Biomedical Research 2017; 28 (9): 3917-3922 *ISSN 0970-938X*
www.biomedres.info

Effect of type 2 diabetes mellitus on sputum negative conversion and treatment effects of multi-drug-resistant tuberculosis.

Baodong Yuan[1], Juan Du[1], Xing Lan[1], Meilan Zhou[2], Jianjie Wang[2], Weihua Wang[2*]

[1]Internal Medicine 4th Ward, Wuhan Institute for Tuberculosis Control, Wuhan Pulmonary Hospital, Wuhan, PR China

[2]Global Fund MDR-TB Project Office, Wuhan Institute for Tuberculosis Control, Wuhan Pulmonary Hospital, Wuhan, PR China

Abstract

The aim of this study was to investigate the effect of Type 2 Diabetes Mellitus (T2DM) on sputum negative conversion and treatment of Multi-Drug-Resistant Tuberculosis (MDR-TB). We included a total of 359 MDR-TB patients for comparing the sputum negative conversion rates at 2, 6, and 12 months after initiating treatment and the recovery (treatment success) rates after completion of treatment for patients with T2DM (Group 2DM+) versus those without (Group 2DM-). A total of 20.6% of the patients (74/359) had T2DM; there were no significant differences in the sputum negative conversion rates between Group 2DM+ and Group 2DM- at 2 and 6 months (P>0.05), but the sputum negative conversion rate in Group 2DM+ at 12 months was significantly lower than that in Group 2DM- (P<0.05); the treatment success rates in Group 2DM+ and Group 2DM- were 56.8% and 79.3%, respectively, and the difference was statistically significant (P<0.05). MDR-TB patients with T2DM had a higher recurrent sputum positive rate at the end of the 12-month treatment, and the success rate was relatively low. Therefore, these patients should undergo early screening for MDR-TB and be supervised during the entire treatment course; standardized management and treatment may be able to improve the treatment success rate.

Keywords: Tuberculosis, Multi-drug resistance, Diabetes mellitus.

Accepted on January 30, 2017

Introduction

Multi-Drug-Resistant Tuberculosis (MDR-TB) is defined as infection with a *Mycobacterium tuberculosis* strain that shows resistance to two or more drugs, at least simultaneously to Rifampin (R) and isoniazid (H). MDR-TB has become an important source of infection because of the required long treatment time, difficulty of treatment, high cost of treatment, low cure rate, and high mortality. It constitutes a heavy burden on society and a threat to global Tuberculosis (TB) control, and has become an urgent problem to be solved.

The World Health Organization (WHO) estimates that there have been 480 thousand patients infected with MDR-TB. Among them, approximately 190 thousand patients have died, and only around 50% of cases have been successfully treated [1]. China is one of the 22 countries with the highest burden of TB in the world. A national survey of MDR-TB in China revealed 52 thousand MDR-TB cases in 2014.

Over the past few years, the relationship between TB and other diseases has been supported by mounting evidence. Diabetes Mellitus (DM) has been found to be one of the diseases linked with TB, something that has been suspected for decades [2]. Owing to their immune-compromised status, people with DM are more vulnerable to infections and suffer from relatively more severe illness, especially with TB. A report from India found that the proportion of TB patients with DM was about 13% [3], while the corresponding proportion in China was 16.0%-24.0%.

Two systematic reviews have highlighted the higher risk among people with DM for active TB, and other research over the same period shows the relative risk as 3.1 (95% CI 2.3-4.3); case-control studies have reported odds ratios of 1.2 to 7.8 [4,5]. These findings have confirmed that the overall risk among people with DM also suffering from TB is three times higher than that among the general population [6].

DM also increases the risk of relapse of TB; five studies reported the relative risk of relapse as 3.89 (95% CI 2.43-6.23) [7]. The incidence of both DM and TB worldwide are increasing over time, and so is the number of patients with both diseases. Therefore, the increasing incidence of both diseases poses a severe challenge for controlling TB in China.

