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The prevalence of diabetes mellitus among the patients with tuberculosis in Qom, Iran, during 2004-2016

Abolfazl Mozafari[1], Maryam Hendiani[1]

1 Department of Medical Sciences, Islamic Azad University, Qom Branch, Qom, Iran

Original Article

Abstract

BACKGROUND: Several studies have indicated the increasing risk of active tuberculosis (TB) due to diabetes mellitus (DM). The increasing prevalence of DM in areas with endemic TB may adversely influence spreading of TB. The current study is undertaken aiming to assess the prevalence of DM in patients with pulmonary TB.

METHODS: This case control study was conducted on 522 participants during a period of 12 years from 2004-2016 in Qom city, central Iran. The control group was symptomatic respiratory patients without preceding history of active pulmonary TB in the same clinic (n = 261). The case and control groups were compared using the Chi-square test. In addition, adjusted odds ratios (OR) and 95% confidence interval for comparison of the DM prevalence among patients with TB across different groups were calculated by multivariate logistic regression.

RESULTS: Mean age of the case and control patients were 51.0 ± 20.5 and 54.0 ± 14.9 years, respectively and 40.4% of all participants were males. The prevalence of DM was higher in patients with TB compared to the control patients and the rate was found to be 26.5% with adjusted OR of 3.54. The DM prevalence was significantly associated with TB in patients with older age (P < 0.001).

CONCLUSION: The prevalence of DM is significantly higher among patients with TB compared to the general population. Moreover, the mean age of patients with TB with DM is significantly higher than expected in patients with TB without DM.

KEYWORDS: Tuberculosis; Risk Factors; Diabetes Mellitus

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Introduction

Tuberculosis (TB), an air born infection caused by Mycobacterium Tuberculosis, is a major global health concern. It infects millions of people each year and is the second deadly infectious disease worldwide, after the human immunodeficiency virus (HIV).[1] It has been estimated that in 2017, 10 million new cases were diagnosed worldwide, the majority (95%) of whom living in the low and middle income regions. However, the number of TB deaths and incidence rate continuously fall globally.[1] The incidence rate of TB in Iran is 16 cases per 100000 population and at present, 16,000 people suffer from the disease. Moreover, the annual death rate due to TB is 2000 among Iranians.[2]

Diabetes mellitus (DM) describes a group of metabolic disorders characterized by increased blood glucose concentration. DM is a mainly asymptomatic disease, as a result it is diagnosed in late stages. The global prevalence of DM in adults has been increased over the recent decades following population aging, urbanization, alteration of diet, and reduction of physical activity patterns leading to increasing obesity.

The main portion (≃ 80%) of the 415 million estimated DM cases globally are from low and

Corresponding Author:
Abolfazl Mozafari; Department of Medical Sciences, Qom Branch, Islamic Azad University, Qom, Iran
Email: a_mozafari@hotmail.com

middle income countries. It has been proposed that the DM prevalence will be exponentially increased in regions with high TB incidence over the next 30 years.[3] In 2011, impaired fasting glucose and total DM prevalence rates were 14.60% and 11.37% among Iranian adults, respectively. Moreover, in 2005-2011, trend analysis revealed a 35.1% increase in DM prevalence in Iran.[4]

Several risk factors are involved in prevalence and incidence of TB, including age, gender, asthma, smoking habits, and family history of contact with patients with TB. People with suppressed immune system are susceptible to developing the latent to active TB. Factors such as poverty, homelessness, wars, immigration, malnutrition, renal insufficiency, alcoholism, social disorders, HIV infection, and especially DM play significant roles in growth of TB rates.

The risk of progression of latent to active TB in patients with DM is 2-3 times higher than in subjects without DM.[5] A study using dynamic TB transmission models to analyze the potential effects of DM on TB epidemiology in 13 countries with high burden of TB determined that stopping the growth of DM would decrease almost six million incidence of TB and more than one million TB deaths in 20 years.[6] Therefore, it is of crucial importance to evaluate the prevalence of DM and its contribution to TB. Furthermore, DM may negatively influence TB treatment outcomes in patients with active TB, by delaying the time for microbiological response, decreasing the chance of favorable consequences, growing the risk of relapse, deaths, and drug resistance.[7]

The prevalence of DM has been elevated in developing countries where TB is highly endemic. As a result, the co-incidence of DM and TB has been increased, warning about emerging concern in this field.[8] Therefore, the current study was designed to assess the prevalence rate of DM in patients with pulmonary TB.

