Influence of Diabetes Mellitus on the Development of Multi Drug Resistant-Tuberculosis in Yogyakarta

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ABSTRAK

Latar belakang: *hubungan antara diabetes melitus (DM) dan Multi Drug Resistant Tuberculosis (MDR-TB) belum pernah diteliti di antara pasien Tuberkulosis (TB) di Indonesia, sedangkan DM diketahui dapat mengganggu respons kekebalan tubuh dan memengaruhi farmakokinetik obat TB sehingga dapat menyebabkan kegagalan pengobatan TB dan terjadinya MDR-TB. Penelitian ini bertujuan untuk menganalisis pengaruh DM pada perkembangan MDR-TB.* ***Metode:*** *studi kohort retrospektif dilakukan dengan melibatkan 356 pasien TB di Balai Pengobatan Paru-paru (BP4) dan Rumah Sakit Sardjito, Yogyakarta, Indonesia pada tahun 2010-2014. Diagnosis MDR-TB ditentukan dengan GeneXpert atau drug sensitivity testing, sementara DM ditentukan berdasarkan kriteria pedoman nasional. Beberapa variabel demografik, epidemiologi, dan hasil pengobatan dikumpulkan. Rasio odds (OR) dan selang kepercayaan 95% (95% CI) dianalisis dengan simple logistic regression.* ***Hasil:*** *di antara 356 pasien TB, 23 orang adalah pasien dengan DM, sedangkan 333 pasien tidak menderita DM. Pasien dengan tuberkulosis dan diabetes melitus memiliki risiko 6,8 lebih besar (95% CI:2,0-23,7, p=0,003) untuk berkembang menjadi MDR-TB. Individu dengan tuberkulosis dan diabetes melitus memiliki kemungkinan 4,4 lebih besar (95% CI:1,5-12,9, p=0,008) untuk memiliki hasil sputum positif pada bulan kedua pengobatan yang mengindikasikan keterlambatan dalam proses penyembuhan dari tuberkulosis.* ***Kesimpulan:*** *terdapat hubungan yang bermakna antara diabetes melitus dengan perkembangan MDR-TB. Oleh karenanya, direkomendasikan bagi klinisi di semua lapis pelayanan kesehatan untuk melakukan tes skrining MDR-TB di antara pasien kelompok ini. Penelitian kohort prospektif perlu dilakukan untuk mengkonfirmasi hasil dari penelitian pendahuluan ini.*

Kata kunci: *diabetes melitus, tuberkulosis, faktor risiko, Indonesia.*

ABSTRACT

Aim: *the correlation between diabetes mellitus (DM) and Multi-Drug-Resistant Tuberculosis (MDR-TB) has never been studied among patients with tuberculosis (TB) in Indonesia, while DM has been identified to alter immune response and pharmacokinetics of TB medications that may lead to a failure of TB treatment and develop MDR-TB. Our study aimed to analyze the influence of diabetes mellitus on the development of MDR-TB.* ***Methods:*** *a retrospective cohort study was carried out on 356 TB patients at the Provincial Lung Clinics and Sardjito Hospital, Yogyakarta, Indonesia between 2010 and 2014. Diagnosis of MDR-TB was established based on GeneXpert or drug sensitivity testing, while DM was determined based on the criteria in the National Guidelines. Demographic, epidemiological and outcome variables were collected. Odds ratios and 95% confidence intervals (95% CI) were analyzed using simple logistic regression.* ***Results:*** *among 356 TB patients, 23 patients were with binomial TB-DM, while 333 patients did not suffered from DM. Patients*

with TB-DM presented a 6.8-fold (95% CI:2.0-23.7, p=0.003) higher risk of developing MDR-TB. Individuals with TB-DM had a 4.4-fold (95% CI:1.5-12.9, p=0.008) greater chance to have positive sputum smear by the second month of treatment indicating a delay in the resolution of the tuberculosis infection. ***Conclusion:*** *there was a significant correlation between diabetes mellitus and MDR-TB development. Therefore, it is suggested that clinicians at all levels of health care service should conduct any kind of screening test for MDR-TB in such group of patients. Further prospective cohort study is needed to confirm the findings of this preliminary study.*

