Vitamin D, Calcium Serum Levels and Biomolecular Parameters in Active Tuberculosis Patients in North Sumatera, Indonesia

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Keywords: Vitamin D, Calsium, Biomolecular Parameters, Tuberculosis.

Abstract: Background: Inflammation in tuberculosis affecting nutrition status in tuberculosis patient. Malnutrition is an important risk factor for tuberculosis (TB) because of high protein as the optimal cell immunity activity in the cell. Objective: We determine to find vitamin D, calcium serum level, and biomolecular such albumin and hs-CRP in active tuberculosis patients. Design: We conducted a cross-sectional study of 25 man and women aged 18-60 years with active tuberculosis in North Sumatera, Indonesia. Parameters were 25(OH)D and calcium serum level, body mass index, fat mass, and biomolecular parameters such as albumin and hs-CRP also assessed. The data reported as numerical and categorical data using statistical program. Results: the mean of study subject age were 35.3±5.9 years old and BMI were 20.8±5.4 kg/m^2. There were 88% subjects categorized into vitamin D deficiency-insufficiency and 12% categorized into vitamin D sufficiency. There were 92% subjects categorized into normal calcium level, and 8% were hypocalcemia. Based on biomolecular analysis, there was 90% in normal range level of albumin and most of them had higher hs-CRP (96%). Conclusions: based on this result, although there was higher vitamin D deficiency, yet found calcium and albumin in normal level, but there higher hs-CRP showed inflammation status reflecting tuberculosis progression.

1 INTRODUCTION

Malnutrition in tuberculosis have reported in many research, related to immunity activity in the cell that would affect inflammation process. There are three risk in tuberculosis (TB) progression caused of malnutrition: the risk of becoming infected with Mycobcterium tuberculosis, infection progressing to active disease, and lower nutrition status. it could described it as viscious cycle between malnutrition and inflammation process (Sotgiu et al., 2015; Subotic et al., 2016).

Both TB and malnutrition are linked to poverty, it is very important to analize the socio-economic problem in North Sumatera, Indonesia areas. Higher point prevalence of infection in malnutrition patients or community dwellers; would results worse and more frequent complications of infection in underweight patients, higher mortality in undernourished populations; and higher rates of infectious diseasess (Sotgiu et al., 2015).

Malnutrition such as vitamin D deficiency also affect TB progression, previous research showed higher vitamin D deficiency in North Sumatera areas (Sari, 2017a, 2017b, 2017c). The malnutrition host-pathogen interaction and involvement of vitamin D-calcium (Ca) signaling in tuberculosis infection is crucial and plays a significant role in tuberculosis pathogenesis [rosen, sharma]. Vitamin D has a potential role in the prevention and treatment of infection, supports induction of pleiotropic antimicrobial responses and immunomodulatory effects (Gill, 2006). Vitamin D is an essential factor for the intestinal absorption of dietary calcium and skeletal mineralization (Gill, 2006; Sharma & Meena, 2017).

Biomolecular parameter such as albumin that reflects protein status and hs-CRP that reflects

Sari, D., Dharmajaya, R., Sari, M., Masyithah, D. and Hutagalung, S.
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DOI: 10.5220/0010085707210725
In *Proceedings of the International Conference of Science, Technology, Engineering, Environmental and Ramification Researches (ICOSTEERR 2018) - Research in Industry 4.0*, pages 721-725
ISBN: 978-989-758-449-7

inflammation process, can be part of tuberculosis progression. This inflammatory response is tightly regulated by both the host and the bacterium during different stages of infection.

The aims of this study were to find vitamin D, calcium serum level, and biomolecular such albumin and hs-CRP in active tuberculosis patientst to our knowledge, this is would be the based to increased the quality of tuberculosis patient's nutrition status in Medan, North Sumatera, Indonesia. Based on this study, we could also find the nutrition problem and support it until tuberculosis eradicated in these areas.

2 METHOD

We conducted a cross-sectional study of 25 man and women aged 18-60 years in North Sumatera, Indonesia May to July 2018, during the dry season (dry season in Indonesia is between April and October, when there was abundant sunlight exposure). The location of recruitment was in Sumatera Island (Medan, North Sumatera, Indonesia) with latitude: 3.57 N and longitude 98.65 E, average temperature: ±32ºC (90ºF). The areas are: Community Health Center 'Teladan' and 'Amplas', that located in Medan city. This study was carried out after ethical approval was obtained from the Health Research Ethics Committee of Sumatera Utara University Medical School (No. 96/TGL/KEPK FK USU-RSUP HAM/2018) and all participants were given written informed consent to the study procedures.

