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Comparison of Pulmonary TB Patients with and without Diabetes Mellitus Type II

Parvaneh Baghaei [1], Payam Tabarsi [1], Zoha Abrishami [2], Mehdi Mirsaeidi[1], Yazdan Ali Faghani [2], Seyed Davood Mansouri [3], Mohammad Reza Masjedi [4]

[1] Mycobacteriology Research Center, NRITLD, Shahid Beheshti University M.C., [2] Azad Medical University, [3] Lung Transplantation Research Center, [4] Chronic Respiratory Disease Research Center, NRTLD, Shahid Beheshti University M.C. TEHRAN-IRAN.

ABSTRACT

Background: *There are several studies on the effect of diabetes mellitus (DM) on clinical symptoms and radiological findings of multi- drug resistant tuberculosis (MDR-TB) and bacteriological findings in pulmonary tuberculosis patients. Considering the contradictory results of these studies, this study was conducted for further investigation in this regard.*

Materials and Methods: *This was a case – control study conducted in Masih- Daneshvari Hospital in Tehran. Forty-seven patients with tuberculosis infection and diabetes type II were selected as the case group and 102 TB cases without diabetes were considered as controls.*

Results: *There were significant differences in hemoptysis, dyspnea and loss of appetite between the two groups, but no significant difference was found in cough, sputum production, chest pain, night sweat, fever or weight loss.*

Also, there was no significant difference between the 2 groups in terms of MDR-TB and bacteriological findings.

On CXR, diabetic patients had a higher prevalence of typical presentations along with cavitary lesion(s) but no significant difference was found between the 2 groups in terms of radiological presentation.

Conclusion: *In this study, diabetes type II did not have much influence on clinical symptoms and bacteriological findings of TB patients. However, PTB–DM type II cases may be considered more contagious due to the higher prevalence of cavitary lesions compared to those without DM. Prevalence of MDR-TB was the same in both groups.* ***(Tanaffos 2010; 9(2): 13-20)***

Key words: *Tuberculosis, Diabetes Mellitus, Multi-drug resistant tuberculosis*

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disease which, if untreated, raises the risk for developing significant complications including an increased susceptibility to infectious diseases. Prior to the development of modern treatment options such as insulin injections, the prognosis for a person diagnosed with DM type I was less than five years due to the high possibility of developing a complication and the most common cause of death

Correspondence to: Masjedi MR

Address: NRITLD, Shaheed Bahonar Ave, Darabad, TEHRAN 19569, P.O:19575/154, IRAN

Email address: mrmasjedi@nritld.ac.ir

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for those with DM was tuberculosis (TB) (1).

Despite modern treatment options for DM, its association with TB has remained strong. In fact, the relative risk of developing bacteriologically confirmed Pulmonary Tuberculosis (PTB) is five times greater in diabetic patients (2). Therefore, DM remains a well-established risk factor for TB (3).

The prevalence of DM and TB in the Middle East is astounding. In 2000, an estimated 15.2 million people had a positive diagnosis of TB in the Middle East, which includes Iran. This figure is expected to increase to around 42.6 million by 2030 (4). Meanwhile, over one-third of the world's population act as hosts of TB bacterium, and new infections occur at a rate of one per second (5). In Iran alone, the incidence of TB was 28 cases per 100,000 people in 2004. With a population of 72 million, new cases of TB were estimated to be over 20,000 for that year (6).

Although DM type I is a well-established risk factor for TB, little is known of how type II of this metabolic disease influences the clinical presentation of TB. Paradoxical reports were recently published on clinical characteristics and prevalence of drug resistant form of Pulmonary Tuberculosis-Diabetes Mellitus (PTB–DM) suggesting that the clinical and radiological presentation of PTB may be different in diabetic patients. For example, PTB–DM patients may be more likely to present with atypical radiological images, while others suggested a more specific difference like an increase in lower lung field involvement, cavitary lesions, cavity in lower lung fields, and multiple cavities (7). Although the data on the clinical presentation of PTB–DM may be limited and inconsistent, there is no research on the incidence of PTB–DM in different geographical regions with a higher prevalence of DM and TB. The aim of this study was to compare the clinical, radiological and bacteriological characteristics of TB patients with and without DM type II.

MATERIALS AND METHODS

A cross-sectional study was performed on confirmed PTB patients admitted to the Masih Daneshvari Hospital in Tehran, Iran during a 2-year period. All data were prospectively collected using a case report form during hospitalization by a trained physician.

The data quality was reviewed for discrepancies and inconsistencies and validated by two infectious disease specialists prior to entering the database. This study was approved by the Institutional Review Board of the National Research Institute of Tuberculosis and Lung Diseases in Tehran, Iran. An informed consent was obtained from all patients.

