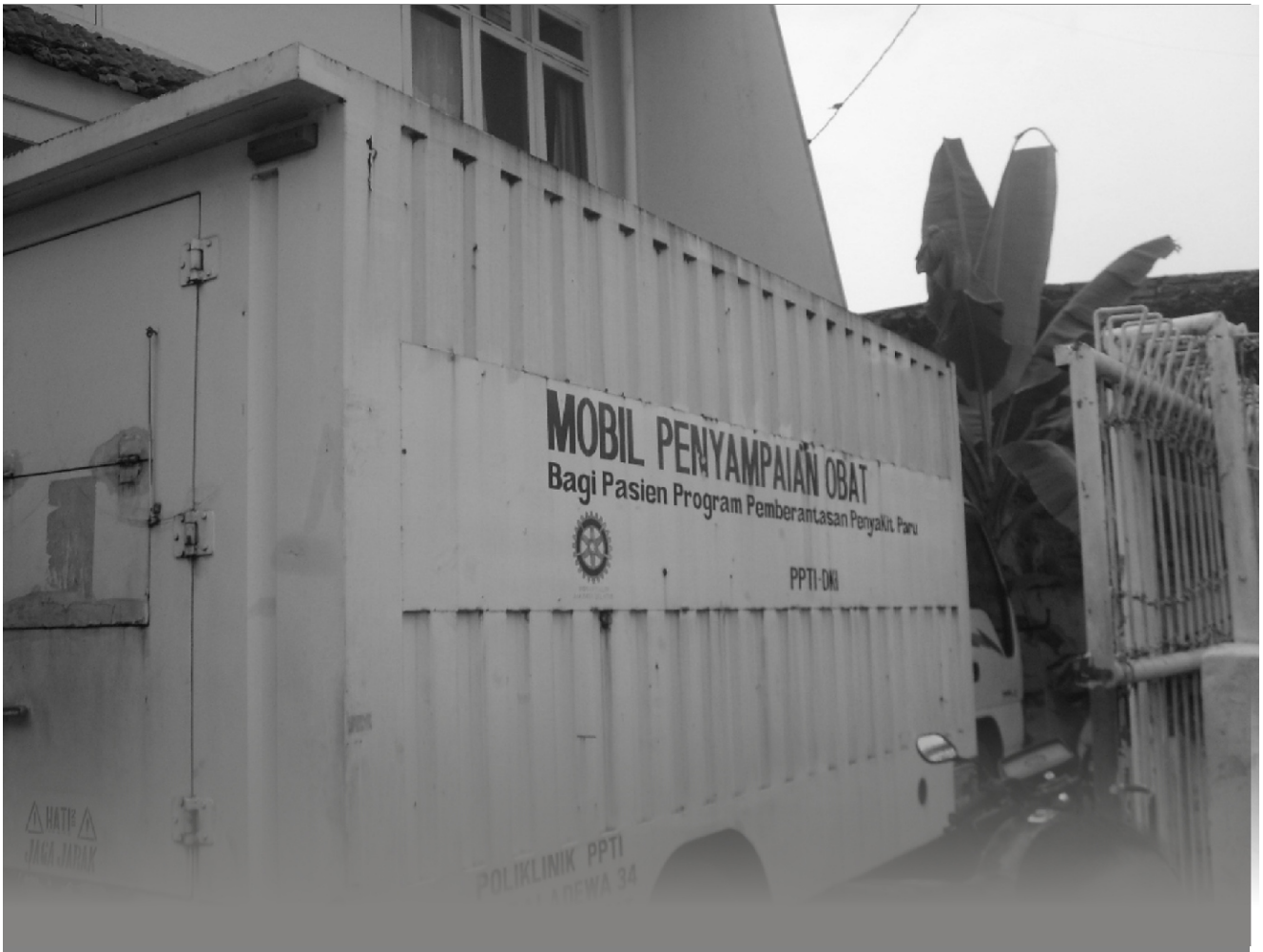
Innate and adaptive host responses and their genetic control in tuberculosis : studies in Indonesia, a highly TB endemic setting

Sahiratmadja, E.K.



Mobile TB drugs distribution

Clinical Infectious Diseases. 2007;45(4):428-435
reprinted with permission

7

The Effect of Type 2 Diabetes Mellitus on the Presentation and Treatment Response of Pulmonary Tuberculosis

Bachti Alisjahbana,[1] **Edhyana Sahiratmadja**,[3]
Erni J. Nelwan,[4] Anugrah M. Purwa,[1] Yana Ahmad,[1]
Tom H.M. Ottenhoff,[5] Ronald H.H. Nelwan,[4] Ida Parwati,[2]
Jos W.M. van der Meer[6] and Reinout van Crevel [6]

[1] Dept. Internal Medicine and [2] Clinical Pathology, Medical Faculty Padjadjaran University, Bandung, Indonesia
[3] Eijkman Institute for Molecular Biology, Jakarta, Indonesia
[4] Infectious Diseases Working Group, Medical Faculty University of Indonesia, Jakarta, Indonesia
[5] Dept. Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands
[6] Dept. Internal Medicine, Radboud University Nijmegen Medical Center Nijmegen, The Netherlands

SUMMARY

Background. Diabetes Mellitus (DM) is a known risk factor for tuberculosis (TB), and with the increasing prevalence of type 2 DM in less developed regions, many patients with TB will have concomitant DM. Presently, little is known about the effect of DM on the clinical presentation and treatment outcome of TB.

