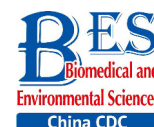# Letter to the Editor

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

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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,

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