ORIGINAL ARTICLE

The effect of diabetes control status on treatment response in pulmonary tuberculosis: a prospective study

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ABSTRACT

Background Uncontrolled diabetes, unlike controlled diabetes, is associated with an impaired immune response. However, little is known about the impact of the status of diabetes control on clinical features and treatment outcomes in patients with pulmonary TB (PTB). We conducted this study to evaluate whether the status of diabetes control influences clinical manifestations and treatment responses in PTB.

Methods A multicentre prospective study was performed between September 2012 and September 2014. The patients were categorised into three groups according to the glycated haemoglobin (HbA1C) level: PTB without diabetes mellitus (non-DM), PTB with controlled diabetes (controlled-DM) and PTB with uncontrolled diabetes (uncontrolled-DM). The primary outcome was the sputum culture conversion rate after 2 months of intensive treatment.

Results Among 661 patients with PTB, 157 (23.8%) had diabetes and 108 (68.8%) had uncontrolled diabetes (HbA1C≥7.0%). The uncontrolled-DM group exhibited more symptoms, positive sputum smears (p<0.001) and presence of cavities (p<0.001) than the non-DM group. Regarding treatment responses, patients with uncontrolled-DM were more likely to have a positive culture after 2 months (p=0.009) and either treatment failure (p=0.015) or death (p=0.027) compared with the non-DM group. In contrast, those with controlled-DM showed similar treatment responses to the non-DM group. In multivariable analysis, uncontrolled diabetes was an independent risk factor for a positive sputum culture after 2 months of treatment (adjusted OR, 2.11; p=0.042) and either treatment failure or death (adjusted OR, 4.11; p=0.022).

Conclusions Uncontrolled diabetes is an independent risk factor for poor treatment response in PTB.

Key messages

What is the key question?

- Does diabetes control status affect the manifestations and treatment outcomes of pulmonary TB (PTB)?

What is the bottom line?

- In this study, we found that patients with uncontrolled diabetes showed more severe presentations of PTB and weaker responses to treatment compared with patients without diabetes, and uncontrolled diabetes was an independent risk factor for poor treatment response in PTB.

Why read on?

- This study is the first prospective study to compare PTB presentation and treatment responses while accounting for diabetes control status, and to investigate whether improved glucose control may reduce the influence of diabetes on the prognosis of PTB.

INTRODUCTION

The association between diabetes mellitus (DM) and TB has been described for centuries. However, following development of anti-TB medication and insulin in the early 20th century, it was widely believed that TB and DM can be controlled, and the relationship between the two diseases was somewhat neglected.[1] However, the rapid increase in the incidence of TB where DM is epidemic shows that DM is a risk factor for TB.

DM is associated with impaired macrophages, T cells and cytokine generation.[2 3] Therefore, individuals with DM are at higher risk for developing TB.[4] Recent studies have also shown that in TB, individuals with DM have different clinical manifestations and clinical outcomes compared with those without DM.[5 6] However, the controversy remains, as data from some studies have shown that DM has no effect on these measures.[7–11] These discrepant findings might be attributed to not recognising the status of DM control. However, only a few studies have evaluated the impact of the status of DM control on the clinical features and treatment outcomes of patients with TB. One retrospective study showed that patients with uncontrolled DM have a higher instance of positive initial smear and positive culture at 2 months compared with patients without DM.[12] Another study showed that the status of glucose control in patients with DM influenced the radiographic findings. Moreover, the presence of cavities was associated with glycated haemoglobin (HbA1C) level.[13] A recent study suggested that poor glucose control

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was related to poor outcomes of pulmonary TB (PTB).[14] However, these studies were retrospective in design and not all populations were assessed for diabetes control status. Also, the effect of glucose control during PTB treatment on the treatment outcome has not been thoroughly evaluated.

Therefore, we conducted this prospective study to evaluate whether the status of diabetes control influences the clinical manifestations and treatment responses of PTB.

METHODS

Study design and patients

We conducted a multicentre prospective cohort study from September 2012 to September 2014 in South Korea. We included patients with PTB (aged 18–75 years) from 10 referral hospitals. Patients were excluded if they were alleged to have HIV infection, or could not use first-line anti-TB drugs due to abnormal hepatic laboratory tests. Enrolled patients were classified as not having DM (non-DM), having controlled DM (controlled-DM) and having uncontrolled DM (uncontrolled-DM). The trial protocol was approved by the institutional review board at all sites. All patients provided written informed consent before enrolment. This trial was registered to the Clinical Research Information Service of the Republic of Korea as KCT0000760 (available from: https://cris.nih.go.kr/cris/search/search_result_st01_en.jsp?seq=2852&type=).