Methods. In an urban setting in Indonesia, 737 patients with pulmonary TB were screened for DM and were followed up prospectively during TB treatment. Clinical characteristics and outcome were compared between patients with TB who had DM and patients with TB who did not have DM.

Results. DM was diagnosed in 14.8% of patients with TB and was associated with older age and a greater body weight. On presentation, diabetic patients with TB had more symptoms but had no evidence of more-severe TB. After 2 months, results of sputum microscopic examination was more often positive in diabetic patients (18.1% vs. 10.0%). After 6 months, 22.2% of cultured sputum specimens from diabetic patients were positive for *Mycobacterium tuberculosis* (adjusted odds ratio, 7.65; $P = .004$).

Conclusion. DM seems to have a negative effect on the outcome of TB treatment. The underlying mechanisms for the different response to treatment in diabetic patients with TB must be explored. Screening for DM and subsequent glycemic control may improve the outcome of TB treatment.

BACKGROUND

Diabetes mellitus (DM) was a well-known risk factor for tuberculosis (TB) in the past,[1,2] but this was largely forgotten during the second half of the 20th century, with the advent of widely available treatment for both diseases. Now, with the current global increase in cases of type 2 DM,[3] the association between TB and DM is re-emerging. The greatest increase in cases of type 2 DM will occur in developing countries, where TB is highly endemic.[3] As a result, a growing number of patients with TB worldwide will present with DM. Indeed, recent studies show that 10%-30% of patients with TB may also have DM.[4-9] We have confirmed the association between DM and TB in Indonesia, which has the third highest number of patients with TB[10] and the fourth highest number of person with DM worldwide.[3] We previously found type 2 DM in 13.3% of patients with TB and 3.2% of age-matched control subjects (OR, 4.7; 95% CI, 2.7-8.1).[4]

With regard to the possible effects of DM on the presentation and outcome of TB, recent data are more scarce. In the era before insulin therapy, patients with DM appeared to be doomed to die of pulmonary TB if they survived the diabetic coma.[2] After the introduction of insulin in 1922, TB remained a serious and deadly threat to patients with DM,[1] but with effective anti-TB treatment, their prognosis improved dramatically.[11] More recent studies exploring the possible effects of DM on the presentation and outcome of TB have had conflicting results.[7,9,12] In a prospective cohort study in an Indonesian region, we examined whether DM was associated with more-severe TB or with a less favorable response to treatment.

METHODS

Study design and patient population

In a prospective cohort study, we included consecutive new patients with pulmonary TB who were aged $\geqslant$ 15 years and who presented at 3 outpatient TB clinics in Jakarta and Bandung in Indonesia from October 2000 through December 2005. Diagnosis of TB was made on the basis of clinical presentation and chest radiograph findings and was confirmed by microscopic detection of acid-fast bacilli. All patients with confirmed TB were screened for

DM by measurement of fasting blood glucose (FBG) concentrations. No anti-DM agents were received within 48 h before blood samples were obtained, and DM was diagnosed if FBG concentration was > 126 mg/dL at 2 different time points; FBG concentrations of 110-126 mg/dL were considered to indicated impairment, in accordance with international criteria.[13] In all patients, we measured FBG concentrations before and after 1 month of anti-TB treatment. TB treatment consisted of a standard regimen of daily rifampicin, isoniazid, pyrazinamid, and ethambutol for 2 months (the intensive phase) and rifampicin and isoniazid for another 4 months (the continuation phase), according to World Health Organization guidelines.[14] In accordance with national guidelines, patients in whom DM was established initiated oral anti-DM drugs after 2-4 weeks of TB treatment. No patient received insulin. Written informed consent was obtained from all subjects, and the study was approved by the ethical committee of the Faculty of Medicine, University of Indonesia, Jakarta, and the Faculty of Medicine, Padjadjaran University, Hasan Sadikin Hospital, Bandung, Indonesia.

Patient characterization and follow-up

Signs and symptoms were recorded before the initiation of TB treatment, and additional history was obtained for the presence of DM or DM treatment, previous TB treatment, TB contacts, other comorbidities, and medication use. A symptom score (0-6) was calculated on the basis of the presence of cough, hemoptysis, dyspnea, fever, night sweats, and weight loss (1 point for each item). Patients with a symptom score >4 were classified as having highly symptomatic disease. The performance status of each patient was determined by field physicians, using the Karnofsky index, based on questioning of the patient and, if possible, the patient's family or friend.[15] A Karnofsky score of 80% corresponds with the inability to do work or perform normal daily activities. For evaluating disease severity, we used sputum mycobacterial load measurements, chest radiograph findings, and anemia and blood inflammatory markers. Microscopic examination of Ziehl-Neelsen-stained sputum slides was performed for acid-fast bacilli, and sputum mycobacterial load was graded as +, ++ or +++.[14] Culture for *Mycobacterium tuberculosis* was performed on Ogawa 3% medium, and *M. tuberculosis* drug-susceptibility testing for rifampicin and isoniazid was performed using an absolute concentration method with supranational control. This method has shown to have an

accuracy of 96%-100% in 10 rounds of World Health Organization/International Union Against Tuberculosis and Lung Disease proficiency testing.[16] Examination of blood samples included a C-reactive protein level measurement, complete blood count, liver and kidney function testing, and HIV testing (Determine dipsticks; Abbott). Anemia was defined as a hemoglobin concentration <12 mg/dL (in female patients) or <13 mg/dL (in male patients). Chest radiographs were read independently by 2 experienced professionals, and abnormalities were classified as mild, moderate, or severe.[17] Persons involved in clinical scoring, microscopic examination reading, and chest radiograph examination were unaware of the patients' DM classification.

