ASSOCIATION BETWEEN VITAMIN D LEVELS WITH MDR-TB PATIENTS WITH HOUSEHOLD CONTACTS AND HEALTHY PEOPLE AS COMPARISON

[1]Nina Herlina, Bintang Yinke Magdalena Sinaga[1*], Parluhutan Siagian[2], Erna Mutiara[3]

[1]Faculty of Medicine, Universitas Malikussaleh, Kampus Unimal Uteunkot Cunda Lhokseumawe, Aceh Utara, Indonesia

[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Kampus USU Padang Bulan 20155, Medan, Indonesia

[3]Faculty of Public Health, Universitas Sumatera Utara, Kampus USU Padang Bulan 20155, Medan, Indonesia

dr.ninaherlina@unimal.ac.id

Abstract

Background: The high incidence of pulmonary tuberculosis (TB) progressing into multidrug-resistant TB (MDR-TB) has become a serious concern and caused a high mortality rate. The incidence of MDR-TB was 3.3% of new cases and 20% of cases of recurrent treatment. Low levels of vitamin D is a predisposing factor of MDR-TB, and family members in contact with the patient also show risk of infection. Currently, there is no study that compares vitamin D levels between MDR-TB patients and their household contact.

Method: This is a case control study, with the number of samples of each group (MDR-TB patients, household contact, healthy controls) 40 subjects, respectively. Each member of each group were checked for vitamin D levels using enzyme-linked immunosorbent assay (ELISA) technique.

Result: Mean levels of vitamin D in MDR-TB patients are 32.21, contact families 31.7 and healthy controls 26.86. There is a significant relationship between vitamin D levels and MDR-TB incidence (p=0.006).

Conclusion : There was no significant association between vitamin D deficiency level with MDR-TB. Vitamin D insufficiency was a protective factor for MDR-TB than in healthy control.

Keyword : *multidrug resistant tuberculosis, vitamin D, household contact*

BACKGROUND

MDR-TB is a TB caused by *M. tuberculosis* resistant to at least two of the most potent anti-tuberculosis (ATD) drugs rifampicin and isoniazid, with or without other first line ATDs. MDR-TB cases are more complicated due to worse prognosis, prolonged treatment, the risk of transmission to others, expensive cost, and the success rate of treatment by 50%, although by 2015 the success of MDR-TB treatment reaching ≥75 % has been achieved by 43 out of 127 countries. (Saltini et al, 2006; WHO, 2015)

Prevention of infection and early diagnosis of TB and drug-resistant-TB patients are often delayed. This is due to the tracking of close contacts not implemented optimally. A close contact with the symptoms of TB is one of a criterion of suspected drug resistance TB. (Ministry of Health, 2014). A study by Lutong et al (2000) reported that the prevalence of TB infection among household contacts was found to be 41-49%.

Vitamin D deficiency (VDD) as predisposing factor to the occurrence of TB has been suspected for a long time. The 80% source of vitamin D comes from sunlight, only about 20% comes from food including fortified fish, meat and food, which have previously been used as treatment in pre-antibiotic TB era. (Howthorne, 2011). Vitamin D plays a role in improving the immune factor and bone homeostasis. The active form of vitamin D is 1,25 dihydroxyvitamin D [1,25 (OH) 2D3] which has been shown to inhibit the growth of M. tuberculosis through innate immune enhancement (Yamshchikov et al, 2011). The role of vitamin D against MDR-TB has not been widely studied, but some studies have show that there is a relationship between low vitamin D levels and MDR-TB incidence. Research conducted by J. Rathored et al (2012) concluded that vitamin D deficiency may predispose to MDR-TB. Edem et al (2015) in Nigeria studied plasma vitamin D in patients with MDR-TB and found low-vitamin D levels in patients with MDR-TB before treatment.

METHOD

This study is a case control study, conducted by measuring vitamin D levels of MDR-TB patients, household contact and control of healthy people. This study was conducted in Haji Adam Malik Hospital Medan, North Sumatera, from August 2016 to April 2017.

