

Original Article

Tuberculosis in Diabetics: Features in an Endemic Area

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SUMMARY: Diabetes mellitus (DM) is known as one of the factors that increases the risk of tuberculosis (TB). TB can also show atypical clinical presentation and localization in diabetics. The aim of the study was to evaluate the features of TB in diabetics in our region. Between 1997 and 2003, all cases of diabetic TB patients and an equal number of non-diabetics treated and followed at the Esrefpasa Tuberculosis Dispensary were analyzed retrospectively. A total of 78 (7.3%) TB cases in DM patients was encountered among 1,063 TB cases. Cavity formation and atypical localization were more often found in diabetics ($P < 0.05$). Duration of treatment was longer in diabetics ($P < 0.05$). The rate of drug resistance was higher in DM cases, but cure rates were similar between groups. A diagnosis of TB should be considered in diabetics with an abnormal chest radiograph, in the presence or absence of specific clinical symptoms, in endemic regions. Diabetic TB cases should be followed especially closely in terms of cure time and drug resistance.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that weakens the immune system. The incidence of pulmonary tuberculosis (PT) has been reported to be higher in diabetics than in non-diabetics (1,2). The relatively high frequency of concomitant tuberculosis (TB) and DM is well recognized (3,4). Diabetic patients have been found to exhibit a tendency to develop TB and pulmonary fungal infections. DM has been characterized as a condition that may predispose previous TB patients to reactivated infection. Ketosis due to DM provides suitable conditions for the reactivation of TB. An oversynthesis of adrenocorticotrophic hormone (ACTH), vitamin A deficiency, overproduction of glycerol, and deposition of lipids in the reticuloendothelial system (RES) all have been shown to reduce immunobiological responses to TB. Alterations in the bactericidal and phagocytic functions of polymorphonuclear leucocytes play important roles in the pathogenesis of TB (5).

Postprimary or reinfection with TB is the most common form of TB in adults, and this form typically involves the apical and posterior segments of the upper lobes, and the posterior segments of the lower lobes of the lungs (6). Patients with immunocompromising diseases can exhibit atypical clinical and radiological presentation and localization. Multilobar and atypical pulmonary lesions have also been reported in diabetics (7,8).

The country of Turkey has a moderate prevalence of TB with a 26:100,000 notification rate and a total of 18,500 reported cases in 2003 (9). Approximately 3 million people in Turkey are thought to have DM. According to data from the Turkish Statistical Institute, DM accounted for 1.85% of all hospitalizations in 2004 (10).

In this study, we aimed to determine whether or not DM alters treatment outcomes, or the demographic, clinical or radiological presentation of TB patients. To this end, we

reviewed case histories to compare features associated with DM/TB patients with those of non-diabetic TB patients.

PATIENTS AND METHODS

Setting: Case histories of patients with TB who had been seen at the Esrefpasa Tuberculosis Dispensary (Izmir, Turkey) between 1997 and 2003 were investigated.

Study subjects: Diabetic patients (study group) and a randomly selected, equal number of non-diabetic patients with no other underlying diseases (control group) were included into the study. The patients with manifest DM were receiving insulin or an oral hypoglycemic agent at the time of the TB diagnosis. All patients in the study group had type II DM and PT.

The data for the study were obtained from patients' charts. The following factors were considered in the analysis: demographic characteristics (age, sex, smoking history, and alcohol use), clinical features (symptoms, the course between the time of diagnosis of DM and that of TB, anti-diabetic treatment), diagnostic methods (smear and culture positivity, resistance to anti-TB drugs, time interval at which the sputum culture became negative, tuberculin skin test (TST) reactivity, radiographic features [including localization and characteristics of the infiltrates], presence of pleural involvement), localization of illness, treatment regimens, and results of treatment. Diabetic patients were also evaluated in terms of the time interval between the diagnoses of DM and TB.

Ethical consent was not obtained from patients seen at the hospital, as the study was a retrospective analysis of TB dispensary records. Instead, the dispensary manager approved the study.

Diagnosis of TB: PT was diagnosed according of any of the following criteria:

1. Isolation of *Mycobacterium tuberculosis* organisms from a culture of sputum or other body fluid.
2. Biopsy specimen showing caseification in a granuloma with or without acid-fast bacilli (AFB), or a biopsy specimen showing non-caseification in a granuloma in cases of response to treatment.