We followed up with patients biweekly during the intensive phase and monthly thereafter. History, physical examination, blood testing, and microscopic examination and culture of sputum samples were repeated after the intensive phase (at 2 months) and at the end of treatment (at 6 months). We measured adherence by interview and pill count. In accordance with the national TB program, specific definitions were used to classify treatment response and outcome.[10]

Data analysis and statistics

We compared findings for patients with TB who had DM with finding for patients with TB who did not have DM. We used Pearson's χ^2 test to compare ratios, Student's *t* test for normally distributed continuous variables, and nonparametric Mann-Whitney *U* test for nonnormally distributed continuous variables. Univariate and multivariate logistic regression were used to calculate ORs for factors associated with disease presentation and bacteriological response at 2 and 6 months after initiation of TB treatment. Study site and patient age, sex, and body mass index (BMI; calculated as the weight in kilograms divided by the square of height in meters; which is associated with DM), as well as parameter that are logically related to the end points analyzed, were included as independent variables in logistic regression models. Data were analyzed using SPSS, version 12.01 (SPSS).

RESULTS

Patient characteristics

Of 737 new patient with TB who were screened, 15 were excluded because of HIV seropositivity ($n = 7$), other co-morbidity ($n = 7$), or missing data ($n = 1$). An additional 88 patients were excluded because of FBG concentrations indicating impairment (110-126 mg/dL; $n = 29$), or undetermined status of DM (1 measurement only; $n = 59$). All of the remaining 634 patients had positive sputum microscopic examination results. Five hundred thirty-four (92.1%) of 580 patients had culture results that were positive for *M. tuberculosis*. Of 634 patients, 540 had normal FBG concentrations, and 94 patients (14.8%) received diagnoses of concomitant DM. The prevalence of DM among patients with TB was 17.1% in Jakarta and 11.6% in Bandung. DM was newly diagnosed in 57 patients (61.3%) and was confirmed to be type 2 DM. No insulin deficiency was found in 14 randomly selected diabetic patients (data not shown), and among patients with a history of DM, none were using insulin. As expected, patients with TB who had type 2 DM were older and had a higher BMI (table 1).

NOTE. Data are percentage of patients, unless otherwise indicated. BCG, bacille Calmette-Guérin; BMI,body mass index (calculated as the weight in kilograms divided by the square of height in meters); FBG,fasting blood glucose; INH, isoniazid; IQR, interquartile range; MDR, multidrug resistant; RIF, rifampicin.

a $P < .001$
b $P < .01$
c Data are for 76 patients with TB who had DM and 491 patients with TB who did not have DM.
d Because of insufficient quality of radiographs, the presence of cavities could only be evaluated for 60 patients with TB who had DM and 433 patients with TB who did not have DM.
e Data are for 84 patients with TB who had DM and 497 patients with TB who did not have DM.
f Data are for 56 patients with TB who had DM and 272 patients with TB who did not have DM.
g Reference parameter (not tested).

Table 1. Characteristics of patients with tuberculosis (TB) who had diabetes (DM) and patients with TB who did not have DM

Characteristic	Patients with TB who had DM (*n* = 94)	Patients with TB who did not have DM (*n* = 540)
Male sex	55.3	51.9
Age, median years (IQR)[a]	45.0 (39.8-52.0)	27.0 (22.0-35.0)
History of TB contact	44.7	52.4
Previous treatment for TB	6.4	4.8
Signs and symptoms		
Duration, median weeks (IQR)	8	8 (4-16)
Cough	98.9	97.8
Hemopthysis	42.6	40.7
Dyspnea	69.1	63.7
Fever	80.9	73.9
Night sweats	79.8	70.2
Weight loss[a]	96.8	80.4
Symptom score >4	63.8	48.5
Median BMI (IQR)[a]	21.1 (18.9-22.8)	17.5 (16.0-19.1)
Karnofsky score ≤80% [b]	45.7	29.4
BCG scar present	43.6	42.6
Severity of chest radiograph findings		
Advanced [c]	52.6	50.9
Cavity present [d]	40.0	52.4
Sputum microscopy		
Positive	29.8	38.9
Sputum culture result [a]		
Negative and/or contamination	13.1	7.0
Positive for *Mycobacterium tuberculosis*	86.9	93.0
Drug susceptibility testing,[f] no. (%) of patients		
INH resistant	5	42 (15.4)
RIF resistant	1 (1.8)	18 (6.6)
MDR	1	13 (4.8)
Laboratory test result		
Haemoglobin level, median mg/dL (IQR)[a]	13.1 (11.6-13.8)	11.9 (10.6-13.1)
Leucocyte count, median leukocytes x 10^3/mL (IQR)	8.7 (10.0-13.5)	10.8 (8.7-13.1)
Blood sedimentation rate, median mm/h (IQR)	93 (66-110)	82 (55-108)
C-reactive protein level, median mg/dL (IQR)	49	56 (26-86)
FBG concentration, median mg/dL (IQR) [g]	215 (154-290)	81 (72-90)

Disease presentation

There was a slight difference in disease presentation between patients with TB who had DM and patients with TB who did not have DM (table1). Patients with TB who had DM presented with more symptoms and a lower performance status (according to the Karnofsky index). Symptom score and Karnofsky index did not show a statistically significant correlation. After adjustment for possible confounding factors, including age, sex, chest radiograph abnormalities (mild, moderate, or severe), sputum mycobacterial load (+, ++, or +++), and BMI, DM remained associated with a Karnofsky index ≤80% (adjusted OR, 3.04; P <.001) and a symptom score >4 (adjusted OR, 2.90; P = .001; table 1).

