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Research Report

PREVALENCE AND RISK FACTORS OF DIABETES MELLITUS IN TUBERCULOSIS PATIENT AT PATRANG DISTRICT INDONESIA

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ABSTRACT

Tuberculosis (TB) is one of cause of death in infectious disease domain. The control of TB is complicated because the inclination of case numbers people with Diabetes Mellitus. Diabetes Mellitus (DM) is an important risk factor for TB development, with prove that more than ten percent of TB patient is DM patient. People with DM have risk three times more likely to suffer from TB than people without DM. The results of TB treatment with comorbid DM will be easier to be failed. Puskesmas Patrang have the highest bacteriologically confirmed BTA TB cases and DM cases in Jember during 2014 until 2016. The aim of this research is to know the DM prevalence in TB patients and to analyze the correlation between DM risk factors in TB patient to TB-DM incidence at Puskesmas Patrang Jember in 2017. The research uses observasional analytic with cross sectional approach. The sampling technique uses simple random sampling with 47 samples. The independent variables include respondent characteristics (age, sex, type of TB, medication category, and family history of DM), central obesity and smoking behavior. While the dependent variable is the DM status. The result shows that the prevalence of DM in TB patients at Puskesmas Patrang Jember regency is 23.4%. Factors associated with TB-DM are age (p -value = 0.012), family history of DM (p -value = 0.003), and smoking status (p -value = 0.035). Factors that do not associated with TB-DM are sex (p -value = 0.731), type of TB (p -value = 0.170), treatment category of TB (p -value = 0.560), central obesity (p -value = 0.435), the number of cigarette (p -value = 1.000) and smoking duration (p -value = 1.000). The most important factor of TB-DM is family history of DM that 10,850 times higher of getting TB-DM than patients without family history of DM.

Keywords: TB, DM, risk factors of DM

ABSTRAK

Tuberkulosis (TB) adalah salah satu penyebab kematian dalam kelompok penyakit menular. Pengendalian TB dipersulit karena kecenderungan kasus penderita Diabetes Melitus. Diabetes Melitus (DM) merupakan faktor risiko penting untuk perkembangan TB, dengan bukti bahwa lebih dari sepuluh persen penderita TB merupakan penderita DM. Penderita DM berisiko 3 kali lebih tinggi untuk menderita TB dibandingkan dengan orang tanpa DM. Hasil pengobatan TB dengan komorbid DM akan lebih mudah mengalami kegagalan. Puskesmas Patrang memiliki kasus TB BTA terkonfirmasi bakteriologis dan DM tertinggi di Kabupaten Jember selama tahun 2014 sampai 2016. Penelitian ini bertujuan untuk mengetahui prevalensi DM pada pasien TB dan mengetahui hubungan faktor risiko DM pada pasien TB terhadap kejadian TB-DM di Puskesmas Patrang Kabupaten Jember tahun 2017. Penelitian ini menggunakan metode penelitian analitik observasional dengan pendekatan cross sectional. Teknik pengambilan sampel menggunakan metode simple random sampling dengan jumlah sampel sebanyak 47 orang. Variabel bebas penelitian meliputi karakteristik responden (usia, jenis kelamin, jenis TB, kategori pengobatan, dan riwayat DM pada keluarga), obesitas sentral dan perilaku merokok. Sedangkan variabel terikat penelitian yaitu status DM. Hasil penelitian menunjukkan bahwa prevalensi DM pada pasien TB di Puskesmas Patrang Kabupaten Jember yaitu sebesar 23,4%. Faktor yang berhubungan secara signifikan dengan kejadian TB-DM yaitu usia (p -value = 0,012), riwayat DM pada keluarga (p -value = 0,003), dan status merokok (p -value = 0,035). Sedangkan faktor yang tidak berhubungan secara signifikan dengan kejadian TB-DM yaitu jenis kelamin (p -value = 0,731), jenis TB (p -value = 0,170), kategori pengobatan TB (p -value = 0,560), obesitas sentral (p -value = 0,435), jumlah rokok yang dihisap (p -value = 1,000) dan lama merokok (p -value =

1,000). Faktor yang paling berhubungan terhadap kejadian TB-DM adalah riwayat DM pada keluarga dengan risiko sebesar 10.850 kali untuk menderita TB-DM dibandingkan pasien tanpa riwayat DM pada keluarga.