Outcomes

The primary outcome was sputum culture positivity at 2 months of treatment. Secondary outcomes included differences in initial symptoms, microbiologic findings, radiographic findings and final treatment outcomes.

Definitions

Diagnosis of PTB was made according to guidelines from the American Thoracic Society.[15] The treatment outcomes were defined according to the revised WHO guidelines.[16] DM was diagnosed by either past history of DM with prior use of anti-diabetic medication or a plasma HbA1C level≥6.5% at the time of PTB diagnosis. We defined uncontrolled-DM as a plasma HbA1C level≥7.0%.[17]

Data collection

Symptoms and additional past medical history were recorded before the initiation of PTB treatment. A symptom score was calculated from 0 to 6 based on the presence of cough, sputum, haemoptysis, fever, night sweat and weight loss (one point for each item). We defined a higher symptom score by symptom score ≥4. In all patients with DM, we measured plasma HbA1C level initially and follow-up HbA1C was recommended at 3 months after treatment initiation.

Chest radiographs were reviewed by the pulmonary radiologist, blinded to status of diabetes control, at each study centre. Monthly sputum smear and culture for TB were obtained during the intensive phase of treatment. Patients were asked to collect morning sputum for analysis. However, after initiation of PTB treatment some patients were not able to expectorate sputum, despite repeated requests. In these cases, sputum was not induced and these patients were excluded from primary outcome analysis. Sputum samples were cultured in solid culture media at all centres, and in addition in liquid culture media (MGIT tube; Becton-Dickinson and Co., Sparks, Maryland, USA) at nine centres. Culture was considered positive if *Mycobacterium tuberculosis* was identified in either solid or liquid media. A TB nurse confirmed compliance at 2-week intervals over a 1-month period, and thereafter on a monthly basis until the end of treatment by interview.

Statistical analysis

To evaluate the primary endpoint, we assumed a 15% rate of positive culture in non-DM with a 9% difference between non-DM and uncontrolled-DM. Thus, with $\alpha=0.05$, a two-tailed analysis and a power of 80%, 1124 patients were needed. We assumed that 10% of the enrolled patients would not undergo culture at 2 months of treatment, 5% would be lost to follow-up and 4% would not use rifampin. Therefore, a final total of 1384 patients were needed for this study.

For overall comparisons, the data distribution was first evaluated for normality using the Shapiro–Wilk test. As body mass index was normally distributed, it was compared among non-DM, controlled-DM and uncontrolled-DM patients using analysis of variance with Tukey's post hoc analysis. As age was abnormally distributed, it was compared using the Kruskal–Wallis test. Descriptive variables were analysed using the χ^2 test or Fisher's exact test, as appropriate. When variables were statistically significant in overall comparisons, pairwise comparisons were performed using the Mann–Whitney U test, χ^2 test or Fisher's exact test. In these cases, we applied the Bonferroni correction method to adjust the p value, considering the potential false-positive rate incurred by multiple comparisons.

Logistic regression analysis was used to assess the risk factors of treatment outcomes. Further, variables that were associated with the outcome at $p<0.1$ in univariate analysis were including multivariable logistic regression analysis. Assessment of the applicability of multi-collinearity indicated no multi-collinearity issues (condition indices <30 and VIF values <10) between the chosen independent variables in this study. All analyses were performed using SPSS V.18.0 (IBM Corp., Armonk, New York, USA) and p values <0.05 were considered statistically significant.

RESULTS

Patients

Patient enrolment started on 15 October 2012 and 691 patients were screened before the end of September 2014. The sample size obtained during this time period included fewer than the target number determined by our power calculations. However, we had to do the interim analysis because we were funded for 2 years by the Korea Centers for Disease Control and Prevention (KCDC) and Korean Institute of Tuberculosis (KIT). With the sample size obtained, there was 92.0% power for analysis of the primary endpoint (instance of a positive culture at 2 months) and 94.8% power for analysis of the secondary endpoint (final outcomes) between the non-DM and uncontrolled-DM groups.

Among 691 new patients with PTB, 30 were excluded either due to missing data (n=17) or a change in diagnosis to a non-tuberculous mycobacterium (n=13). Finally, 661 patients were included in this study. Among the 661 patients, 157 (23.8%) had DM and 108 of these (68.8%) had uncontrolled status (figure 1). Among the 157 patients with DM, 104 were diagnosed previously and 53 (33.8%) were newly diagnosed with DM during the workup of PTB. Of the 53 newly diagnosed patients with DM, 25 were grouped as controlled-DM while the remaining 28 were grouped as uncontrolled-DM.