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3. Positive TST and signs and symptoms compatible with active TB disease, such as an abnormal unstable chest radiograph or clinical evidence of active TB disease (e.g., fever, night sweats, cough, weight loss, hemoptysis) and report of satisfactory results with anti-TB medications.

Extrapulmonary TB (EPT) was diagnosed by fine-needle aspiration cytology or biopsy of an affected organ showing a granuloma with or without a positive *M. tuberculosis* culture. Case definitions and treatment outcomes were classified as defined by the World Health Organization (WHO) (11).

Bacteriological culture and drug susceptibility tests (DSTs): Mycobacterial cultures were performed on the Lowenstein-Jensen (LJ) media. DST was by determining the proportion on the critical concentration method and LJ media, as previously described by Canetti et al. (12). TST reactivity was measured by the Mantoux method (13).

Radiological evaluation: Radiological data were collected using the posterior-anterior (PA) radiographic images obtained at the time of diagnosis. Atypical localization was defined as middle- and lower-zone involvement on a PA chest radiogram. Presence or absence of the following findings on chest radiograms were recorded: cavity, heterogeneous infiltration, pleural effusion, mass lesion, abscess, hilary enlargement, miliary appearance, parenchymal infiltration plus pleural effusion, atelectatic band, parenchymal or subpleural nodular appearance, etc).

Treatment: All patients received anti-TB treatment according to the WHO treatment categories. The typical treatment regimen consisted of an initial phase of isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol given daily for 2 months followed by isoniazid and rifampin for 4 months. This standard regimen was modified or extended, depending on the rate of response to treatment and the occurrence of drug resistance.

Statistical analysis: Data are expressed as mean \pm standard deviation (SD). The statistical analysis was conducted with SPSS 9.05 (SPSS, Chicago, Ill., USA). The features of the two groups were compared using Fisher's exact test. A *P* value of <0.05 was considered statistically significant. Randomization for the selection of non-diabetic TB patients was carried out by an interactive random-number generator using Graphpad, an open-source software package available on the internet (<http://www.graphpad.com/quickcalcs/randomN1.cfm>).

RESULTS

DM was detected in 78 patients (7.3%) as a concomitant disease in 1,063 TB cases seen at the dispensary between 1997 and 2003. The mean age of diabetic and non-diabetic patients was 53.55 ± 12.66 (19-74) and 34.19 ± 14.77 (29-83) years old, respectively (<0.001). The difference was more significant in patients older than 50 years than in younger patients ($P = 0.000$). Although male gender was dominant in both groups, the difference was significant in the non-DM group ($P = 0.0005$). Smoking habit was found at a higher rate in non-diabetics ($P = 0.014$). The demographic data are presented in Table 1.

Reliable data regarding the time interval between the diagnoses of TB and DM were available for 65 diabetic patients. A diagnosis of both DM and TB was made simultaneously in 23 (35.38%) patients. The time interval between the diagnoses of the two diseases was <10 years in 26 (40%) patients, and ≥ 10 years in 16 (24.6%) patients. All patients

Table 1. Demographic characters of case groups

	Diabetic (%)	Non-diabetic (%)	<i>P</i>
Age mean (range)	53.55 ± 12.66 (19-74)	34.19 ± 14.77 (29-83)	<0.001
Age (>50)	44 (56.4)	11 (14.1)	0.000
Sex Male	44 (56.4)	54 (69.2)	0.181
Female	34 (43.6)	24 (30.8)	0.118
Smoker	24 (30.8)	39 (50)	0.014
Alcohol use	8 (10.3)	10 (12.8)	0.616

Table 2. Symptoms of cases

Symptom	Diabetic (%)	Non-diabetic (%)	<i>P</i>
Cough	63 (80.8)	51 (65.4)	0.030
Night sweating	46 (59)	41 (52.6)	0.420
Sputum expectoration	45 (57.7)	38 (48.7)	0.261
Weight loss	20 (25.6)	20 (25.6)	1
Malaise	19 (24.4)	21 (26.9)	0.714
Loss of appetite	9 (11.5)	10 (12.8)	0.807
Chest pain	9 (11.5)	8 (10.3)	0.797
Hemoptysis	–	15 (19.2)	0.000
Other	11 (14.1)	18 (23.1)	0.150

