Letter to the Editor

Role of Diabetes Mellitus on Treatment Effects in Drug-susceptible Initial Pulmonary Tuberculosis Patients in China*

MA Yan[1,2,3,^], HUANG Mai Ling[1,2,3,^], LI Tao[4,^], DU Jian[1,2,3], SHU Wei[1,2,3], XIE Shi Heng[1,2,3], WANG Hong Hong[1,2,3], ZHU Guo Feng[5], TAN Shou Yong[6], FU Yan Yong[7], MA Li Ping[8], ZHANG Lian Ying[9], LIU Fei Ying[10], HU Dai Yu[11], ZHANG Yan Ling[12], LI Xiang Qun[5], LIU Yu Hong[1,2,3,#], and LI Liang[1,2,3,#]

We assessed the role of diabetes mellitus (DM) on treatment effects in drug-susceptible initial pulmonary tuberculosis (PTB) patients. A prospective study was conducted in eight provinces of China from October 2008 to December 2010. We enrolled 1,313 confirmed drug-susceptible initial PTB patients, and all subjects received the treatment regimen ($2H_3R_3E_3Z_3/4H_3R_3$) as recommended by the national guidelines. Of the 1,313 PTB patients, 157 (11.9%) had DM; these patients had more sputum smear-positive rates at the end of the second month [adjusted odds ratios (a*OR*) 2.829, 95% confidence intervals (*CI*) 1.783-4.490], and higher treatment failure (a*OR* 2.120, 95% *CI* 1.565-3.477) and death rates (a*OR* 1.536, 95% *CI* 1.011-2.628). DM was a contributing factor for culture-positive rates at the end of the second month and treatment failure and death of PTB patients, thus playing an unfavorable role in treatment effects of PTB.

Key words: Tuberculosis; Diabetes mellitus; Treatment outcome

Tuberculosis (TB) is still a serious threat to public health globally. World Health Organization (WHO) reported an estimated 10.4 million new TB cases and 1.4 million TB deaths in 2015. China has 0.918 million TB patients, which is the third highest number globally next to India and Indonesia. With the growing epidemic of diabetes mellitus (DM) worldwide, there are major health and socioeconomic impacts, especially in developing countries. The first Global Report on Diabetes indicated that in 2012, there were 422 million adults with diabetes, 80% of cases occurred in low-and middle-income countries, and DM caused 1.5 million deaths. China has the highest DM burden in the world; almost 10% of all adults in China (about 110 million people) have DM currently, and the number may increase to 150 million by 2040.

China has a high double-burden of both diseases; the rapid and global rise of diabetes put forward challenges in the prevention and treatment of TB. Previous studies confirmed[1-2] that DM was associated with increased risk of TB and poor TB outcomes. In this study, we analyzed the characteristics of pulmonary tuberculosis (PTB) patients with and without DM, and explored the role of DM on treatment effects in PTB patients, which may provide reference evidence to develop prevention and control strategies for PTB with DM.

This prospective study was conducted in eight provinces in China from October 2008 to December 2010, based on the levels of TB burden in 2007; namely, Tianjin, Shanghai, Chongqing, Guangdong,

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1. Beijing Chest Hospital, Capital Medical University, Beijing 101149, China; 2. Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing 101149, China; 3. Administration Office, Clinical Center on Tuberculosis Control, Chinese Center for Disease Control and Prevention, Beijing 101149, China; 4. National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China; 5. Shanghai Municipal Center for Disease Control and Prevention, Shanghai 200336, China; 6. Guangzhou Chest Hospital, Guangzhou 510095, Guangdong, China; 7. Tianjin Centers for Disease Control and Prevention, Tianjin 300041, China; 8. Department of TB Control, Henan Center for Disease Control and Prevention, Zhengzhou 450016, Henan, China; 9. Hebei Center for Disease Control and Prevention, Shijiazhuang 050021, Hebei, China; 10. Department of TB Control, Guangxi Center for Disease Control and Prevention, Nanning 530021, Guangxi, China; 11. Chongqing Anti-tuberculosis Institute, Chongqing 400050, China; 12. Yunnan Center for Disease Control and Prevention, Kunming 650022, Yunnan, China

Hebei, Henan, Yunnan, and Guangxi were selected for the study, which are eight regions that are situated in Eastern, Western, Central, and Metropolitan regions. Laboratory examinations, such as sputum smear examinations, sputum culture examinations, and drug sensitivity tests were carried out in every study area. Cultures for *Mycobacterium tuberculosis* were grown using Lowenstein-Jensen media; drug-susceptibility testing was performed using proportional methods.

