Impact of Diabetes on Treatment Outcomes and Long-Term Survival in Multidrug-Resistant Tuberculosis

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Key Words

Diabetes mellitus · Multidrug-resistant tuberculosis · Treatment · Outcome · Survival

Abstract

Background: Few studies have investigated the impact of diabetes mellitus (DM), a globally increasing metabolic disease, on treatment outcomes and long-term survival in patients with multidrug-resistant forms of tuberculosis (MDR-TB). **Objectives:** We analyzed outcomes in a large cohort to assess the impact of DM on treatment outcomes of patients with MDR-TB. **Methods:** MDR-TB patients newly diagnosed or retreated between 2000 and 2002 and followed for 8–11 years were retrospectively analyzed with respect to the effect of DM as a comorbidity on their treatment outcome and long-term survival. **Results:** Of 1,407 patients with MDR-

TB, 239 (17.0%) had coexisting DM. The mean age and body mass index were higher in MDR-TB patients with DM [MDR-TB_{DM(+)}] than in those without DM [MDR-TB_{DM(-)}]. Patients with MDR-TB and a comorbidity of DM had a significantly lower treatment success rate than those without a history of DM (36.0 vs. 47.2%, $p = 0.002$). In addition, DM was the negative predictor for MDR-TB treatment success in multivariate analyses [odds ratio 0.51, 95% confidence interval (CI) 0.26–0.99]. Mean survival times were also lower in MDR-TB_{DM(+)} than in MDR-TB_{DM(-)} patients (102 vs. 114 months, $p = 0.001$), with DM as a significant predictor of poor long-term survival in multivariate analyses (hazard ratio 1.59, 95% CI 1.01–2.50). **Conclusions:** Among MDR-TB patients, DM was a relatively common comorbidity. In patients undergoing treatment for MDR-TB and followed for 8–11 years, it was found to be independently associated with an increased risk of both treatment failure and death.

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Introduction

In 2011, 366 million people were living with diabetes mellitus (DM). Based on current predictions, the number will increase to 552 million by 2030, with 80% of affected individuals living in low- and middle-income countries [1]. Moreover, a recent meta-analysis showed that diabetes patients have a 2- to 3-fold higher risk of tuberculosis (TB) [2] as well as an increased risk of failure and death during treatment of the infection [3]. Consequently, global efforts aimed at controlling both diseases have included collaborative efforts in terms of research and management [4–6].

Multidrug-resistant TB (MDR-TB), defined as TB resistant to the first-line drugs isoniazid and rifampicin, remains a serious threat to public health and has complicated the efforts of TB control programs worldwide [7]. MDR-TB poses a therapeutic challenge because the second-line drugs used to treat these patients are less potent and not well tolerated, resulting in a lower likelihood of treatment success [8]. Patients with extensively drug-resistant TB (XDR-TB), in which the disease shows additional resistance to fluoroquinolones (FQNs) and at least one second-line injectable drug (amikacin, capreomycin or kanamycin), have an even worse outcome [9–12]. Additional risk factors for poor MDR-TB treatment outcome are lower body mass index (BMI) [11], human immunodeficiency virus (HIV) coinfection and a positive acid-fast bacilli (AFB) smear [13].

The majority of the 10 countries in which the number of estimated cases of DM in 2000 and the number predicted for 2030 are highest [1] are also among the 10 countries currently estimated to have the highest prevalence of MDR-TB [14]. However, the impact of the two diseases as comorbidities on treatment outcome and long-term survival has not been well analyzed. Such studies are highly relevant given that TB control programs, especially those targeting MDR-TB, may need to be modified in populations with a high incidence of DM. The long duration of morbidity, complex medications and lower likelihood of treatment success of MDR-TB require more attention to comorbidities in order to improve the treatment outcomes.

In South Korea, the prevalence of DM in the population over the age of 30 years in 2005 was estimated to be 9.1%, based on the Korean National Health and Nutritional Examination Survey (KNHANES) [15]; among MDR-TB patients, however, it was between 14 and 23% [9, 11, 12, 16]. To determine the effect of DM on treatment outcomes and long-term survival among patients with MDR-

TB, we analyzed outcomes in a large cohort of patients with MDR-TB with respect to the presence or absence of diabetes as a comorbidity.