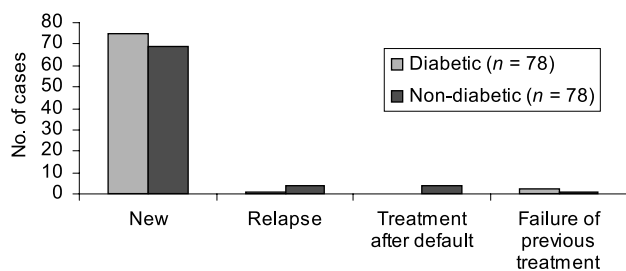


Fig. 1. Distribution of cases in groups.

were examined at least once by an internal medicine specialist. According to the patients' charts, the medications of six patients were switched from oral to insulin anti-DM treatment. Afterward, all of these six patients showed blood glucose maintenance at levels <140 mg/dl. During treatment at the dispensary, glucose blood levels were assessed on a monthly basis, as were liver enzymes.

BCG scarring was present in 33 (42.3%) of the diabetics and in 49 (62.8%) of the non-diabetics ($P = 0.015$). Tuberculin skin testing was performed in 67.9% (53 cases) of the diabetics and in 71.8% (56 cases) of the non-diabetics, and the test was found to be positive in 39.6% (21 cases) and 28.5% (16 cases) of each group, respectively ($P = 0.233$).

In both groups, the subjects were primarily new patients at the dispensary. Four non-diabetic patients were described as being treated after non-compliance (Figure 1).

PT and EPT was diagnosed in 64 (82.1%) and 7 (9%) diabetic cases, respectively; EPT and PT were concomitant in 7 (9%) cases in the DM group. In the non-DM group, the following diagnoses were made: PT in 54 (69.2%), EPT in 19 (24.4%), and PT-plus-EPT in 5 (6.4%) patients. Cases of EPT were more frequent in non-DM patients ($P = 0.016$), whereas the frequency of PT or PT-plus-EPT did not differ between groups ($P = 0.092$ and $P = 0.765$, respectively).

The distribution of symptoms is shown in Table 2.

Diagnostic methods and bacteriologic findings are shown in Table 3. Smear positivity was found in 59 (84.28%) diabetic patients and in 51 (75%) non-diabetic patients ($P = 0.218$). A pathologic diagnosis was more frequently made in

non-diabetics, due to the higher ratio of EPT.

The radiological findings for all cases are shown in Table 4. Atypical localization was found in 37.2% (29 cases) of

Table 3. Diagnostic methods and bacteriological results of cases

	Diabetic (%)	Non-diabetic (%)	<i>P</i>
Bacteriological	65 (83.3)	59 (75.6)	0.160
Pathological	7 (9)	17 (21.8)	0.026
Clinical + radiological	8 (10.3)	3 (3.8)	0.118
Bacteriology			
Smear (+) Culture (+)	59 (75.6)	46 (59)	0.026
Smear (-) Culture (+)	6 (7.7)	7 (9)	0.772
Smear (+) Culture (-)	-	5 (6.4)	0.023
Smear (-) Culture (-)	5 (6.4)	10 (12.8)	0.174
Smear× Culture×	8 (10.3)	10 (12.8)	0.616

×, not performed.

Table 4. Radiological findings of cases

	Diabetic (%)	Non-diabetic (%)	<i>P</i>
Cavity	45 (57.7)	22 (28.2)	0.000
Heterogeneous infiltration	28 (35.9)	12 (15.4)	0.003
Pleurisy	4 (5.1)	-	0.043
Mass	1 (1.3)	-	0.316
Abscess	-	1 (1.3)	0.316
Hilary enlargement	2 (2.6)	-	0.155
Miliary	2 (2.6)	-	0.155
Parenchymal infiltration + pleurisy	4 (5.1)	-	0.043
Other	-	51 (65.4)	0.000

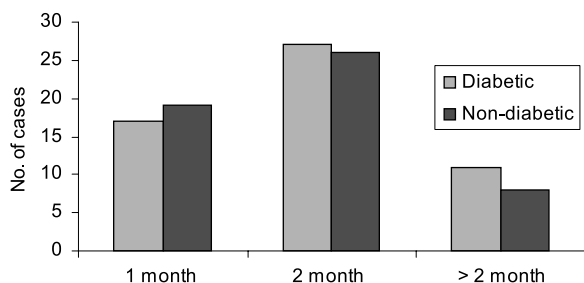


Fig. 2. Bacteriological conversion times of cases.

diabetics, and 14% (22 cases) of non-diabetics ($P = 0.000$).