Currently, most studies have reported that TB patients with DM have higher rates of treatment failure [8,9], but there is still controversy as to whether DM significantly increases the risk of acquiring MDR-TB. The effect of DM on the treatment

of MDR-TB is rarely reported, especially its effect on the sputum negative conversion rate. Therefore, we applied Observed Treatment Short course (DOTS) management during the whole treatment course for MDR-TB patients, aiming to investigate the sputum negative conversion rate and the success rate of treating MDR-TB patients with and without Type 2 Diabetes Mellitus (T2DM).

Materials and Methods

Study design

This study used a case-control design.

Subjects

All of the cases were collected from the fifth-round China Global Fund MDR-TB project (the 1st stage), China Global Fund MDR-TB integrated project, and prolonged project, which were consecutively implemented in Wuhan from December 2006 to June 2014. During the implementation period, a total of 4870 suspected MDR-TB cases were screened throughout Wuhan and after strain identification and susceptibility tests, 593 MDR-TB patients were diagnosed and included in the management, treatment, and 18-24 month follow-up. A total of 359 cases had complete treatment outcomes and were registered, including 74 patients who also had T2DM and 285 patients without T2DM. The patients with T2DM included those with a history of diabetes or newly diagnosed with diabetes. Definitions of MDR-TB and diabetes as defined by WHO were used for this project [10,11]. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Wuhan Pulmonary Hospital. Written informed consent was obtained from all participants.

Data variables and data collection

All of the MDR-TB patients had a TB sputum smear and culture performed once every month during the injection period after initiation of treatment and once every 2 months during the non-injection period. The sputum negative conversion rate was compared between the two groups 2, 6, and 12 months after initiation of treatment.

Criteria of treatment outcomes

The results of laboratory sputum smear and culture were set as the primary evidence of the treatment outcomes; the treatment outcomes were divided into six categories, namely “cured,” “treatment completed,” “treatment failed,” “died,” “lost to follow up,” and “not evaluated” [12], among which “cured” and “completed” were considered as successful treatment, but the rest were considered as unsuccessful in accordance with the WHO guidelines.

Analysis and statistics

SPSS v. 19.0 software was used for the statistical analysis. The interactions of multiple factors were analysed using logistic regression analysis, and the count data were analysed using the χ^2 test or Fisher's exact test, with $P<0.05$ defined as statistically significant.

Results

General situations

A total of 359 MDR-TB patients were enrolled into DOTS who were registered, had treatment outcomes, and completed the 18-24-month follow-up from December 1, 2006 to June 30, 2014, including 74 cases with MDR-TB and T2DM (Group 2DM+, 61 men and 13 women, aged 30 to 68 years, mean age (50.59 ± 9.77 years), and 285 cases with MDR-TB without T2DM (Group 2DM-, 199 men and 86 women, aged 18 to 72 years, mean age (41.82 ± 13.79 years). The $\chi 2$ test showed no statistically significant difference in sex between the two groups ($P>0.05$) but there was for age ($P<0.01$); further analysis revealed that the prevalence of MDR-TB combined with T2DM in patients aged 35-54 and>55 years old was higher than that in the age group of 18 to 34 years old, and the difference was statistically significant ($P<0.01$). There were also statistically significant differences between groups in drinking habits, liver and kidney diseases, first or re-treatment, and the presence of a pulmonary cavity ($P<0.05$) (Table 1).

Table 1. *Demographic and clinical characteristics of MDR-TB patients with and without DM, Wuhan, 2006-2014.*

Population features	2DM+ (n=74)	2DM- (n=285)	T/χ^2	P
BMI	20.94 ± 3.30	19.36 ± 2.61	4.39	<0.01
Gender			0.57	>0.05
M	55 (74.3)	199 (69.8)		
F	19 (25.7)	86 (30.2)		
Age			25.28	<0.01
18~34	6 (8.1)	98 (34.4)		
35~54	37 (50.0)	129 (45.3)		
55~	31 (41.9)	58 (20.4)		
Drinking history			21.78	<0.01
Yes	33 (45.2)	54 (18.9)		
No	40 (54.8)	231(81.1)		
Combining with liver disease			9.34	0.002
Yes	18 (24.7)	31 (10.9)		
No	55 (75.3)	254 (89.1)		
Combing with renal disease			5.56	0.033
Yes	5 (6.8)	5 (1.8)		