Materials and Methods

This case control study was carried out in Qom City located in central Iran (34°38′24″N 50°52′35″E). Medical records of 1500 patients suffering from pulmonary TB during a period of 12 years (April 2004 to March 2016) referred to Tuberculosis and Leprosy Control Office of Communicable Disease Management Center were analyzed. Pulmonary TB cases were defined based on the World Health Organization (WHO) and Iranian national TB guidelines. According to the guidelines, at least three sputum samples should be taken from the suspected cases of pulmonary TB in the early morning and sent for TB microscopy and culture before starting possible treatments. Spontaneously produced sputum is preferred, if it is not possible, induction of sputum or bronchoalveolar lavage (BAL) should be used. A case of pulmonary TB is considered to be smear-positive if 1-9 bacilli are observed in each microscopic field and graded as 1+, 2+, and 3+. In smear negative pulmonary TB, no bacilli can be seen in microscopic field, but growth is positive in cultures or radiological findings are consistent with active pulmonary TB.[9]

DM was defined based on the diagnostic criteria described by the American Diabetes Association (ADA) as follows:

A fasting plasma glucose (FPG) level of 126 mg/dl or higher, a two-hour plasma glucose level of 200 mg/dl or higher during a 75-g oral glucose tolerance test (OGTT), or a random plasma glucose of 200 mg/dl or higher in a patients with classic symptoms of hyperglycemia or hyperglycemic crisis.[10]

The study inclusion criteria included pulmonary TB and age above 15 years old. The exclusion criteria included HIV positive patients, intravenous (IV) drug abuser, previous history of gastric bypass surgery, end stage renal disease (ESRD), cancer, leukemia and lymphoma, immunocompromised patients, and patients on oral corticosteroid or immunosuppressant drugs. The control group were symptomatic respiratory patients from the same health units without prior history of

active pulmonary TB who matched to the same age and gender subcategory in the case group. Considering the inclusion and exclusion criteria, finally 261 patients with TB as the case subjects and 261 symptomatic respiratory patients as the control subjects were selected for the study. The sociodemographic parameters were monthly family income (minimum, medium, and high wage), marital status (single, married), age, gender, nationality, residency (urban, rural), education (undergraduate, graduate), and body mass index (BMI).

All the information obtained was kept confidential. The study was initiated after the approval from the Ethics Review and Research Committee, Islamic Azad University. Permission from the health authorities was also taken prior to the study.

Descriptive statistics including mean and standard deviation (mean ± SD) were used to present data. Comparisons between groups were made using the Chi-square test or Fisher's exact test as appropriate for qualitative/categorical variables. Multivariate logistic regression was used to calculate adjusted odds ratios (OR) and 95% confidence intervals for comparison of DM prevalence among patients with TB across different subgroups. A two-way analysis of variance (ANOVA-2) was performed for assessing the effects of demographic parameters and grouping (case and control) on the level of fasting blood sugar (FBS). Data analyses were performed using Statistical Package for Social Science (SPSS) (version 20, IBM Corporation, Armonk, NY, USA) and P values less than 0.050 was considered significant.

Results

Table 1 represents the demographic data and characteristics of the participants. As can be seen, mean age of the case and control patients were 51.0 ± 20.5 and 54.0 ± 14.9 years old, respectively (P < 0.180). Moreover, 44.1% of the patients with TB and 41% of the patients in the control group had age less than 50 years old. Furthermore, 37.5% of the case group and 43.3% of the control group were comprised of men. The proportion of the patients with TB with BMI < 25 was 18.3%, and more than 80% of the participants were Iranians the majority (90.4%) of who were urban residents.