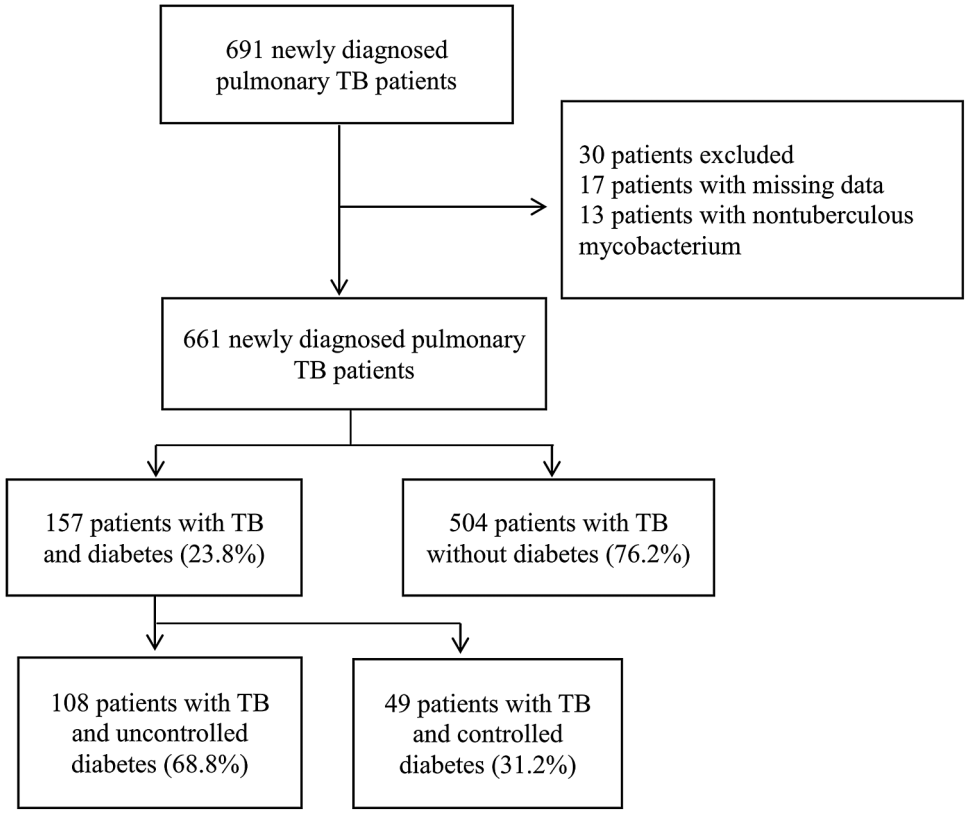

Figure 1 A flow diagram of the study population.

Disease presentation

Patients with DM were older, mostly male, and had a higher history of smoking and heart disease compared with the non-DM group. Regarding symptoms, patients with DM had more instances of cough (p=0.029), sputum (p=0.018), weight loss (p<0.001) and a higher symptom score (p=0.027) than the non-DM group. In bacteriological and radiological examinations, patients with DM had a greater instance of positive smears (p<0.001), cavities (p<0.001), consolidation (p<0.001) and multi-lobe involvement (>3 lobes; p<0.001). However, the instance of drug resistance was not statistically different between the two groups (p=0.076).

To test the effect of diabetes control status, we compared measures from patients in the non-DM, controlled-DM and uncontrolled-DM groups. Regarding baseline symptoms, the uncontrolled-DM group had more instances of cough (p=0.009), sputum (p=0.018) and weight loss (p=0.006) compared with the non-DM group. Bacteriological and radiological examinations showed that those with uncontrolled-DM had a higher instance of a positive smear (p<0.001), cavities (p<0.001), consolidation (p=0.001) and multi-lobe involvement (p<0.001) compared with the non-DM group. However, those with controlled-DM did not show any difference in baseline symptoms, bacteriological and radiological findings compared with the non-DM group (table 1). The incidence of positive smears in the non-DM group, the controlled-DM group, patients with HbA1C 7.0–8.99% and patients with HbA1C≥9% was 42.3% (213/503), 45.1% (23/51), 67.7% (42/62) and 82.6% (38/46), respectively (p for trend <0.001). The presence of a cavity in the non-DM group, those with controlled-DM, patients with HbA1C 7.0–8.99% and patients with HbA1C≥9% was 36.0% (181/503), 45.1% (23/51), 58.1% (36/62) and 73.9% (34/46), respectively (p for trend<0.001).