Keywords: *diabetes mellitus, tuberculosis, risk factors, Indonesia.*

INTRODUCTION

Diabetes mellitus (DM) influences the natural development of tuberculosis (TB) through depressed cellular immunity, alveolar macrophages dysfunction, low interferon gamma level, pulmonary microangiopathy and micronutrient deficiency.[1,2] Globally, 70% of diabetics live in TB endemic countries. Type-2 DM was found in around 2 - 9% of the population in 22 countries with the highest burden of TB.[3] Indonesia, with the second highest burden of TB in the world,[4] has the seventh largest number of diabetics.[5] The prevalence of Type-2 DM among TB patients in Indonesia was relatively low (13.2%). However, it was significantly associated with TB.[6]

Indonesia is also one of the ten countries that currently have been estimated to have the highest number of Multi Drug Resistant-Tuberculosis (MDR-TB).[4] MDR-TB is TB that does not respond to at least isoniazid and rifampicin treatment, the main anti-TB medications.[4] The prevalence of type-2 DM among MDR-TB patients in Indonesia has not yet been known. However, some studies have revealed that type-2 DM has been found among 18.8-23.3% of MDR-TB patients in some public hospitals in Indonesia.[7,8] The association between type-2 DM and MDR-TB is not entirely clear and different studies have revealed conflicting results. Some studies demonstrated that there was no association between type-2 DM and MDR-TB,[9,10] while other reported that the risk of MDR TB increased among diabetic patients.[11,12] However, type-2 DM has been shown to increase the risk of delayed sputum conversion and treatment failure.[6,11,13]

The correlation between type-2 DM and MRD -TB has never been studied among patients with TB in Indonesia. Therefore, our study aimed to analyze the influence of type-2 DM on the development of MDR-TB in Indonesia.

METHODS

As a preliminary study, our retrospective cohort study was carried out involving all TB patients who were admitted to the Provincial Lung Clinics and Dr. Sardjito Referral Hospital, Yogyakarta, Indonesia between 2010 and 2014. The criteria for establishing the diagnosis of type-2 DM was in line with the National Guidelines and was carried out by a physician. Individuals who had fasted for at least 8 hours and showed a plasma glucose concentration of ≥126 mg/dl were considered diabetic.[14] The diagnosis of DM was also made if patients had a history of known DM or had received antidiabetic agents. Diagnosis of TB was established based on clinical examination, positive sputum smear examination for acid-fast bacilli (AFB) and or positive chest X-ray, which were consistent with the National and International Guidelines.[15] All TB patients were treated according to the National and International Guidelines.[15] MDR-TB diagnosis was determined by an examination using GeneXpert MTB/RIF (Cepheid, US) or drug sensitivity testing at the Laboratory of TB, Department of Microbiology, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta. At the beginning of treatment, a routine blood examination was conducted, and Human Immunodeficiency Virus (HIV) testing was performed for all patients.

Patient Selection

All pulmonary TB patients who were treated at the Provincial Lung Clinics and Dr. Sardjito Hospital were included in our study. MDR-TB patients were selected based on the

results of drug sensitivity or GeneXpert testing, which were registered in their medical records. Exclusion criteria were those who were less than 18 years old and had incomplete medical record. The study was conducted in accordance to the Helsinki Declaration of 2008 and had been approved by the Medical and Health Research Ethics Committee at Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia on November 3rd, 2012 with reference number KE/FK/855/EC. Based on the calculation of sample size formula for a cohort study ($Z\alpha$=1.96, p0=2.8%, p1=23.3%, $Z\beta$=0.80, and m=6.58; based on previous data on DM prevalence of TB and MDR-TB patients in Indonesia), the minimum sample needed in the exposed group was 24 patients. Since it was a preliminary study, 23 patients were considered as acceptable sample size.