Table 1. Demographic data and characteristics of the participants

Variable	Group	Case (%)	Control (%)	Total (%)	P
Gender	Male	98 (37.5)	113 (43.3)	211(40.4)	0.180
	Female	163 (62.5)	148 (56.7)	311 (59.6)	
Nationality	Domestic	165 (63.2)	256 (98.5)	422 (80.8)	< 0.001
	Foreigner	96(36.8)	5(1.5)	100(19.2)	
Residency	Urban	233 (89.3)	239 (91.6)	472 (90.4)	0.370
	Rural	28 (12.3)	22 (8.4)	50 (10.1)	
Marriage	Single	54 (20.7)	39 (14.9)	93 (17.8)	0.086
	Married	207 (79.3)	222 (85.1)	429 (82.2)	
Education	Undergraduate	226 (86.6)	194 (74.3)	420 (80.5)	< 0.001
	Graduated	35 (13.4)	67 (25.7)	102(19.5)	
Income	Low	181 (69.3)	139 (53.3)	320(61.3)	< 0.001
	Medium	70 (26.8)	63 (24.1)	133(25.5)	
	High	10 (3.8)	59 (22.6)	69(13.2)	
Age (years)	Below 50	115 (44.1)	107 (41.0)	222 (42.5)	0.470
	Above 50	146 (55.9)	154 (59.0)	300 (57.5)	
BMI	Below 25	48 (18.3)	42 (16.0)	90 (17.2)	0.480
	Above 25	213 (81.7)	219 (84.0)	432 (82.8)	
FBS (mg/dl)	Below 100	117 (44.8)	202 (77.3)	319 (61.1)	< 0.001
	Between 100-126	75 (28.7)	27 (10.3)	102 (19.6)	
	Above 126	69 (26.5)	32 (12.4)	101 (19.3)	

BMI: Body mass index; FBS: Fasting blood sugar

Table 2. Comparison of diabetes mellitus (DM) prevalence among patients with tuberculosis (TB) across different groups

Variable	Categories	TB (%)	TB + DM	Prevalence (%)	OR	95% CI	P
Age (years)	< 50	115 (44.1)	10	8.7	7.14	3.43-14.70	< 0.001
	> 50	146 (55.9)	59	40.4			
Gender	Male	98 (37.5)	22	22.4	1.40	0.78-2.50	0.250
	Female	163 (62.5)	47	28.8			
Nationality	Iranian	165 (63.2)	54	32.7	2.62	1.38-4.98	0.003
	Foreigner	96 (36.8)	15	15.6			
BMI	< 25	48 (18.4)	12	25.0	1.09	0.53-2.25	0.800
	> 25	213 (81.6)	57	26.8			
Marital status	Single	54 (20.7)	10	18.5	1.75	0.82-3.71	0.130
	Married	207 (79.3)	59	28.5			
Residency	Urban	233 (89.3)	64	27.5	0.57	0.20-1.57	0.270
	Rural	28 (10.7)	5	17.9			
Education	Undergraduate	226 (86.6)	60	26.5	0.95	0.42-2.16	0.910
	Graduated	35 (13.4)	9	25.7			
Income	Low	181 (69.3)	49	27.1	1.01	0.61-1.66	0.480
	Medium	70 (26.8)	16	22.9			
	High	10 (3.8)	4	40.0			

TB: Tuberculosis; DM: Diabetes mellitus; OR: Odd ratio; CI: Confident interval; BMI: Body mass index

The frequency of DM was higher in patients with TB compared to those in the control group. 69 of the patients with TB and 32 of the control ones had DM and the prevalence of DM in the case and control groups were found to be 26.5% and 12.4%, respectively [P < 0.001, crude OR = 2.57 (1.62-4.07), adjusted OR = 3.54 (2.13-5.88)]. Consistently, mean of FBS in the patients with TB and the control individuals was 125.2 ± 57.5 and 99.8 ± 33.6 mg/dl (P < 0.001), respectively.

Comparing the DM prevalence among various subcategories of patients with TB described in table 2 revealed that significant differences were present among only the two demographic variable of age [crude OR = 7.14, (3.43-14.7) with adjusted OR = 6.77 (3.25-14.1) and nationality [crude OR = 2.62, (1.38-4.98) with adjusted OR = 2.36 (1.20-4.63)].

ANOVA-2 was conducted to examine the effects of demographic parameters and grouping (case and control) on the level of FBS and statistically significant interaction was noticed only between the age and grouping (F = 16.20, P < 0.001). This means that FBS was significantly higher in patients with TB with the age of more than 50 years old (Table 3).

