Serum vitamin D level and susceptibility to multidrug-resistant tuberculosis among household contacts

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Abstract. Low levels of vitamin D is a predisposing factor for Multidrug-resistant tuberculosis. Family members in contact with the patient are also at risk of infection. Currently, there is no study that compares vitamin D levels between MDR-TB patients and household contact. This study aims to identify the association between level vitamin D within MDR-TB occurrence. This was a case-control study, with the number of samples in each group (MDR-TB) patients and household contacts were 40 people. Each member of each group was checked for vitamin D levels using enzyme-linked immunosorbent assay (ELISA) technique. Statistical analysis was by using Chi-Square analysis using SPSS. Mean levels of vitamin D in MDR-TB patients were 32.21, household contact 31.7. There was a significant association between vitamin D levels and MDR-TB occurrence (p=0.01). No significant association between vitamin D level with the MDR-TB occurrence.

1. Introduction

The problem that arises in efforts to eradicate TB is multidrug-resistant tuberculosis (MDR-TB) caused by Mycobacterium tuberculosis resistance to anti-tuberculosis treatment (ATT). According to WHO (2011), there were an estimated 500,000 cases of TB resistant to isoniazid (INH) and rifampicin (MDR-TB) each year with a mortality rate of about 150,000 and only about 10% were diagnosed and treated. Globally, MDR-TB was reported to occur in 3.3% of new TB cases and 20% of previously treated cases, which has increased in recent years. In 2014, 480,000 cases were found and an estimated 190,000 people died from MDR-TB.[1] ATT resistance surveys in Indonesia had been conducted, among them were in Timika, Papua in 2004, where MDR-TB in new TB cases was 2%, whereas, in Central Java in 2006, it was 4.1% were new cases and 19.2% were previously treated cases (Ministry of Health, 2014). According to the data at Adam Malik Center General Hospital (RSUP HAM) Medan in 2015.

There were 142 MDR-TB patients. In 2016 there were 219 cases and as many as 215 from January to July 2017. This number indicates that the MDR-TB problem in North Sumatera and its surrounding areas is a serious problem and should be anticipated by finding more ways to therapy, mainly preventive and supportive.[2] Prevention of transmission and early diagnosis of both TB and MDR-TB is often delayed. It is due to screening detection of household contacts have not been implemented optimally. Household contact with the patient increases the risk of infection and develops into TB
especially if there is a decrease in the immune system. According to Lutong et al. (2000), the prevalence of TB among household contacts was between 41-49%. In addition to bacterial infections, environmental factors, lifestyle and genetic factors also contribute to causing illness.[3]

Factors that cause the occurrence of susceptibility and incidence of TB apart from the germ factor itself, is also caused by immune factors, namely the ability of the body's defense mechanism against infection (King, 2004). Vitamin D deficiency (VDD) as a predisposing factor to the occurrence of TB has been suspected since long. The richest source of vitamin D is acquired from sunlight and 10-20% comes from varieties of food, especially fortified ones, which have previously been used to treat TB in the era of pre-antibiotic treatment.[4]

The role of vitamin D against MDR-TB has not been widely studied. Rathored et al. (2012) concluded that vitamin D deficiency was thought to predispose the occurrence of MDR-TB. Another study conducted by Rathored et al. (2015) found low vitamin D levels in MDR-TB patients compared with TB patients and healthy people. Edem et al. (2015) in Nigeria studied plasma vitamins in patients with MDR-TB and found low levels of vitamin D in MDR-TB patients before treatment, then increased vitamin D levels in the fourth and sixth months of treatment.[5,6,7]

Based on the data above, there are allegations that vitamin D plays a role in the TB and MDR-TB occurrence. There is no study on vitamin D levels in MDR-TB patients compared to household contact with MDR-TB patients in Indonesia we conduct this research to see the role of vitamin D levels MDR-TB occurrence.