No	68 (93.2)	280 (98.2)		
First or re-treatment			3.86	0.049
First treatment	26 (35.1)	68 (23.9)		
Re-treatment	48 (64.9)	217 (76.1)		
Pre-treatment sputum smear			1.83	0.176
Positive	32 (43.2)	99 (34.7)		
Negative	42 (56.8)	186 (65.3)		
Resistant to levofloxacin			2.8	0.246
Yes	9 (12.2)	65 (11.6)		
No	32 (43.2)	137 (48.1)		
Pulmonary cavity			6.77	0.009
Yes	45	125		
No	29	160		

The sputum negative conversion rate

There were no significant differences in the sputum negative conversion rates between Group 2DM+ and Group 2DM- at 2 and 6 months (χ^2=5.61 and 0.41, respectively, P>0.05); however, at 12 months, 59 cases in Group 2DM+ were negative, and 242 cases in Group 2DM- were negative, a statistically significant difference (χ^2=8.78, P<0.05) (Table 2).

Table 2. *Smear status of sputum culture-positive MDR-TB patients with and without DM at the end of the 2nd-, 6th- and 12th-month, Wuhan, 2006-2014.*

	Sum (n=359)	**2DM+ (n=74 (%))**	**2DM- (n=285 (%))**	**χ^2**	**P**
2nd-month					
Negative	303	66 (89.2)	237 (83.2)	5.61	0.06
Positive	49	5 (6.8)	44 (15.4)		
No sputum retained	7	3 (4.1)	4 (1.4)		
6th-month					
Negative	302	64 (86.5)	238 (83.5)	0.41	0.815
Positive	16	3 (4.1)	13 (4.6)		
No sputum retained	41	7 (9.5)	34 (11.9)		
12th-month					
Negative	301	59 (79.7)	242 (84.9)	8.78	0.012
Positive	8	5 (6.8)	3 (1.1)		
No sputum retained	50	10 (13.5)	40 (14.0)		

Treatment outcomes

The overall treatment success rate in these 359 MDR-TB patients was 74.7%, among whom Group 2DM+ had 32 unsuccessful cases, a cure rate of 56.8%; 59 cases in Group 2DM- were unsuccessful, a cure rate of 79.3%. The success rate in Group 2DM+ was much lower than Group 2DM-, and the difference was statistically significant (χ^2=15.76, P<0.05) (Table 3).

Table 3. *Treatment outcomes for MDR-TB patients with and without DM, Wuhan, 2006-2014.*

Treatment outcome	**2DM+ (n=74 (%))**	**2DM- (n=285 (%))0**	**χ^2**	**P**
Successful treatment				
Cured	42 (56.8)	226 (79.3)		
Treatment completed	0	0		
Unsuccessful treatment	32 (43.2)	59 (20.7)	15.76	0
Treatment failed	14 (18.9)	28 (9.8)		
Died	2 (2.7)	2 (0.7)		
Lost to follow up	13 (17.6)	28 (9.8)		
Not evaluated	3 (4.0)	1 (0.4)		

Logistic regression analysis of possible confounding variables

Taking T2DM as the dependent variable, logistic regression analysis was performed for age and sex. Single factor analysis showed that the therapeutic effect was correlated with T2DM (OR: 2.92, 95% CI: 1.70-5.02). After correction for age and sex, both T2DM and older age were correlated with a

therapeutic effect (OR: 2.27, 95% CI: 1.29-3.99; OR: 0.51, 95% CI: 0.26-0.99; OR: 0.36, 95% CI: 0.17-0.76) (Table 4).

Table 4. Logistic regression analysis of effect of therapeutic effect.