A total of 1,313 drug-susceptible initial PTB patients with and without DM were analyzed by inclusion and exclusion criteria in this study. All subjects satisfied the following criteria: 1) Informed consent; 2) Initial diagnosis at 15 years of age or older; 3) Not an nontuberculous mycobacteria (NTM) strain infection; 4) Strains susceptible to Isoniazid (H), Rifampicin (R), and Ethambutol (E); 5) No other comorbidity except for DM; and 6) Culture-positive PTB cases.

Treatment regimens of the participants were administered under China's National TB Control Program (NTP)[3]. A regular 6-month standard short-course chemotherapy was $2H_3R_3Z_3E_3/4H_3R_3$ with H, R, Pyrazinamide (Z), and E in 2-month intensive phases, in addition to H and R in 4-month continuation phases. In the present study, the treatment outcomes were divided into four categories (i.e., successful treatment, failure, died, and transferred out) with definitions according to NTP guidelines in China[3].

Every patient was diagnosed with DM before they started anti-TB therapy. DM was diagnosed if the fasting plasma glucose (FPG) concentration was ≥ 7 mmol/dL at two different time points (within a period of one week); FPG concentrations between 6.1 and 7 mmol/L were considered as impaired fasting glucose (IFG) levels, according to the 1999 WHO guidelines[4].

Chest X-rays were assessed by chest physicians and radiologists who were blinded to TB patients' DM status, and included assessments of lung lesions and cavities (Table 1), which were according to 'Tuberculosis Fascicle, Guideline on Clinical Diagnosis and Treatment'[5].

Assessment of patients on smoking status at the time of enrolment: 1) Non-smoker: Patients who had never smoked; 2) Ex-smoker: A person who was previously a smoker, but had quit smoking for three months before the study; or 3) Current smoker: A patient at the time of the study who had smoked in the last three months.

This study was approved by the Institutional Ethics Review Committee of Beijing Chest Hospital, and selected 8 provincial TB Control and Prevention Centers (TB special hospital).

A total of 2,142 patients with smear-positive PTB were enrolled during the 3-year study period. Of these, 67 NTM cases, 54 culture-negative cases, 383 drug-resistance cases, 154 cases with other comorbid diseases (except DM), and 171 re-treatment cases were excluded. Finally, 1,313 drug-susceptible initial PTB cases were determined eligible and used for further analysis in the study. Among 1,313 patients, 157 (11.9%) cases had DM and 1,156 (89.1%) cases had only TB. Proportion of cases with DM were male, older, attending junior middle school and high school, DM are shown in Table 2. Compared to the group of PTB patients without DM, a higher ex-smokers and smokers, and had body mass index (BMI) values of 18.5-23.

We further analyzed manifestations of chest X-rays between PTB with and without DM after patients completed the treatment period of six months. As expected, there was a higher proportion of no change (6.1% *vs*. 4.9%) or deterioration (3.5% *vs*. 1.2%) in lesions of the lungs on chest X-rays among the PTB with DM patient group; meanwhile, patients with DM were more likely to have cavities with no changes (11.8% *vs*. 7.4%) or increasing (1.8% *vs*. 0.6%), as seen in Table 3.

Table 1. Lesions Absorption and Cavities Closure

Characteristic	Evaluated Index
Lesions	
Significant absorption	Absorption of all lesions ≥ 1/2 of primary lesion
Absorption	Absorption of all lesions < 1/2 of primary lesion
No change	No significant change of all lesions
Deterioration	Lesions enlarge or spread
Cavities	
Decreased	Cavities decreased ≥ 1/2 of primary cavities diameter
No change	Cavities decreased or increased < 1/2 of primary cavities diameter
Increase	Cavities decreased or increased > 1/2 of primary cavities diameter

