

# Association of Obesity and Negative Acid-Fast Bacilli Finding Among Pulmonary Tuberculosis Patients with Type 2 Diabetes Mellitus

## Hubungan Obesitas dan Temuan Bakteri Tahan Asam (BTA) Negatif Pada Pasien Tuberkulosis Paru dengan Diabetes Melitus Tipe 2

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### ABSTRAK

Obesitas merupakan faktor protektif terhadap terjadinya tuberkulosis paru (TB Paru) pada populasi non-diabetes. Namun, pengaruh obesitas pada pasien dengan diabetes melitus tipe II (DMT2) belum banyak diketahui. Studi ini bertujuan untuk mengetahui hubungan obesitas dan TB Paru pada pasien dengan DMT2. Studi merupakan studi potong lintang yang dilakukan di instalasi rawat inap, Departemen Penyakit Dalam, Rumah Sakit Umum Pusat Fatmawati pada bulan Januari 2015 sampai dengan Desember 2017. Kriteria inklusi pada penelitian ini adalah pasien DMT2 yang telah terdiagnosa dengan TB paru dan berusia  $\geq 18$  tahun. Pada studi ini, hasil Bakteri Tahan Asam (BTA) negative didefinisikan sebagai tidak ditemukannya BTA pada pemeriksaan mikroskopik sputum subjek, sementara obesitas didefinisikan sebagai index massa tubuh  $> 24.9$  kg/m<sup>2</sup>. Dari 363 subjek dengan TB paru dan DMT2, 22.59% subjek mengalami obesitas. Prevalensi BTA negative pada pasien dengan TB paru dan DMT2 adalah 81.82%, temuan tersebut diketahui berhubungan dengan kejadian obesitas ( $p:0.002$ ,  $OR=6.36$ ,  $95\%CI 1.9-21$ ). Kesimpulan dari penelitian ini adalah pada pasien TB paru dan DMT2 dengan obesitas, hasil pemeriksaan sputum cenderung memberikan hasil negative. Oleh karena, itu perlu kewaspadaan dalam mendiagnosa TB paru pada pasien dengan DMT2 yang mengalami obesitas, karena tidak dapat semata-mata disingkirkan hanya berdasarkan hasil pemeriksaan sputum.

**Kata kunci:** Tuberkulosis, diabetes, obesitas, bakteri tahan asam

### ABSTRACT

Obesity is known as protective factors of pulmonary tuberculosis (PTB) in non-diabetes mellitus population. However, its effect on PTB in type 2 diabetes mellitus (T2DM) patient is unclear. The study aims to determine the association between obesity and PTB in patient with T2DM. A cross-sectional study was held in in-patient, The Department of Internal Medicine, Fatmawati General Hospital from January 2015 to December 2017. This study includes patient with T2DM who had been diagnosed with PTB and age  $\geq 18$  years old. In this study negative Acid-fast-bacilli (AFB) founding defined as patient's sputum is negative by smear microscopy, while obesity define as body mass index  $> 24.9$  kg/m<sup>2</sup>. From 363 PTB patient with T2DM, 22.59% were obese. Results showed that prevalence of negative AFB founding in PTB patients with T2DM was 81.82% and it was solely associated with obesity ( $p:0.002$ ,  $OR=6.36$ ,  $95\%CI 1.9-21$ ). Obese patients were likely to have negative AFB founding. It suggested that diagnosing PTB in patient with T2DM and obese can't be solely based on bacteriological confirmation.

**Key words:** Tuberculosis, diabetes, obesity, acid-fast bacilli

### Introduction

Tuberculosis is the ninth leading cause of death worldwide. It was estimated 10.4 million incident cases of TB worldwide in 2016.<sup>1</sup> Most of the estimated number (45%) occurred in South-East Asia, including Indonesia.<sup>1</sup> The increase of non-communicable disease such as diabetes is recognized as a re-emerging risk and challenge to tuberculosis control. Epidemiological studies have elucidated the association between diabetes and tuberculosis, people with diabetes have triple risk of developing tuberculosis, and 15% of TB cases globally were linked to diabetes.<sup>2-5</sup>

Since diabetes prevalence has increased worldwide, the risk of having obesity as result of lifestyle changes, population aging, and urbanization was also increased. Obesity is known as major

However, obesity has long known as protective factors of pulmonary tuberculosis (PTB).<sup>7-9</sup> The effect of obesity on tuberculosis suggested that obese individual had more CD4+ T cells and leptin hormone which was play important role in immune protection and reduce the risk of active tuberculosis.<sup>10-12</sup> Unfortunately, the effect of obesity on PTB in type 2 diabetes mellitus (T2DM) patient is unclear.