Kata kunci: TB, DM, faktor risiko DM

INTRODUCTION

Tuberculosis (TB) is infectious disease that caused by *Mycobacterium tuberculosis* (*M.tb*) which can attack various organs especially the lungs.¹ TB is one of 10 causes of death in the world and the leading cause of death in the world in infectious disease domain.² Diabetes Mellitus (DM) is a metabolic disorder disease characterized by elevated blood sugar levels due to decreased insulin secretion by pancreatic beta cells and or insulin function i.e. insulin resistance. Diabetics are three times more likely to have TB than people without DM.³ TB patients with DM were at risk for the failure of sputum conversion after undergoing TB treatment, 1.69 times higher risk for treatment failure, 1.24 times higher for anti tuberculosis drug resistance, 3.89 times higher for relapse, and 4.95 times higher risk for death during treatment than those without DM.⁴ Previous TB-DM studies have found that age, sex, pulmonary TB, and family history of DM are associated with TB-DM incidence.⁵ Other studies were found that age, family history of DM, alcohol consumption, and central obesity were associated factors with TB-DM incidence.^{6,7}

TB-DM is a problem in TB endemic countries with lower middle income because 70% of DM patients live in TB endemic countries and 80% of DM patients live in lower middle income countries.^{8,9} Indonesia is in 4th highest TB cases below India, China and South Africa with 48,000 cases.¹⁰ East Java is in second place of highest bacteriologically confirmed BTA TB cases after West Java and is included in the top 10 of DM patients in Indonesia.^{11,12} Jember has the second largest number of bacteriologically confirmed BTA TB cases after Surabaya and has DM patients of 8619 people by 2012.^{13,14} Puskesmas Patrang has the highest cases of TB BTA confirmed bacteriology and DM cases with 111 cases of TB BTA confirmed bacteriology and 371 DM cases by 2016.

Studies on the effect of DM on TB epidemiology in 13 high TB burden countries were showed that 6 million TB cases and 1.1 million TB deaths can be avoided through DM control.⁸ Previous studies have suggested that risk factors for DM incidence in TB patients include race, age, sex, type of TB, treatment category, family history of DM, central obesity, smoking, and alcohol. Race is thought to be due to genetic factors that contribute to the incidence of insulin resistance. People who have black skin are more susceptible to DM than people with white skin. TB-DM patients are generally occur in old age especially after the age of 40 years. The aging process causes the ability of pancreatic beta cells in producing insulin reduced.^{15,16} TB-DM is more common in men than women as a result of risk factors such as smoking and alcohol consumption.¹⁷

Based on type of TB, DM is more common in pulmonary TB patients than extrapulmonary TB.¹⁸ The prevalence of recurrent TB is higher in TB-DM patients than TB without DM. TB-DM patients are 3.9 times more likely to get TB relapse than TB without DM.¹⁹ DM tends to be inherited so the family members of patients with DM have the possibility of 2-6 times suffering DM compared with family members who do not suffer from DM.²⁰ Another factor is central obesity which can lead to insulin resistance due to excess fat that makes insulin work difficult so that blood sugar levels rise.¹⁵ Based on the previous research, majority of TB-DM patients had ever use tobacco (78,3%). The effect of nicotine causes a decrease in insulin release due to catecholamine hormone activation, a negative effect on insulin action, impairment of pancreatic β cells and leads to insulin resistance.²¹ Alcohol can affect the endocrine glands by releasing epinephrine that leads to transient hyperglycemia and hyperlipidemia so that alcohol consumption is contraindicated with diabetes.²²

The problem of TB-DM in Jember especially in Puskesmas Patrang tends to be in the top three highest cases of bacteriologically confirmed BTA TB and DM during 2014-2016. A bacteriologically confirmed BTA TB cases for three consecutive years i.e 94, 107 and 111 and DM cases for three consecutive years i.e 2049, 1011 and 371 cases. The declining of DM cases may be caused by undiagnosed patients. DM patients are usually asymptomatic but it is still a risk of TB-DM incidence. Moreover, TB-DM problem in Jember has not been studied more deeply, therefore we need to know the risk factors of DM incidence in TB patient at Puskesmas Patrang Jember in 2017 for preventing and controlling DM incidence in TB patient considering its impact if TB and DM occur together. The purpose of this research is to know the risk factors of DM incidence in TB patients at Puskesmas Patrang Jember in 2017.