Data Collection

Epidemiological and clinical variables were obtained from medical records. The collected data variables were age, sex, body mass index (BMI), smoking status, an ethnic group, history of TB contact, history of TB treatment, result of sputum smear taken at the time of diagnosis and after two months of treatment, presence of a cavitary lesion on chest X-ray, and results of drug resistance test. Study participants were followed-up retrospectively through medical record until the end of treatment.

Data Analysis

Bivariate analysis was carried out using Chi square test or Fisher's exact test. A logistic regression was carried out to determine whether the type-2 DM was associated with multi drug resistance tuberculosis. Univariate test were done to type-2 DM and other factors. Factors with $p<0.20$ then were included in the multivariate model, $p<0.05$ was considered significant. Odds ratios (OR) and 95% confidence intervals (95% CI) were also calculated. SPSS software program version 24.0 (IBM, USA) was used for the calculations.

RESULTS

We excluded 35 patients due to incomplete data. **Table 1** shows general characteristics of 356 individuals included in the study. Among the 356 TB patients, 23 patients were with binomial tuberculosis – diabetes mellitus and 333 TB patients did not suffered from diabetes mellitus. Demographic characteristics were similar between TB patients with and without DM. Patient with DM had more cavitary lesion (p=0.005) and positive sputum smear examination after two months treatment (p=0.2) than those without DM.

Table 1. Characteristics of TB patients with and without diabetes mellitus (DM)[a]

Characteristics (N=356)	TB-DM n (%)	TB-nonDM n (%)	Total n (%)
Age (years), mean (SD)	42.48 (14.23)	36.79 (14.89)	37.01 (0.79)
Age >37 years	12 (52.17)	131 (39.30)	143 (40.20)
Male sex	17 (73.91)	205 (61.56)	222 (62.36)
BMI <18.5 or >25 kg/m^2	17 (73.91)	262 (78.68)	279 (78.37)
Ethnic group:			
- Javanese	21 (91.30)	304 (91.29)	325 (91.29)
- Others (Sundanese, Batak, others)	2 (8.70)	29 (8.71)	31 (8.71)
History of smoking	7 (30.4)	113 (33.9)	120 (33.7)
History of TB contact	5 (21.7)	93 (27.9)	98 (27.53)
Previous TB treatment	3 (13.0)	17 (5.1)	20 (5.6)
Cavitary disease	12 (52.2)	84 (25.2)	96 (26.97)
Positive SSM result at diagnosis	22 (95.65)	316 (94.89)	338 (94.94)
Positive SSM result at 2 mo of treatment	5 (21.7)	20 (6.01)	25 (7.0)
MDR-TB	4 (17.4)	10 (3.0)	14 (3.93)

SD: standard deviation; SSM: sputum smear examination; [a] Data are n (%) unless otherwise stated

Table 2 shows factors significantly associated with MDR-TB development, which include age older than 37 years old (p=0.04), female (p=0.04), had previous TB treatment ($p<0.001$) and was with DM (p=0.009). Among the TB-DM patients, 4 patients (17.4%) developed MDR-TB. The univariate analysis showed that patients

with binomial tuberculosis - diabetes mellitus presented a 6.8-fold (95% CI:2.0-23.7, p=0.003) higher risk of developing MDR-TB compared to those without DM (**Table 3**). Meanwhile, the effect of DM increased (OR=17.9, 95%CI: 3.3-96.8) when analyzed together with other factors. Factor of previous TB treatment was not included in the multivariate analysis because of its wide confidence interval. Individuals with binomial tuberculosis- diabetes mellitus had a 4.4-fold (95% CI:1.5-12.9, p=0.008) greater chance to have positive tuberculosis result of sputum smear after the second month of treatment indicating a delay in the resolution of the tuberculosis infection (**Table 4**).

