PREVALENCE OF ACTIVE TUBERCULOSIS & MTB-INFECTION AMONG DIABETIC POPULATION IN SOUTHERN OF IRAN, 2016

Vahid Rahmanian [1], Karamatollah Rahmanian *[2], Elham Mansoorian [3], Narges Rahmanian[4], Heshmatollah Shakeri[5], Mohammad Ali Rastgoofard[6]

1. *MSC in Epidemiology, MPH in Health Policy , Research Center For Social Determinants of Health, Jahrom University of Medical Sciences ,Jahrom, Iran*
2. *Associate Professor in Community Medicine, Research Center For Social Determinants Of Health, Jahrom University of Medical Sciences ,Jahrom, Iran*
3. *MSC student in Health Education And Health Promotion, Research Center For Social Determinants Of Health, Jahrom University Of Medical Sciences ,Jahrom, Iran*
4. *Emergency Medicine Specialist ,Research center for social Determinants of Health, Jahrom University of Medical Sciences ,Jahrom, Iran*
5. *Assistant Professor , Infectious Disease and Tropical Medicine Specialist, Research center for social Determinants of Health, Jahrom University of Medical Sciences ,Jahrom, Iran*
6. *Bsc in public Health, Research Center For Social Determinants Of Health, Jahrom University Of Medical Sciences ,Jahromn*

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ABSTRACT

Background and objectives: Mycobacterium tuberculosis (MTB) infection can occur at any age. Upon infection, the person can remain infected for years and even for his entire lifetime. The aim of this study was to determine the prevalence of MTB infection and active tuberculosis in people with type-II diabetes.
Method: A cross-sectional study was conducted on 705 patients with type-II diabetes. All patients were tested for MTB infection by Mantoux test. Induration size of greater than 10mm was considered as positive reaction, and people suspected to have active TB were examined by sputum smear test. Data was analyzed with descriptive statistics and Chi-square test at α=0.05 using SPSS16.
Results: Patients had a mean age of 58±11.06 years and mean diabetes duration of 4.13±2.25 years. 27.2% of patients had uncontrolled diabetes and 25.2% of them had underlying conditions. In 26.4% of patients induration size was less than 5 mm (negative), in 20.1% it was 5-9 mm (borderline), in 25.7% it was 10-14 mm (positive), and in 27.8% it was 15 mm or greater (strongly positive). MTD infection was significantly associated with presence of an underlying condition, duration of diabetes, night sweats, weight loss, and uncontrolled diabetes (p<0.05). In total, 2 patients with smear-positive active pulmonary tuberculosis were identified.
Conclusion: The prevalence of MTB infection among the studied population of diabetic patients was 53.47%. The prevalence of active pulmonary TB in this population was estimated to 283 per 100,000 people, which is 166 times higher than the prevalence of active TB in normal population of the same region in the same year (1.7 per 100,000 people).

Introduction

Tuberculosis (TB) is a life-threatening infectious disease caused by Mycobacterium tuberculosis (MTB) and is associated with a wide range of clinical conditions. Approximately 85% of TB cases are pulmonary and the rest appear in extrapulmonary forms [1, 2]. TB has specific clinical signs such as fever, night sweats, weight loss, appetite loss, and

Corresponding Author: Karamatollah Rahmanian. Email: k. rahmanian @ jums.ac.ir

fatigue. In 90% of cases, pulmonary TB causes coughing. Initially, this is only dry coughing at morning but as the disease progresses patients starts to cough up sputum and blood [3].

In WHO's ranking of global burden of diseases (based on Disability-Adjusted Life Years (DALY), TB was ranked seventh in 1990, and is expected to remain in this rank at least until 2020. This is while most other infectious diseases have fallen in this ranking [1]. According to WHO statistics, in 2015, approximately 10.4 million people including 5.9 million men (56%), 3.5 million women (34%) and 1 million children (10%) contracted active TB. This included 1.2 million new cases among people with HIV/AIDS (11%), 480,000 new cases of Multidrug-resistant TB (MDR TB), and 100,000 new cases of Rifampicin-resistant TB (RR-TB). It is notable that in that year, this disease took the life of approximately 1.4 million people [4].