Materials and Methods

Study Participants and Data Collection

1,407 Korean patients with MDR-TB were enrolled between January 2000 and December 2002; the details of these patients were described previously [11]. In brief, 1,407 patients with culture-proven MDR-TB were enrolled from all national TB hospitals ($n = 360$), all Korean National Tuberculosis Association (KNTA) chest clinics ($n = 836$) and eight randomly selected university hospitals near Seoul ($n = 211$). Medical records were retrospectively reviewed for demography, TB treatment history, comorbidities, AFB cultures and drug susceptibility test (DST) results, chest radiographs, treatment modalities and outcomes. Patients were considered to be diabetic if they had a previous history of DM and were using insulin and/or oral hypoglycemic agents at the time of MDR-TB diagnosis. All patients had been followed for 8–11 years after the commencement of treatment. Information on vital status as of December 2010 was obtained from the death registry of the Korean National Statistical Office; however, this registry does not provide information on the cause of death. This study was approved by the Institutional Review Board of the Asan Medical Center and other institutions.

AFB Cultures and DST

AFB were examined by Ziehl-Neelsen staining and culturing on egg-based Ogawa medium. DSTs for isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, kanamycin, cycloserine, p-aminosalicylic acid, prothionamide, and ofloxacin (OFX) were performed at all participating laboratories. Enviomycin-capreomycin susceptibility was determined at the Korean Institute of Tuberculosis, the Supranational TB Reference Laboratory (Seoul, South Korea), and one private laboratory. DSTs were carried out according to the proportion method and the pyrazinamidase test, performed at the Korean Institute of Tuberculosis. Among the FQNs and second-line aminoglycosides, only OFX and kanamycin susceptibility tests, respectively, were done routinely as part of the study. Thus, for amikacin and other FQNs, DSTs were not evaluated.

Definitions of Study Measures

XDR-TB was defined as MDR-TB with bacillary resistance to both OFX and a second-line injectable drug (kanamycin, capreomycin or enviomycin).

Treatment outcomes were grouped into seven categories, consisting of the six WHO recommended categories (cure, treatment completion, transfer out, default, death and treatment failure) [17] and short-term treatment completion [11]. Adequate treatment duration was defined as 18 months, including 12 months after culture conversion. Short-term treatment completion was defined as: (1) inadequate treatment duration, but >6 months; (2) three consecutive negative cultures before treatment completion, and (3) treatment completion, as assessed by a physician and based on a favorable treatment response. Treatment success was defined as the sum of cure, treatment completion

Table 1. Clinical characteristics of 1,407 MDR-TB patients with or without DM

Characteristics	MDR-TB _{DM(+)} (n = 239)	MDR-TB _{DM(-)} (n = 1,168)	Total (n = 1,407)	p value
Mean age, years	49.9±11.3 (20–80)	41.5±15.1 (13–89)	42.9±14.9 (13–89)	<0.001
Male	203 (84.9)	836 (71.6)	1,039 (73.8)	<0.001
BMI	20.7±3.6 (13.3–32.0)	18.8±3.0 (12.0–28.3)	19.2±3.2 (12.0–32.0)	<0.001
Previous history of TB treatment (n = 1,359)	234	1,125	1,359	0.086
No history	79 (33.8)	306 (27.2)	385 (28.3)	
First-line drugs only	130 (55.6)	661 (58.8)	791 (58.2)	
Second-line drugs	25 (10.7)	158 (14.0)	183 (13.5)	
≥2 previous TB treatments (n = 1,335)	50/232 (21.6)	320/1,103 (29.0)	370/1,335 (27.7)	0.021
Other comorbidities				0.245
Chronic liver disease	6 (2.5)	20 (1.7)	26 (1.8)	
Malignancy	3 (1.2)	10 (0.86)	13 (0.9)	
Others ¹	8	32 (2.7)	40 (2.8)	
HIV seropositive (n = 66)	0/14 (0)	1/52 (1.9)	1/66 (1.5)	1
Extrapulmonary TB	10 (4.2)	43 (3.7)	53 (3.8)	0.88
Positive AFB smear at treatment initiation	165 (69.0)	793 (67.9)	958 (68.1)	0.73
Radiologic severity (n = 1,251)				0.119
Minimal	12 (5.9)	83 (7.9)	95 (7.6)	
Moderate advanced	135 (65.9)	609 (58.2)	744 (59.5)	
Far advanced	58 (28.3)	354 (33.8)	412 (32.9)	
Cavitary disease	108 (45.2)	491 (42.0)	599 (42.6)	0.369
Bilateral disease (n = 1,190)	136/194 (70.1)	744/996 (74.7)	880/1,190 (73.9)	0.182
XDR-TB	14 (5.9)	61 (5.2)	75 (5.3)	0.69
Surgical treatment	8 (3.3)	52 (4.5)	60 (4.3)	0.44

