

The Negative Clinical Impact of Diabetes on Tuberculosis: A Cross-Sectional Study in New Jersey

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Context: Numerous studies have investigated a link between tuberculosis (TB) and type 2 diabetes mellitus (DM) in high-incidence countries. There is a need to characterize the relationship of TB and DM in the United States.

Objective: To characterize the clinical and demographic differences in patients with TB with and without DM.

Design: Cross-sectional.

Setting: This study was performed at an institutional center providing TB care for New Jersey.

Patients or Other Participants: A total of 353 cases of TB were seen at the Lattimore Clinic between 2009 and 2014. After excluding those with HIV infection and those under 19 years of age, 73 cases of TB were reviewed.

Intervention(s): No interventions performed.

Main Outcome Measure(s): Sputum culture positivity, time to culture conversion, extent of disease on chest x-ray, and degree of cavitation on chest x-ray. Outcome measures were determined prior to data collection.

Results: Extent of disease on chest x-ray was higher for DM+ cases compared with DM- cases ($P = 0.007$). A total of 24% of DM+ cases had evidence of cavitation on chest x-ray compared with 5% of DM- cases ($P = 0.03$). DM+ cases were slightly more likely to have positive sputum cultures than were DM- cases ($P = 0.07$). The median time to sputum culture conversion was 27.5 days in the DM+ group vs 18.0 days in the DM- group ($P = 0.26$).

Conclusions: Extent of disease on chest x-ray was significantly more severe in the DM+ group than in the DM- group.

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Freeform/Key Words: diabetes, tuberculosis

Abbreviations: CDC, Centers for Disease Control and Prevention; DM, diabetes mellitus; MDR, multidrug-resistant; TB, tuberculosis.

An estimated 33% of the world's population is infected with latent tuberculosis (TB) [1]. Although the rate of TB in the United States has decreased significantly by ~65% since the 1992 peak, ~9557 cases were reported in 2015, an increase from 2014 according to the Centers for Disease Control and Prevention (CDC) [2]. Diabetes affects 9.3% of the US population as of 2014, and an estimated 27.8% of those people are undiagnosed [3]. Several large-scale studies have demonstrated a higher TB incidence rate in patients with diabetes than in those without diabetes [4]. In addition, the radiographic presentation of TB has been shown to be more severe in the population with diabetes [5]. Studies examining the time to sputum culture conversion and acid-fast smear positivity have also shown differences in patients with diabetes vs those without diabetes [6, 7]. Due to the larger TB burden abroad, the majority of these studies examining TB and diabetes have been performed internationally [4]. As a result, there is need for further study of the relationships between TB and diabetes clinically in the United States. Of primary concern is that the relationship between TB and diabetes may be underappreciated, and, as a result, the population of patients with both TB and diabetes may be undermanaged. To begin characterizing this relationship in the United States, this study was performed to compare and contrast the demographics of patients with TB with and without diabetes and compare and contrast the severity of TB in patients with and without diabetes on the basis of chest x-ray findings, sputum culture results, drug resistance profiles, and length of required treatment. This information can then be used to improve our approach to caring for the population with both TB and diabetes.

