ORIGINAL ARTICLE

The Prevalence of Diabetes Mellitus among Hospitalized Tuberculosis Positive Case Admitted in Hajj Hospital, Surabaya, Indonesia

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ABSTRACT

Introduction: Tuberculosis (TB) is the cause of significant health and death problems worldwide. Indonesia is known as the second highest country with TB burden in the world after India. The incident of TB is further increasing in diabetes mellitus patients. Diabetes mellitus disrupts the body's immune function; thus, patients are more susceptible to infection, including TB. The purpose of this study was to determine the prevalence of diabetes mellitus history (DM) among newly diagnosed TB patients in Surabaya. **Methods:** 160 patients were grouped into two groups; the first group (67 patients) was positive for TB and diabetes mellitus, and the second group (93 patients) was positive for TB only. Data were collected from TB patients based on acid-fast bacilli stain (AFB) and positive Xpert MTB/RIFF. Blood glucose level was collected from 2hrPPG, and glycated hemoglobin (HbA1c). **Results:** The prevalence of TB related with DM history was 42% from 55 ± 9.52 years old. Patients with TB-DM showed poor glucose blood level, their 2hrPPG was 301.43 ± 126.80 mg/dl, and the HbA1c result (> 6.5%) was 82%. The rifampicin resistant level result was not significantly different between TB and TB-DM (4.4% and 3% respectively). **Conclusions:** Our results highlight the incidence of DM history in TB positive patient that was hospitalized in Hajj Hospital. Therefore, it is important to monitor the prevalence of DM in TB newly diagnosed cases to assist practitioner to choose better treatment while considering the risk of DM interference.

Keywords: Tuberculosis, DM, rifampicin sensitive

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INTRODUCTION

Tuberculosis has remained a cause of global health problem. Tuberculosis is caused by *Mycobacterium tuberculosis*. This bacterium is known as a slow-growing bacterium, which is also known as a single infectious agent that can be included as one of the ten highest causes of death in the world. In 2017, it was estimated around 10 million patients infected with TB and 1.6 million patients have died (1). Indonesia has ranked second in the highest burden of TB, and TB cases in Indonesia have never reduced since many cases were undetected. Based on data by the Ministry of Health in 2017, 360.700 cases were found to be TB positive, and among them, 168.412 cases were acid-fast bacilli smear-positive (2). At the same time, Indonesia also has a high burden for diabetes. According to Ministry of Health, diabetes prevalence in adult (2013) is around 6.9%. These numbers reduce to 6.3% in 2017. Indonesia has been ranked in the seventh position for diabetes prevalence in the world (3). The bidirectional association between TB and DM is one of the significant concerns worldwide with the correlation between diabetes and tuberculosis which is increasingly being recognized and managed (4).

Diabetes mellitus (DM) is categorized as a metabolic disease which is caused by abnormalities in insulin secretion, insulin action or both; thus, it will lead to high blood glucose levels (hyperglycemia). Patient with diabetes showed impaired innate immune system caused by the high level of blood glucose (5). Diabetes can disrupt the activation and function of macrophages, monocytes, lymphocytes, pulmonary microangiopathy, renal dysfunction and vitamin deficiency. Patient with poor control of hyperglycemia is more susceptible to TB infection compared to a patient with good control of hyperglycemia (6). Prevalence of TB was increased threefold in people with diabetes (7). Thus, it is necessary to monitor the prevalence of TB infection in DM patients in Surabaya.

The objective of the present study is to describe the prevalence of DM history in patients with TB positive cases. These data are necessary to raise awareness in an attempt to reduce the susceptibility of TB from DM patient and reduce the mortality rate caused by these dual epidemics. Tuberculosis infection among diabetes mellitus patients in Indonesia is still interested since now Indonesia has faced a double threat not only from TB but also from DM.