Treatment response during the intensive phase of treatment

To evaluate treatment response, we excluded those who did not use rifampin (n=43), according to the WHO guidelines.[16] Of 618 patients, 142 (23.0%) had diabetes and 99 (69.7%) of them had uncontrolled-DM. The occurrence of transfer or default during the intensive phase of treatment did not differ between patients with DM and the non-DM group (p=0.353). A total of three patients with DM (2.1%) died during the intensive phase of treatment, but this did not reach statistical difference compared with the non-DM group (p=0.083). Microbiological examination of sputum during the intensive phase of treatment was performed for 485 patients. In the non-DM group, 28 of 367 (7.6%) presented with a positive culture at 2 months of treatment and 19 of 118 (16.1%) patients with diabetes had a positive culture at 2 months of treatment (OR, 2.32; 95% CI 1.25 to 4.34, p=0.007). When treatment response was assessed according to the status of diabetes control, those with uncontrolled-DM showed a higher instance of positive cultures at 2 months of treatment (p=0.009) compared with the non-DM group; however, those with controlled-DM did not show any difference compared with the non-DM group (p=0.755; table 2). When occurrence of positive cultures at 2 months was assessed according to the HbA1C level, the frequency of positive cultures in the non-DM group, the controlled-DM group, patients with HbA1C 7.0–8.99% and patients with HbA1C≥9% was 7.6% (28/367), 5.7% (2/35), 11.9% (5/42) and 34.3% (12/35), respectively (p for trend<0.001).

Table 1 Characteristics of patients with pulmonary TB, according to diabetes control status

	Non-DM N=504	Controlled-DM N=49	Uncontrolled-DM N=108	p Value
Age, years median (IQR)	41.0 (29.4–56.8)	62.1 (50.3–70.0)*	56.1 (49.1–65.7)*	<0.001
Sex, male	324/504 (64.3)	37/49 (75.5)	92/108 (85.2)*	<0.001
BMI, mean±SD (kg/m^2)	20.6±3.2	21.8±3.9*	20.9±3.0	0.034
Any smoking history	198/503 (39.4)	28/48 (58.3)*	73/108 (67.6)*	<0.001
TB history	96/504 (19.0)	12/49 (24.5)	26/108 (24.1)	0.373
Symptom				
Cough	332/504 (65.9)	31/49 (63.3)	87/108 (80.6)*	0.009
Sputum	264/504 (52.4)	27/49 (55.1)	71/106 (67.0)*	0.023
Haemoptysis	57/503 (11.3)	6/49 (12.2)	13/107 (12.1)	0.959
Weight loss	141/504 (28.0)	21/49 (42.9)	46/108 (42.6)*	0.002
Fever	129/503 (25.6)	13/49 (26.5)	37/107 (34.6)	0.168
Night sweating	50/504 (9.9)	5/49 (10.2)	19/107 (17.8)	0.064
Symptom score (≥4)	75/504 (14.9)	9/49 (18.4)	26/107 (24.3)	0.056
Microbiologic findings				
Smear positivity	213/504 (42.3)	22/49 (44.9)	80/108 (74.1)*†	<0.001
Drug resistant (any drug)	59/399 (14.8)	10/43 (23.3)	19/93 (20.4)	0.190
INH resistant	48/401 (12.0)	6/43 (14.0)	15/94 (16.0)	0.567
MDR	18/401 (4.35)	4/43 (9.3)	6/94 (6.4)	0.342
Chest radiograph				
Cavity	181/504 (35.9)	22/49 (44.9)	70/108 (64.8)*	<0.001
Consolidation	277/504 (55.0)	32/49 (65.3)	79/108 (73.1)*	0.001
Multi-lobe involvement‡	132/504 (26.2)	20/49 (40.8)	49/108 (45.4)*	<0.001
Underlying disease				
Heart disease	37/497 (7.4)	16/49 (32.7)*	26/107 (24.3)*	<0.001
Cancer	15/503 (3.0)	1/49 (2.0)	4/108 (3.7)	0.846
ESRD	2/501 (0.4)	1/49 (2.0)	2/108 (1.9)	0.162

Data are presented as the number (%) of subjects, unless otherwise indicated.
*p<0.05 compared with non-DM, †p<0.05 compared with controlled-DM.
‡Multi-lobe involvement indicates lung involvement of more than three lobes.
BMI, body mass index; DM, diabetes mellitus; ESRD, end-stage renal disease; INH, isoniazid; MDR, multidrug resistant.