	Model 1			Model 2		
Variable	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Combined diabetes						
Yes	1			1		
No	2.92	1.70-5.02	<0.001	2.27	1.29-3.99	0.004
Age						
18-34 years old				1		
35-54 years old				0.51	0.26-0.99	0.049
≥ 55 years old			0.36	0.17-0.76	0.007	
Gender						
Male				1		
Female				1.58	0.86-2.92	0.14

Model 1 is single factor analysis, and model 2 contains gender and age.

Discussion

This study reported, for the first time, the effect of T2DM on the sputum negative conversion rate and treatment success of MDR-TB in Wuhan, China. In this study, the prevalence of T2DM in patients with MDR-TB was 20.6% (74/359). Studies in other countries also reported higher prevalence's of T2DM in MDR-TB patients [13-16]; for example, studies from India, the Philippines, Spain, and Peru showed that the prevalence of DM in MDR-TB patients was 10-23%, consistent with this study.

Some limitation studies have shown that negative sputum culture results after 2 months of treatment can better predict the treatment outcomes of MDR-TB [17]. Holtz et al. [18] found poor treatment outcomes in patients who still had positive sputum culture results at the end of the 2nd month of treatment; Dembele et al. [19] confirmed the above results. They followed up patients and found higher cure rates in the patients with negative sputum culture results at 2 months. However, these studies merely analysed the effect of the sputum negative conversion rate at 2 months on final outcomes, but did not analyse the subsequent sputum negative conversion rate.

We found no significant differences in the sputum negative conversion rate between Group 2DM+ and Group 2DM- at 2 and 6 months, but at 12 months, the proportion of patients with positive sputum culture results in Group 2DM+ was higher than in Group 2DM-, indicating that the patients in Group 2DM+ suffered from a higher failure rate than those in group 2DM-.

Currently, there is controversy about the impact of T2DM on the sputum negative conversion rate in TB patients, especially in MDR-TB patients, but reports targeting the latter are rare. Recently, Magee's study [16] found that after treatment, there was no statistically significant difference in the sputum negative conversion rate between patients with and without T2DM, but Salindri et al. [20] reported close relationships between T2DM and the sputum negative conversion rate in MDR-TB patients. Therefore, for MDR-TB patients with T2DM, it is necessary to pay attention to the sputum culture results at 12 month after initiation of treatment.

In this study, the re-positive rate of sputum bacteria in MDR-TB T2DM patients was higher, and there may be several reasons for this: a. obesity and glycaemic control during anti-TB treatment causing alterations in immunity [21], making them more prone to be re-infected by MDR-TB bacteria; b. most T2DM patients have severe lung lesions and cavities, and in this study, the incidence of pulmonary cavities in the patients with T2DM was higher, which has been defined by Kempker et al. [22] as one risk factor for patients to develop new drug resistance. A cavitary lesion is an ideal setting for acquired resistance, and given high bacterial loads, it can activate mycobacterial replication, reduce host defenses, and result in potentially low penetration by drugs; c. a relatively long conversion time among Armenians was found to be correlated with the presence of a high level of ofloxacin resistance [23]; d. unstable blood sugar control or long-term high blood sugar levels can make the internal environment acidic, which thus leads to low immunity, helps pathogens to regrow, and results in a higher risk of recurrence [24]. These are just some possibilities, and more clinical trials and studies need to be performed to investigate the reason(s) in the future.

This study found that the treatment success rate in Group 2DM + (56.8%) was lower than Group 2DM- (79.3%), similar to the results of previous studies. After correction for sex and age, both T2DM and older age were found to be risk factors that lead to a lower curative ratio in patients with MDR-TB. Kang et al. [25] studied 1407 MDR-TB patients and found that the treatment success rate in the MDR-TB patients with T2DM was lower than in those without T2DM (36.0% *vs.* 47.2%, P=0.002); meanwhile, it has also been found that DM is an independent factor that can increase the treatment failure rate and mortality of MDR-TB. Choi et al. [26] reported that older age, T2DM, Body Mass Index (BMI)<18.5 and MDR-TB are risk factors for failure, death, and recurrence during TB treatment. They also found that MDR-TB patients with T2DM are relatively older, and this may be a contributory factor to treatment failure.