The aim of this study is to know the association between obesity and acid-fast bacterial finding (active tuberculosis) in patient with PTB and T2DM, and investigated the factors affecting negative bacterial findings in patient with PTB and T2DM.

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## Methods

A cross-sectional study held in in-patient, department of Internal Medicine, Fatmawati General Hospital from January 2015 to December 2017 through consecutive sampling method with a minimum study subject calculated using Lemeshow formula ( $P1=0.0317$ ,  $P2=0.2167$ , a 5% ( $Z_{\alpha/2}=1.96$ ), and  $Z1-b=0.84$  for power 80%), we got 50 subjects for each group as minimum sample for our study. We use secondary data from medical records of patients admitted with following inclusion criteria: patients with type 2 diabetes mellitus, diagnosed with pulmonary tuberculosis and age  $\geq 18$  years old. The exclusion criteria were patient without bacteriological confirmation data or Body Mass Index (BMI) data or diagnosed with miliary TB.

From 383 PTB patients with T2DM who admitted to our hospital, we found 363 patients eligible to conducted in our study. Negative acid fast-bacilli founding defined as patient's sputum is negative by smear microscopy or Xpert MTB/RIF, while obesity define as body mass index  $> 24.9$  kg/m<sup>2</sup> as recommended by World Health Organization (WHO) Asia-Pacific Task Force.<sup>13</sup> Educational status was categorized by high (university and high school graduates) and low (below high school graduate). Category for glycemic control used HbA1c and fasting blood glucose (FBG) level which was divided into poor ( $HbA1c \geq 7\%$  or  $FBG < 80$  mg/dL or  $> 130$  mg/dL) and good ( $HbA1c < 7\%$  or  $FBG 80-130$  mg/dL) according to Indonesian society for endocrinology (PERKENI) guidelines. Duration of diabetes was defined as length time since patient get diagnosed with diabetes until current admission.

The data analyses were performed using STATA version 12. All data were expressed in categorical parameters. Chi-square test was performed to find an association between obesity and AFB-founding in PTB patient with T2DM. Multivariate analysis using logistic regression was performed to find an association between obesity and AFB-founding in PTB patient with T2DM after controlling covariate variables. All p values

## Results

From 383 patients between January 2015-December 2019, 363 patients met the inclusion and without exclusion criteria. From 363 subjects, 22.59% were obese and 81.82% were found negative in acid-fast bacilli examination. Most of the subjects were age  $< 60$  years old (65.29%), female (62.29%), high educational status (63.89%), non-smoking (69.55%),

poorly controlled HbA1c (75.61%), poorly controlled FBG (74.78%) and has been diagnosed with T2DM  $< 10$  years (85.77%) (Table 1).

**Table 1. Demographic and Clinical Characteristics of The Subjects**

Characteristics	N (%)
Body Mass Index	
Obese	82 (22.59)
Not-obese	281 (77.41)
Acid-fast bacilli founding	
Negative	297 (81.82)
Positive	66 (18.18)
Age	
$< 60$ years	237 (65.29)
$\geq 60$ years	126 (34.71)
Sex	
Female	226 (62.26)
Male	137 (37.74)
Educational status	
High	220 (63.89)
Low	130 (36.11)
Smoking	
No	233 (69.55)
Yes	102 (30.45)
HbA1c control	
Good	30 (24.39)
Poor	93 (75.61)
FBG Control	
Good	58 (25.22)
Poor	172 (74.78)
Duration of diabetes	
$< 10$ years	223 (85.77)
$\geq 10$ years	37 (14.23)