MATERIAL AND METHOD

This research uses observational analytic method with cross sectional approach. The research was conducted at Puskesmas Patrang Jember in August 2017. The number of samples were 47 TB patients using simple random sampling technique.

The variables of this research consist of independent and dependent variables. The independent variables include respondent characteristics (age, sex, type of TB, medication category, and family history of DM), central obesity and smoking behavior. While the dependent variable is the DM status.

Table 1. Prevalence of Diabetes Mellitus in Tuberculosis Patient at Puskesmas Patrang in 2017

DM Status	Frequency (people)	Percentage (%)
TB-DM	11	23.4
TB	36	76.6

Sources of research data consist of primary data and secondary data. Primary data was obtained from interview and measurement of abdominal circumference in TB patients. Secondary data was obtained from the data of quarterly reports of new cases of TB BTA confirmed bacteriologic finding in Health Office Jember district during 2014-2016, DM report data at Health Office Jember district during 2014-2016 and form TB 01 at Puskesmas Patrang Jember district in 2017.

Data collection techniques are conducted through interview, measurement and observation. Instrument of data collection was determined using questionnaire and meter measuring tool. Data analysis techniques used univariate, bivariate analysis using chi-square, and multivariate using logistic regression.

RESULT AND DISCUSSION

Prevalence of Diabetes Mellitus in Tuberculosis Patient at Puskesmas Patrang Jember in 2017

Patients with TB as respondents in the study were 47 respondents. The respondents were divided into TB-DM patients and TB patients. TB-DM patients were TB patients who also were diagnosed by health professionals suffering from DM or taking DM drug while TB patients were those who only suffer TB. Prevalence of DM in TB patient can be seen in Table 1.

In Table 1, the prevalence of DM in TB patients is 23.4%. This figure exceeds the prevalence of DM only in the population in Indonesia that is 3.2%. In addition, Alisjahbana found that DM is more common in patients with TB than in control subjects. Of 454 TB patients, 60 patients (13.2%) have DM rather than of 556 non TB patients, 18 patients (3.2%) have DM.²³ Guptan and Shah (2000) were stated that impaired glucose tolerance (IGT) in TB is much higher than overt DM. According to the National Diabetes Data Group of NIH, one to five per cent of patients with IGT may progress to overt DM. In 1990, Fong Y et al was stated that glucose intolerance due to TB occurs because of increased cytokines IL-1 and TNF alpha which can stimulate the anti insulin hormones. In addition, in 1993, Sinurova et al was stated that cortisol which controls blood sugar levels also decrease. Even, TB germs are able to release toxins through the bloodstream or TB germs directly attack the pancreas that causes the production of amyloid (abnormal protein) in the pancreas which further inflict DM.^{24,25} The mechanism is the reason why DM is more prevalent in people with TB than in general population. The exceeds of the DM prevalence in

Table 2. Distribution of Tuberculosis Patient Characteristics by Age, Gender, Type of Tb, Treatment Category, and Family History of DM in Puskesmas Patrang Jember in 2017

Characteristics	Frequency (people)	Percentage (%)
Age		
≥ 45 years old	18	38,3
< 45 years old	29	61,7
Sex		
Male	26	55,3
Female	21	44,7
Type of TB		
Pulmonary	39	83,0
Extrapulmonary	8	17,0
Treatment Category		
Category 2	3	6,4
Category 1	44	93,6
Family History of DM		
Yes	12	25,5
No	35	74,5

TB patient rather than in general population also occurs in countries where TB and DM cases are most prevalent.⁸ Another research which conducted by Raghuraman *et al* in India also found higher prevalence of DM in TB patients that is 29% than the prevalence of DM in the population. The population is 7% because India is included in high load TB cases that have a growing number of DM cases.⁶