Patients with T2DM often have metabolism disorders, low immunity, and a higher bacterial load, which easily leads to bacterial clearance delays. Meanwhile, elderly patients also tend to have low immunity, decreased drug metabolism, and an increased incidence of adverse reactions, and these are all likely to affect the therapeutic effects.

There also exist studies that reported no correlation between T2DM and the treatment outcomes of TB; for example, Prasad et al. [27] reported no statistically significant difference in the treatment success rate between the TB patients with/without

T2DM (91% *vs.* 84%, P=0.06). In short, the treatment of MDR-TB combined with DM is much more complex, and its cure rate is affected by many factors; hence, multiple follow-up studies are needed for further confirmation.

Although this study found that the treatment success rate in Group 2DM+ was lower than in Group 2DM-, it was still higher than other studies (36.0% in Kang [25]). This suggests that joint expert treatments, which integrate multiple disciplines (including experts in endocrinology, psychiatrics, psychology, and surgery) and perform simultaneous treatment, monitoring, and standardized management against the two diseases, can achieve results better than expected. Therefore, treatments with full-process supervision and standardized management against MDR-TB combined with T2DM are particularly important.

There still exist certain shortcomings in this study. It was a single-center study, and there may have been bias when enrolling the patients, such as those patients unable to maintain an effective treatment regimen or refused treatment were not included, and some patients were lost to follow-up for diverse reasons. We also did not perform multivariate analysis of the factors that may influence the sputum bacteria, such as smoking, comorbidities, and blood sugar level, and these factors may have an effect on the final outcomes. In the future, high-quality, prospective, randomized, controlled, and multi-center clinical trials are required so as to further optimize the treatment and management protocols for MDR-TB patients with T2DM.

Conclusions

In summary, in this study, the prevalence of T2DM in MDR-TB patients was 20.6%, and the positive rate of sputum culture in these patients at the end of 12 months of treatment was high, indicating that the recovery rate was low. Therefore, we recommend that patients with both TB and T2DM should be screened for MDR-TB in the early stages and undergo full-procedure supervision and standard management therapies to attempt to improve their cure rate.

Acknowledgements

This study was supported by the China Global Fund MDR-TB project (CHN-S10-G14-T); Major Projects of National Science and Technology in "Eleventh Five-Year Plan" (2009ZX10003-019).

Conflicts of Interest

The authors declare no conflict of interest.

References

1. World Health Organization. Global tuberculosis report 2015. France: WHO Press 2015.
2. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health 2007; 7: 234.
3. Indian Diabetes Mellitus-Tuberculosis Study Group. Screening of patients with diabetes mellitus for tuberculosis in India. Trop Med Int Health 2013; 18: 636-645.
4. Stevenson CR, Critchley JA, Forouhi NG, Roglic G, Williams BG. Diabetes and the risk of tuberculosis: a neglected threat to public health? Chronic Illn 2007; 3: 228-245.
5. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 2008; 5: e152.
6. Lönnroth K, Roglic G, Harries AD. Improving tuberculosis prevention and care through addressing the global diabetes epidemic: from evidence to policy and practice. Lancet Diabetes Endocrinol 2014; 2: 730-739.
7. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med 2011; 9: 81.
8. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clin Infect Dis 2007; 45: 428-435.
9. Harries AD, Murray MB, Jeon CY, Ottmani SE, Lonnroth K. Defining the research agenda to reduce the joint burden of disease from diabetes mellitus and tuberculosis. Trop Med Int Health 2010; 15: 659-663.
10. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: a report of a WHIO/IDF consultation. Geneva: WHO 2006.
11. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: WHO 2006.
12. World Health Organization. Companion handbook to the WHO Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: WHO 2014.
13. Singh R, Gothi D, Joshi J. Multidrug resistant tuberculosis: role of previous treatment with second line therapy on treatment outcome. Lung India 2007; 24: 54-57.
14. Aragon J, Litonjua A, Tupasi T. Prevalence of type 2 diabetes among multi-drug resistant tuberculosis (MDR-TB) patients seen in Makati Medical Center under the directly observed therapy plus (DOTS PLUS) program. Philippine J Intern Med 2003; 41: 7-10.
15. Tanrikulu AC, Hosoglu S, Ozekinci T, Abakay A, Gurkan F. Risk factors for drug resistant tuberculosis in southeast Turkey. Trop Doct 2008; 38: 91-93.
16. Magee MJ, Blossb E, Shin SS, Contreras C, Huaman HA, Ticona JC, Bayona J, Bonilla C, Yagui M, Jave O, Cegielski JP. Clinical characteristics, drug resistance, and treatment outcomes among tuberculosis patients with diabetes in Peru. Int J Infect Dis 2013; 17: e404-412.
17. Shariff NM, Safian N. Diabetes mellitus and its influence on sputum smear positivity at the 2nd month of treatment among pulmonary tuberculosis patients in Kuala Lumpur,