Sixty-six (84.6%) diabetic and 61 (78.2%) non-diabetic patients required hospitalization ($P = 0.303$) for TB. The mean hospitalization time in diabetics and non-diabetics was 45.72 ± 23.36 and 41.92 ± 20.03 days, respectively ($P = 0.326$).

At the end of 2 months, the conversion ratios of smear-positive cases were 74.5 and 88.2% for the diabetic and non-diabetic groups, respectively. The duration of bacteriological conversion intervals did not significantly differ ($P > 0.05$). Conversion times are given in Figure 2.

Drug resistance was found in 26.1 and 5.6% in culture-positive DM and non-DM cases, respectively ($P = 0.0031$). Resistant cases were all new cases, and resistance was described as primary resistance. Although the total resistance rate was significantly higher in the DM group, no significant difference was noticed for each individual drug ($P > 0.05$). Two multidrug-resistant (MDR) cases were also detected in the DM group.

Treatment regimen, duration of treatment, and outcomes are provided in Table 5. Longer than 6 months was required to achieve a cure in the diabetic group ($P = 0.000$). Two diabetic patients (2.6%) died during therapy. One diabetic (1.3%) and four non-diabetic (5.1%) patients abandoned treatment.

Cases were evaluated at the end of 3 years. Recurrence was detected in one diabetic in three non-diabetic patients.

Seropositivity for human immunodeficiency virus (HIV) was not detected in either the DM or the non-DM group.

DISCUSSION

The association between DM and TB has long been acknowledged. Early in the 20th century, diabetic patients who did not die in a coma were likely to die from TB. However, the proportion of deaths attributable to TB among diabetic patients fell dramatically from the 1920s to the 1970s. In the 1930s, TB occurred in 8% of diabetic patients within 3 years of recovery from a diabetic coma (and in 20% of such patients within 5 years), and the development of TB appeared to follow the onset of DM in 85% of cases. Moreover, the risk of TB is correlated with the severity of DM (14-16).

The incidence of TB in diabetics is higher than that of the general population. Coker et al. pointed out that DM increases the risk of developing TB infection, as do other factors (e.g.,

Table 5. Treatment regimens, duration and results of cases

		Diabetic (%)	Non-diabetic (%)	<i>P</i>
Treatment regimen	HRZE	70 (89.7)	56 (71.8)	0.004
	HRZS	3 (3.8)	17 (21.8)	0.001
	Retreatment	1 (1.3)	5 (6.4)	0.006
	Other	3 (3.8)	-	0.080
Treatment duration	6 m	15 (15.2)	62 (79.5)	0.000
	8 m	9 (11.5)	7 (9)	0.598
	9 m	29 (37.2)	7 (9)	0.000
	12 m	13 (16.7)	2 (2.6)	0.003
	>12 m	2 (2.6)	-	0.155
	>6 m	5 (6.4)	-	0.023
Treatment results	Currently being treated	5 (6.4)	-	0.023
	Cure	27 (34.6)	27 (34.6)	1
	Completed therapy	43 (55.1)	45 (57.7)	0.747
	Transfer to another center	-	2 (2.6)	0.155
	Left therapy	1 (1.3)	4 (5.1)	0.173
	Death	2 (2.6)	-	0.155
	Continuing therapy	5 (6.1)	-	0.023

living with TB patients, illicit drug use, overcrowding) (17). The risk of developing an active TB infection is reported to be 3 to 7 times higher in diabetics than in non-diabetics (18,19). The progression of latent infection to active disease is primarily determined by endogenous host factors (20). Previously, diabetic patients were not necessarily considered to be at increased risk of acquiring *M. tuberculosis* infection (21). However, one recent study has reported a greater risk in terms of reactivation or reinfection, as determined by molecular epidemiological methods (19). Olmos et al. reported the incidence of TB at 4.8% in DM cases, while this rate was determined to be 0.8% in the general population in Chili (22). Some studies have reported even higher incidences of notification (e.g., 12.3% national notification, and 14.8%—and even 25.2%—in the international literature) (18,23,24). Here, we found that the incidence of TB in DM patients was slightly higher than that of the general population of Turkey (7.3%).

The duration of DM has been strongly associated with the risk of development of TB. A diagnosis of TB was synchronous with a diagnosis of DM in 16-25% of TB patients in the literature (25). In our study, DM and TB were diagnosed simultaneously in 1/3 of subjects in the DM group; the duration of diabetes in 40% of the patients was <10 years. Uncontrolled blood glucose levels have been claimed to be associated with earlier TB infections. The manifestation of TB was reported in 85% of badly managed DM cases in the first 10 years of DM (15). Jabbar et al. reported observing the highest incidence of TB among DM patients who had had DM for more than 10 years (2).