Values are number (%) or mean ± SD (range).

¹ Chronic lung disease (n = 9), chronic renal disease (n = 4), hypo- or hyperthyroidism (n = 5), connective tissue disease (n = 3), psychiatric disease (n = 5), malnutrition and postgastrectomy state (n = 14).

and short-term treatment completion. All outcomes were the initial treatment outcomes during the study period and were analyzed based on AFB culture results.

Statistical Analysis

Data are expressed as mean ± SDs. Comparisons of clinical characteristics between MDR-TB patients with and without DM were performed using χ^2 tests or Fisher's exact tests for categorical variables and Student's *t* tests for continuous variables. χ^2 tests and Fisher's exact tests were used to compare the treatment success proportion between those with and without DM. To elucidate the predictors of initial treatment success, we compared selected clinical variables between treatment success and other groups through univariate comparison and subsequent multiple logistic regression. In regression, backward selection procedures were used to select clinically relevant variables to be maintained in the final model, with use of a *p* value <0.05 as the criterion for statistical significance. Cox regression analysis was used to evaluate predictors for all-cause mortality of MDR-TB patients. Cumulative survival for patients with MDR-TB with and without DM was estimated by the Kaplan-Meier method, and the log-rank test was used for comparison. All statistical analyses were carried out using SPSS software (SPSS Inc., Chicago, Ill., USA), version 18.0.

Results

Baseline Characteristics of MDR-TB Patients with and without DM

Among the 1,407 patients with MDR-TB, 239 (17%) also had diabetes [MDR-TB_{DM(+)} group] while the remaining 1,168 (83%) did not [MDR-TB_{DM(-)} group] (table 1). The mean age and BMI of patients in the MDR-TB_{DM(+)} group was higher (age 49.9 years, range 20–80; BMI 20.7, range 13.3–32, respectively) than that of the MDR-TB_{DM(-)} group (age 41.5 years, range 13–89; BMI 18.8, range 12.0–28.3, respectively). Other comorbidities did not show a significantly different distribution between the two groups. A history of at least two previous TB treatments was more common in the MDR-TB_{DM(-)} group (21.6% in MDR-TB_{DM(+)} vs. 29.0% in MDR-TB_{DM(-)}, *p* = 0.02). There were no significant differences between the MDR-TB_{DM(+)} and MDR-TB_{DM(-)} groups in terms of AFB smear positivity at treatment initiation, extrapulmonary TB, radiologic severity on simple chest radiograph, and the presence of XDR-TB.

Table 2. Initial treatment outcomes of MDR-TB patients with or without DM

Treatment outcomes	MDR-TB _{DM(+)} (n = 239)	MDR-TB _{DM(-)} (n = 1,168)	Total (n = 1,407)	p value (0.078)
Cure	59 (24.7)	366 (31.3)	425 (30.2)	0.041
Treatment completion	13 (5.4)	80 (6.8)	93 (6.6)	0.42
Short-term treatment completion	14 (5.9)	105 (9.0)	119 (8.5)	0.11
Failure	15 (6.3)	50 (4.3)	65 (4.6)	0.18
Transfer out	21 (8.8)	87 (7.4)	108 (7.7)	0.48
Default	86 (36.0)	367 (31.4)	453 (32.2)	0.17
Death	31 (13.0)	113 (9.7)	144 (10.2)	0.13
Treatment success	86 (36.0)	551 (47.2)	637 (45.3)	0.002
Relapse (n = 637)	9/86 (10.5)	59/551 (10.7)	68/637 (10.7)	0.95
Culture conversion (n = 1,314)	133/217(61.3)	730/1,097 (66.5)	863/1,314 (65.7)	0.136

