susceptibility to the risk of TB infection⁽⁹⁻¹²⁾

The results of this study are expected to add research evidence on supplementation of vitamin D in the treatment of pulmonary TB patients. It can be used as evidence in policy making by the government in the use of vitamin D as an additional supplement for TB patients. This study aims to provide the effect of vitamin D supplementation on the speed of sputum conversion in pulmonary TB patients

METHODS

The experimental study used a randomized controlled trial design in pulmonary TB patients. The main inclusion criteria chosen as the study subjects were new cases of pulmonary TB patients with smear positive direct smear sputum, age ≥ 15 years, willing to follow the study by signing informed consent. This research was conducted from March-October 2019. The research sample was collected in 2 (two) Puskesmas in the Deli Serdang working area (Puskesmas Pancurbatu and Puskesmas Mulioorejo) with consecutive sampling method.

Subjects who met the inclusion criteria were interviewed, and given pots of sputum for each subject to take sputum at weeks 2,4,6 and 8 in the morning. 80 TB patients who met the inclusion criteria were given TB drugs and oral vitamin D₃ cholecalciferol (Biotech) treatment at week 8, 0.2,4, and 6. Dose of vitamin D given 100,000 iu with four times the administration at week 0,2,4 and week 6. Sputum TB patients are taken to the public health center to be examined when taking TB drugs.

Researchers worked with TB officers to schedule the taking of TB drugs that were the subject of research every 2 weeks according to the schedule for vitamin D and sputum examination, so that researchers made sure the subjects took vitamin D. Sputum is examined by the puskesmas laboratory staff where the patient is treated. Kruskal Wallis and Mann Whitney test was performed to assess the effect of vitamin D administration on sputum conversion. This study has passed the ethical review from the health research ethics commission agency.

RESULTS

Subject Characteristics

Based on the result of the research on 82 subjects being treated in the Puskesmas Pancurnatu and Puskesmas Mulioorejo, Deli Serdang, for pulmonary TB patients using TB drugs with vitamin D and only TB drugs, it was found that.

From the Table 1, Table 2, Table 3 and Table 4, it could be found that TB patients with vitamin D supplementation based on characteristics with highest frequency is with male sex (58.5%), an age range of 26-45 years, Toba tribe (31.7%), AFB +1 status (70.7%); while TB patients without vitamin D supplementation with male sex (65.9%), an age range of 46-65 years, Toba tribe (56.1%), AFB +2 status (48.8%).

Table 1. Distribution of TB patients based on gender

Gender	With vitamin D		Without vitamin D	
	Frequency	Percentage	Frequency	Percentage
Male	24	58.5	27	65.9
Female	17	41.5	14	34.1

Table 2. Distribution of TB patients based on age

Age	With vitamin D		Without vitamin D	
	Frequency	Percentage	Frequency	Percentage
Adolescent (12-25) years	9	22.0	6	14.6
Adult (26-45) years	20	48.8	17	41.5
Elderly (46-65) years	10	24.4	18	43.9
Old man (>65 years)	2	4.9	0	0

Table 3. Distribution of TB patients based on health center

Health center	With Vitamin D		Without Vitamin D	
	Frequency	Percentage	Frequency	Percentage
Health center "Pancurbatu"	14	34.1	20	48.8
Health center "Mulioarjo"	27	65.9	21	51.2

Table 4. Distribution of TB patients based on AFB status

AFB status	With vitamin D		Without vitamin D	
	Frequency	Percentage	Frequency	Percentage
• +1	29	70.7	7	17.1
• +2	7	17.1	20	48.8
• +3	5	12.2	14	34.1

Sputum Conversion Time

Table 5. sputum conversion time difference in both groups

Sputum conversion time	Intervention		Mean Rank	p
	With Vitamin D	Without Vitamin D		
Not conversion	0	4	2.5	
2 nd week	18	1	14.0	
4 nd week	15	19	40.5	0.000
6 nd week	3	11	64.5	
8 nd week	5	6	77.0	

The results in table 5, sputum of all pulmonary TB patients in the group with vitamin D supplementation were all conversion, while the group without vitamin D supplementation there were 4 people who did not convert within two months of treatment.