Although patients with TB who had DM were more symptomatic, blood testing and bacteriological and radiological examination did not reveal more-severe disease in patients with TB who had DM (table 1). Diabetic patients revealed less anemia in univariate analysis, but after adjustment for other factors, including age, sex, BMI, and duration of disease, this association was no longer statistically significant (adjusted OR, 0.53;95% CI, 0.27-1.03). Diabetic patients also had fewer pulmonary cavities and a slightly lower sputum mycobacterial load (table 1), but after adjustment for other factors, neither cavities (adjusted OR, 0.76;95% CI, 0.39-1.48) nor mycobacterial load (adjusted OR, 1.71;96%, 0.90-3.25) were significantly associated with DM. Table 2 displays crude and adjusted ORs for all predictive factors examined for the Karnofsky index, symptom score, pulmonary cavities, anemia, and sputum mycobacterial load.

NOTE. BMI, body mass index (calculated as the weight in kilograms divided by the square of height in meters); DM, diabetes mellitus.

[a] DM was defined as a fasting blood glucose concentration >126 mg/dL; no DM was defined as a fasting blood glucose concentration <110 mg/dL.

[b] As a continuous variable in years.

[c] Abnormalities were classified as mild or moderate versus severe.[17]

[d] Jakarta, Indonesia, was the other study site.

[e] Categorized as <1 month, 1-3 months, and 1>3 months.

Table 2. All dependent variables at disease presentation examined in multivariate regression analysis.

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)
Karnofsky Index ≤80%		
DM [a]	2.02 (1.2.9-3.16)	3.05 (1.65 - 5.64)
Age[b]	1.01 (1.00 - 1.03)	1.00 (0.98 - 1.02)
Female sex	1.05 (0.75 - 1.47)	1.17 (0.81 - 1.71)
Severe chest radiograph abnormalities[c]	2.05 (1.51 - 2.79)	1.87 (1.35 - 2.59)
BMI	0.93 (0.87 - 0.98)	0.89 (0.82 - 0.96)
Study site Bandung[d]	0.82 (0.58 - 1.16)	0.87 (0.59 - 1.28)
Symptom score >4		
DM [a]	1.87 (1.19 - 2.95)	2.92 (1.58 - 5.40)
Age[b]	1.00 (0.99 - 1.01)	0.99 (0.97 - 1.01)
Female sex	1.12 (0.82 - 1.54)	1.16 (0.82 - 1.63)
Severe chest radiograph abnormalities[c]	1.15 (0.89 - 1.49)	1.01 (0.76 - 1.33)
BMI	0.97 (0.91 - 1.02)	0.91 (0.85 - 0.97)
Study site Bandung[d]	0.60 (0.43 - 0.82)	0.60 (0.42 - 0.85)
Anemia		
DM [a]	0.34 (0.21 - 0.56)	0.53 (0.27 - 1.03)
Age[b]	0.98 (0.96 - 0.99)	0.99 (0.97 - 1.01)
Female sex	2.03 (1.44 - 2.85)	2.76 (1.82 - 4.18)
Severe chest radiograph abnormalities[c]	2.51 (1.74 - 3.61)	2.22 (1.62 - 3.04)
Duration of disease[a]	1.22 (0.99 - 1.50)	1.06 (0.82 - 1.37)
BMI	0.91 (0.65 - 1.27)	0.85 (0.78 - 0.92)
Study site Bandung[d]	0.82 (0.77 - 0.88)	0.64 (0.42 - 0.98)
Pulmonary cavities		
DM [a]	0.60 (0.35 - 1.05)	0.76 (0.39 - 1.48)
Age[b]	1.00 (0.99 - 1.02)	1.01 (0.99 - 1.03)
Female sex	0.68 (0.48 - 0.97)	0.75 (0.51 - 1.09)
Duration of disease[a]	1.41 (1.12 - 1.76)	1.20 (0.94 - 1.54)
BMI	0.86 (0.81 - 0.92)	0.86 (0.80 - 0.93)
Study site Bandung[d]	0.53 (0.37 - 0.76)	0.63 (0.42 - 0.93)
Sputum mycobacterial load +++		
DM [a]	1.04 (0.66 - 1.65)	1.71 (0.90 - 3.25)
Age[b]	1.01 (0.99 - 1.02)	1.01 (0.99 - 1.03)
Female sex	1.20 (0.97 - 1.66)	1.09 (0.76 - 1.58)
Severe chest radiograph abnormalities[c]	1.77 (1.25 - 2.51)	1.65 (1.13 - 2.39)
Duration of disease[a]	0.97 (0.79 - 1.19)	0.95 (0.75 - 1.21)
BMI	0.94 (0.89 - 1.00)	0.91 (0.84 - 0.98)
Study site Bandung[d]	1.46 (1.04 - 2.04)	1.77 (1.19 - 2.62)