According to the same statistics, in 2015, there were 10416 new cases of TB in Iran, of which 170 were MDR-TB and 1425 were RR-TB. In that year, the TB mortality rate among Iranians was 2.03 deaths per 100,000 people [5, 6].

Tuberculosis infection refers to any case of infection with mycobacterium tuberculosis, but it is not a generally concerning condition provided that bacteria are low in numbers and are under the control of immune system; a state that is called latent tuberculosis. In fact, there are many people who have MTB infection and are considered completely healthy [7].

MTB infection can occur at any age, and later, a chronic impairment of immune system caused by other conditions such as uncontrolled diabetes may allow TB bacilli to reproduce and cause active TB. On the other hand, MTB infection may stay latent for years and even for the patient's entire lifetime [7, 8].

The chance of developing active TB is greatest within a short time after initial infection, but decreases with time [7].

Diabetic people are estimated to have 2 to 4 times greater risk of developing active tuberculosis [9]. Thus, with the 250 million new cases of diabetes mellitus in the world and prediction of 100% increase in the number of diabetic patients in the next 20 years, WHO has expressed great concerns about the effect of diabetes on the control of tuberculosis [10].

In a meta-analysis conducted in 2008, people with diabetes were found to be 3.11 times more likely to develop tuberculosis [11].

The combination of tuberculosis and diabetes mellitus is a global health threat [9]. The exact mechanism of association between these two conditions is yet unknown, but it is believed that diabetes triggers TB activation and disease progression by suppressing the immune responses and affecting bactericidal activity of leukocytes. It is also believed that with appropriate medication, the risk of such TB activation can be reduced by 90% [12].

Reports on the prevalence of active TB among diabetic patients vary with the country and region. For example, this prevalence has been reported to be 5.8% in Ethiopia [13], 13.2% in Japan [14], 18.4% in India [15] and 9.4% in Kuala Lumpur [16]. This indicates that there is indeed a need for further clinical study on diabetes as a risk factor for TB, especially in developing countries.

Despite its deficiencies as diagnostic tool for active TB in adults, the Mantoux tuberculin skin test can serve as a convenient screening tool to determine whether a person is infected with MTB [17]. This test has been recommended by many scientific publications for active screening of tuberculosis among diabetic people. Furthermore, Iran's national TB manual has stressed the importance of chemoprophylaxis for diabetic patients that test positive in Mantoux test under the supervision of specialist [7].

In Iran, TB activation and relapse are often diagnosed long after emergence of symptoms and there is currently no standard preventive measure for high-risk groups. Screening is also performed passively and usually upon patient's request following the failure to treat symptoms based on other diagnoses. Determining the probable count of latent tuberculosis or early diagnosis can mitigate the risk of active TB and contribute to controlling TB in high risk populations, preventing new infections, and reducing the complications and mortality of tuberculosis.

The aim of this study was to determine the prevalence of TB in patients with type-2 diabetes.

Materials and Methods

This cross-sectional study was carried out in 2016 on the patients with type-2 diabetes in the villages of Jahrom County. The patients had been previously diagnosed in a screening program conducted in the county's health centers. Study was conducted using the census method, and accordingly, all 705 patients who met inclusion/exclusion criteria entered the study.

The names of diabetic patients diagnosed in the screening program were obtained from the screening forms. Data collection tool was a checklist devised in accordance with Iran's national TB manual [7], which included demographic information, medical records, contact information and history, complaints, and clinical symptoms associated with TB. In the next stage, all patients were tested for MTB infection using Mantoux tuberculin skin test.

Uninfected people (tested negative in two Mantoux tests administered 10 days apart and showing no sign of active TB), people with MTB infection (tested positive in Mantoux test but not showing any sign of active TB) and people with active TB (tested positive in AFB test or having pathologic/radiologic signs suggesting active TB) were differentiated from each other [7].