Relationship between Respondent Characteristics with TB-DM Incidence in Tuberculosis Patients at Puskesmas Patrang Jember in 2017. Characteristics are the attributes or things possessed by an element. Characteristics of respondents in this study include age, sex, type of TB, treatment category, and family history of DM. The distribution of TB patient characteristics can be seen in Table 2. Based on Table 2, out of 47 patients were enrolled for this research, most TB patients are < 45 years old (61,7%). Indonesia's Health Profile (2017) was also stated that the highest proportion of TB cases are found in the < 45 years old. During 2012-2016, the proportion is 61.48%, 60.96%, 60.26%, 60.31%, and 59.91%.²⁶ TB can attack anyone, especially the productive age (15-50 years old). People with productive age are easy to interact with others, high mobility makes it possible to transmit bacteria to others. Infant or younger than 4 years old also have greater risk of experiencing the progression of TB infection because the T-cell mediated immune response of young children is not fully developed (immature) so it works inefficiently to antigen challenge.²⁷⁻²⁹

This research was also found that most TB patients are males (55,3%). Males are at higher risk of developing TB than females because they have smoking habit that makes lung function impaired, damages the macrophages as cells that can eat bacteria, making it easier to get TB.^{28,30} Based on National Health Indicator Survey (SIRKESNAS) in 2016, the prevalence of smoking in male is 59% and female is 1.6%.²⁶

Table 2 also was showed that most of respondents had pulmonary tuberculosis (83%). According to the definition, TB is a contagious infectious disease caused by *Mycobacterium tuberculosis* that can attack various organs especially the lungs. TB transmission occurs through sputum sparks containing TB bacteria that are transmitted when people with TB cough or sneeze, so that pulmonary TB is the most common clinical manifestation compared to other organs.^{1,31}

Most TB patients in this research are in undergoing category 1 treatment (93,6%) especially TB BTA confirmed bacteriologically. The number of TB BTA confirmed bacteriology cases can be used as an indicator of TB patient discovery to achieve National indicators. National indicators are indicator of TB programs that can measure the success of a program.³² It means more getting TB BTA confirmed bacteriologically patients among suspected sputum examination, getting treated faster.

The result was showed that the majority of TB patients have no family history of DM. In this study, family history of DM was not associated with the incidence of TB. Patient who has family history of DM is 2-6 times higher to get DM. DM is characterized by hyperglycaemia due to insulin secretion defect, insulin work or both. Hyperglycaemia is capable of causing immune disorders i.e decreased gamma interferon function (IFN γ) which serves to stimulate macrophages to kill *M.tuberculosis* through the mechanism of endocytosis into the macrophages. This indicates that in this study there are other risk factors that cause TB such as

close contact with untreated TB patients, lack of nutritional status, low immunity, and smoking habits.^{28,33}

The relation between the characteristics of respondents with TB-DM incidence could be identified through bivariate analysis. The related factors of TB-DM incidence were age and family history of DM. The unrelated factors of TB-DM incidence were sex, type of TB, and treatment category. Table 3 gives the bivariate analysis of the relation between respondent characteristics and TB-DM incidence at Puskesmas Patrang Jember in 2017.

Table 3 was showed that TB-DM was associated with older age. This result is in line with research by Raghuraman et al (2014) that found the median age of TB-DM patients that was 49.5 ± 11.8 .⁶ While Mansuri et al (2015) found the average age of TB-DM patients is 47 ± 16 .⁷ TB-DM tends to be experienced by people with old age as a result of DM cases often found in old age.^{8,34} The risk of developing DM usually appears after 45 years old. At that age there is a physiological decline in humans that affects the reduced ability of pancreatic beta cells in the production of insulin.^{15,16}

Family history of DM was also significantly related to TB-DM incidence. Most patients with family history of DM tend to suffer from TB-DM (14.9%) than suffering TB (10.6%). These results are in line with other research that the family history of DM is associated with TB-DM incidence.⁶ DM tends to be inherited rather than transmitted. Family members of patients with diabetes (diabetics) are 2 to 6 times more likely to suffer DM compared to family members who do not have DM.²⁰

This research has not found any significant association between sex and TB-DM. Similar results were reported by researches by Raghuraman *et al* and Mansuri *et al*.^{6,7} But the other study by Suwanpimolkul *et al* was stated that men was associated with TB-DM. Men are 1.66 times more likely to have TB-DM than women.³⁵ In this research, most of the men (40.4%) and women (36.2%) only had TB.