All adult patients (≥ 18 years of age) with a new diagnosis of PTB presenting to Masih Daneshvari Hospital were consecutively screened for this study. A new diagnosis of TB was made on the basis of clinical signs and symptoms for more than two weeks (cough, sputum production, fever, night sweats, and weight loss), chest radiography (CXR), and a confirmed positive culture for *Mycobacterium tuberculosis*. A new diagnosis of DM was made if the fasting blood glucose was >126 mg/dl, a criterion in accordance with the "World Health Organization" (WHO) guidelines (8). Patients with a previous clinical diagnosis of DM type II with a glucose level of <127 mg/dl under treatment for DM were also enrolled in this study. Excluded from this study were patients with a diagnosis of Human Immunodeficiency Virus (HIV) infection, regardless of CD4+ lymphocyte count. After obtaining a written consent, HIV test was performed for all patients. Patients with other immunodeficiency states including recent diagnosis of a malignancy

except squamous cell carcinoma and basal cell carcinoma, current immunosuppressive therapy, radiotherapy, and chronic use of corticosteroids were also excluded from the study. Finally, patients already receiving anti-TB therapy for more than one month prior to admission or patients with a history of TB were excluded as well. All PTB–DM patients were categorized into three main forms of DM: type I, type II, and gestational diabetes (occurring during pregnancy) according to WHO definition (8). Only patients considered to have DM type II were evaluated in this study.

Demographic and clinical characteristics of all patients were recorded on the case report form at the time of admission by face to face interviews.

The pulmonary findings were detected by using patient's CXR interpreted by a chest radiologist blinded to the DM status of the patient. The radiological data was categorized as mild, moderate, or extended involvement. Mild involvement was defined as slight involvement of one or both lungs but in no more than one zone. If several zones in one or both lungs were involved but intact areas were present between the involved areas, the involvement was considered moderate. Otherwise, the involvement was considered extended. Upper lobe involvement with or without cavitary lesion(s) on CXR was defined as typical pulmonary involvement. Every other radiological presentation was classified as atypical pulmonary involvement. Only CXR findings were collected; no results from CT-scans were used for analysis in this study.

Microscopic detection of acid fast bacilli was performed for all patients. The sputum samples were also cultured in a Lowenstein-Jensen medium and drug-susceptibility testing was performed by the standardized method of proportion (9-11). Susceptibility was determined on the basis of the following drugs and concentrations: isoniazid 0.2 µg/ml, rifampin 40 µg/ml, ethambutol 2 µg/ml, and streptomycin 4 µg /ml. Drug-susceptibility testing was not done for pyrazinamide. Resistance was labeled if the colony numbers on the drug-containing medium was more than 1% of the colony numbers on drug-free medium. Multi-drug resistant tuberculosis (MDR–TB) was defined by resistance to both rifampin and isoniazid.

Patients with PTB–DM type II were selected as the case group. Control subjects were selected consequently from confirmed TB patients with no history of DM who met the inclusion and exclusion criteria. Control subjects were matched with cases in terms of age and sex.

The data were analyzed using SPSS for Windows version 14 software. Central tendency was calculated for quantitative variables. Normal variables were analyzed using Chi–Square, and when necessary, Fisher's Exact test. For variables that did not have normality, the Mann Whitney U test was utilized. A p-value $\leq$ 0.05 was considered statistically significant.

RESULTS

Case group criteria were met by 47 PTB–DM patients. Of the patients who met the inclusion and exclusion criteria for the control group after matching sex and age with the case group, 102 were selected. The mean ± SD age of the PTB–DM group and the control group was 57.8 ± 13.6 and 55.28 ± 12 years, respectively ($p>0.5$). The demographic characteristics of the case and control subjects are shown in Table 1.

Among the clinical signs and symptoms, no significant difference was found in cough, sputum production, night sweat, fever, weight loss, and chest pain. Despite this, data analysis indicated that the

prevalence of hemoptysis in the PTB–DM group was significantly higher than in the control group, while the prevalence of dyspnea and appetite loss was higher in the case group as shown in Table 2.

Based on the inclusion criteria, all patients enrolled in this study had positive sputum culture for *Mycobacterium tuberculosis*. In further bacteriological analysis, 42 (89.4%) of the case group and 84 (82.4%) of the controls had positive sputum smears (p>0.05).

Two patients from the control group (2%) were infected with MDR–TB. No cases of MDR–TB were present in the PTB–DM group. This difference between the two groups was not statistically significant.

The patients' CXR results were also compared. The PTB–DM group had a higher frequency of typical pulmonary involvement in CXR as compared to the control group (p=0.025)(Table 3).