**Table 2. Association Between Obesity and Acid-Fast Bacilli Founding In PTB Patients with T2DM**

Variable	Total n (%)	AFB Negative n (%)	Bivariate	
			OR (95% CI)	p-value
Body mass index				
Obese	82 (22.59)	77 (93.90)	4.27 (1.64-14.08)	0.001
Age				
$\geq 60$ years	126 (34.71)	108 (85.71)	1.52 (0.82-2.93)	0.161
Sex				
Male	137 (37.74)	113 (82.48)	1.07 (0.60-1.96)	0.799
Educational Status				
Low	130 (36.11)	97 (74.62)	0.48 (0.27-0.85)	0.007
Cigarette				
Yes	102 (30.45)	81 (79.41)	0.78 (0.42-1.48)	0.398
HbA1c control				
Poor	93 (75.61)	70 (75.27)	0.47 (0.15-1.46)	0.190
FBG control				
Poor	172 (74.78)	140 (81.40)	0.80 (0.31-1.88)	0.595
Length of T2DM diagnosed				
$\geq 10$ years	37 (14.23)	33 (89.19)	1.91 (0.65-5.62)	0.236

Negative acid-fast bacilli founding was significantly more common in obese PTB patient with T2DM, risk of negative AFB founding in obese patient with T2DM was nearly 4.3 fold higher than those without obese (p: 0.001, odds ratio [OR] = 4.27, 95% Confidence Interval [CI] 1.64-14.08). However, negative AFB founding was less common in patient with low educational status

( $p$ : 0.007, OR=0.48, 95% CI 0.27-0.85) (table 2). Meanwhile, the effect of obesity increased ( $p$ : 0.002, OR=6.36, 95% CI 1.9-21) when analyzed together with another factors. Factors of age, HbA1c and FBG control and length of T2DM diagnosed were not included in the multivariate analysis because of their cell's values were too small (Table 3).

**Table 3. Multivariate Analysis**

Variabel	Beta	SE	OR	95%CI	P-value
Obesity	1.85	0.61	6.36	1.9-21	0.002
Educational status	-0.48	0.31	0.62	0.1-1.7	0.114
Smoking	-0.32	0.35	0.73	0.8-16.6	0.368
Sex	-0.26	0.28	0.77	0.1-2.0	0.458

## Discussion

Our study showed that obesity were significantly associated with negative AFB founding in PTB patients with T2DM. Our results are consistent with those of several published studies, Lai Y et al. 2017. Reported a lower risk of active tuberculosis in obesity and overweight patient.<sup>11</sup> Leung G et al. 2015. Reported obesity is associated with a lower risk of active tuberculosis in older population of Hongkong.<sup>7</sup> Umakanth M, 2017. Reported obesity and overweight were associated significantly with lower risk of both clinically active and cultured-confirmed tuberculosis.<sup>14</sup> This findings indicate that obesity is still a protective factor in development of active tuberculosis even in T2DM patients. This results also suggested that screening or diagnosing tuberculosis especially in obese patient with T2DM are not sufficient enough if the test is just solely by sputum smear or geneXpert MTB/Riff test.

This mechanism could be explained as people with obesity has an increased frequency of CD3+ and CD4+ T cells.<sup>10</sup> Leptin levels are suppressed in tuberculous patients and low leptin levels may contribute to increase susceptibility to infections. In humans, leptin levels are correlated with fat mass and can be decreased by hunger.<sup>15</sup> Recent studies showed that basal leptin levels in obese patients are significantly higher than non-obese patients.<sup>16</sup> The administration of leptin in patients with human congenital leptin deficiency has demonstrated beneficial effect on T-cell hyporesponsiveness, obesity, neuroendocrine and metabolic deficiency.<sup>7</sup> The immune-modulating effect of leptin may also account for the lower risk of active TB incidence in obese/overweight person since it could enhance the T-cell-mediated immune function.<sup>17</sup>

this might produce bias since not all patients who had negative test results on sputum smear test were went to geneXpert MTB/riff examinations. Also, the covariates presented in this study may not be sufficient to conclude that the associations between obesity and negative AFB findings in PTB patients with T2DM are truly independent. For example, pharmacological treatment, recent TB diagnosis and comorbidities which may have effects on these association were not included in this study. Another (major) limitations of our study is causal relations and postulated relationships cannot be established from a cross-sectional study design. With the potential clinical implications of our observation, further cohort studies are warranted to confirm these findings in other population groups. More basic research and animal studies are also indicated to explore underlying mechanisms.

## Conclusion

Obesity associated with developing negative AFB findings in microbiological test for PTB in patients with T2DM. Therefore, it suggested that clinicians should conduct sufficient diagnosis test for PTB in obese patient with T2DM even if AFB findings were negative.

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