Treatment Outcomes of MDR-TB Patients with and without DM

The overall treatment success rate of the 1,407 patients was 45.3% (cure 30.2%, treatment completion 6.6%, and short-term treatment completion 8.5%). However, in the MDR-TB_{DM(+)} group, treatment success rate was significantly lower than in the MDR-TB_{DM(-)} group (36.0 vs. 47.2%, $p = 0.002$). By contrast, between the two groups, neither the culture conversion rate nor the relapse rate differed significantly: 61.3 vs. 66.5% ($p = 0.14$) and 10.5 vs. 10.7% ($p = 0.95$) for the MDR-TB_{DM(+)} group and MDR-TB_{DM(-)} group, respectively (table 2). Similar results were obtained in the 75 patients with XDR-TB, in whom a comorbidity of DM did not cause a significant difference in the treatment success rate (XDR-TB + DM: 28.6% vs. XDR-TB only: 29.5%, $p = 1.00$).

Impact of Diabetes on Treatment Outcomes and Long-Term Survival

In multivariate logistic regression analysis of the clinical variables included in the univariate comparison between treatment success and other groups, DM as a comorbidity was the independent negative predictor of treatment success [odds ratio (OR) 0.51, 95% confidence interval (CI) 0.26–0.99, $p = 0.049$] (table 3). The same was true for BMI <18.5 (OR 0.38, 95% CI 0.21–0.66, $p = 0.001$) and XDR-TB (OR 0.17, 95% CI 0.04–0.8, $p = 0.03$).

Death was the initial treatment outcome in 144 patients, with 326 additional deaths occurring during 6–10 years of follow-up. Overall, the mean survival time of the 1,407 MDR-TB patients was 112 months (95% CI 109.3–114.4). The mean survival time of patients in the MDR-TB_{DM(+)} group was 102 months, which was significantly less than that of patients in the MDR-TB_{DM(-)} group (114 months,

Fig. 1. Kaplan-Meier survival analysis estimates for all-cause mortality in MDR-TB patients with and without DM. Patients with MDR-TB_{DM(+)} had a significantly shorter median survival time (102 vs. 114 months, $p = 0.001$). The solid line indicates MDR-TB_{DM(+)} and the dashed line indicates MDR-TB_{DM(-)}.

$p = 0.001$; fig. 1). However, there was no significant interaction between the time to death and DM when interaction was evaluated between the binary variable of time (≤ 18 months vs. > 18 months) and DM status ($p = 0.13$). Diabetes was a significant predictor of poor long-term survival, as determined in multivariate analyses [hazard ratio (HR) 1.59, 95% CI 1.01–2.50, $p = 0.047$] (table 4). As expected, independent predictors of poor long-term survival were: age > 40 years (HR 2.13, 95% CI 1.38–3.30, $p = 0.001$), BMI <18.5 (HR 1.94, 95% CI 1.24–3.05, $p = 0.004$), far advanced disease (HR 2.05, 95% CI 1.32–3.18, $p = 0.001$) and XDR-TB (HR 4.39, 95% CI 2.35–8.20, $p < 0.001$).