Table 2 Treatment response and outcome of patients with pulmonary TB, according to diabetes control status

	Non-DM	Controlled-DM	Uncontrolled-DM	p Value
Intensive phase	N=476	N=43	N=99	
Death	2/476 (0.4)	0/43 (0)	3/99 (3.0)	0.026
Transfer or default	10/476 (2.1)	0/43 (0)	5/99 (5.1)	0.125
No culture result	97/476 (20.4)	3/43 (7.0)	13/99 (13.1)	0.033
Positive culture	28/367 (7.6)	2/40 (5.0)	17/78 (21.8)*	<0.001
Final outcome	N=452	N=40	N=93	
Favourable	403/452 (89.2)	35/40 (87.5)	74/93 (79.6)	0.057
Cured	241/452 (53.3)	25/40 (62.5)	45/93 (48.4)	0.366
Treatment complete	162/452 (35.8)	10/40 (25.0)	29/93 (31.2)	0.266
Unfavourable	49/452 (10.8)	5/40 (12.5)	19/93 (20.4)*	0.044
Death	2/452 (0.4)	0/40 (0)	4/93 (4.3)*	0.003
TB-related death	0/452 (0)	0/40 (0)	2/93 (2.2)	
Treatment failure	3/452 (0.7)	1/40 (2.5)	5/93 (5.4)*	0.003
Transfer or default	44/452 (9.7)	4/40 (10.0)	10/93 (10.8)	0.965

Data are presented as the number (%) of subjects, unless otherwise indicated.
*p<0.05 compared with non-DM.
DM, diabetes mellitus.

Treatment response at the end of treatment

Of 618 patients, 33 (5.3%) continued receiving treatment. The frequency of patients continuing treatment did not differ between the patients with DM (24/476) and the non-DM group (9/142; p=0.547). Of 585 patients, unsuccessful treatment occurred in 15 patients, with six deaths (1.0%) and nine treatment failures (1.5%). Among the six patients who died, there were two TB-related deaths, while four were due to other causes. All of the TB-related deaths occurred in those with uncontrolled-DM. When we compared the non-DM,

controlled-DM and uncontrolled-DM groups, more patients with uncontrolled-DM experienced treatment failure (p=0.015) and death (p=0.027) compared with the non-DM group. However, the frequencies of treatment failure (p=0.288) and death (p=1.000) did not differ between the controlled-DM and non-DM groups (table 2).

Risk factors for positive sputum culture at 2 months of therapy

Of 618 patients, 113 could not expectorate sputum after initiation of treatment. When patients who could not expectorate sputum at 2 months (n=113) were compared with those with culture results (n=485), those who could not expectorate sputum had lower incidence of cavity on initial chest radiograph (33.3% vs 42.1%; p=0.09), lower incidence of initial smear positive rate (28.9% vs 48.7%; p<0.01) and lower rate of symptom score ≥4 (8.0% vs 17.5%; p=0.01). After exclusion of defaulted cases (n=10), transferred cases (n=5), death (n=5), and those who could not expectorate sputum after treatment initiation (n=113), we evaluated the risk factors for a positive sputum culture at 2 months of treatment in 485 patients. In a univariate analysis, factors that were related to a positive culture at 2 months included a higher symptom score, a positive sputum smear, uncontrolled diabetes, the presence of a cavity, the presence of consolidation and multi-lobe involvement on chest radiography (table 3). In the multivariable analysis, uncontrolled diabetes (adjusted OR (aOR), 2.11; 95% CI 1.03 to 4.31) and a positive sputum smear (aOR, 6.12; 95% CI 2.17 to 17.25) were independent risk factors for positive sputum culture at 2 months (table 3).

Risk factors for treatment failure or death

After exclusion of patients who received ongoing treatment (n=33), defaulted cases (n=39) and transferred cases (n=19), 527 cases were evaluated for risk factors associated with treatment failure or death. In univariate analysis, factors that were associated with treatment failure or death included age over 60 years, a history of smoking, uncontrolled diabetes, multi-lobe involvement, presence of comorbidity and a positive sputum smear (table 4). In the multivariable analysis, current smoking (aOR, 6.23; 95% CI 1.16 to 33.50), uncontrolled diabetes (aOR, 4.11; 95% CI 1.23 to 13.78) and multi-lobe involvement (more than three; aOR, 3.73; 95% CI 1.02 to 13.71) were associated with treatment failure or death (table 4).