In the PPD test, 0.1 ml of 5-unit tuberculin solution provided by the Pasteur Institute of Iran was injected into the inner surface of the middle third section of the patient's forearm in a featureless area (without scar, burn marks, etc.). The result was read 48 to 72 hours after injection. Any reaction before 48-hour mark was considered irrelevant. As expected, every test

resulted in an allergic reaction in the form of erythema (redness) and induration (swelling and hardening). Diameter of the indurated area was measured across the forearm (perpendicular to the forearm axis) in millimeters (diameter of erythema is unimportant). In the cases where there was no induration at the site of injection, the result was reported as zero millimeters. Test results were interpreted in accordance with Iran's national TB manual: <5 =negative; 5-9 mm = borderline; 10-14 mm=positive; > 15 mm = strongly positive [7].

In the cases that tested positive in PPD test and AFB test of sputum smear, the patient and immediate family were respectfully and privately introduced to Jahrom's health center to receive necessary medical services. It should also be noted that this study was approved by the ethics committee of research department of Jahrom University of Medical Sciences (ID: IR.jums.REC.1396.029). Finally, data was analyzed with descriptive statistics and Chi-square test at significant level of α = 0.05 using SPSS16.

Results

A total of 705 patients with type-2 diabetes in the villages of Jahrom County were tested for MTB infection and smear-positive pulmonary tuberculosis. Patients had a mean age of 58±11.06 years and an age range of 35-90 years. Of 705 patients, 554 (78.6%) were women and 151 (21.4%) were men; 590 (83.7%) were married; 494 (70.15%) were illiterate, 180 (25.5%) had elementary education, 25 (3.5%) had high school diploma, and 6 (0.85%) had higher education; and 529 people (75%) were housewives. Diabetes of 480 patients (68.1%) was controlled with medication, diabetes of 33 patients (7.4%) was controlled without medication, and diabetes of 192 patients (27.2%) was uncontrolled. The mean duration of diabetes among patients was 4.13±2.25 years. 33 patients (4.7%) had addiction and 178 patients (25.2%) had underlying conditions such as renal problems, hypertension, immunodeficiency disorders, etc. (Table 1).

In terms of TB-associated clinical symptoms, 84 patients (11.9%) had chronic coughing for more than two weeks, 62 patients (8.8%) were coughing up sputum for more than two weeks, 8 patients (1.1%) were coughing up bloody sputum, 54 patients (7.7%) had experienced weight loss, 42 patients (6%) were experiencing a loss of appetite, 40 patients (5.7%) had fever, 90 patients (12.8%) had night sweats, 45 patients (6.4%) had dyspnea, and 3 patients (0.4%) had swollen lymph nodes.

7 patients (1%) had a history of exposure to pulmonary tuberculosis, but none of the patients had a history of TB diagnosis or anti-TB medication.

In 186 patients (26.4%) induration diameter was less than 5 mm (negative), in 142 patients (20.1%) it was 5-9 mm (borderline), in 181 patients (25.7%) it was 10-14 mm (positive), and in 196 patients (27.8%) it was 15 mm or more (strongly positive).

As suggested by the majority of scientific resources, induration diameters of more than 10 mm were classified as positive MTB infection. Table 2 shows the prevalence of MTB infection among different groups of patients with type-2 diabetes. As shown in this table, there was a significant relationship between MTB infection and underlying condition, duration of diabetes, night sweats, weight loss and uncontrolled diabetes (p <0.05) (Table 2).

Of 78 patients who had notable signs of active pulmonary TB and were eligible for direct smear microscopy, 7 were excluded because of lack of cooperation in sputum sampling. For the remaining 71 patients, three sputum samples (per patient) were collected in accordance with Iran's national TB manual.

For 69 patients, the result of Ziehl-Neelsen's sputum smear staining was negative, and they recovered after 14 days of treatment with broad-spectrum antibiotic. Overall, 2 cases of smear-positive active pulmonary tuberculosis were identified.

The first case was an 81-year-old woman with history of 14 years of uncontrolled type-2 diabetes, who had chronic coughing (for more than two weeks), was coughing up sputum, was experiencing appetite loss, had fever and night sweats, and tested positive in PPD test (22 mm). Her sputum smear was +++.