Remarkable experimental studies have investigated the association between DM and TB. Sugawara et al. indicated in their two well-designed studies that diabetic rats were more susceptible to *M. tuberculosis* infection than were non-diabetic rats. The researchers observed no significant difference between the phagocytosis of tubercle bacilli by alveolar macrophages of type 1 versus type 2 rats. However, the authors also demonstrated that alveolar macrophages of neither type 1 nor type 2 diabetic rats were not fully activated by *M. tuberculosis* infection (26,27).

In general, more males than females receive a diagnosis of TB. This has been mostly attributed to socio-cultural factors that lead to a higher risk of exposure to *M. tuberculosis* in men, and/or to a higher frequency of underdiagnosis in women, primarily resulting from fewer opportunities among women of obtaining medical services (28,29). Pérez-Guzmán et al. reported finding an association between DM and changes in the male/female ratio of PT with increasing age. Namely, they found a higher proportion of elderly diabetic women with TB than non-diabetic women with TB (30). Although male gender was dominant in both groups in our study, the difference was only significant in the non-DM group. However, the distribution of gender did not generate a significant difference between groups.

Atypical localization is seen more often in diabetics with TB than in non-diabetics with TB (10-25%) (3,31,32). Sosman and Stidl reported a higher rate of lower-lung involvement of TB in their diabetic patients (3). Pérez-Guzmán et al. suggested that in older patients and in diabetics, increased alveolar oxygen pressure in the lower lobes favors the development of lower-lobe disease in these groups (33). Bacakoğlu et al. also concluded that DM was associated with lower-lung disease, but only in older patients (23). Multilobar involvement of TB has been reported to be more frequent in diabetics than in the general population (32). The specific

reported incidence of cavitory lesions has varied among studies finding a higher rate of cavitory disease in diabetics (31,34-37). In our study, atypical radiological (PA chest radiogram) findings of middle- and lower-zone involvement were seen in 37.2% of the diabetic group and 14% of the non-diabetic group. Cavitation and a wider range of pulmonary infiltration were much more frequently seen in diabetics than in non-diabetics.

We also detected higher rates of smear positivity and a greater incidence of cavitory disease in DM cases, as also indicated by the studies of Törün et al. (25) and Stevenson et al. (24). Thus, a higher smear-positivity rate is likely to be associated with greater cavity formation and wider pulmonary damage due to DM.

The American Thoracic Society has recommended tuberculin skin testing of all diabetic patients. Those with a positive skin test (induration of 10 mm or more in response to purified protein derivative) who have never been treated should receive isoniazid and pyridoxine for 6 to 12 months, regardless of their age (38). Studies need to be performed in order to ascertain the appropriate threshold for TST induration in diabetic patients, and whether some anergic diabetic patients might benefit from isoniazid prophylaxis treatment.

Ataç et al. detected that DM as the main factor affecting bacteriological conversion time (39). Güler et al. had reported that the presence of DM and diffuse pulmonary lesions were dependent factors for a prolonged conversion period (40). However, we found similar conversion time intervals in both groups in our study.

Wada et al. reported a higher relapse rate in diabetics with TB than in the general of TB population (41). In our study, while there were more relapse cases in the non-diabetic group, the difference was not found to be statistically significant. Bashar et al. concluded that DM creates a predisposition for MDR-TB (42). Bacakoğlu et al. reported a total drug resistance of 19.6% in DM, and 23.9% in non-DM patients (23). Our groups had similar cure rates. However, MDR-TB was found in two cases in the diabetic group, and there was no MDR-TB in the non-diabetic group. Drug resistance rates, except for that to isoniazid, were similar between the two groups.

Discrepancies in the literature regarding various features of patients with both DM and TB are bound to be partly due to differences in the degree to which glucose control has been achieved in these patients. DM is a known risk factor for TB in endemic area, and this risk increases with age. In general, TB is a disease that should be considered in diabetic patients with an abnormal chest radiograph. Diabetic TB patients should be closely observed for drug resistance for the duration of treatment, and the appropriate time to stop treatment should be carefully determined. Maintaining stable control of the blood glucose level is among the most important issues in the management of diabetic patients with TB.

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