Initial response to TB treatment

Twenty-four patients (3.8%) defaulted and 11 (1.7%) were transferred during the intensive phase of TB treatment. Among the remaining 599 patients, 2 patients with DM died within 2 months after initiation of treatment. Symptomatic improvement, weight gain and reduction of blood inflammatory markers were similar in both groups (not shown). Treatment adherence was estimated to be 98% in the group of patients with TB who had DM and 91% in the group of patients with TB who did not have DM on the basis of patient's reports and pill counts. Microscopic examination of sputum samples at 2 months was performed for 593 patients; 18.1% of diabetic patients and 10% of non-diabetic patients had positive result (table 3). However, after adjustment for age, sex, BMI, study site, chest radiograph abnormalities, and sputum mycobacterial load before initiation of treatment, the association between DM and sputum smear positivity was no longer statistically significant (table 3). Sputum culture at 2 months, performed for 413 patients, was not associated with DM in either univariate or multivariate analysis (table 3).

Outcome after six months treatment

During the continuation phase of TB treatment, 42 additional patients (7.0%) defaulted, and 11 (1.8%) were transferred. Adherence was similar in diabetic and nondiabetic patients (not shown). No more deaths were witnessed, and symptomatic improvement was similar in both groups. Microscopic examination of sputum samples at 6 months, performed for 532 patients, revealed positive result for 3.1% of control patients and was not associated with DM in univariate analysis or after adjustment for age, sex, BMI, sputum examination results at 2 months, drug resistance, and adherence (table 3). Severe chest radiograph abnormalities and positive sputum microscopic examination at 2 months were the only factors that were significantly associated with positive sputum microscopic examination results at 6 months (table 4).

Sputum cultures after 6 months were performed for 360 (66.3%) of 543 patients; 6 patients with DM (22.2%) and 32 control patients (6.9%) still receiving treatment had positive culture results at this point. DM was significantly associated with positive sputum culture results after 6 months of treatment; this association remained after adjustment for age, sex, BMI, chest radiograph abnormalities, sputum mycobacterial load after 2 months,

Table 3. Treatment response and outcome of patients with tuberculosis (TB) with and without diabetes mellitus (DM).

Period, variable	No. (%) of patients with TB		Crude OR (95% CI)	Adjusted OR (95% CI)
	With DM (n = 94)	Without DM (n = 540)		
Intensive phase				
AFB negative [a]	67 (71.3)	455 (84.3)	...	...
AFB positive	17 (18.1)	54 (10.0)	2.14 (1.17-3.9)	1.90 (0.82-4.42)
No sputum available, hospital transfer, and/or study default	8 (8.5)	31 (5.7)	...	...
Death	2 (2.1)	0 (0)	...	...
Culture result positive for *Mycobacterium tuberculosis*	7/41 (17.1)	68/372 (18.3)	0.92 (0.39-2.16)	0.90 (0.30-2.68)
End of treatment				
AFB negative[a]	70 (74.5)	435 (80.6)	...	...
AFB positive	4 (4.3)	17 (3.1)	1.46 (0.48-4.47)	1.06 (0.17-6.60)
No sputum available, hospital transfer, and or study default	18 (19.1)	88 (16.3)	...	...
Death	2 (2.1)	0 (0)	...	...
Culture result positive for *M. tuberculosis*[b]	6/27 (22.2)	32/333 (9.6)	2.69 (1.01-7.14)	7.65 (1.89-30.95)

NOTE. The intensive phase was the first 2 months of treatment, and end of treatment was at 6 months. AFB, acid-fast bacilli.
[a] Reference value.
[b] $P < .05$.

noncompliance, and drugresistance (adjusted OR, 7.65; P = .004; table 3). Besides DM, only sputum examination results at 2 months remained significantly associated with sputum culture at 6 months (table 4).

DISCUSSION

In our study in Indonesia, we found type 2 DM in a significant proportion of patients with TB. Before the initiation of TB treatment, diabetic patients had more symptoms but had no evidence of more-severe TB on blood testing and on bacteriological and radiological examination. At the end of 6 months of TB treatment, DM was strongly associated with positive sputum culture results - even more so after adjustment for possible confounding factors.

Table 4. All dependent variable at follow-up examined in multivariate analysis.