The second case was a 42-year-old woman with history of 5 years of medication-controlled type-2 diabetes, who had chronic coughing (for more than two weeks), was coughing up blood, was experiencing appetite loss and chest pains, and tested positive in PPD test (10 mm). Her sputum smear was ++.

Discussion

Before the discovery of antibiotics, pulmonary TB was known to be the cause of half of deaths among diabetic people. According to recent studies, pulmonary TB is 3 to 4 times more prevalent among diabetic patients than among normal populations. Thus, diagnosis of latent tuberculosis with tuberculin skin test is of particular importance for these patients [18]. However, PPD test does not have a high sensitivity and specificity and is known to give false negatives in old patients or those with severe malnutrition and immunodeficiency. Sometimes these false negatives can be detected by retest in the first

3 weeks, so we also conducted a second PPD test 10 day after the first one to rule out interference from age, malnutrition and immunodeficiency.

There are also other diagnostic methods, such as analysis of response of lymphocytes to MTB by measuring Th1 response to the release of interferon-α, but because of affordability and accessibility of PPD test, it is still the method of choice for diagnosis of MTB infection in developing countries, even among people with diabetes.

In this study, the prevalence of MTB infection in diabetic patients in Jahrom was found to be 53.47%, which is higher than the figures reported for some other parts of Iran including Isfahan (20%), Qazvin (12.3%) and Zahedan (6.25%) [10, 19, 20].

In recent years, diagnosis of latent TB infection in diabetic patients has received growing attention and there is now little disagreement over the necessity of chemoprophylaxis in these patients. In Iran, the only acceptable chemoprophylaxis for TB is the daily consumption of 5mg of Isoniazid per kg of body weight for at least 6 months. Chemoprophylaxis with Isoniazid reduces the likelihood of TB activation by 90% and has life-long protective effects (in the absence of re-infection) [7, 21].

The present study also found a significant relationship between MTB infection and underlying conditions (p <0.001), as 62.4% of patients who had underlying conditions such as hypertension, immunodeficiency, renal problems etc. tested positive in tuberculin test, whereas only 43.4% of patients who did not had these underlying conditions tested positive. It can be argued that the presence of underlying conditions that weaken the body predisposes the patient to TB activation.

This study also found a significant relationship between the duration of diabetes and MTB infection, as 58.3% of people who had diabetes for more than 4 years tested positive for TB infection, but only 42.1% of those had diabetes for less than 1 year tested positive (P-value = 0.005). In contrast, the study of Meena did not find this particular relationship to be significant [22].

Also, 55.6% of patients who had weight loss, 52.2% of those who had night sweats, and 69.2% of those who had uncontrolled diabetes tested positive for MTP infection, which was statistically significant (p <0.05). On the other hand, there was no significant relationship between PPD test results and gender, age, education, and addiction, or chronic coughing, coughing up sputum, coughing up blood, and loss of appetite (p> 0.05).

In a study by Alisjahbana et al. (2007) in Indonesia, it was found that chronic coughing, night sweats, painful and shallow breathing, weight loss, appetite loss, and fever were three times more common in TB patients who had diabetes [23].

In a case-control study by Meena, 31 out of 92 patients (33.69%) had positive PPD tests, and there was a significant relationship between the levels of Hemoglobin, INR, HbA1c, and the history of tuberculosis and the mean induration size (in PPD test), but there was no significant relationship between mean induration size and age, BMI, duration of disease, fasting blood sugar, serum albumin and total protein [22].

The close association of diabetes with tuberculosis and the role of diabetes as a risk factor for TB activation and development of smear-positive active tuberculosis have been underscored in many studies. Although the majority of studies report a concurrence between tuberculosis and diabetes, they have not been able to determine which of these two facilitates the other [19]. But overall, the evidence accumulated over the past 40 years confirms that diabetes does in fact increase the risk of tuberculosis. The result of a study by Jeon and Murray on 17 researches published from 1983 to 2007 on 700,000 people including approximately 18,000 people with MTB infection has shown that diabetes triples the risk of tuberculosis, but in different studies, this risk elevation may ranges between 0.98 and 7.83. According to this study, diabetes has been responsible for over 10% of cases of tuberculosis in China and India [11].