Data continued with mann whitney test with test results as in the table 3.

Table 3. mann whitney test results based on sputum conversion time

	Mann Whitney U	Wilcoxon W	Z	Asymp.Sig. (2-tailed)
2 nd week-4 nd week	0.000	171.000	-5.657	0.000
2 nd week-6 nd week	0.000	171.000	-4.472	0.000
2 nd week-8 nd week	0.000	171.000	-4.690	0.000
4 nd week-6 nd week	0.000	120.000	-4.123	0.000
6 nd week-8 nd week	0.000	120.000	-4.359	0.000

Mann Whitney-U test results show that vitamin D supplementation given to TB patients is more effective at 4th and 6th week.

DISCUSSION

Characteristics of Subjects

Subjects with male sex more than female sex in two groups. This is influenced by the lifestyle of them. Men are head of families who work for a living with more activities outside than women. Men are mostly active smokers, which can be a risk factor for lung TB infection. According to the results of regional health research in 2018 the number of smokers in Indonesia increased from 7.2 in 2013 to 9.1 in 2018. Other risk factors are high alcohol consumption, alcoholic beverages consumption is more carried out by men than women.⁽¹³⁾ The results of our brief interviews with several subjects showed that habitual consumption of alcoholic beverages was common in his daily life before suffering from pulmonary TB.

Based on the age of subjects, the adult group with an age range of 26-45 years more than the other in the group with vitamin D supplementation, while in the group without vitamin D 46-65 years more than the other. Basic health research data (Risksedas) in 2013 recorded the age of pulmonary TB patients in Indonesia at most ages 24-34 years by 21.4%, ages 35-44 years 19.41% and ages 45-54 years 19.39%. WHO in the Global Tuberculosis Report 2018 reported the most TB incidents in Indonesia at the age of 25-34 years both in male and female sex.^(1,14)

The difference in the number of pulmonary TB patients by age of study subjects is due to the physiological processes of the body that are different in each age range. The role of hormone interactions with pulmonary TB infection is one of the physiological processes of the body that is different at the age level. The results of previous studies found an interaction between dehydroepiandrosterone (DHEA) with glucocorticoids which affect several lymphocyte functions. Active TB disease is characterized by decreased DHEA levels and elevated cortisol levels. Disruption of the ratio of cortisol to DHEA results in changes in the concentration of key cytokines in TB, namely gamma interferon.⁽¹⁵⁾

Sputum Conversion Time (With Vitamin D Supplementation)

To help diagnose tuberculosis (TB) and infections caused by other Mycobacterium species, which are known as acid-fast bacilli (AFB). AFB smear refers to the microscopic examination of a fluorochrome stain of a clinical specimen, with the results of AFB +1 (few), AFB +2 (moderate) and AFB +3 (many) of TB germs. The AFB sputum conversion time was measured every 2 weeks after the subjects were given the intervention of TB drugs and vitamin D. The number of subjects who converted in the group with supplementation vitamin D were subjects with AFB + 1 status was 29 people, AFB + 2 were 7 people and AFB + 3 were 5 people. The results of the examination showed smear pulmonary TB patients +1 experienced conversion at 2nd week (18 people) and 4th week (11 people), AFB+ 2 conversion time at 4th week (4 people) and 6th week (3 people), AFB+3 all had conversions in the 8th week (5 people).