1. Materials and Methods

A protocol was submitted and approved by the Rutgers Newark Health Science Internal Review Board (Pro2013002938). A list of all patients with TB being managed at the Lattimore Clinic at New Jersey Medical School and who were first seen at the Lattimore clinic between the years of 2009 and 2014 was obtained. A total of 353 cases were identified. The list included HIV status, diabetes mellitus (DM) diagnosis, and age. Although not explicitly excluded, none of the subjects had type 1 diabetes, and thus, all cases of diabetes were type 2 diabetes. Because HIV status might be a confounding factor when studying the relationship between DM and TB, we decided to include only patients who were HIV negative. In addition, we limited this investigation to adults, so only those 19 years of age and older at the time of diagnosis were included (n = 81). Pharmacologic immunosuppression was not a criterion for exclusion. The remaining patients included subjects who had DM (DM+) at the time of TB diagnosis (n = 34) and those who did not (DM-; n = 47). Patient charts were retrieved from a secure file room and reviewed, and study data were transcribed onto a standard data collection form, without personal identifiers. Charts of 33 subjects with both diabetes and TB and 40 subjects with only TB were able to be reviewed; 8 charts could not be located and were therefore excluded from the analysis. Demographic and clinical characteristics were abstracted from all patient charts. Grading of chest x-rays was made based on the radiologist reports at time of initial diagnosis. Extent of disease on chest x-ray was graded using a scale from A to C (A/limited, <25% involvement of thoracic cavity; B/moderate, 25% to 50% involvement; and C/severe, >50% involvement). Cavitation was graded using a scale from 1 to 3 (1, absent; 2, <4 cm aggregate diameter cavitation; and 3, ≥ 4 cm aggregate diameter cavitation). Study data were entered into an Excel file that resides on the university secure server. Throughout the duration of the study, patient charts and paper data collection forms were kept in a secure office in a locked room. Once the data were entered, they were analyzed using JMP Pro 12 SAS software [8]. Data analysis included the generation of summary statistics; comparisons were made using Fisher exact and χ^2 testing for nominal data, *t* tests for normally distributed continuous data, and nonparametric rank tests for nonnormally distributed data. All significance testing was conducted at the $\alpha = 0.05$ level.

2. Results

The prevalence of DM in our study population was 34 out of 81 (42.0%; 95% CI 31.8% to 52.9%). Table 1 presents the demographic characteristics of the study population by DM status. No considerable differences were observed for these variables.

Table 1. Demographic Characteristic of Lattimore Clinic Patients With TB With and Without DM at the Time of Diagnosis, 2009–2014

Demographic Characteristics	DM+, Number (%) (N = 33)	DM–, Number (%) (N = 40)	Total	P Value
Sex				
Male	21 (64)	21 (53)	42	0.35 ^a
Female	12 (36)	19 (48)	31	
Hispanic origin				
Yes	9 (28)	15 (38)	24	0.45 ^a
No	23 (72)	24 (62)	47	
Race				
Black	16 (48)	15 (38)	31	0.63 ^b
White	7 (21)	11 (28)	18	
Other	10 (30)	14 (35)	11	

^aFisher exact test.^bPearson χ^2 .

Clinical characteristics of subjects appear in [Table 2](#). Substantial group differences were observed for the extent of TB disease and for cavitation on the initial chest x-ray. A total of 55% of DM+ patients were characterized as B or C on initial chest x-ray compared with only 29% among DM– patients. Notably, all members of the DM+ group had evidence of disease on chest x-ray, whereas six members of the DM– group showed no evidence of pulmonary disease on chest x-ray. Degree of cavitation was further grouped into presence or absence because of the small sample size. The presence of cavitation in the DM+ group is 24% compared with only 5% in the DM– group ($P = 0.03$).

Initial sputum culture results were marginally different between groups (81% positive among those who were DM+ compared with 62% positive among those who were DM– ($P = 0.07$). Those who were DM+ were more likely to be sputum positive at the time of diagnosis. Although not statistically significant, the median time to sputum conversion was longer in the DM+ subject compared with DM– (27.5 vs 18 days) ($P = 0.26$).

Smear grade at time of initial presentation was not significantly different in the DM+ group compared with the DM– group ($P = 0.995$). No notable differences were observed by DM status for body mass index at time of TB diagnosis, type of TB (presence or absence of extrapulmonary TB), or multidrug-resistant (MDR) status.