Table 3. Predictors of initial treatment success in 1,407 MDR-TB patients

Variables	Treatment success (n = 637)	Other ¹ (n = 770)	Univariate analysis OR ² (95% CI)	p value	Multivariate analysis OR ² (95% CI)	p value
Age >40 years	308 (48.4)	435 (56.5)	0.72 (0.58–0.89)	0.002	0.94 (0.54–1.64)	0.82
Female	178 (27.9)	190 (24.7)	1.18 (0.93–1.50)	0.165		
BMI <18.5	60/184 (32.6)	125/231 (54.1)	0.41 (0.27–0.61)	<0.001	0.38 (0.21–0.66)	0.001
Previous TB treatment with second-line drugs	50/618 (8.1)	133/741 (17.9)	0.40 (0.29–0.57)	<0.001	0.84 (0.27–2.57)	0.76
≥2 previous TB treatments	141/607 (23.2)	229/728 (31.5)	0.66 (0.52–0.84)	0.001	0.52 (0.25–1.06)	0.07
Far advanced disease	146/563 (25.9)	229/688 (38.7)	0.56 (0.44–0.71)	<0.001	0.83 (0.45–1.52)	0.54
Bilateral disease	357/538 (66.4)	523/652 (80.2)	0.49 (0.37–0.63)	<0.001		
Cavitary disease	286 (44.9)	313 (40.7)	0.84 (0.68–1.04)	0.11		
Positive AFB smear at treatment initiation	426 (66.9)	532 (69.1)	0.90 (0.72–1.13)	0.38		
Surgical treatment	41 (6.4)	19 (2.5)	2.72 (1.56–4.73)	<0.001	2.52 (0.86–7.40)	0.09
XDR-TB	22 (3.5)	53 (6.9)	0.48 (0.29–0.80)	0.005	0.17 (0.04–0.8)	0.03
DM	86 (13.5)	153 (19.9)	0.63 (0.47–0.84)	0.002	0.51 (0.26–0.997)	0.049
TB drugs used previously, n	2.9±2.3	3.5± 2.7	0.92 (0.88–0.97)	<0.001	1.02 (0.88–1.18)	0.76
Potentially effective TB drugs, n	3.6±1.5	3.3± 1.6	1.15 (1.07–1.23)	<0.001	1.02 (0.84–1.24)	0.82

Values are number (%) or mean ± SD.

¹ Includes failed, defaulted and transferred-out patients, and patients who died as treatment outcomes.

² OR was for treatment success.

Table 4. Predictors of all-cause mortality in 1,407 MDR-TB patients

Variables	Deaths (n = 470)	Univariate analysis HR ¹ (95% CI)	p value	Multivariate analysis HR ¹ (95% CI)	p value
Age >40 years	338 (71.9)	2.72 (2.23–3.33)	<0.001	2.13 (1.38–3.30)	0.001
Male	381 (81.1)	1.64 (1.30–2.07)	0.002	0.76 (0.48–1.18)	0.22
BMI <18.5	101/175 (57.7)	2.06 (1.53–2.78)	<0.001	1.94 (1.24–3.05)	0.004
Previous TB treatment with second-line drugs	105/447 (23.5)	2.46 (1.98–3.06)	<0.001	1.20 (0.57–2.49)	0.64
≥2 previous TB treatments	159/436 (36.5)	1.66 (1.37–2.02)	<0.001	1.25 (0.78–2.00)	0.35
Far advanced disease	235/432 (54.4)	3.17 (2.62–3.83)	<0.001	2.05 (1.32–3.18)	0.001
Bilateral disease	355/403 (88.1)	3.09 (2.29–4.18)	<0.001		
Cavitary disease	197 (41.9)	0.97 (0.80–1.16)	0.71		
Positive AFB smear at treatment initiation	346 (73.6)	1.37 (1.12–1.68)	0.003	1.28 (0.75–2.19)	0.37
Surgical treatment	7 (1.5)	0.30 (0.14–0.63)	0.002	0.16 (0.02–1.20)	0.075
XDR-TB	46 (9.8)	2.54 (1.87–3.44)	<0.001	4.39 (2.35–8.20)	<0.001
DM	102 (21.7)	1.47 (1.18–1.83)	0.001	1.59 (1.01–2.50)	0.047
TB drugs used previously, n	3.65±2.79	1.09 (1.05–1.14)	<0.001	0.99 (0.89–1.11)	0.88
Potentially effective TB drugs, n	3.11±1.71	0.86 (0.82–0.91)	<0.001	1.09 (0.95–1.25)	0.23

Values are number (%) or mean ± SD.

¹ HR was for all-cause mortality.

Discussion

In this large MDR-TB cohort analysis, 17.0% of the patients with MDR-TB had coexisting DM, although the latter was determined based solely on medical records. In

these patients, the presence of the two diseases was independently associated with an increased risk of treatment failure and death. Specifically, MDR-TB_{DM(+)} patients had a significantly lower treatment success rate and a shorter mean survival than MDR-TB_{DM(-)} patients.