In this study, as shown in Table 4, we determined the sputum culture status of 1,128 patients at the end of the second month of TB treatment, rather than of 1,313 patients, mainly because they presented with no sputum. PTB patients with DM remained culture-positive (26.4% *vs.* 10.5%) at 2 months, with lower treatment success (74.5% *vs*. 85.6%), and higher treatment failure rate (8.3% *vs*. 5.0%) and death rate (3.8% *vs.* 1.4%) after treatment for six months. Multivariate logistic regression analysis also revealed that DM was associated with an increased culture-positive rate [adjusted odds ratios (a*OR*) 95% confidence intervals (*CI*)]: [2.829 (1.783-4.490)] at the end of the second month of PTB, and treatment failure [a*OR* (95% *CI*): 2.120 (1.565-3.477)] and death [a*OR* (95% *CI*):

Table 2. Characteristics of Initial PTB Patients with and without DM

Characteristic	Total	PTB Patients without DM	PTB Patients with DM	*P* Value
	N (%)	*N* (%)	*N* (%)	
Sex				
Male	915/1,313 (69.7)	785/1,156 (67.9)	130/157 (82.8)	Reference
Female	398/1,313 (30.3)	371/1,156 (32.1)	27/157 (17.2)	< 0.001
Mean (SD) age (years)	40.7 (16.9)	39.1 (16.9)	52.4 (11.5)	< 0.001
Degree of education				
Illiteracy	118/1,313 (9.0)	106/1,156 (9.2)	12/157 (7.6)	Reference
Primary school	298/1,313 (22.7)	269/1,156 (23.3)	29/157 (18.5)	0.053
Junior middle school and high school	747/1,313 (56.9)	637/1,156 (55.1)	110/157 (70.1)	0.189
College degree and above	150/1,313 (11.4)	144/1,156 (12.4)	6/157 (3.8)	0.893
Smoking				
Non-smoker	632/1,313 (48.1)	585/1,156 (50.5)	47/157 (30.0)	Reference
Ex-smoker	461/1,313 (35.1)	395/1,156 (34.3)	66/157 (42.0)	< 0.001
Smoker	220/1,313 (16.8)	176/1,156 (15.2)	44/157 (28.0)	< 0.001
BMI value[a]				
< 18.5	500/1,299 (38.5)	467/1,142 (40.9)	33/157 (21.0)	Reference
18.5-	721/1,299 (55.5)	621/1,142 (54.4)	100/157 (63.7)	< 0.001
≥ 24.0	78/1,299 (6.0)	54/1,142 (4.7)	24/157 (15.3)	< 0.001

Note. [a]Since 14 patients refused to measure height, thus only data of BMI 1,299 cases.

Table 3. Comparison Manifestations of Chest X-ray between TB Patients with and without DM Group when Completely Treatment

Variables	Total	PTB Patients without DM	PTB Patients with DM	Crude *OR* (95% *CI*)	*P* Value
	N (%)	*N* (%)	*N* (%)		
Lesions[b]					
Absorption[*]	980 (93.5)	877 (93.9)	103 (90.4)	Reference	
No change	53 (5.1)	46 (4.9)	7 (6.1)	1.312 (0.566-3.046)	0.527
Deterioration	15 (1.4)	11 (1.2)	4 (3.5)	3.136 (0.966-10.180)	0.057
Cavities[c]					
Decreased	374 (91.2)	323 (92.0)	51 (86.4)	Reference	
No change	33 (8.1)	26 (7.4)	7 (11.8)	0.874 (0.295-2.589)	0.807
Increase	3 (0.7)	2 (0.6)	1 (1.8)	3.167 (0.282-35.560)	0.350

Note. [b]Only 1048 TB cases were analyzed include 934 cases without DM and 114 cases with DM; [c]Only 410 TB cases were analyzed include 351 cases without DM and 59 cases with DM. [*]Absorption include significant absorption and absorption.

1.536 (1.011-2.628)], respectively.

Some published literature reported that 5.4%-44.0% of PTB patients have DM[1-2,6]; in the present study, 11.9% of PTB patients had DM, which was similar to a proportion reported from India (11.61%)[2]. WHO reported that there were DM occurred in 10% of TB patients in 2011[7]; however, a study from India highlighted that DM was as high as 44% among TB patients[6]. Inaddition, in Brazil, only 5.4% of TB patients presented with DM[1]. Different research results have great variation; this may be related with study settings, high burdens of both diseases, study design, methods of diagnosing DM, or outcome definitions.