2. Methods
It was a case-control study designed to measure vitamin D levels in patients with MDR-TB and compare with household contact. This research was at Haji Adam Malik Hospital, Medan, North Sumatera from August 2016 until April 2017. Research subjects were 80 people (40 MDR-TB patients and 40 household contacts that fulfilled the criteria of the study, and purposed sampling technique is used. The inclusion criteria for patients with MDR-TB were new cases of MDR TB (untreated or had been treated in less than seven days), with GeneXpert test results showing a positive result for M.tuberculosis rifampicin-resistant, male and female age 18-65 years and agree to participate (informed consent). The inclusion criteria for the household contacts were those who are in contact with patients with MDR-TB over 24 hours who are healthy from clinical examination, Chest X-ray, and blood sugar tests. The exclusion criteria for the two groups were Human Immunodeficiency Virus (HIV), diabetes mellitus, kidney disease and liver disease as well as other serious illnesses, were taking vitamin D supplements, immunosuppressants such as corticosteroids and cancer chemotherapy. During the study, 3 ml venous blood sampling was performed, serum vitamin D (25-OHD) examination was performed using enzyme-linked immunosorbent assay (ELISA) method in the laboratory medical faculty of University of Sumatera Utara. Vitamin D deficiency if levels were <20 ng / mL, vitamin D insufficiency if levels were 20-29 ng / mL, and sufficient levels were ≥30 ng / mL. Results of serum vitamin D (25-OHD) were on the data collection sheets, and then data processing was performed using the SPSS program.

3. Results
The demographic characteristics of study subjects by gender, age, education, occupation, and BMI are in table 1. The highest proportion of sex in MDR-TB group was male (n=24, 60%). In household contact group there were 21 men (52.5%), no significant difference was between the two groups (p=0.26). The highest age proportion in the two study groups ranged from 22-40 years; there was no aspecific difference between the two groups (p=0.36). Most subjects in the two groups were employed, and there was aspecific difference between both groups (p<0.001). Most subjects in the two groups were senior high school graduates, and there were significant differences between the two groups (p=0.04). Based on BMI, subjects in MDR-TB group mostly were underweight (n=39, 97.5%) and in household contact mostly werenormomweight(n=29, 72.5%) and there was a significant difference between the two groups (p<0.001).
Table 1. Demographic characteristic of MDR-TB patients, household contact.

| Characteristic    | MDR-TB n (%) | Household Contact n (%) | P Value |
|-------------------|--------------|-------------------------|---------|
| Gender            |              |                         |         |
| Male              | 24 (60)      | 19 (47.5)               | 0.26    |
| Female            | 16 (40)      | 21 (52.5)               |         |
| Age               |              |                         |         |
| 17-21 years       | 3 (7.5)      | 2 (5)                   |         |
| 22-40 years       | 19 (47.5)    | 17 (42.5)               |         |
| 41-60 years       | 16 (40)      | 14 (35)                 | 0.36    |
| >60 years         | 2 (5)        | 7 (17.5)                |         |
| Occupation        |              |                         |         |
| Unemployed        | 9 (22.5)     | 15 (37.5)               |         |
| Employed          | 31 (77.5)    | 25 (62.5)               | P<0.001 |
| Education         |              |                         |         |
| None              | 1 (2.5)      | 0 (0)                   |         |
| Elementary School | 0 (0)        | 4 (10)                  |         |
| Middle School     | 6 (15)       | 14 (35)                 | 0.04    |
| High School       | 29 (72.5)    | 21 (52.5)               |         |
| D3/S1/S2/S3       | 4 (10)       | 1 (2.5)                 |         |
| BMI               |              |                         |         |
| Underweight       | 39 (97.5)    | 5 (12.5)                |         |
| Normoweight       | 1 (2.5)      | 29 (72.5)               | P<0.001 |
| Overweight        | 0 (0)        | 6 (15)                  |         |

Chi-square

Frequency distributions based on the history of anti-TB treatment use in the MDR-TB group were mostly in the withdrawal of category 1 medication (n=14.35%). In the household contact there is no history of previous use of anti-TB treatment and otherwise did not suffer from TB according to clinical and radiological examination.

Table 2. Frequency distribution of anti-TB treatment history in MDR-TB patients.

| History of ATT                                 | MDR-TB n (%) |
|-----------------------------------------------|--------------|
| Relapse after category 1<sup>a</sup> ATT       | 2 (5%)       |
| Failed with category 1 ATT                    | 2 (5%)       |
| Drug withdrawal in category 1 ATT             | 14 (35%)     |
| Relapse after category 2<sup>b</sup> ATT       | 8 (20%)      |
| Failed with category 2 ATT                    | 4 (10%)      |
| Drug withdrawal in category 2                 | 10 (25%)     |
| Total                                         | 40 100%      |

<sup>a</sup>Category 1 (2RHZE/4RH)<br><sup>b</sup>Category 2 (2RHZES/5RHE)

3.1. Statistical Analysis

There was no significant difference in vitamin D levels between MDR-TB group and household contact group (p=1.0). The mean vitamin D levels in MDR-TB were 32.21 +/- 11.5 and household contact 31.7 +/- 9.11.
Table 3. It is a comparison of vitamin D levels between MDR-TB and household contact.