Variable	Patients with positive result	Patients with negative results	Crude OR (95% CI)	Adjusted OR (95% CI)
Sputum microscopic examination results at 2 months				
No. of patients	71	522		
Diabetes[a]	17 (23.9)	67 (12.8)	2.14 (1.17-3.90)	1.90 (0.82-4.42)
Study site Bandung[b]	50 (70.4)	193 (36.8)	4.09 (2.39-7.02)	3.80 (2.10-6.88)
Male sex	27 (38.0)	276 (52.9)	1.83 (1.10-3.04)	1.36 (0.78-2.38)
Sputum mycobacterial load ++ or +++ before treatment	56 (78.9)	325 (62.3)	2.26 (1.25-4.11)	1.21 (0.87-1.68)
Age, median years (IQR)	30 (24-44)	28 (22-40)	1.02 (1.00-1.04)	1.01 (0.98-1.04)
Median BMI (IQR)	18.2 (16.8-0.5)	17.7 (16.2-19.7)	1.06 (0.97-1.15)	1.00 (0.90-1.12)
Severe chest radiograph abnormalities[c]	31/64 (48.4)	237/472 (50.2)	0.93 (0.55-1.57)	1.04 (0.59-1.84)
Sputum culture at 2 months				
No. of patients	75	338		
Diabetes[a]	7 (9.3)	34 (10.1)	0.92 (0.39-2.16)	0.90 (0.30-2.68)
Study site Bandung[b]	32 (42.7)	156 (46.2)	0.87 (0.52-1.44)	0.83 (0.48-1.45)
Male sex	42 (44.0)	164 (51.5)	1.35 (0.82-2.23)	1.42 (0.83-2.44)
Sputum mycobacterial load ++ or +++ before treatment	57(76.0)	211 (62.4)	1.91 (1.07-3.38)	1.31 (0.96-1.81)
Age, median years (IQR)	27 (22-40)	28 (23-38)	1.00 (0.98-1.02)	1.00 (0.97-1.03)
Median BMI (IQR)	17.4 (16.1-18.8)	17.7 (16.2-19.5)	0.96 (0.87-1.05)	0.93 (0.83-1.05)
Severe chest radiograph absnormalities[c]	31/69 (55.1)	150/317 (47.3)	1.36 (0.81-2.30)	1.19 (0.68-2.07)
Sputum microscopic examination at 6 months				
No. of patients	21	505		
Diabetes[a]	4 (19.0)	70 (13.9)	1.46 (0.48-4.47)	1.06 (0.17-6.60)
Study site Bandung[b]	12 (57.1)	198 (39.2)	2.07 (0.86-5.00)	1.10 (0.37-3.30)
Male sex	5 (23.8)	252 (49.9)	3.19 (1.15-8.83)	2.48 (0.81-7.60)
Age, median years (IQR)	30 (23.5-43.0)	29 (23-40)	1.00 (0.96-1.04)	0.97 (0.92-1.03)
Median BMI (IQR)	18.2 (16.9-20.4)	17.8 (16.2-19.8)	1.06 (0.92-1.22)	1.05 (0.84-1.31)
Severe chest radiograph absnormalities[c]	15 (75.0)	225 (48.6)	3.17 (1.13-8.87)	4.48 (1.35-14.90)
Nonconversion at week 8[d]	12 (57.1)	46 (9.1)	2.93 (1.13-7.59)	14.86 (5.19-42.54)
Sputum culture at 6 months				
No. of patients	38	322		
Diabetes[a]	6 (15.8)	21 (6.5)	2.69 (1.01-7.14)	7.65 (1.89-30.95)
Study site Bandung[b]	11 (28.9)	109 (33.9)	0.80 (0.38-1.67)	0.67 (0.26-1.73)
Male sex	20 (52.6)	159 (49.4)	0.88 (0.45-1.72)	0.84 (0.38-1.89)
Age, median years (IQR)	26 (22.8-40.2)	28 (23-38)	0.99 (0.96-1.03)	0.96 (0.91-1.00)
Median BMI (IQR)	17.5 (15.9-18.8)	17.5 (16.0-19.5)	0.98 (0.86-1.11)	0.92 (0.78-1.10)
Severe chest radiograph[c]	20/31 (64.5)	147/302 (48.7)	1.92 (0.89-4.14)	1.90 (0.79-4.54)
Nonconversion at week 8[d]	10 (26.3)	32 (9.9)	3.24 (1.44-7.27)	5.44 (2.11-13.99)

NOTE. Data are no. (%) of patients, unless otherwise indicated. BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters); IQR, interquartile range.
[a] Diabetes was defined as a fasting blood glucose concentration >126 mg/dL; no diabetes was defined as a fasting blood glucose concentration <110 mg/dL.
[b] Jakarta, Indonesia, was the other study site.
[c] Abnormalities were classified as mild or moderate versus severe.[17]
[d] Categorized as sputum microscopic examination results at week 8.

Type 2 DM increases the risk of developing active TB,[4-6,18] but less is known about the possible effects of DM on the severity and outcome of TB. Recently, a number of studies have compared disease presentation between diabetic and nondiabetic patients with TB. Studies in Malaysia,[19] Saudi Arabia,[9] and Turkey[12] did not find major differences in presenting symptoms, but a recent, large study in the Mexico-Texas border region reported a higher rate of fever and hemoptysis among diabetic patients.[7] Of note, in that particular study, DM was self-reported, and patients were not systematically screened for the disease. Unlike our study, the cited studies provided relatively little information about possible confounding factors, which is unfortunate, because presentation is influenced by many factors, including age, sex, nutritional status, accessibility to health care (resulting in a delay in patient presentation), and comorbidity. We were able to correct for most of these factors and still found that diabetic patients had more symptoms than nondiabetic patients. Some of the symptoms should, therefore, be ascribed to DM itself (which was often untreated and poorly controlled). Similar to previous studies, we found a higher frequency of "atypical" images with fewer cavities in patients with DM,[20-22] although others researchers have reported a higher frequency of pulmonary cavities in patients with DM.[7,23,24]