Vitamin D is an organic substance that is less soluble in water, and very soluble in fat. The biomarker of vitamin D status is 25-hydroxyvitamin D₃ with active metabolite 1,25- (OH) D. The role of vitamin D in the body including increases bone mineralization, decreases PTH synthesis and release, increases absorption of calcium and phosphate, induces differentiation in immune cells, improves hematopoiesis, and inhibits clonal proliferation. The role of vitamin D is very important in the body's defense against TB through its action on increasing phagocytosis of macrophages. Vitamin D, either endogenously (Vitamin D₃) or consumed (vitamin D₂ or vitamin D₃), must be activated to produce an effect. In the case of TB using anti-tuberculosis drugs, it makes TB resistant in some patients, vitamin D as an immunomodulatory hormone is used as one of the healing therapies.⁽¹⁶⁻¹⁹⁾

Calcitriol as an active metabolite of vitamin D has antibacterial activity, this metabolite modulates host response to mycobacterial infections by inducing reactive nitrogen and oxygen intermediates, inhibiting matrix metalloproteinase enzymes that play a role in the cavity formation process by upregulating IL-10 receptors thereby inducing IL-10 synthesis, and induces the antimicrobial activity of cathelicidin which induces autophagy.^(5,19-21)

Sputum Conversion Time (Without Vitamin D Supplementation)

Results of sputum conversion in the group treated without vitamin D supplementation, there were 4 people who did not convert with initial AFB+2 and AFB+3 status. Subjects with AFB + 1 conversion at 2 weeks (1 person), 4 weeks (4 people), and 6 weeks (2 people). Subjects with AFB+2 conversions at week 4 (9 people), week 6 (6 people), and week 8 (3 people). Subjects with AFB + 3 conversions at week 4 were 96 people, week 6 (3 people), and week 8 (3 people).

Patients with TB have low levels of vitamin D in their bodies when compared to healthy populations. Research in Spain says that people who are more often associated with TB patients have low 25 (OH) D levels and this is thought to be due to the body's immune process against tuberculosis. Other studies in India prove that vitamin D is associated with susceptibility to TB and the risk of developing infection to TB disease. Similar results in Pakistan with a cohort design in 129 patients proved vitamin D deficiency increased the risk of developing TB.⁽²²⁻²⁴⁾

There were 4 TB patients who were not converted in the group without vitamin D supplementation, TB patients who have consumed TB drugs and supplemented it will provide resistance to M. tuberculosis germs theoretically^(7,18) The response of some M. tuberculosis germs besides dying against the host immune system will be responded to by doing dormancy. Research in India states that the number of more TB bacilli in AFB + 3 has a higher risk of developing drug-resistant mutants than AFB+2 and AFB+1.⁽²⁵⁾

Assessed the speed of sputum conversion in both groups

AFB sputum examination with a microscope is the main diagnostic supporting examination in developing countries. This examination is the most effective (efficient), easy, inexpensive, and fast, while the culture examination is a gold standard examination to determine the diagnosis of TB. One indicator used to monitor and assess treatment (evaluation of therapy) is to look at sputum conversion. Sputum conversion is a change (conversion) of sputum examination results of smear positive pulmonary TB patients into negative AFB after undergoing a period of treatment or intensive therapy.^(26,27)

The results of this study showed that all pulmonary TB patients given intervention (suplementation vitamin D) had sputum conversion. Subjects with the most initial AFB+1 status conversions at 2nd weeks, AFB +2 at 4nd weeks, and AFB +3 at 8nd weeks. This is in line with previous studies conducted by Parikh et al., 2012 in India, stating that AFB + 3 pulmonary TB patients require more time for conversion than AFB + 2 and AFB + 1.

The results of this study prove that vitamin D significantly accelerates sputum conversion in TB patients. Provision of vitamin D in TB patients is highly recommended as one way to break the chain of TB infection. Vitamin D supplementation can increase the immune system of TB patients by inducing the production of cathelisin which plays a role in fighting TB germs.⁽²⁸⁻³⁰⁾

CONCLUSION

Vitamin D supplementation accelerates the sputum conversion of TB patients with the recommended supplementation time of 4 to 6 weeks.

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