3. Discussion

The relationship of TB to DM has been well studied outside the United States [4]. The Center for Disease Control (CDC) reported ~9557 new cases of TB in the United States (3.0 cases per 100,000 persons), which is a decline from the 1992 peak of ~26,000 new cases of TB [2]. However, 2015 marked the first increase in number of new TB cases in the United States in over a decade [2]. This recent increase in TB incidence and the increasing prevalence of DM in the US population highlights the need for further studies exploring the relationship between TB and DM within the United States. The prevalence of DM in our study population is 45.2%, and this number could be expected to climb if the CDC's estimation that DM will double or triple by 2050 is correct [9]. Also of note are the similarities and differences between this study population and those of other major studies, notably the ongoing Effects of Diabetes on Tuberculosis Severity study in South India, where the prevalence of DM in the TB population is 54.1%, comparable with this study population [10]. A major difference is the demographic differences in ethnicity among South India, other major international areas of TB and DM study, and the population at Lattimore Clinic in Newark, NJ.

The Lattimore Clinic in Newark, NJ, is a center that treats patients with TB from throughout northern New Jersey in Essex and surrounding counties. Case management and

Table 2. Clinical Characteristics of Lattimore Clinic Patients With TB With and Without DM at the Time of Diagnosis, 2009–2014

	DM+	DM–	Total	<i>P</i> Value
BMI at time of TB diagnosis				
Mean (SD)	24.2 (4.8)	23.6 (4.7)		0.65 ^a
n	26	22	48	
TB type, number (%)				
Presence of extrapulmonary (includes cases with both)	8 (24)	10 (25)	18	0.94 ^b
Pulmonary only	25(76)	30 (75)	55	
MDR TB, number (%)				
Yes	2 (7)	1 (3)	3	0.47 ^b
No	27 (93)	32 (97)	59	
Initial sputum results, number (%)				
Positive	26 (81)	24 (62)	50	0.07 ^b
Negative	6 (19)	15 (38)	21	
Time to culture conversion (in d)				
Median (25%,75% values)	27.5 (0.5, 56.0)	18.0 (0 ^c , 47.3)		0.26 ^d
Sputum smear grade at time of TB diagnosis, number (%)				
0	21 (66)	27 (69)	48	0.995 ^d
1+	3 (9)	3 (8)	6	
2+	1 (3)	1 (3)	2	
3+	4 (13)	4 (10)	8	
4+	3 (9)	4 (10)	7	
Extent of disease (initial chest x-ray), number (%)				
0	0 (0)	6 (16)	6	0.007 ^d
A	13 (45)	21 (55)	34	
B	11 (38)	9 (24)	20	
C	5 (17)	2 (5)	7	
Cavitation (initial chest x-ray), number (%)				
Presence	7 (24)	2 (5)	9	0.03 ^e
Absence	22 (76)	36 (95)	58	

Abbreviation: BMI, body mass index.

^a*t* test.

^bPearson χ^2 .

^cNegative at time of TB diagnosis.

^dWilcoxon rank-sum test.

^eFisher exact test.

universal directly observed therapy are used on almost every patient, achieving adherence rates >98%. As of a 2015 census, the population of Essex County has a high proportion of blacks (41.8%), white (49.6%), and Hispanic (22.4%) [11]. The population meeting criteria for this study was of similar distribution with a slight increase in the proportion of Hispanic and non-white-identifying subjects. There is known racial disparity in TB incidence in the United States as demonstrated by CDC statistics, notably in the non-Hispanic black population, which has sustained higher rates of TB despite an overall downtrend in TB cases since the 1992 peak [12]. Considering this, there were no significant differences in racial demographics between DM+ and DM– patients ($P = 0.69$). There were also no significant differences in Hispanic origin between DM+ and DM– patients ($P = 0.45$).

Only 10 out of 33 of the patients in the DM+ group had recorded HbA_{1c} results within 3 months of their TB diagnosis. The range of HbA_{1c} in our DM+ group was 6.6% to 15.3%. There were no statistically significant differences in HbA_{1c} and extent of TB disease ($P = 0.39$). However, this analysis is limited by the small sample size. It is unclear whether these

patients were being tested for HbA_{1c} by another physician or if they were not being tested at all, but this demonstrates inconsistencies in monitoring patients with TB and DM less than a decade ago. Recent studies have suggested a pathologic relationship between TB and DM in which TB leads to poor glycemic control and accelerates diabetic complications [4, 6, 13, 14]. There have also been suggestions that metformin, a first-line drug used in type 2 DM management, may have beneficial effects in management of TB through inhibiting intracellular growth of TB and increasing the efficacy of many anti-TB drugs [15].