The sample size was 120 people overall (40 MDR-TB patients, 40 household contacts and 40 healthy controls) who met the inclusion and exclusion criteria. The inclusion criteria for MDR-TB patients are those who have been diagnosed with MDR-TB based on the results of GeneXpert examination and have not been treated (have been taking ATD less than 7 days); male or female aged 18-65 years; willing to follow the research by informed consent. Household contact inclusion criteria are families that have direct contact with patients with MDR-TB for at least 24 hours; was declared healthy from clinical examination, chest X-Ray, blood glucose and urine examination; male or female age 18-65 years and willing to follow the research. The inclusion criteria for healthy control are no symptoms of pulmonary TB based on clinical and radiological examination; male or female 18-65 years of age and willing to follow studies expressed with informed consent. While exclusion criteria in all three subjects were HIV, diabetes mellitus, kidney disease, liver disease and other severe illnesses; were taking vitamin D supplements; were taking immunosuppressive drugs such as corticosteroids and cancer chemotherapy.

Examination of vitamin D levels from venous blood samples was performed using the Enzyme-Linked Immunosorbent Assay (ELISA) method in an integrated laboratory of North Sumatra University Faculty of Medicine, with criteria of vitamin D levels (25-OH vitamin D) divided into three groups including vitamin D less than 20 ng / ml (vitamin D deficient), vitamin D levels of 20-29 ng / ml (vitamin D insufficient), vitamin D levels more than or equal to 30 ng / ml (vitamin D sufficient). The results of vitamin D examination were processed by using a computer program.

RESULTS

The study included 120 research subjects. The highest proportion of sex in the MDR-TB group were male of 24 people (60%), household contact group were female of 21 people (52.5%), while in healthy people 31 people (77.5%) were male. There were significant differences based on gender characteristics of the three study subjects ($p = 0.02$). The distribution of frequency by age in the three groups was highest in the age range 22-40 years, i.e. 19 people (47.5%) in the MDR-TB group, 17 people (42.5%) in the household contact group and 23 people (57.5%) in healthy people group, there was no significant differences between groups ($p = 0.06$). Distribution of frequency based on occupation showed that most subjects in

MDR-TB group had “other” jobs (based on Table I) as many as 11 people (27,5%),

Table 1. Demographic Characteristics of the subjects in MDR-TB, household contact and healthy control

Karakteristik	TB-MDR		Household Contact		Healthy People		p-value
	n	(%)	n	(%)	N	(%)	
Gender							
Male	24	(60)	19	(47.5)	31	(77.5)	0.02
Female	16	(40)	21	(52.5)	9	(22.5)	
Age							
17-21 years	3	(7.5)	2	(5)	7	(17.5)	
22-40 years	19	(47.5)	17	(42.5)	23	(57.5)	0.06
41-60 years	16	(40)	14	(35)	8	(20)	
>60 years	2	(5)	7	(17.5)	2	(5)	
Occupation							
Unemployed	9	(22.5)	16	(40)	12	(30)	
Farmer	4	(10)	7	(17.5)	3	(7.5)	
Labor	7	(17.5)	4	(10)	5	(12.5)	0.07
Entrepreneur	4	(10)	11	(27.5)	6	(15)	
Government/Military	5	(12.5)	1	(2.5)	4	(10)	
Others	11	(27.5)	1	(2.5)	10	(25)	
Education							
None	1	(2.5)	0	(0)	1	(2.5)	
Elementary School	0	(0)	4	(10)	0	(0)	0.00
Secondary School	7	(17.5)	14	(35)	2	(5)	
High School	27	(67.5)	21	(52.5)	20	(50)	
BMI							
Underweight	39	(97.5)	5	(12.5)	9	(22.5)	
Normoweight	1	(2.5)	29	(72.5)	31	(77.5)	0.00
Overweight	0	(0)	6	(15)	0	(0)	

whereas most people in household contact group and healthy control group were unemployed (16 people (40%) and 12 people (30%), respectively). There was no

significant difference between groups (p=0.07). Based on the highest level of education, most people in the three groups of subjects studied high school (27 people (67.5%) in MDR-TB group, 21 people (52.5%) in household contact group and 20 people (50%) in healthy control group). And the highest frequency distribution based on BMI in MDR-TB group was 39 (97.5%) underweight, whereas most subjects in other groups were normoweight (29 people (72.5%) in household contact group and 31 people (77,5%) healthy control group).