The effect of glucose-lowering treatment on PTB treatment outcome

Among 157 patients who had DM, 131 (83.4%) were evaluated for plasma HbA1C level at 3 months of treatment. In the initial characterisation of diabetes status, 88 exhibited uncontrolled-DM and 43 had controlled-DM. Among the 88 patients with uncontrolled-DM, 59 (67.0%) remained in the uncontrolled state at 3 months of treatment and 29 (33.0%) exhibited a change to a controlled state at 3 months of treatment. The two groups did not show a difference in frequency of a positive initial smear (86.2% vs 69.5%; p=0.088), the presence of a cavity (65.5% vs 67.8%; p=0.83), multi-lobe involvement (51.7% vs 67.0%; p=0.41), initial median HbA1C level (8.3% vs 9.0%; p=0.164) or use of insulin (24.1% vs 37.3%; p=0.217). With regards to treatment response, the two groups did not show differences in the occurrence of a positive 2-month culture (OR, 0.68; 95% CI 0.23 to 2.05, p=0.49) and

Table 3 Risk factors for a positive culture at 2 months of pulmonary TB treatment

	Culture conversion before 2 months N=438	Positive culture at 2 months N=47	Unadjusted OR (95% CI), p value	Adjusted OR (95% CI), p value
Age over 60 years	117/438 (26.7)	10/47 (21.3)	0.74 (0.36 to 1.54), 0.421	
BMI				
BMI<18.5	111/438 (25.3)	16/47 (34.0)	1	
18.5≤BMI<25	280/438 (63.9)	28/47 (59.6)	0.83 (0.45 to 1.54), 0.556	
25≤BMI	47/438 (10.7)	3/47 (6.4)	0.57 (0.17 to 1.90), 0.358	
Smoking status				
Non-smoker	244/438 (55.7)	17/47 (36.2)	1	1
Past smoker	59/438 (13.5)	9/47 (44.7)	1.52 (0.70 to 3.31), 0.290	1.55 (0.61 to 3.91), 0.355
Current smoker	135/438 (30.8)	21/47 (44.7)	1.81 (0.99 to 5.34), 0.056	1.49 (0.70 to 3.18), 0.307
Symptom score ≥4	69/438 (15.8)	16/47 (34.0)	2.76 (1.43 to 5.32), 0.002	1.07 (0.51 to 2.23), 0.865
Status of DM				
Non-DM	339/438 (77.4)	28/47 (59.6)	1	1
Controlled-DM	38/438 (8.7)	2/47 (4.3)	0.64 (0.15 to 2.78), 0.549	0.54 (0.12 to 2.50), 0.537
Uncontrolled-DM	61/438 (13.9)	17/47 (36.2)	3.37 (1.74 to 6.54), <0.001	2.11 (1.03 to 4.31), 0.042
Positive smear	194/438 (44.3)	42/47 (89.4)	10.57 (4.10 to 27.21), <0.001	6.12 (2.17 to 17.25), 0.001
Drug resistant (any drug)	43/437 (9.8)	3/46 (6.5)	0.64 (0.19 to 2.15), 0.466	
Cavity	170/438 (38.8)	34/47 (72.3)	4.12 (2.12 to 8.04), <0.001	1.33 (0.60 to 2.94), 0.488
Consolidation	259/438 (59.1)	37/47 (78.7)	2.56 (1.24 to 5.28), 0.007	1.46 (0.66 to 3.20), 0.352
Multi-lobe involvement*	128/438 (29.2)	27/47 (57.4)	3.27 (1.77 to 6.04), <0.001	1.54 (0.77 to 3.08), 0.218
Comorbidity†	64/438 (14.6)	7/47 (9.9)	1.02 (0.44 to 2.38), 0.959	
Compliance <95%	27/436 (6.2)	5/47 (10.6)	1.80 (0.66 to 4.93), 0.223	

Data are presented as the number (%) of subjects, unless otherwise indicated.
*Multi-lobe involvement indicates lung involvement of more than three lobes.
†Comorbidities include end-stage renal disease, heart disease and cancer.
BMI, body mass index (kg/m^2).