Table 2. Factors associated with MDR-TB[a]

Characteristics	MDTR-TB		Total (N=356)	P value[b]
	Yes	No		
Age >37 years	11 (78.6)	132 (38.6)	143 (40.2)	0.004
Female sex	9 (64.3)	125 (36.5)	134 (37.6)	0.04
BMI <18.5 or >25 kg/m^2	14 (100)	265 (77.5)	279 (78.37)	0.05
Ethnic group:				
- Javanese	14 (100)	311 (90.9)	325 (91.29)	0.62
- Others (Sundanese, Batak, others)	0 (0.0)	31 (9.1)	31 (8.71)	
History of smoking	2 (14.3)	118 (34.5)	120 (33.7)	0.15
History of TB contact	2 (14.3)	96 (28.1)	98 (27.53)	0.37
Previous TB treatment	13 (92.9)	7 (2.0)	20 (5.6)	<0.001
Cavitary lung lesion on radiology	1 (7.1)	95 (27.8)	96 (26.97)	0.12
Positive SSM result at diagnosis	12 (85.7)	326 (95.3)	338 (94.94)	0.15
Positive SSM result after 2 mo of treatment	2 (14.3)	23 (6.7)	25 (7.0)	0.26
Presence of DM	4 (28.6)	19 (5.6)	23 (6.5)	0.009

[a] Data are n (%) unless otherwise stated.
[b] Chi square test or Fisher's exact test were used when appropriate

Table 3. Analysis between the significant factors associated with MDR-TB and the development of MDR-TB

Variables	Total n (%)	MDRTB n (%)	Bivariate		Multivariate	
			OR (95% CI)	P-value[a]	OR (95% CI)	P-value[b]
Age>37 years	160 (44.94)	10 (71.43)	5.8 (1.6-21.3)	0.01	6.7 (1.7-26.3)	0.01
Female sex	134 (37.6)	9 (64.3)	3.12 (1.0-9.5)	0.045	6.1 (1.4-26.8)	0.02
History of smoking	120 (33.7)	2 (14.3)	0.3 (0.1-1.4)	0.14	0.3 (0.1-1.7)	0.20
Previous TB treatment	20 (5.6)	13 (92.9)	622.1 (71.2-5434.2)	<0.001	-	-
Cavitary lung lesion on radiology	96 (27.0)	1 (7.1)	0.2 (0.03-1.6)	0.12	0.1 (0.01-1.1)	0.06
Positive SSM result at diagnosis	338 (94.9)	12 (85.7)	0.3 (0.1-1.4)	0.13	0.4 (0.1-2.2)	0.30
DM	23 (6.5)	4 (28.6)	6.8 (2.0 – 23.7)	0.003	17.9 (3.3-96.8)	0.001

[a] Calculated with simple logistic regression; [b] Calculated with multiple logistic regression.

Table 4. Association between DM and positive SSM result after 2 months of treatment

Variables	Total - n (%)	TB-DM - n (%)	TB-non DM - n (%)	OR (95% CI)	P value
Positive SSM result at 2 mo of treatment	25 (7)	5 (21.7)	20 (6)	4.4 (1.5-12.9)	0.008

[a] Calculated with simple logistic regression

DISCUSSION

Our study showed that type 2 DM was significantly associated with the development of MDR-TB in Yogyakarta, Indonesia. The mechanism could be explained by lower plasma concentrations of anti TB drugs, particularly rifampicin,[16] due to altered drug absorption, distribution, metabolism and excretion in TB patients with DM. The intestinal motility in diabetics is also lower, thus reduces gastric emptying, changes the pH levels and results in delayed absorption of some drugs. Moreover, a study showed that TB diabetic patients had rifampicin serum levels that were 53% lower in TB non-diabetic patients.[16] The low plasma level of anti-TB drugs was proposed to cause poor treatment outcome, in which risk on treatment failure was almost nine folds higher in patients with low drug exposure compared to patients with higher drug exposure. Furthermore, it also has an association with acquired drug resistance.[17,18] Another hypothesis includes the mutations of katG gene. The gene has a function to protect the Mycobacterium tuberculosis against oxidative stress and to encode catalase-peroxidase that induces isoniazid into its active form. In diabetic patients, there might be improved production of reactive oxygen species, thus the strains with such mutations are more likely to survive.[19,20]