Table 1. Distribution of ATT usage history among MDR-TB patients

History of ATT	MDR-TB	
	n	(%)
Relaps after category 1 ATT	2	(5%)
Failed with category 1 ATT	2	(5%)
Drug withdrawal in category 1 ATT	14	(35%)
Relaps after category 2 ATT	8	(20%)
Failed with category 2 ATT	4	(10%)
Drug withdrawal in category 2	10	(25%)
	40	100 %

*Category 1(2RHZE/4RH) *Category 2 (2RHZES/5RHE)

Table 2. Comparison of Vitamin D levels between MDR-TB, household contact and healthy control

	TB-MDR		Household Contact		Healthy control		p Value
	Mean	SD	Mean	SD	Mean	SD	
Vitamin D levels	32.21	11.15	31.7	9.11	26.86	6.22	0.021

* Kruskal wallis test

There was a significant difference of vitamin D levels between the three study groups (p = 0.021). The highest vitamin D levels were found in the MDR-TB group (32.21 ± 11.5), followed by vitamin D levels in the household contact (31.7 ± 9.11) and fthe lowest vitamin D levels were in the healthy group (26.86 ± 6.22).

By further analysis, it was found that significant differences were found between MDR-TB patients and healthy people (p = 0.029). Whereas between MDR-TB with household contact and between household contact with healthy person no significant differences were found (p=1.0 and p=0.055,

respectively). The results of the analysis are shown in table 4.

Table 4. Difference in mean vitamin D levels between groups

Group	Group in Comparison	p-Value
MDR-TB	Healthy control	0.029
	Household contact	1.0
Household contact	Healthy control	0.055

Association in Vitamin D levels between study subjects

Table 5. Association in Vitamin D levels between MDR-TB patients and household contacts

		MDR-TB		Household contact		p value	OR	95%CI
		n	(%)	N	%			
Vitamin D	Deficient	4	(10)	1	(2.5)	0.23	4	0.41-3.81
	Insufficient	13	(32.5)	16	(40)	0.66	0.81	0.32 -2.66
	Sufficient	23	(57.5)	23	(57.5)	-	1	1
	Total	40	100	40	100			

*logistic regression test

Table 6. Association in Vitamin D levels between MDR-TB patients and healthy controls

		MDR-TB		Healthy control		p value	OR	95%CI
		n	(%)	n	(%)			
Vitamin D	Deficient	4	(10)	4	(10)	0.299	0.435	0.09 – 2.69
	Insufficient	13	(32.5)	26	(65)	0.003	0.217	0.08 – 0.58
	Sufficient	23	(57.5)	10	(25)	-	1	1
	Total	40	100	40	100			

* logistic regression test

Table 6 shows the results of logistic regression test of vitamin D levels relationship to MDR-TB incidence with healthy people. Insufficient vitamin D levels is a protective factor for the incidence of MDR-TB (p = 0.003; OR = 0.217; 95% CI

0.08-0.58). While deficient vitamin D levels was not associated with MDR-TB incidence (p = 0.299; OR = 0.435; 95% CI 0.09 - 2.69).

DISCUSSION

The results of gender-based frequency distributions in this study showed there were more men in the MDR-TB group (n=24, 60%). L Surkova et al, (2012) stated that men are significantly easier to develop MDR-TB.

In this study we found low BMI or underweight in patients with MDR-TB as many as 39 (97.5%), there were significant differences between groups based on BMI (p = 0.00). BMI does not describe a person's vitamin D levels. In obese people (BMI> 27) the levels of 25 (OH) D were lower than those without obesity (Wortsman et al 2000). The low serum 25 (OH) D concentration is caused by increased serum 25 (OH) D absorption in fatty tissue, increased basal metabolic rate and the lifestyle of obese people who tend to be less fond of outdoor activities resulting in less sun exposure (Saliba et al, 2012). Hyun Oh Park et al in Korea found that low BMI is also a risk of failure of MDR-TB therapy. Lagunova et al (2009) found that people with IMT> 40 had low vitamin D levels, and a study conducted in Persahabatan Hospital (2012) found that low BMI prolonged sputum conversion time in MDR-TB patients.