Discussion

In the current study, the prevalence of DM in patients with TB was found to be 26.5% which was higher than that in the control group (12.4%) with OR more than 3. Similar findings have been reported by other researchers.[11,12] The association between TB and DM has previously been confirmed and several epidemiologic studies have reported a significant correlation in this regard,[13,14] Patients with DM are at 2-3 folds higher risk of developing active TB compared to the general population.[15] A systematic review of 13 observational studies demonstrated that DM was associated with an increased risk of TB [relative risk = 3.11, 95% confidence interval (CI) 2.27-4.26] and case-control studies were heterogeneous with ORs of 1.16 to 7.83.[16] Additionally, systematic review of the literature determined that in the top 10 countries with the highest prevalence of TB, 12.6% (95% CI 9.2-17.3) of the new cases had to be attributed to DM in 2030.[17]

Table 3. Comparison of fasting blood sugar (FBS) level among the case and control subjects in different groups

Variable	Categories	TB	Control	P
		FBS (mean ± SD)	FBS (mean ±SD)	
Age (years)	< 50	105.4 ± 47.6	98.0 ± 32.0	< 0.001
	> 50	140.8 ± 59.8	101.0 ± 34.0	
Gender	Male	119.3 ± 48.7	99.6 ± 35.4	0.270
	Female	128.8 ± 62	99.9 ± 32.3	
Nationality	Iranian	131.2 ± 60.4	100.0 ± 33.8	0.860
	Foreigner	114.9 ± 50.6	87.7 ± 14.2	
BMI	< 25	121.3 ± 49.5	96.0 ± 23.6	0.980
	> 25	126.1 ± 59.2	100.5 ± 35.2	
Marriage	Single	116.2 ± 58.9	98.3 ± 25.4	0.380
	Married	127.5 ± 57	100.1 ± 34.9	
Residency	Urban	127.1 ± 59.4	99.1 ± 32.4	0.059
	Rural	109.2 ± 34.2	107.7 ± 44.8	
Education	Undergraduate	125.1 ± 56.4	99.3 ± 34.8	0.930
	Graduated	126.1 ± 64.6	101.3 ± 30.3	
Income	Low	125.7 ± 56.8	99.0 ± 32.8	0.700
	Medium	122.4 ± 59.6	101.5 ± 41.2	
	High	135.9 ± 53.7	100.4 ± 27.8	

TB: Tuberculosis; FBS: Fasting blood sugar; SD: Standard deviation; BMI: Body mass index

The present study findings showed a significantly higher prevalence of DM in older patients with TB with an OR of more than 7 for the age of above 50 years old. In support of this finding, it has been claimed that type 2 DM appears to be a critical risk for the onset of TB, particularly for adults in their 40s and early 50s, the period which coincides with the onset of type 2 DM in the general population.[18,19] Despite the improvement of health care services, better living conditions, and changing life styles, the prevalence of DM is rising. Continuous screening and distinguishing of pre-diabetic stage play an important role in the reduction of TB incidence.

Contrary to other studies, higher BMI was not observed in patients with TB and DM compared patients without DM with TB in this study.[18] However, few other studies have shown a lower BMI in patients with DM.[20] The current findings suggest that screening for DM is necessary in patients with TB even in case of the lack of a high BMI among them.

Several studies have offered convincing biological evidence in support of the causal association between DM and impaired host immunity for TB activation.[21,22] It has been demonstrated that the expression of adaptive immunity is delayed in chronic diabetic mice compared to euglycemic mice. This is evidenced by declined early production of gamma interferon (IFN-γ) and interleukin-12 (IL-12) in the lung and the presence of fewer *M. tuberculosis* antigen early secreted antigen 6 kilodaltons (ESAT-6)-responsive T cells within the first month of infection, marking a diminished T helper 1 (Th1) adaptive immunity; this plays a crucial role in controlling TB infection.[23] In another study, to investigate the immune cell profile alterations in patients with TB with type 2 DM, it was noticed that patients with TB with coincident type 2 DM had higher percentages of Th2 and Th17 cells after stimulation with TB antigens, while they had unchanged Th1 cells and decreased $CD8^+$ cytotoxic T cells compared to patients with TB without type 2 DM.[24]

This study was constructed on the data obtained from observational studies which could be confounded by variables associated with both DM and TB. To decrease the interference, it was tried to match important

parameters of sociodemographic status with the application of adjustment. However, the samples were representative of the population with definite TB, because all the patients were registered at one of the reference TB centers in Qom.

Conclusion

In summary, the current findings indicate that the prevalence of DM is significantly higher in patients with TB. DM can activate latent TB by suppressing immune system, therefore, people with DM, especially the elderly, may be important targets for assessment for active case finding and management of latent TB and efforts to diagnose, detect, and treat DM may have a beneficial impact on the control of TB.

Conflict of Interests

Authors have no conflict of interests.

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