MATERIALS AND METHODS

A cross sectional study was conducted at General Hospital Hajj, Surabaya between January to December 2017. All patients were TB positive. Inclusion criteria were set; patients with all gender and all age, positive TB which were confirmed by sputum smears positive for Acid Fast Bacteria (AFB), or were confirmed by rapid diagnostic tests such as Xpert MTB/RIF only or sputum smears positive for AFB and positive with a rapid diagnostic test such as Xpert MTB/RIF. All patients were verified with DM history. Diabetes positive was confirmed with a random blood sugar of greater than 200mg/dl, fasting plasma glucose higher than 126 mg/dl and glycated hemoglobin (HbA1c) of greater than 6.5% before taking anti-tuberculosis therapy. All data were statistically analyzed (descriptive and analytical statistics) using Microsoft Excel for Mac version 16.25. Correlation analysis were performed using Chi-Square Test and difference among samples were analyzed with t-test.

RESULTS

Sputum Smear and Xpert MTB/RIF Combination Method Result in Higher Detection of Patient with Positive Tuberculosis

Among 160 patients, combinations method by using sputum smear and Xpert MTB/RIF yield a higher result in detecting tuberculosis positive (Table I). However, our statistical analysis failed to detect any significant difference among those three methods in detecting TB positive regarding patients' gender. Though it was noticed that there was male predominance in TB and TB-DM infection (86 male patients and 74 female patients), but this was not significant between female and male patients (χ^2 = 1, p =0.75, Table I).

The prevalence of DM among patient with TB positive

From 160 patients with TB positive cases, it was found later from medical record that 67 patients (42%) were known to have been diagnosed with DM. Meanwhile, 93 patients (58%) did not have DM history. Table I shows that smear sputum result showed positive results in 47 patients (45.6%) with DM and other 56 patients (54.4%) without DM. Smear sputum result showed that both TB and TB-DM patients were predominantly positive 1 according to International Union Against Tuberculosis and Lung Disease (IUATLD) scale (Figure 1). From Xpert MTB/RIF result (Xpert MTB/RIF only or Xpert MTB/RIF and smear sputum) showed that 53 patients (39%) with DM and other 83 patients (61%) without DM showed a positive result for TB.

Table I: Distribution of TB positive cases as regards different methods of identification

	Sputum Smear	Xpert MTB/RIF	Sputum Smear & Xpert MTB/RIF	Total	Chi Square	p-value
Gender					0.7	0.70
Female	13 (8.1)	23 (14.4)	38 (23.8)	74 (46.25)		
Male	11 (6.9)	28 (17.5)	47 (29.4)	86 (53.75)		
Total	24	51	85	160		

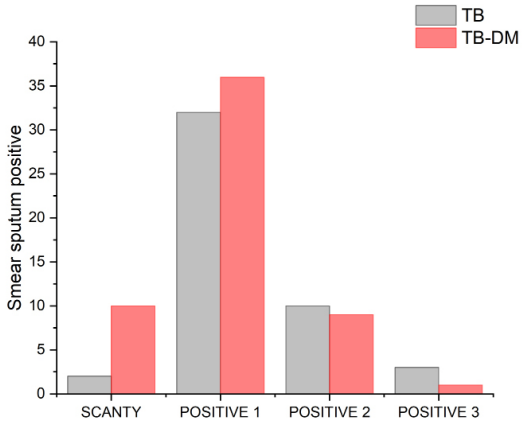

Figure 1: Distribtuion of smear sputum result based on IUATLD scale. TB and TB-DM patient were categorized as positive one was found significantly higher as compared to other scales. Scanty means 1 to 9 AFB in 100 fields; Positive 1 means 10 to 99 AFB in 100 fields; Positive 2 means 1 to 10 AFB per field in at least 50 fields; Positive 3 means > 10 AFB per field in at least 20 fields.

We want to check whether prevalence of DM history in TB positive cases were affected by different in gender, ages or rifampicin resistance. Our results showed gender did not contribute in the prevalence of DM history in TB positive cases χ^2 (1,160) = 1 with p= 0.75). Meanwhile, different in ages showed a correlation with the prevalence of TB-DM ((χ^2 (2, 157) = 26.60; p< 0.001, Table II). Mean age of TB and TB-DM patients was significantly different (p<0.05) Figure 2) since patient age variance among TB was greater compared to those data from TB-DM patients.