| Vitamin D level | MDR-TB | Household Contact | p-value |
|-----------------|--------|-------------------|---------|
|                 | Mean   | SD    | Mean | SD   |         |
| Kruskal-Wallis test | 32.21 | 11.15 | 31.7 | 9.11 | 1.0     |

To see the association of vitamin D levels with confounding variables such as gender, age, occupation, education, and BMI, multivariate analysis was conducted. Of the five variables, three of them showed significant differences, occupation, education, and BMI. In education and BMI, variables cannot be continued with multivariate analysis because there was a zero value on the distribution of education and BMI. The only occupation could be continued with multivariate analysis table 4.

Table 4. Association of vitamin D levels - occupation between MDR-TB and household contact.

| Level vitamin D | MDR-TB | Household Contact | p-value | OR | 95% CI |
|-----------------|--------|-------------------|---------|----|--------|
|                 | n (%)  | n (%)             |         |    |        |
| Deficient       | 4 (10) | 1 (2.5)           | 0.14    | 5.89 | 0.55-62.1 |
| Insufficient    | 13 (32.5) | 16 (40)       | 0.80    | 0.88 | 0.34-2.30 |
| Sufficient      | 23 (57.5) | 23 (57.5)      | -       | 1.00 | 1.00    |
| Occupation      | Unemployment | 9 (22.5)   | 0.09    | 0.40 | 0.14-1.15 |
|                 | Employment  | 31 (77.5)   | -       | 1.00 | 1.00    |

Logistic Regression Test

Table 4 shows the results of logistic regression test of vitamin D levels association to MDR-TB incidence with household contacts as a control. Deficient vitamin D levels and insufficiency did not associate with MDR-TB incidence (p>0.05). Occupational status was also not significantly related to the incidence of MDR-TB.

4. Discussion

The incidence of MDR-TB associated with several influencing factors, such as gender, age, education, occupation, and BMI. The results of agender-based frequency distribution in this study showed that men in MDR-TB group were 24 people (60%), while women 16 people (40%). L Surkova et al. stated that men are significantly more susceptible to develop into MDR TB, whereas Rathored et al. showed that sex has nothing to do with the incidence of MDR TB.

A study in China by Li Xin-Xuet al(2015) showed that educational level was an independent predictor of MDR-TB occurrence. In this study, the demographic characteristics of education in the two largest groups were high school, and there were significant differences between the two study groups (p= 0.04). There were also significant differences between the two groups based on occupation, but after a multivariate analysis with logistic regression testing, we found no significant association between the work and the incidence of MDR-TB.

In this study, we found that low BMI or underweight in the MDR-TB group were 39 people (97.5%), there were significant differences in the two study groups based on BMI (p<0.001). Many studies linking BMI to the incidence of MDR-TB and vitamin D levels, such as Hyun Oh Park et al in Korea, suggested that low BMI was a risk of failure of MDR-TB patients therapy.[9] Shown that BMI more than 40 had low vitamin D levels, and in PersahabatanHospital (2012) it was shown that low BMI prolongs sputum conversion time in MDR-TB patients.

Historical use of anti-TB treatment can affect the occurrence of MDR-TB, in this study the most category was found in category 1 drug withdrawal, as many as 14 people (35%). It could be due to negligence and disobedience of patients in consuming anti-TB treatment, the patient tended to feel better after consuming the drugs for 2 to 4 months and they stopped for themselves before the regiment was completed.
It is the first study comparing vitamin D level of patients with MDR-TB with household contact as control. The author chose this group as a control with the assumption that the household contact lives in the same house as the patient so that the food is eaten and exposure to sunlight are similar. In this study, there is a nonsignificant association between vitamin D levels and MDR-TB occurrence. Rathored et al (2015) showed that vitamin D was a predisposing factor for MDR-TB. Iftikhar R et al (2013) that showed low vitamin D was present in people with TB. This study in line the research of Jon et al in Medan concluded that vitamin D levels did not significantly associate with pulmonary TB incidence. In this may be due to vitamin D was not the only cause of MDR-TB and many factors could influence the incidence of MDR-TB.

5. Conclusion
There was no significant association between vitamin D deficiency and MDR-TB occurrence. Vitamin D levels of most MDR-TB sufferers are sufficient, as well as household contacts. The mean vitamin D levels between MDR-TB and household contact patients did not differ significantly, and there is no significant association between occupational status and the occurrence of MDR-TB.

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