The second hypothesis that we examined in our cohort was whether DM is associated with a less favorable response to TB treatment. Indeed, after 2 months of treatment, 2 patients with DM had died, and sputum microscopic examination results were more frequently positive among diabetic patients. However, after adjustment for possible confounding factors, the association between sputum microscopic examination results and DM was no longer statistically significant, and culture results at 2 months (a more important parameter) were not significantly associated with DM. The 2-month data should, therefore, be interpreted with caution. At 6 months, more than twice as

many diabetic patients as nondiabetic patients had a sputum culture result that was positive for *M. tuberculosis*, and DM remained a strong and independent prognostic factor after adjustment for possible confounding factors. Previous studies dealing with this subject have had conflicting results. Some studies found no effect of DM on TB cure rates,[9,19] and others did report significant effects on treatment outcome.[25-28] Similar to our findings, a recent large retrospective study involving the Texas-Mexico border region revealed a significantly higher rate of sputum smear positivity during the first months of treatment among patients with self-reported DM.[7] Importantly, none of these studies have used sputum culture results after treatment as an end point. Of note, other factors that may be related to treatment outcome, including incarceration, and drug or alcohol use,[29] were absent in our cohort.

The conclusions of studies like ours very much depend on the quality of case definitions and proper evaluation of end points. We used strict definitions to establish or exclude DM. Diagnosis of DM in patients with pulmonary TB can be confounded by disease activity, but DM was confirmed by repeated FBG concentration during TB treatment and measurement of insulin in a subset of patients. In a recent study in the same region, the mean HbA1c was 10.5 for diabetic patients and 5.6 for nondiabetic patients (J. Stalenhoef, personal communication). We previously found that only 3% of cases of DM in patients with TB reverse after TB treatment.[4]

With regard to end points, careful data collection was performed. Drop-out rates were very low, especially considering the region of this study. Sputum microscopic examination results were available for 93.8% of patients at 2 months and 84% of patients at 6 months. For sputum culture, which is not routinely performed in this region, results were available for 61.5% of patients at 2 months and 57.8% of patients at 6 months. On the basis of sputum microscopic examination results, the treatment failure rate was 3.1% in the control group; 5.9% of control patients who completed 6 months of treatment had a positive sputum culture result. These figures are comparable to results in a recent large trial in Africa that used a similar regimen.[30] All patients were tested for HIV infection and HIV-seropositive patients were excluded from analysis. Possible confounding factors were recorded in detail and accounted for. Unfortunately, no follow-up was performed after completion of treatment to see if DM was also associated with increased relapse rates.

If DM indeed has a negative effect on TB treatment, what could be the possible mechanism(s)? Noncompliance may lead to treatment failure, but,

treatment adherence was actually better among diabetic patients. Drug-resistance, another strong determinant of treatment failure in TB, was also lower among diabetic patients. We speculated about other possible explanations. In this respect, pharmacokinetic aspects of TB treatment may be relevant. The available evidence suggests that the efficacy of rifampicin is dependent on exposure to the drug or on the maximum drug concentrations achieved.[31] We have recently found that exposure (are under the curve, 0-6 h) to rifampicin was 2-fold lower in patients with TB who had DM than in patients who did not have DM.[32] Similar differences were found for the maximal plasma concentrations of rifampicin; the maximal plasma concentration of rifampicin was above the target concentration of 8 mg/L[33] in 6% of patients with TB who had DM, compared with 47% of patients who did not have DM. These pharmacokinetic differences might lead to easier acquisition of drug resistance and might explain the lower bacteriological response in diabetic patients with TB. Additional studies are needed to clarify these issues.

To summarize, we have examined the effect of type 2 DM on presentation and outcome of pulmonary TB in an Indonesian region. DM was associated with more symptoms but not with increased severity of TB and had a negative effect on the outcome of anti-TB treatment. The findings of this study underline the need to improve the care for patients with concomitant DM and TB, especially in developing countries. Therefore, we advocate to screen patients with TB for DM, especially those aged >35 years. Prospective studies are needed to determine the effects of tighter glycemic control on TB treatment and outcome.

Acknowledgments

We thank Dr. H. Danusantoso and Dr. M. Pangaribuan (Central Jakarta Tuberculosis Association Clinic, Jakarta, Indonesia), Prof. C.B. Sudjana Prawira (Hasan Sadikin General Hospital, Bandung, Indonesia), and Dr. H.B. Sampoerno (Bandung Tuberculosis and Lung Clinic, Bandung, Indonesia), for encouraging and accommodating research in their institutions. We are grateful for the assistance of Dr. M. den Heijer, H. Straetman, and C. Tack (Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands), for their consultation and input in the preparation of this manuscript.