Cases of TB in which extrapulmonary sites were involved, either with coexisting pulmonary TB or without, were grouped and separated by DM status. There were no significant differences in presence of extrapulmonary manifestations of TB between DM+ and DM- patients ($P = 0.94$). The overall prevalence of extrapulmonary TB in this study population was 32.7%. There were also no significant differences in MDR status between study groups ($P = 0.47$).

Chest x-ray is a common imaging test ordered for patients in whom TB is suspected. Chest CT scans are more accurate for identifying extent of disease; however, chest x-ray is the initial radiographic imaging modality performed. Several studies performed internationally have shown more extensive disease on chest x-ray as well as increasing presence of cavitation on chest x-ray reaching statistical significance [5, 16, 17]. The results of this study are consistent with these findings, demonstrating more extensive disease on chest x-ray in the DM+ group as determined by the CDC grading scale ($P = 0.007$). Additionally, the DM+ group had a higher prevalence of cavitation than the DM- group, reaching statistical significance ($P = 0.03$). These findings are consistent with the hypothesis that DM+ patients present with more severe disease than DM- patients.

There was a marginally significant difference in initial sputum culture positivity between the two groups ($P = 0.07$), with DM+ being more likely to present with a positive sputum culture. In this study, time to sputum culture conversion was measured to determine treatment success, whereas several other studies used sputum smear conversion. The median time to sputum culture conversion was 27.5 days in the DM+ group vs 18.0 days in the DM- group, but the difference was not statistically meaningful. There have been mixed results in the literature on the relationship of time to sputum smear conversion and DM status [17–20]. However, there is a general trend toward longer sputum conversion times in this study, supporting the hypothesis that DM+ patients respond more slowly to TB treatment than those who are DM-. This trend is consistent with the interim results of the Effects of Diabetes on Tuberculosis Severity study, which have also not reached statistical significance [10]. Additionally, sputum smear status is an indicator of infectivity, and in this study, no significant differences in initial smear grade were found ($P = 0.995$).

The exact mechanisms by which DM negatively affects TB are undetermined, but several explanations in the literature have been proposed. Notably, a recently published study measured the levels of 27 different cytokines in patients with TB, DM, and TB/DM. They concluded that levels of several cytokines were uniquely elevated in the TB/DM cluster compared with TB and DM alone [14]. Additionally, recent literature has identified defective alveolar macrophage function in diabetic mice, possibly contributing to TB susceptibility [13, 21, 22]. Other proposed mechanisms include poor drug absorption in patients with diabetes and interference with tissue drug absorption and immune cell functions resulting from hyperglycemia [23].

In conclusion, despite lower prevalence of TB within the United States compared with TB abroad, it is still a public health concern in the United States. Given the rising prevalence of DM in the United States and projected increases by 2050, it is anticipated that DM within the TB population will also increase in the future. Considering the results of international studies as well as this study on the population with TB and DM, there are unique concerns that must be considered when managing a patient affected by both of these diseases. Namely, chest x-ray findings have been found to be significantly more severe in the DM+ population, and, although not found in this study, response to treatment as measured by time to sputum culture conversion has also trended toward slower response in the DM+ population. These findings support recommendations to screen for and consider TB among patients with

diabetes with a high likelihood for infection. Limitations of this study are mainly due to small sample size and, even more importantly, a lack of documentation of several variables of interest, including tobacco use, drug use, and HbA_{1c} within 3 months of diagnosis. Also, it is possible that results of this study are unique to the Lattimore Clinic population and that the results may not be indicative of the rest of the TB and TB/DM population in the United States. Ultimately, the TB/DM+ population must be further studied within the United States to better determine proper management of this unique and increasing population.

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