a. Study participants

The subjects of this study consisted tuberculosis patients in two community health centers with the higher tuberculosis prevalence in Medan, North Sumatera, Indonesia, man and women with various occupations, and taken purposively, there were 25 subjects The inclusion criteria were tuberculosis patients within the range of 18-60 years old. Exclusion criteria were subjects with history of diabetes mellitus, myocardial infarction, renal orliver dysfunction. In addition to those exclusion criteria, subjects who were pregnant and lactating were also excluded.

b. Anthropometry, status body fat, and blood pressure

Anthropometry included height (to the nearest 0.5 cm), weight (to the nearest 0.1 kg), waist ircumference using a standardized measuring tape in centimetres, systolic and diastolic blood pressure measurement, and body mass index (calculated as kg/m^2). Categorized BMI was based on Asia Pacific [6], <18.5 classified as underweight, 18.5-22.9 classified as normoweight, 23-24.9 classified as overweight/at risk, 25-29.9 classified as obese I, and >30 classified as obese II. Assessment of body fat percentage were using Body Composition Monitor with Scale (*HBF-362, KaradaScan-Omron*). Body fat percentage refered to the amount of body fat mass in regards to the total body weight expressed as a percentage, the following classified: normal ≤29.9% and high >30.0% based on Bioelectrical Impedance.

c. Laboratory analysis

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 (insuficiency), 30-100 ng/mL (suficiency) [7]. To convert ng/mL to nmol/L is multiply with 2.496. Calsium 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.

We measured albumin serum using architect C800 with colorimetry method and to measured hs-CRP, we also use architect C800 with different method which are turbidimetry/ immuno-turbidimetry.

d. Statistical analysis

This research presented data in two variables which were continuous and categorical variables. Continuous variables were expressed as continuous variables as mean±SD. Categorical variables were expressed as percentage proportions We used SPSS program (version 11.5; SPSS Inc, Chicago, IL) to perform the analysis.

3 RESULTS AND DISCUSSIONS

The results will be discussed in 4 subsections, they are characteristic of study participants, anthropometry and blood pressure, vitamin D and

calcium, and biomoleculer parameters: albumin and hs-CRP.

a. Characteristic of study participants

The aim of this study was to report parameters which were vitamin D, calcium status and biomolecular parameters. In **Table 1** showed the demographic of study subject. The mortality, morbidity, and disease progression of tuberculosis varies between different age groups. Based on these difference, we had a better understanding of the immunological mechanisms underlying disease and protection for cell immunity of the body.

Table 1. Demographic and clinical characteristics

Variables	n(%)
Age (mean±SD)	35.3±5.9
Age classification	
18-30	4(16
31-40	16(64)
41-50	4(16)
51-60	1(4)
Gender	
Male	20 (80)
Female	5 (20)
Ethnic	
Javanese	6 (24)
Bataknese	8 (32)
Minang	8 (32)
Others	3 (12)
Occupation	
Student	5 (20)
Employed	8 (32)
Unemployed	8 (32)
Housewife	4 (16)
Smoking history	
Yes	20 (80)
No	5 (20)

Abbreviations:
SD: Standart Deviation

Most of the subject had smoking history, tobacco smoke increases risk of Mycobaterium tuberculosis infection by several means: alteration of muco-ciliary clearance, reduced alveolar macrophage activity; immune-depression of pulmonary lymphocytes, reduction of cytotoxic activity of natural killer cells, alteration of the activity of the pulmonary dendritic cells. Both active and passive smoking increases the risk of latent tubercular infection and of pulmonary and extra-pulmonary tuberculosis (Cegielski & McMurray, 2004).

b. Anthropometry and blood pressure

A low body mass index (BMI) was associated with a 3-fold increased risk of tuberculosis when compared with patients with a normal BMI, and an increased BMI was associated with a 50% decreased risk of tuberculosis. In this study, most of the study subjects were underweight (Casha & Scarci, 2017; Lyons & Stewart, 2013; Subotic et al., 2016) as presented in **Table 2**. In this study, most of the study subjects had lower fat mass, this was because of malnutrition condition.