Table 4 Risk factors for treatment failure or death

	Favourable outcome N=512*	Poor outcome N=15†	Unadjusted OR (95% CI), p value	Adjusted OR (95% CI), p value
Age over 60 years	133/512 (26.0)	8/15 (53.3)	3.26 (1.16 to 9.15), 0.033	3.18 (0.84 to 12.03), 0.088
BMI				
BMI<18.5	121/512 (23.6)	4/15 (26.7)	1	
18.5≤BMI<25	338/512 (66.0)	9/15 (60.0)	0.77 (0.27 to 2.21), 0.772	
BMI≥25	53/512 (10.4)	2/15 (13.3)	1.33 (0.29 to 6.07), 0.711	
Smoking status				
Non-smoker	495/512 (96.7)	2/15 (13.3)	1	1
Past smoker	70/512 (13.7)	5/15 (33.3)	3.16 (1.05 to 9.51), 0.041	4.79 (0.84 to 12.03), 0.078
Current smoker	139/512 (27.1)	8/15 (53.3)	3.07 (1.09 to 8.62), 0.033	6.23 (1.16 to 33.50), 0.033
Symptom score ≥4	79/512 (15.4)	5/15 (33.3)	2.74 (0.91 to 8.23), 0.074	1.82 (0.42 to 7.85), 0.421
Status of DM				
Non-DM	4.3/512 (78.7)	5/15 (33.3)	1	1
Controlled-DM	35/512 (6.8)	1/15 (6.7)	2.30 (0.26 to 20.26), 0.452	0.97 (0.10 to 9.59), 0.978
Uncontrolled-DM	74/512 (14.5)	9/15 (60)	9.80 (0.32 to 30.07), <0.001	4.11 (1.23 to 13.78), 0.022
Positive smear	224/512 (43.8)	11/15 (73.3)	3.54 (1.11 to 11.25), 0.023	1.21 (0.30 to 4.99), 0.788
Drug resistant (any drug)	46/510 (9.0)	2/14 (14.3)	1.68 (0.37 to 7.74), 0.373	
Cavity	194/512 (37.9)	8/15 (53.3)	1.87 (0.67 to 5.25), 0.225	
Multi-lobe involvement‡	139/512 (27.1)	11/15 (73.3)	7.38 (2.31 to 23.56), <0.001	3.73 (1.02 to 13.71), 0.047
Consolidation	301/512 (58.8)	11/15 (73.3)	1.93 (0.61 to 6.14), 0.259	
Comorbidity§	70/512 (13.7)	6/15 (40.0)	4.21 (1.45 to 12.19), 0.013	2.09 (0.55 to 7.99), 0.283
Compliance <95%	22/512 (4.3)	1/12 (8.3)	2.02 (0.25 to 16.39), 0.420	

Data are presented as the number (%) of subjects, unless otherwise indicated.
*Favourable outcomes include cure or treatment completion.
†Poor outcomes include treatment failure or death.
‡Multi-lobe involvement indicates lung involvement of more than three lobes.
§Comorbidities include end-stage renal disease, heart disease and cancer.
BMI, body mass index (kg/m^2).

treatment failure or death (OR, 0.52; 95% CI 0.13 to 2.14, p=0.36).

DISCUSSION

In this multicentre prospective cohort study, we compared initial presentation and treatment responses in PTB according to the status of diabetes control. In this study, we found that differences in disease presentations and treatment responses were associated with initial diabetes control status. Upon initial presentation, patients with uncontrolled-DM showed a higher frequency of positive smears, more cavitary lesions on chest radiographs and more symptoms than the non-DM group. After 2 months of intensive treatment, patients with uncontrolled-DM had higher instances of positive culture and treatment failure or death compared with the non-DM group; however, there were no differences between the controlled-DM and non-DM groups. In addition, we found that initial smear positivity and HbA1C≥7% were independent risk factors for positive culture at 2 months of treatment.

Several studies have compared disease presentation in TB between patients with DM and non-DM. However, the results from these studies have been conflicting.[6 7 18–20] According to our data, these differences may be due to differences in study populations and, specifically, the number of patients with controlled-DM included in the study cohort. We found that the controlled-DM and non-DM groups exhibit similarities in measures of smear positivity, frequency of having cavities and symptoms. However, patients with uncontrolled-DM showed differences in disease presentation compared with the non-DM group. In addition, the frequency of having cavities and a positive smear was positively associated with HbA1C levels. A possible hypothesis stems from differences in the cytokine response. An animal study showed that acute diabetic and euglycaemic mice had similar bacterial burdens in the lung. However, chronic diabetic mice had a higher bacterial burden in the lung than euglycaemic mice. In addition, in lungs of a chronic diabetic mouse, there was a reduction in early production of IFN-γ.[21] The results from this animal study suggest that chronic hyperglycaemia is an offensive condition in TB progression. In addition, a recent human study showed that *M tuberculosis*-specific IFN-γ was negatively associated with fasting blood glucose levels.[22] Another possible explanation is that severe infection may result in significant alterations in glucose metabolism and stress-induced hyperglycaemia. However, when we measured HbA1C levels at 3 months of treatment, 67% of those with initially uncontrolled-DM remained with uncontrolled status. Moreover, when we compared the uncontrolled-DM and controlled-DM groups at 3 months of treatment, the two groups did not show statistical differences in initial severity, including smear positivity, presence of cavity and multi-lobe involvement. Therefore, whether the diabetes control status is uncontrolled or controlled, rather than the presence or absence of diabetes, may influence the disease presentation of PTB.