Our study also revealed that diabetic TB patients had delayed resolution of tuberculosis infection as shown by positive tuberculosis result of sputum smears in the second month of treatment. The findings are consistent with results of previous study that has identified a longer sputum conversion time in diabetic TB patients compared to non-diabetics.[21] It might be related to altered immune response against tuberculosis found in diabetic patients, thus leading to higher baseline mycobacterial burdens in comparison to non-diabetic patients and resulting in longer sputum conversion time.[21,22] Moreover, another study in Indonesia revealed that despite the similarity of culture conversion proportions for diabetic TB patients and non-diabetic TB patients after 2 months of treatment, the rate of treatment failure among diabetic TB patients was higher (22.2%) compared to the rate among non-diabetic TB patients (9.6%).[23] Meanwhile, patients with previous treatment failure will obtain longer treatment duration, which will increase the likelihood of developing drug-resistant mutation.

We also found that patients with DM in our study had more cavitary lesions. Our finding is in accordance with results of some previous studies,[22,24] and the reason proposed was due to uncontrolled glycemic level (HbA1c≥7) or insulin dependency.[9] However, we could not collect data of neither HbA1c levels nor insulin dependency. Therefore, we could not confirm the hypothesis. In addition to the presence of diabetes mellitus, our data also revealed that being older than 37 years old, female and had previous TB treatment gave higher risk of developing MDR-TB. Previous studies indicated conflicting results for older age as a predisposing factor for MDR-TB.[25,26] However, in our study, it might be caused by the delayed diagnosis of MDR-TB since the free-cost and prompt diagnosis device for MDR-TB (GeneXpert) in Yogyakarta was just available recently in 2012. Female gender as a risk factor for the development of MDR-TB may be explained by low health-care seeking behavior among women when the disease was still not progressive, which corresponds with results of an earlier study.[27] However, the role of this factor needs further investigation. Meanwhile, a history of previous TB treatment has already been stated as one of the strongest predisposing factors of MDR-TB by WHO and some previous studies. It may be caused by multi-factorial causes, such as non-adherence, low level of drugs, poor health system, and human error.[4,10,28] In 2015, WHO reported that 12% of TB patients in Indonesia who were treated for TB in the past were estimated to develop MDR-TB.[4]

To prevent the development of MDR-TB among TB diabetic patients, clinicians need to pay attention on the co-management of TB and DM. A glycemic control could be hindered by TB infection, especially in the early stage of TB treatment. In this stage, increased inflammation would occur due to early bacterial killing, which may escalate insulin resistance.[29] Furthermore, there is a drug-drug interaction between TB and DM drugs. Rifampicin decreases the plasma levels of some oral anti-diabetic drugs, especially

sulphonylureas and biguanides; while in patients using isoniazid, worse glycemic control may occur due to sulphonylureas.[30] Moreover, rifampicin serum levels in TB diabetic patients are lower than TB non-diabetic patients.[16] In addition, the side effects of co-administrating TB and diabetes medications might influence patient adherence, which is another predisposing factor for developing MDR-TB. Therefore, a strict glycemic control together with monitoring the blood levels of anti-diabetes and anti-TB drugs during TB treatment may give benefits to improve treatment outcome. Despite having high numbers of estimated cases of DM and MDR-TB,[4,5] the integrated systems for communicable and non-communicable diseases have not yet been well developed in Indonesia.

There are some limitations in our study. The results of sputum examination is limited to the results of sputum smear on microscopic examination since culture examination is expensive and rarely conducted although culture would provide more information. Our study also has a relatively small sample size, thus our findings need to be confirmed in larger sample and in this way, we may assess other risk factors for drug resistance.

CONCLUSION

Our study shows that diabetes mellitus increases the risk of developing MDR-TB. Therefore, it is suggested that clinicians at all levels of health care service should make an appropriately targeted early clinical suspicion and conduct any kind of screening test of MDR-TB for such group of patients. Further prospective cohort study should be conducted to confirm these preliminary findings.

ACKNOWLEDGMENTS

The work was supported by the Directory of General Higher Education (DGHE) of Indonesia. Authors retain the copyright to their work. The authors declare no competing financial interests.

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