DM patient has poor diabetes control

Diabetes mellitus patients were presented with 2-hour post-prandial blood glucose (2hrPPG) control of glucose blood level ≥ 200 mg/dL dan HbA1C > 6.5% (8,9). Post prandial blood glucose (2hrPPG) in TB-DM patients was 301.43 ± 126.80 mg/dl (N=54). Among 54 TB patients, 83.3% of the patients (N=45) were categorized as patients with poor glycemic control (2hrPPG ≥ 200 mg/dL). Meanwhile, 7.04% of the patients (N=4) were categorized as impaired or poor glucose tolerance (2hrPPG from 140 to < 200mg/dL) and 9.3% of the

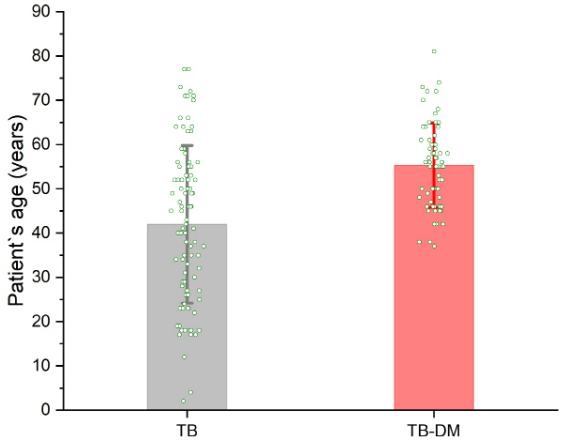

Figure 2: . Distribution of TB and TB-DM as regards of patient age. Scatter plot showed all data. The bars showed mean for each group meanwhile the error bar represent +/- standard deviation

Table II: Distribution of TB and TB-DM cases as regards patient gender, age and Xpert MTB/RIF

	TB (%)	TB-DM (%)	Total (%)	Chi Square	#p
Gender				0.11	0.75
Female	42 (56.8)	32 (43.2)	74 (100)		
Male	51 (59.3)	35 (40.7)	86 (100)		
Total	93 (58.1)	67 (41.9)	160 (100)		
Age					
< 40 years	38 (24.2)	3 (1.9)	41 (26.1)	26.60	1.66E-06
40-60	40 (25.5)	45 (28.7)	85 (54.1)		
>60	14 (8.9)	17 (10.8)	31 (19.7)		
Total	92 (58.6)	65(41.4)	157 (100)		
Xpert MTB/RIF					
MTB/RIF SENSITIVE	77 (56.6)	49 (36)	126	0.005	0.95
MTB/RIF RESISTANCE	6 (4.4)	4 (3)	10 (7.4)		
Total	83 (61)	53 (39)	136 (100)		

*2 patients age was unknown The data showed number of cases (%)

patients were normal. According to HbA1C level, 86.7% of the patients showed poor glycemic control (N=13) with HbA1C >6.5% bad control of glucose blood level.

Rifampicin resistance among TB and TB-DM patients

Rifampicin resistance/sensitive test showed that among 136 patients who were diagnosed with Xpert MTB/RIF method, 10 patients (7.4%) showed resistance to rifampicin. Group of TB-DM patient and TB patient showed 3% and 4.4% resistance to rifampicin respectively. The pattern of rifampicin resistance does not have any correlation with the prevalence of TB-DM since the number of rifampicin sensitivity in both cases (TB and TB-DM) were high (($\chi^2(1,136) = 0.005$, $p > 0.05$, Table II).

DISCUSSION

The prevalence of DM in TB positive case is high considering the previous studies showed that the prevalence of DM among TB patients was 13.2% (14) and 14.8% (12). These discrepancies are probably due to the different sample size from the previous studies (400-600 patients while our samples 160 patients).