Type of TB was found to be statistically insignificant. Previous research also was found that the type of TB was not significantly related to TB-DM incidence.⁷ Different results were found by Workneh *et al* (2016) that pulmonary TB was significantly associated with TB-DM incidence. The prevalence of pulmonary TB among TB-DM patient was higher (64.2%) than TB patient (58.1%).⁵ While in this research, patients with pulmonary TB tend to suffer from TB (59.6%) than TB-DM (23.4%). It is also known that all extrapulmonary TB patients suffer from TB with percentage of 17%.

Treatment category was also found to be statistically insignificant. There are two treatment category i.e category 1 that consists of TB BTA confirmed bacteriology, pulmonary TB patients diagnosed clinically, and extrapulmonary TB and category 2 that consists of relapse, drop out, and fail treatment.³² This result is in line with other researchers that also found that treatment category 2 was not significantly associated with TB-DM.^{6,7} But, research which was conducted by Mi et al (2013) found that category 2

Table 3. Bivariate Analysis of The Relation between Respondent Characteristics and Tb-DM Incidence in Tuberculosis Patients at Puskesmas Patrang Jember in 2017

Characteristics	Status DM		p-value	OR (95% CI)
	TB-DM n	TB N		
Age				
≥ 45	8	10	0,012*	6,933 (1,525-31,515)
< 45	3	26		1
Sex				
Male	7	19	0,731	1,566 (0,389-6,298)
Female	4	17		1
Type of TB				
Pulmonary	11	28	0,170	-
EP	0	8		-
Treatment Category				
Category 2	1	2	0,560	1,700 (0,139-20,749)
Category 1	10	34		1
Family History				
Yes	7	5	0,003*	10,850 (2,304-51,101)
No	4	31		1

EP = extrapulmonary

*Significant $\leq \alpha$ (0,05)

Table 4. Bivariate Analysis of The Relation Central Obesity and TB-DM Incidence in Tuberculosis Patients at Puskesmas Patrang Jember in 2017

Central Obesity	DM Status		p-value	OR (95% CI)
	TB-DM	TB		
	n	N		
Yes	4	8	0,435	2,000 (0,465-8,597)
No	7	28		1

*Significant $\leq \alpha$ (0,05)

significantly associated with TB-DM. They found a higher prevalence of treatment category 2 in patients with TB-DM (13.8%) than TB patients (7.9%). They also were stated that the risk of patient with category 2 treatment was 1.7 times more likely suffering TB-DM than patient with category 1 treatment.¹⁹ In this research, the prevalence of patient with treatment category 2 among TB group (4.3%) is higher than TB-DM group (2.1%). Furthermore, the prevalence of patient with treatment category 1 among TB group (72.3%) is higher than TB-DM group (21.3%).

Relationship between Central Obesity and TB-DM Incidence in Tuberculosis Patient at Puskesmas Patrang Jember in 2017 Cental obesity is fat accumulation in the abdominal area that exceeds normal value. Respondents were classified as central obesity if the abdominal circumference is ≥ 90 cm for men and ≥ 80 cm for women. The relation between central obesity and TB-DM incidence is shown in Table 4.

In Table 4, central obesity is not significantly related to TB-DM incidence (p-value = 0.435). This result is in line with a study by Raghuraman *et al* (2014) who found central obesity was not statistically related to TB-DM incidence.⁶

In central obesity occurs fat accumulation in the body exceeds the normal value in the abdominal area.³⁶ Futhermore, fat in the stomach causes fat cells to secrete proinflammatory chemicals that make the body less insensitive to insulin by disrupting the function of insulin responsive cells and the ability of cells to respond insulin. The more fat deposits in the stomach, the more difficult the insulin works so that blood sugar rises.^{15,37} But, in this research, majority of respondent or 74.5% are not categorized to central obesity that respectively is 59,6% for TB patients and 14,9% for TB-DM patients. Research by Raghuraman *et al* was also found that majority of respondent were not categorized to central obesity (90,3%).⁶ Relationship between Smoking Behaviour with TB-DM Incidence in Tuberculosis Patients at Puskesmas Patrang Jember in 2017.