A study[2] reported that PTB patients with DM had higher sputum-positive rates at the end of the second month, which was also shown in our studies, as DM was an independent risk factor of culture-positive rates of the end of the second month. This was mainly because DM patients had a history of metabolic disorders and low immunity; thus, tuberculosis bacteria could not be easily killed. Whether DM could increase unfavorable outcomes of TB patients is a controversial topic, although some data indicated that prognosis did not significantly difference between PTB patients with and without DM[8]; however, more studies documented that DM could further increase the risk of unfavorable outcomes[1-2]. This study revealed that DM is a risk factor for increasing treatment failure and death. At present, there are still no special treatment regimens for PTB patients with DM. Some experts suggested that the treatment course of PTB patients with DM should be prolonged according to individual patient statuses[9]. Treatment courses of re-treatment and initial PTB patients with DM should be extended beyond 12 months and 8 months, respectively, which may improve the absorption of lung lesions and cavites closure outcomes.

Our data indicated that radiological manifestations such as lesions absorption and cavites closures were more severe among patients with DM. Previous studies have confirmed greater multiple cavities on chest radiography in PTB patients with DM[9]; however, previous studies have also reported no differences in chest radiography[10]. Thus, further study is still required to explore the impact of DM on lung lesions absorption and cavites closures in PTB patients.

To sum up, DM is associated with increasing risk of culture-positive rates at the end of the second month, treatment failure, and death. Hence, we should pay more attention to early prevention, timely detection, and standard treatment and care for PTB patients with DM. We suggest that DM prevention and control strategies should be added to TB control programs, and to evaluate their effectiveness, carry out further research to explore some important questions on optimal treatment courses of PTB patients with DM. In this way, the growing TB-DM co-epidemic may be controlled through the above measures.

Strengths and Limitations This study has several strengths as follows. To the best of our knowledge, this might be the first prospective, multicenter, large-sample study to investigate treatment effects and outcomes in PTB patients with and without DM. Our study data demonstrated that DM occurred in about 11.9% of drug-susceptible initial PTB patients, and further confirmed that DM is an independent risk factor to increase culture-positive rates at the end of the second month, failure rates, and death rates.

Table 4. Multivariate Regression Analysis for DM Associated with TB Treatment Effect

Variables	PTB without DM	PTB with DM	Unadjust		Adjusted	
	N (%)	*N* (%)	*OR* (95% *CI*)	*P* Value	*OR* (95% *CI*)	*P* Value
Sputum-culture of the end of 2nd month						
Negative	898 (89.5)	92 (73.6)				
Positive	105 (10.5)	33 (26.4)	3.068 (1.964-4.792)	< 0.001	2.829 (1.783-4.490)	< 0.001
Treatment outcome						
Treatment success	990 (85.6)	117 (74.5)				
Failure	58 (5.0)	13 (8.3)	2.326 (1.412-3.833)	0.001	2.120 (1.565-3.477)	0.002
Died	16 (1.3)	6 (3.8)	2.144 (1.121-2.168)	0.023	1.536 (1.011-2.628)	0.031
Others[a]	88 (8.1)	21 (13.4)	2.655 (0.955-7.379)	0.061	0.841 (0.101-7.028)	0.873

Note. [a]Others include defaulted and transferred out cases.

Of course, there are still several limitations in our study. First, blood glucose levels across different months can further reveal associations between DM and TB. Unfortunately, because the patient data were incomplete, this could not be assessed in the study. Second, because the patients had no follow-up period after completing treatment in our study, we could not further analyze relapse of TB patients with and without DM.

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[^]These authors contributed equally to this study and share first authorship.

[#]Correspondence should be addressed to LI Liang, Fax: 86-10-80885205, Tel: 86-10-89509216, E-mail: liliang@tb123.org; LIU Yu Hong, Fax: 86-10-80885025, Tel: 86-10-89509135, E-mail: liuyuhong0516@126.com

Biographical notes of the first authors: MA Yan, female, born in 1980, Master of public health, majoring in tuberculosis control and prevention; HUANG Mai Ling, female, born in 1980, Master of clinical medicine, majoring in clinical research and treatment; LI Tao, male, born in 1981, Master of public health, majoring in tuberculosis control and prevention.

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