The comparison between gender showed that there was no correlation between the difference in gender and the prevalence of TB-DM although it is often observed that the rate of TB infection is high in men compared to women. It is believed that male dominance in TB infection is caused by the underdiagnosis of TB cases in women (12). One may suggest that female exhibits more-robust immune response to antigenic challenges than man (13). Thus, it is convinced that those rules are also accounted for TB infection.

In age comparison, we showed that TB-DM was more frequently found in 40-60 years range. Similar results also showed TB-DM patients mean age was 53 years vs TB patient was 44 years (14). These results were often seen as DM type 2 is more prevalent in older age.

The previous study by Alisjahbana et al. in 2007 stated that DM was associated with more symptoms but not with the increased severity of TB. Our recent study did not address this issue. However, our study wants to show that DM patients with poor control of their diabetes can be infected with TB. Other studies showed that DM patients had three times chance of developing TB compared to the non-DM population (15-17). Although TB is believed to be strongly associated with immune deficiency disease such as HIV, but the number of people infected with DM is much higher than that of immunocompromised states which make it prominent factor associated with TB at the population level (18). In Asian countries in which TB and DM have coexisted as a dual burden, these dual diseases can exist probably as a result of external (poor glycemic control) and internal factors (specific mechanisms of insulin resistance, genetic susceptibility to DM (19).

Our 2 hrPPG level and HbA1C level results showed similarities with other results from Diabcare-Asia project which conducted the cross-sectional survey from 24.317 patients from Bangladesh, China, India, Indonesia, Malaysia, Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand and Vietnam. The study found that, among diabetic patients, 55% of them had HbA1C level exceeding 8% (20). Persistent hyperglycemia in DM patients can alter the immune response to Mycobacterium tuberculosis (Mtb). This alteration was associated with changes in the innate and cellular cytokine response to Mtb (21). Thus, DM patients have a reasonable reason in increasing their

risk to TB infection. But from our present data, we need to elaborate a greater number of patients with TB and patients with TB-DM in order to give a good clinical picture of DM relation with TB infection in Surabaya.
Other concerns arise from multiple drug resistance-tuberculosis (MDR-TB) cases to rifampicin. Rifampicin resistant TB (RR-TB) can be defined as resistance to rifampicin with or without resistance to other first-line anti TB drugs using genotypic or phenotypic methods. Multidrug resistance TB (MDR-TB) can be caused by Mycobacterium tuberculosis that is resistant to isoniazid (H) and rifampicin (R) with or without resistance to other drugs. MDR-TB is treatable but costly and it requires long time treatment with potential toxic drug (22). The data from WHO estimates that 3.5% of all new TB cases had MDR-TB or rifampicin-resistant TB (23). Our result also showed similar trend with this report. Several studies also showed patients with DM and patients that recently were diagnosed positive for TB had an increased risk of MDR-TB cases (24-26).

Most cases of MDR-TB are emerged from a mixture of physician error, inadequate and incomplete treatment and patient non-compliance during the treatment of susceptible Tb (27-28). Meanwhile, the correlation between increasing number of MDR strains of Mtb in a TB-DM patients can be explained by the association of poor glucose control and dysfunction of phagocytosis, reactive oxygen species (ROS) production, chemotaxis and T-cell reaction in DM patients (29). The other reasons seem caused by less virulent MDR strain of Mtb which is more likely to flourish in an immunocompromised patient with DM (30-31).

Our results suggest that the initial screening for the newly diagnosed patients with TB for its correlation with DM history is important. Our plan will include more patients from another hospital in Surabaya to get a better understanding of the real correlation between DM and TB positive cases in Surabaya. Thus, that information will be useful in choosing TB treatment while considering the risk of DM interference in TB therapy. Patients with DM were also encouraged to control their diabetic level to avoid another infection such as TB.

CONCLUSION

This study showed 42% of the prevalence of Diabetes Mellitus history in recently diagnosed TB patients in Surabaya. Indonesia is widely recognized to have the dual epidemic burden; TB and DM. Therefore, a concerted effort is needed to monitor the prevalence of this dual epidemic for a better outcome.

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