MDR-TB incidence are affected by patient's non-compliance and history of ATD usage. In this study the highest category was in category 1 dropout (n=14, 35%). This could be caused by negligence and disobedience of patients in consuming ATT, oftentimes the patients had felt better after consuming ATT for 2 to 4 months, and they stopped before treatment is complete.

Based on this study, the frequency distribution of vitamin D levels in the three study groups showed that the MDR-TB group and the most vitamin D levels in household family were sufficient, and only 4 (10%) were deficient in patients with MDR-TB and healthy people. It can be concluded that MDR-TB patients and families who are in contact with patients with MDR-TB do not have significantly different levels of vitamin D, this may be influenced by the similar intake of food between the two groups, and according to literature the intake of vitamin D from food comprised 20% of total vitamin D levels, sunlight contributed the most about

80-90% through the synthesis of vitamin D from the skin, so it could be concluded that same house conditions, same sunlight sources between MDR-TB patients and contact families resulted in similar vitamin D levels between groups.

In this study it could be concluded that vitamin D deficiency did not correlate significantly with MDR-TB incidence, in healthy control the insufficient vitamin D level turned out to be a protective factor against MDR-TB incidence. This study is in line with the research of Jon et al in Medan (2015), who found that vitamin D deficiency levels did not correlate significantly with the incidence of pulmonary TB. Similarly, the study of Mashhadi SF et al (2014) in Islamabad also reported that the average vitamin D of MDR-TB patients did not show a significant association with the incidence of the disease. But it is not in line with Rathored et al's (2015) study, which found that vitamin D deficiency is a predisposing factor for MDR-TB. Iftikhar R et al (2013), also said that low vitamin D levels are present in people with MDR-TB. To further analyze the association of vitamin D levels in each group, logistic regression test was performed with no significant results between MDR-TB patients and contact families. Whereas the results of logistic regression test in MDR-TB group and healthy control, it was concluded that insufficient vitamin D levels is a protective factor against MDR-TB incidence (OR: 0.217; 95% CI; 0.08-0.58). Many factors that can lower the levels of vitamin D such as the source of food contained in food consumed, geographical location, duration of exposure to sunlight, weather (season), drugs, and impaired vitamin D absorption.

In this study, vitamin D levels of MDR-TB patients were higher than in household contact and healthy people, this may be possible because medical personnels have provided education to TB patients by advocating the consumption of foods that have high nutritional value, and the patients also received assistance from the government through healthy food provision, so that in patients with MDR-TB vitamin D levels are of sufficient value. Food sources of high vitamin D levels are cod liver oil, sardines and mackerel, salmon, margarine, cereal, milk and liver. In addition to dietary intake, vitamin D levels are also affected by sun exposure factors that contribute as much as 80% -90% in vitamin D synthesis. In this study, most samples of MDR-TB patients have occupations and outdoor activities so it is possible to get more sun exposure than indoor workers.

Vitamin D metabolism in the body is also influenced by vitamin D binding protein (DBP) that converts 7-dehydrocholesterol (7-DHC) to pre-vitamin D3 through ultraviolet B exposure, this is affected by the albumin content of each person. Intestinal malabsorption syndromes including cystic fibrosis, intestinal disease and inflammatory bowel disease may interfere with vitamin D absorption in the gut. (Margulies SL et al, 2015).

In this study, most subjects in healthy control group had low vitamin D levels (20-29ng / dl), this might be due to the samples were mostly taken from employees and medical personnel at the hospital, where most work and activities were indoors therefore acquired less sun exposure, and also influenced by lifestyles that avoid sun exposure, such as the use of sunblock that can cause low levels of vitamin D. Thus healthy control groups still have risk factors for MDR-TB infection, because the incidence of infection is not only due to vitamin D factors, but there are other more dominant factors such as contact history with TB patients. Consider vitamin D supplementation, bask in the sun for 10-15 minutes on healthy control to prevent the incidence of TB infection.

CONCLUSION

There was no significant association between vitamin D deficiency and MDR-TB incidence, low vitamin D levels in healthy control was a protective factor against the incidence of MDR-TB.

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