References

1. Boucot KR, Dillon ES, Cooper DA, Meier P, Richardson R. Tuberculosis amog diabetics: the Philadelphia survey. Am Rev Tuberc 1952; 65:1-50.
2. Root HF. The association of diabetes and tuberculosis. N Eng J Med 1934; 210:1-13.
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27:1047-1053.
4. Alisjahbana B, van Crevel R, Sahiratmadja E, den Heide M, Maya A, Istriana E, Danusantoso H, Ottenhoff TH, Nelwan RH, van der Meer JW. Diabetes mellitus is strongly associated with tuberculosis in Indonesia. Int J Tuberc Lung Dis 2006; 10:696-700.
5. Kim SJ, Hong YP, Lew WJ, Yang SC, Lee EG. Incidence of pulmonary tuberculosis among diabetics. Tuber Lung Dis 1995; 76:529-533.
6. Mugusi F, Swai AB, Alberti KG, McLarty DG. Increased prevalence of diabetes mellitus in patients with pulmonary tuberculosis in Tanzania. Tubercle 1990; 71:271-276.
7. Restrepo BI, Fisher-Hoch SP, Crespo JG, Whitney E, Perez A, Smith B, McCormick JB. Type 2 diabetes and tuberculosis in a dynamic bi-national border population. Epidemiol Infect 2007;135:483-491.
8. Shetty N, Shemko M, Vaz M, D'Souza G. An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. Int J Tuberc Lung Dis 2006; 10:80-86.
9. Singla R, Khan N, Al Sharif N, Ai-Sayegh MO, Shaikh MA, Osman MM. Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. Int J Tuberc Lung Dis 2006; 10:74-79.
10. World Health Organization. Global tuberculosis control: surveillance, planning, financing. WHO report 2006. Geneva, Switzerland: World Health Organization, 2006.
11. Luntz GRWN. Management of the tuberculous diabetic; follow-up of 84 cases in one year. BMJ 1957; 1:1082-1086.
12. Bacakoglu F, Basoglu OO, Cok G, Sayiner A, Ates M. Pulmonary tuberculosis in patients with diabetes mellitus. Respiration 2001;68:595-600.
13. American Diabetes Association. Diagnosis and classification of diabetes mellitus Diabetes Care 2006;29(Suppl 1):S43-S48.
14. World Health Organization. Treatment of tuberculosis: guidelines for national program. Geneva, Switzerland: World Health Organization, 2006.
15. Mor V, Laliberte L, Morris JN, Weimann M. Karnofsky performance status scale: an examination of its reliability and validity in a research setting. Cancer 1984; 53:2002-2007.
16. van Klingeren B, Dessen-Kroon M, van der Laan T, Soolingen D. Drug susceptibility testing of *Mycobacterium tuberculosis* complex using a high throughput, highly reproducible absolute concentration method. J Clin Microbiol (in press).
17. Falk A, O'Connor B, Pratt PC, Webb WR, Wier JA, Wolinsky E. Classification of pulmonary tuberculosis. In: Falk A, ed. standards and classification of tuberculosis. New York: National Tuberculosis and Respiratory Disease Association, 1969: 67-76
18. Ponce-De-Leon A, Garcia-Garcia Md ML, Garcia-Sancho MC, et al. Tuberculosis and diabetes in southern Mexico. Diabetes Care 2004; 27:1584-1590.
19. Nissapatorn V, Kuppusamy I, Jamaiah I, Fong MY, Rohela M, Anuar AK.Tuberculosis in diabetic patients: a clinical perspective. Southeast Asian J Trop Med Public Health 2005; 36(Suppl 4):213-220.

20. Morris JT, Seaworth BJ, McAllister CK. Pulmonary tuberculosis in diabetics. Chest 1992; 102:539-541.
21. Umut S, Tosun GA, Yildirim N. Radiographic location of pulmonary Tuberculosis in iabetic patients. Chest 1994;106:326.
22. Weaver R. Unusual radiographic presentation of pulmonary tuberculosis in diabetic patients. Am Rev Respir Dis 1974; 109:162-163.
23. Shaikh MA, Singla R, Khan NB, Sharif NS, Saigh MO. Does diabetes alter the radiological presentation of pulmonary tuberculosis. Saudi Med J 2003; 24:278- 281.
24. Wang JY, Lee LN, Hsueh PR. Factors changing the manifestation of pulmonary tuberculosis. Int J Tuberc Lung Dis 2005; 9:777-783.
25. Firsova VA, Ovsiankina ES, Kaminskaia GO, Rusakova LI, Grigor'eva ZP, Ryzhova AP, Iatskova TV, Gubkina MF. Carbohydrate metabolism impairment and specific features of the course of tuberculosis in adolescents with diabetes mellitus. Probl Tuberk 2000;4:17-19.
26. Hendy HH, Stableforth D. The effect of established diabetes mellitus on the presentation of infiltrative pulmonary tuberculosis in the immigrant Asian community of inner city area in United Kingdom. Br J Dis Chest 1983; 77:87- 90.
27. Mboussa J, Monabeka H, Kombo M, Yokolo D, Yoka-Mbio A, Yala F. Course of pulmonary tuberculosis in diabetics. Rev Pneumol Clin 2003; 59:39-44.
28. Mos-Antkowiak R. Tuberculosis in patients with alcoholism, peptic ulcer, diabetes mellitus or mental disorders. Pneumonol Alergol Pol 1991; 59:43-47.
29. Coker R, McKee M, Atun R, et al. Risk factors for pulmonary tuberculosis in Russia: case-control study. BMJ 2006; 332:85-87.
30. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet 2004;364:1244-1251.
31. Jayaram R, Gaonkar S, Kaur P, Suresh BL, Mahesh BN, Jayashree R,Nandi V, Bharat S, Shandil RK, Kantharaj E, Balasubramanian V. Pharmacokinetics-pharmacodynamics of rifampin in an aerosol infection model of tuberculosis. Antimicrob Agents Chemother 2003; 47:2118-2124.
32. Nijland HM, Ruslami R, Stalenhoef JE, Nelwan EJ, Alisjahbana B, Nelwan RH, van der Ven A, Danusantoso H, Aarnoutse RE, van Crevel R. Exposureto rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes. Clin Infect Dis 2006; 43:848-854.
33. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs 2002; 62:2169-2183.