Table 1. The demographic characteristics of patients with or without DM type II

	TB-DM group (N=47)	TB group (N=102)	Total N=149	P-value
Sex				
Male	42.6%(N=20)	48.0%(N=49)	46.3%(N=69)	NS
Female	57.4%(N=27)	52.0%(N=53)	53.7(N=80)	
Nationality				
Afghan	10.6%(N=5)	13.7%(N=14)	12.8(N=19)	NS
Iranian	89.4% (N=42)	86.3%(N=88)	87.2%(N=130)	
Residence				NS
City	95.7%(N=45)	92.2%(N=94)	93.3%(N=139)	NS
Village	4.3%(N=2)	7.8%(N=8)	6.7%(N=10)	
Current tobacco use				NS
No	68.1%(N=32)	64.7%(N=66)	65.8%(N=98)	NS
Yes	31.9%(N=15)	35.3%(N=36)	34.2%(N=51)	
Drug use				NS
No	83.0%(N=39)	84.3%(N=86)	83.9%(N=125)	NS
Yes	17.0%(N=8)	15.7%(N=16)	16.1%(N=24)	
Alcohol use				NS
No	95.7%(N=45)	85.3%(N=87)	88.6%(N=132)	NS
Yes	4.3%(N=2)	14.7%(N=15)	11.4%(N=17)	
History of contact				NS
No	78.7%(N=37)	86.1%(N=87)	83.8%(N=124)	NS
Yes	21.3%(N=10)	13.9%(N=14)	16.2%(N=24)	
Site of infection				NS
Pulmonary and Extra- pulmonary	0%(N=0)	7.8%(N=8)	5.4%(N=8)	NS
Pulmonary	100%(N=47)	92.2%(N=5)94	94.6%(N=141)	

Table 2. The Clinical characteristics of patients with or without DM type II.

Symptom	TB-DM	TB	P-value
Cough			
Yes	97.9%(n=46)	93.1%(n=95)	NS
No	2.1%(n=1)	6.9%(n=7)	
Sputum production			
Yes	68.1%(n=32)	73.5%(n=75)	NS
No	31.9%(n=15)	26.5%(n=27)	
Hemoptysis			
Yes	27.7%(n=13)	12.7(n=13)	0.025
No	72.3%(n=34)	87.3%(n=89)	
Dyspnea			
Yes	48.9%(n=23)	78.4%(n=80)	0.000
No	51.1%(n=24)	21.6(n=22)	
Chest pain			
Yes	48.9%(n=23)	53.9%(n=55)	NS
No	51.1%(n=24)	46.1%(n=47)	
Appetite loss			
Yes	63.8%(n=30)	79.4%(n=81)	0.036
No	36.2%(n=17)	20.6%(n=21)	
Night sweat			
Yes	66.0%(n=31)	62.7%(n=64)	NS
No	34.0%(n=16)	37.3%(n=38)	
Fever			
Yes	76.6%(n=36)	71.6%(n=73)	NS
No	23.4%(n=11)	28.4%(n=29)	
Weight loss			
Yes	80.9%(n=38)	89.2(n=91)	NS
No	19.1%(n=9)	10.8%(n=11)	

Table 3. The radiological findings in patients with or without DM. type II

CXR pattern	TB-DM group	TB group	Total	P-value
Typical	73.9%(N=34)	54.9%(N=50)	61.3%(N=84)	0.025
Atypical	23.9%(N=11)	45.1%(N=41)	38.0%(N=52)	
Normal CXR	2.2%(N=1)	0%(N=0)	7%(N=1)	
Total	100%(N=46)	100%(N=91)	100%(N=137)	

Both groups showed similarities regarding the extension of pulmonary involvement (p>0.05). Mild, moderate, and extensive involvements were observed in 21 (46.7%), 14 (31.1%), and 10 (22.2%) patients in the case group and in 32 (35.2%), 35 (38.5%), and 24 (26.4%) patients in the control group, respectively.

A significantly higher number of cavitary lung lesion(s) was found among the PTB–DM patients in comparison to the control group (p=0.004). Cavitary lung lesion(s) were identified in 27 (60%) cases and 32 (34.8%) controls. Bilateral cavitations were identified in 8 (17.8%) patients from the case group and 8 (8.7%) patients from the control group (p=0.001).

DISCUSSION

Our primary findings in this study were as follows: 1) the most common symptoms in the PTB–DM group were cough, weight loss, and fever; however, the prevalence of hemoptysis was higher in diabetics while the prevalence of dyspnea and appetite loss was higher among the non-diabetic patients; 2) there was no statistically significant difference in MDR–TB between the diabetic and non-diabetic patients; 3) a high proportion of diabetic patients had more visible cavitary lesions on their CXR.