Malaysia: A case control study. Int J Mycobacteriol 2015; 4: 323-329.

18. Holtz TH, Sternberg M, Kammerer S, Laserson KF, Riekstina V, Zarovska E, Skripconoka V, Wells CD, Leimane V. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. Ann Intern Med 2006; 144: 650-659.
19. Dembele SM, Ouedraogo HZ, Combary A, Saleri N, Macq J. Conversion rate at two-month follow-up of smear-positive tuberculosis patients in Burkina Faso. Int J Tuberc Lung Dis 2007; 11: 1339-1344.
20. Salindri AD, Kipiani M, Kempker RR, Gandhi NR, Darchia L, Tukvadze N, Blumberg HM, Magee MJ. Diabetes reduces the rate of sputum culture conversion in patients with newly diagnosed multidrug-resistant tuberculosis. Open Forum Infect Dis 2016; 3: 126.
21. Gomez-Gomez A, Magana-Aquino M, Lopez-Meza S, Aranda-Alvarez M, Díaz-Ornelas DE, Hernandez-Segura MG, Salazar-Lezama MA, Castellanos-Joya M, Noyola DE. Diabetes and other risk factors for multi-drug resistant tuberculosis in a mexican population with pulmonary tuberculosis: case control study. Arch Med Res 2015; 46: 142-148.
22. Kempker RR, Kipiani M, Mirtskhulava V, Tukvadze N, Magee MJ, Blumberg HM. Acquired drug resistance in mycobacterium tuberculosis and poor outcomes among patients with multidrug-resistant tuberculosis. Emerg Infect Dis 2015; 21: 992-1001.
23. Hovhannesyan A, Breeze E. Time to sputum conversion in multidrug-resistant tuberculosis patients in Armenia: retrospective cohort study. Global J Med Pub Health 2012; 1: 24-28.
24. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis 2009; 9: 737-746.
25. Kang YA, Kim SY, Jo KW, Kim HJ, Park SK. Impact of diabetes on treatment outcomes and long-term survival in multidrug-resistant tuberculosis. Respiration 2013; 86: 472-478.
26. Choi H, Lee M, Chen RY, Kim Y, Yoon S, Joh JS, Park SK, Dodd LE, Lee J, Song T, Cai Y, Goldfeder LC, Via LE, Carroll MW, Barry CE 3rd, Cho SN. Predictors of pulmonary tuberculosis treatment outcomes in South Korea: a prospective cohort study, 2005-2012. BMC Infect Dis 2014; 14: 360.
27. Prasad P, Gounder S, Varman S, Viney K. Sputum smear conversion and treatment outcomes for tuberculosis patients with and without diabetes in Fiji. Public Health Action 2014; 4: 159-163.

*Correspondence to

Weihua Wang

Global Fund MDR-TB Project Office

Wuhan Institute for Tuberculosis Control

Wuhan Pulmonary Hospital

PR China