TB-DM risk factors also were influenced by smoking behaviour variables. Smoking behavior variables in this study include smoking status, number of cigarettes, and smoking duration. The results of the bivariate analysis between smoking behaviour and TB-DM incidence are listed in Table 5. In Table 5, only smoking status was associated with the incidence of TB-DM (p-value = 0.035).

Table 5. Bivariate Analysis of Smoking Behaviour with TB-DM Incidence in Tuberculosis Patients at Puskesmas Patrang Jember in 2017

Smoking Behaviour	DM Status		p-value	OR (95% CI)
	TB-DM	TB		
	n	n		
Smoking Status				
Yes	3	1	0,035*	13,125 (1,203-143,233)
No	8	35		1
The Number of Cigarettes				
> 10	1	1	1,000	-
≤ 10	2	0		
Smoking Duration				
> 20 years	1	1	1,000	-
≤ 20 years	2	0		

*Significant $\leq \alpha$ (0,05)

While the number of cigarettes (p-value = 1,000) and duration of smoking (p-value = 1,000) are not significantly related to TB-DM incidence.

Research by Viswanathan *et al* was stated that smoking was risk factor for TB-DM. People that smoking is at risk 1.92 times higher than that of non-smokers.¹⁷ Smoking causes inflammation and oxidative stress in the cells of the body thus increasing the risk of developing DM. Nicotine content in cigarettes can lead to decreased insulin secretion, impaired function in pancreatic beta cells, increased beta cell apoptosis and risk of insulin resistance by binding and activating nicotinic acetylcholine receptors (nAChRs) which are part of the transmembrane group of protein chanel ions in the central nervous system and the peripheral nervous system. Activation of nAChRs results in the increase and release of catecholamines in the bloodstream which can result in increased blood pressure, free fatty acid, and blood sugar mobilization/in contrast to the effects of insulin. Exposure to nicotine in a short time (more than 1 $\mu\text{mol/L}$) and within 48 hours can inhibit the release of insulin. The risk of people who smoke is 30-40% higher for DM than nonsmokers.^{21,38} Most Associated Factor with TB-DM in Tuberculosis Patients at Puskesmas Patrang Jember in 2017

The most associated factor with TB-DM in TB patients in Patrang Health Center in Jember Regency in 2017 could be known through multivariate analysis. Based on bivariate analysis, variables that could be analyzed using multivariate analysis were age, family history of DM, and smoking status. The result of multivariate analysis aims to get the most dominant independent variable related to the dependent variable by looking at the biggest OR value. The analysis can be seen in Table 6.

Based on Table 6, it can be seen that the history of DM in the family was the most associated factor with TB-DM incidence. TB patients who had a family history of DM is at risk 18.250 times higher for getting TB-DM rather than TB patients with no family history of DM.

Table 6. Analysis of Most Associated Factor with TB-DM Incidence in Tuberculosis Patient at Puskesmas Patrang Jember in 2017

Variable	Coefficient	p-value	OR	Confidence interval 95%
Age				
≥ 45	2,875	0,016*	17,717	1,710-183,506
< 45			1	
Family History				
Yes	2,904	0,014*	18,250	1,813-183,708
No			1	
Smoking Status				
Yes	1,841	0,174	6,303	0,444-89,439
No			1	

*Significant $\leq \alpha$ (0,05)

This result is similar with research by Sirait *et al* that the risk of DM was 2.4 times greater in those whose parents had a history of DM compared with those whose parents had no history of DM.³⁹ The magnitude of family history is possible because of a genetic defect of pancreatic β cells and is possible due to genetic abnormalities in the action of insulin in the presence of abnormalities in insulin receptors.⁴⁰

CONCLUSION

The conclusion of this research is the prevalence of DM in TB patients in Puskesmas Patrang higher than prevalence of DM in general population in Indonesia. In Indonesia, East Java is in the second place of highest TB cases under West Java. Further the second city of highest TB cases in East Java is found in Jember especially in Puskesmas Patrang which not only tend to be in the top three highest cases of TB but also tend to be in the top three highest cases of DM. Factors associated with TB-DM incidence are age, family history of DM and smoking status. Factors unassociated with TB-DM incidence were gender, type of TB, treatment category, central obesity, number of smoked cigarettes and duration of smoking. Factors most associated with TB-DM incidence is family history of DM.

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