Regarding the clinical presentation of PTB–DM, this study found no significant difference between diabetics and non-diabetics with the exception of hemoptysis. The most common symptoms in the PTB–DM patients were almost similar to those of non-DM group including cough (97.9%), weight loss (80.9%), and fever (76.6%). Bacakoglu and colleagues found similar results regarding the influence of DM on PTB symptoms (12). They believe that DM does not affect the clinical presentation of PTB. Feleke and colleagues also revealed that the more common symptoms were indeed cough and fever (13). The interesting point in our study was the higher prevalence of hemoptysis (27.7%) in diabetic patients and the higher prevalence of dyspnea (78.4%) and appetite loss (79.4%) among the non-diabetic group. Thus far, we

did not find any important diagnostic difference in clinical symptoms between the two groups.

In our study, no significant difference was found between the incidence of MDR–TB in diabetic and non-diabetic patients. This suggests that neither group has a greater tendency of acquiring MDR–TB and therefore, a more aggressive empirical management of TB is not required in those with DM type II. This topic has been examined in literature and there is no consensus on the relationship between MDR–TB and DM. For example, Bashar et al. identified DM as a risk factor for MDR–TB. The results of this study were possibly skewed given the inclusion criteria of patient populations with a higher risk for MDR–TB. For instance, homeless patients were included in both groups, the HIV status for a large percentage of the cases and controls was not available, and the DOTS strategy was not used for patients in both groups (2). In another study, drug resistance to first line anti-TB drugs was found not to be associated with the diagnosis or duration of DM (14). The limitation of this study, however, exists in the rapid increase of MDR–TB over the course of study because of which the outcome data could not be generalized. Finally, a study from India reported a lower incidence of MDR–TB among PTB patients with DM (15). Some researchers believe that the varying outcome can be reconciled by other variables like socioeconomic or unique geographical dynamics. The results of our study were likely influenced by the low incidence of MDR–TB in this particular study population, a percentage that was much lower than a previous study we conducted in Iran (16). Considering all the controversial reports, more research is clearly required in this area in order to further evaluate this correlation.

There is also controversy in the radiological findings in TB patients with and without DM. For example, an increased frequency of atypical involvement in diabetic patients has been identified in several studies (7,17,18). Other studies, however, have shown no significant difference in radiographic presentation of TB between the two groups and have reported that both groups had a higher prevalence of upper lobe involvement (2,19). Our study consented to the latter since the extension of pulmonary involvement was not significantly different between the two groups despite the previous reports regarding the higher extension of pulmonary involvement in PTB-DM patients (20). Additionally, we found that a high proportion of diabetic patients had typical pulmonary involvement and 73.9% of them had upper pulmonary involvement.

The only different radiological characteristic between the two groups was that the PTB–DM patients had a higher frequency of cavitary lesions present on CXR. Cavitary lesion(s) in PTB–DM have also been evaluated in previous studies. Unlike radiological presentation, these studies were consistent in their reports regarding a higher proportion of patients with lesions in the PTB–DM group (7,12,19). Our study results are consistent with previous findings reporting that 60% of the cases in the PTB–DM group had cavitary lesions on CXR, a percentage much higher than 34.8% reported in the non-diabetic controls. Despite these consistent findings, the correlation between the duration of disease and onset of cavitary lesion(s) is unclear. According to another study, prevalence of cavitary lesion(s) in PTB–DM patients is not correlated with the duration of symptoms (14). Considering the crucial immunological response to the occurrence of cavitary lesion(s) in the lungs, several studies document phagocyte and cell-mediated immunity dysfunction in DM which could explain our findings (20-23). Other possibilities for more frequent cavitary lesion(s) in PTB include nationality, race and living in a high burden community which have

been evaluated in earlier studies (24). However, further investigations are required in this regard (7).

Also, bacteriological findings were not affected by the presence of DM. A previous study examined the correlation between positive TB smears and DM and found no relationship (12). Likewise, we found no difference in positive smear results between the two groups in our study.

The primary weakness of our study is its hospital setting. The results of our study could have been strengthened by the inclusion of culture negative TB patients; however, the goal was to demonstrate the probable differences between PTB–DM and non diabetic patients in confirmed cases; therefore, culture negative cases could not be included in this study. Also, Hgb A1c levels were not evaluated to demonstrate the difference between well-controlled versus poorly controlled DM.

In conclusion, there are no notable differences between the clinical presentation of PTB–DM patients and PTB cases without a history of DM with the exception of the greater incidence of hemoptysis. Also, this study indicates that the incidence of MDR–TB is not impacted by the DM status of the patient, suggesting that DM may not be a risk factor for MDR–TB. However, PTB–DM cases may be considered more contagious than those without DM due to the higher prevalence of cavitary lesion(s) in them. Therefore, clinicians should be more aggressive in taking isolation precautions when treating PTB–DM patients.

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Competing interests statement:

The authors declare that they have no competing financial interests.

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