Table 2. Anthropometric characteristics

Parameters	Mean±SD and n(%)
Weight (kg)	54.5±12.3
Height (cm)	161.6±8.2
BMI (kg/m^2)	20.8±5.4
Underweight	23(92)
Normal	2(8)
Overweight	-
Obese	-
Fat mass (%)	20.2±3.7
Low	19(76)
Normal	6(24)
High	-
Abdominal	79.3±21.3
circumference (cm)	25(100)
Normal	-
High	
Blood pressure (mmHg)	110.3±24.5
Sistole	78.5±18.5
Diastole	

Abbreviations:
BMI: body mass indeks

c. Vitamin D and calcium

Based other previous study, women and man were susceptible to vitamin D deficiency (Sari et al., 2017a, 2017c), vitamin D affected calcium level also. Exposure to sunlight is the main source of vitamin D for human. This exposure induces the conversion of 7-dehydrocholesterol to vitamin D3 via previtamin D3 in the skin. This form then converted to 25-hydroxyvitamin D in the liver and is further converted to the bioactive form of vitamin D, $1.25(OH)_2D_3$ in the kidney. Studies have found that it binds to vitamin D receptor (VDR), activates VDR signaling, and induces a series of antimicrobial responses such as induction of autophagy, phagolysosomal fusion, release, and activation of the antimicrobial peptide cathelicidin, and killing of intracellular *Mycobacterium tuberculosis* (Gibney et al., 2008; Kim et al., 2014). This study reported that active tuberculosis patient had deficiency-insufficiency vitamin D (**Table 3**).

What caused this? Propably there were many factors besides low intake of vitamin D food sources,

one of them was lower sunlight exposure. This could be one of the risk factor of lower 25(OH) D serum level, in this study found that most of the subjects were student, employed, and housewife (**Table 3**). This could be the reasons that they would avoid the sunlight. The tuberculosis patient had a job and all of them had to leave their house to stay at work place. Previous study also report that higher percentage women work indoors than outdoors, other factor was sunscreen application that lower the exposure (Sari et al., 2017b, 2017c).

Table 3. Serum levels of 25-hydroxyvitamin D and calcium

Parameters	Mean±SD; n (%)
25-hydroxyvitamin D serum levels (ng/mL)	22.8±5.6
Vitamin D status, n (%)	
Deficiency-Insufficiency	22(88)
Sufficiency	3(12)
Normal in sunny countries	-
Serum calcium (mg/dL)	9.1±0.5
Calcium classification, n(%)	
Low	2(8)
Normal	23(92)

Continues variable: mean ± SD; categorical variable: n (%); SD=standard deviation

Calcium serum level maintain ini normal range, probably because of lower calcium intake, another reason was calcium food sources that abundant in slight. Activity vitamin D in tuberculosis as an immunomodulator, the pathogenesis is when monocytes, and macrophages exposed to a lipopolysaccharide or to *Mycobacterium tuberculosis,* there is an up-regulate the vitamin D receptor gene and the 25-hydroxyvitamin D-1α-hydroxylase gene. This respons resulting an increased production of 1,25-dihydroxyvitamin D3, increase the synthesis of cathelicidin, a peptide capable of destroying *M. tuberculosis*.

Table 4. Serum levels of albumin dan hs-CRP

Parameters	Mean±SD; n (%)
Albumin (g/dL) Low	3.8±0.8
Normal High	6(24)
	19(76)
hs-CRP (mg/dL) Low inflammation	-
Active inflammation	49.1±15.7
	- 25(100)

Abbreviations: Continues variable: mean ± SD; categorical variable: n (%); SD=standard deviation

A reading above 10 mg/L of hs-CRP may signal a need for further testing to determine the cause of such significant inflammation in your body. The highest hs-CRP showed C-reactive protein (CRP) is produced by the liver. Its level rises when there is inflammation in the body. LDL cholesterol not only coats the walls of the arteries, but it also damages them. This damage causes inflammation that the body tries to heal by sending a "response team" of proteins called "acute phase reactants", one of them was CRP (Yoon, Davis, & Cattamanchi, 2013). This study showed that most of the subjects were active TB, and still had inflammation process, that affect malnutrition based on BMI and vitamin deficiency.

A suggestion which was nutritional supplementation in patients with TB is associated with better cure and treatment completion rates as well as better performance status. Limitation of this study that we did not assed parathyroid hormon and albumin serum that affect vitamin D and calcium metabolism.

4 CONCLUSIONS

Higher vitamin D deficiency-insufficiency found in this study, but not affecting calcium serum level. Based on biomolecular parameters such as albumin showed normal level, but there higher hs-CRP showed inflammation status reflecting tuberculosis progression.

ACKNOWLEDGMENTS

The authors gratefully acknowledge that the present research is supported by Ministry of Research and Technology and Higher Education Republic of Indonesia, Research and Community Service, Universitas Sumatera Utara. The support is under the research grant DRPM of Year 2018 Contract Number 263/UN5.2.3.1/PPM/KP-DRPM/2018.

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