DM is considered to be associated with delayed culture conversion and poor treatment outcomes in TB,[5 11 23] although not all reports have demonstrated a similar relationship.[24 25] In our study, we found that the frequencies of positive culture after 2 months of treatment and treatment failure or death were independently associated with HbA1C≥7%. In addition, HbA1C level was positively correlated with positive culture at 2 months of treatment. Efficient mycobacterial eradication of TB by antimycobacterial antibiotics requires the cooperation of a properly functioning immune system.[26] However, chronic hyperglycaemia can induce immune dysfunction, thereby reducing the

efficacy of anti-TB treatment. Another possible explanation is that DM can interact with anti-TB drugs. One study reported that plasma concentrations of isoniazid and rifampicin are decreased in diabetic populations compared with non-diabetic populations.[27] Another study showed that the volume of distribution and the absorption rate constant of rifampicin were affected by DM.[28] In addition, one study suggested that plasma glucose concentration was associated with rifampicin concentration.[29]

It is unclear whether glucose control during anti-TB treatment can affect the treatment outcome of PTB. Previously, it was thought that strict control of glucose during the treatment of PTB may improve treatment outcomes, because an animal study suggested that glucose control could restore an impaired immune system.[30] However, human studies have not been able to confirm this finding. Two retrospective studies failed to find a negative association between the status of DM control during treatment and treatment response.[23 31] However, a prospective study from Peru reported that the hazard rate of culture conversion among those with documented DM control was 2.2 (95% CI 1.1 to 4.1) compared with unrecognised or uncontrolled-DM. However, this study assessed the status of glucose control only by medical records documented by a nurse or physician prior to treatment of TB.[32] One prospective study suggested that joint management of TB and DM improve clinical outcomes.[33] However, in this study, the control groups were extracted from the previous National Register of Cases of TB.

In our study, we measured the HbA1C level after 3 months of treatment, which reflected the status of DM control during the intensive phase of treatment. Our results also did not show any influence of HbA1C level at 3 months of treatment on the treatment response. However, our study was not designed to study the effect of DM treatment intensification in improving short-term and end of PTB treatment outcomes. Therefore, HbA1C levels at 3 months of treatment were not measured in all patients. In addition, this outcome had only 20.8% power to assess differences in final outcome between controlled-DM and uncontrolled-DM at 3 months of treatment. Therefore, a properly designed randomised controlled trial is needed to show whether intensification of diabetes care at the start of PTB treatment can help improve TB treatment outcomes.

Our study has several limitations. First, culture results were available in only 73% of study patients during the intensive phase of treatment. That is because we did not induce sputum in patients who were not producing it. However, these measures are ecologically relevant in the treatment of PTB because patients often cannot expectorate sputum due to the effective reduction in sputum production by anti-TB treatment. Second, we did not obtain our target sample size because we were funded by the KCDC and KIT for only 2 years. However, with the obtained sample size, we had 92.0% power to analyse differences between non-DM and uncontrolled-DM in the frequency of positive cultures at 2 months of treatment. Therefore, our study population was large enough to adequately address the goals of this study. An additional limitation is that chronic inflammation could induce temporary hyperglycaemia. Therefore, overdiagnosis of DM in patients with newly diagnosed DM was a consideration. However, in this study, to exclude temporary hyperglycaemia, we diagnosed DM based on measurement of HbA1C levels, which reflected 3 months of glucose control. In addition, when we followed fasting glucose or HbA1C level at 3 months of treatment, 21 of 25 patients with newly diagnosed controlled-DM continued to meet the diagnostic criteria of DM, in spite of treatment of DM. Therefore, we expect that the possibility of overdiagnosis might be low.

To the best of our knowledge, this study is the first multicentre prospective cohort study designed to evaluate the effect of the status of DM on PTB treatment outcomes. In conclusion, DM itself is not a risk factor for poor treatment response in PTB, but HbA1C≥7% is an independent risk factor.

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Correction

Matharoo J, Arshad A, Sadhra S, *et al*. S126 How does knowledge, perceptions and attitudes towards shisha pipe smoking vary amongst university students? *Thorax* 2016;71:A74. doi:10.1136/thoraxjnl-2016-209333.132

The first affiliation has been corrected. The correct list should be as follows:

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