The prevalence of DM in our MDR-TB cohort was higher than in the general population older than 30 years in South Korea, in which a rate of 9.1% was determined based on the data of the 2005 KNHANES [15]. Considering that the prevalence of DM among our series of MDR-TB patients was similar to the 14–23% reported for other such cohorts in South Korea [9, 11, 12, 16], it appears that DM is a relatively common comorbidity in MDR-TB patients. This finding has important implications for treatment outcomes and thus for national TB control programs. However, evidence for the effect of DM on MDR-TB treatment outcome has been lacking.

The significantly lower treatment success rate of MDR-TB_{DM(+)} patients and the finding that DM was a significant independent predictor of poor outcome of MDR-TB treatment are in agreement with previous reports on drug-susceptible TB patients [18–20]. The negative influence of DM on the response to TB treatment has been explained by a number of factors, including immunologic dysfunction, i.e. alterations in monocyte chemoattraction [21], alveolar macrophage activity [22] and type I cytokine phenotype [23]. An additional aspect is the higher mycobacterial load in DM patients, leading to a delay in microbial clearance which, in turn, can affect treatment success [19, 24]. However, at least in our cohort, this did not appear to be the case since there was no difference in radiologic severity, proportion of cavitory disease and AFB smear positivity at treatment initiation between MDR-TB patients with and without DM. In addition, the relapse rate and culture conversion rate did not significantly differ between the two groups.

A pharmacologic interaction between rifampicin and diabetes medications has also been suggested as the reason for the poor outcome of patients with DM and TB [25]. While an evaluation of these effects was beyond the scope of this study, an important consideration is that the complex medication schedule for patients with these comorbidities can decrease compliance. Indeed, irregular treatment [26] and poor adherence to the drug regimen are matters of concern in the treatment of TB as they increase the likelihood of treatment failure. Although the default rate between the MDR-TB_{DM(+)} and MDR-TB_{DM(-)} patients in our study did not significantly differ, in this cohort as a whole it was relatively high. Thus, together with the fact that directly observed treatment has not been instituted during outpatient care in South Korea, poor compliance may well have been at least a contributing factor explaining the poor outcome of MDR-TB patients with DM.

Long-term studies on the effect of DM on the mortality of MDR-TB patients are still scarce. Based on the more than 8 years of follow-up of our MDR-TB patients, DM was

determined to be an independent predictor of long-term all-cause mortality. This finding is consistent with previous reports dealing with drug-susceptible TB, in which the adjusted OR for death in TB patients with DM compared to those without DM was 4.95 (95% CI 2.69–9.10) [3]. However, we could not fully assess the role of DM in the death of our patients due to the limited amount of available information, although lack of significant interaction between the time to death and DM in our study suggested the possibility that the excess death in people with diabetes may not have been due to TB itself, but rather to DM-related complications. In another study, in which TB treatment outcomes were evaluated in 174 TB patients with positive sputum smears, 62% of the deaths were related to comorbidities rather than directly to TB [27]. Conversely, another study reported that TB-related death was nearly three times higher in patients with DM as a comorbidity than in patients without DM [20]. Thus, the higher mortality of our MDR-TB patients with DM may have been due to its complications, but other explanations cannot be ruled out.

Glycemic control is an important factor in the management of DM and could affect the severity and response to treatment of patients with both DM and TB [28, 29]. Clinicians would therefore be advised to pay greater attention to glycemic control in MDR-TB patients who also have DM, in order to improve long-term outcomes.

This study has several limitations that are inherent to all retrospective studies, as already described [11]. The diagnosis of DM was based on medical records, such that neither glycemic control status nor DM-related complications could be assessed. In addition, information on additional diagnoses of DM during the 8–11 years of follow-up was not available. Long-term survival was analyzed only for all-cause mortality, not for TB-related mortality, because of the rules of the Korea National Statistical Office. Despite these limitations, the large number of patients studied and the careful assessment of fatal outcomes allowed meaningful analyses of the impact of diabetes, as a comorbidity, in the treatment outcomes of patients with MDR-TB.

In conclusion, diabetes was found to be a relatively common comorbid condition among MDR-TB patients, with a negative impact on treatment outcome. Among patients undergoing treatment for MDR-TB, DM was independently associated with an increased risk of both treatment failure and death.

Acknowledgments

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