In the present study, out of 705 diabetic patients studied, 2 tested positive for active pulmonary TB in both PPD and AFB tests. Accordingly, the prevalence of TB in the studied population of diabetic patients was estimated to 283 per 100,000 people, which is 166 times higher than the TB prevalence in normal population of the same county in the same year (1.7 per 100,000 people).

The prevalence of tuberculosis in Iranian diabetic patients is underresearched, but the prevalence of TB in general population in different regions of Iran has been between 10 per 100,000 people (in Sabzevar) and 137 per 100,000 people (in Sistan-Baluchistan) [24]. Therefore, the prevalence of TB among diabetic patients of this study is significantly higher than that of general population in any region of Iran and also the latest global TB prevalence statistics (2015), that is, 140 per 100,000 people [25].

In a study by Feleke (1999) on 1352 diabetic Ethiopians, people with insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) were found to have, respectively, 26 times and 7 times higher probability of developing TB, as compared to normal population [13].

The most common source of MTB infection is the sputum of patients with active pulmonary TB. With each cough, these patients produce up to 3,000 infectious droplet nuclei of less than 5 micrometers in diameter which contain their respiratory secretions and therefore tuberculosis bacilli. These infectious droplets can be released not only by coughing but also by talking, sneezing, spitting, and singing, and can stay in the air for a long time (7). Therefore, early diagnosis and timely treatment of diabetic patients with smear-positive pulmonary tuberculosis can serve as a preventive and inhibitory measure against the spread of TB among other members of population.

Conclusion

In this study, the prevalence of MTB infection among the studied diabetic population was found to be 53.47%. The prevalence of active pulmonary TB in this population was estimated to 283 per 100,000 people, which is 166 times higher than the active TB prevalence in normal population of the same county in the same year (1.7 per 100,000 people).

The figures obtained in this study confirm the higher prevalence of MTB infection and smear-positive pulmonary tuberculosis in studied diabetic population than the figures estimated for normal population and the global prevalence of TB in patients with diabetes mellitus. Therefore, screening of diabetic patients for TB and screening of TB patients for diabetes can be recommended as a way to control both conditions in this region.

Further follow up of the patients may result in more precise recommendations in regard to chemoprophylaxis of diabetic patients with induration size of more than 10mm. Also, introduction of a control group and comparison of prevalence of latent TB among diabetic and non-diabetic people in two groups can be a good avenue for future research.

Conflict and interests:

The authors declare that there is no conflict of interest.

Ethics license:

This study is approved by the ethics committee of research department of Jahrom University of Medical Sciences (ID: IR.jums.REC.1396.029.)

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Table 1: Demographic information of patients with type-II diabetes in Jahrom villages (2016)

Variable	Group	Frequency	Percentage
Gender	Male	151	21.4
	Female	554	78.6
Marital status	Single	4	0.6
	Married	590	83.7
	Widow(er)	108	15.3
	Divorced	3	0.4
Education level	Illiterate	494	70.15
	Elementary/middle school certificate	180	25.5
	High school diploma	25	3.5
	University degree	6	0.85
Occupation	Unemployed	34	4.8
	Farmer	59	8.4
	Worker	27	3.8
	Housewife	529	75
	Government employee	4	0.6
	Other	52	7.4
Underlying conditions	None	527	74.8
	Hypertension	103	14.6
	Renal problem	11	1.6
	Immunodeficiency problem	1	0.1
	Other	63	8.9

Table 2: Frequency distribution of MTB infection among demographic groups of patients with type-II diabetes in Jahrom villages (2016)

Variable	Group	TB infection				Significance
		Negative <5mm	Borderline 5-9mm	Positive 10-14mm	Strongly positive > 15	p-value
Gender	Male	35 (23.2%)	32 (21.2%)	38 (25.2%)	46 (30.5%)	0.71
	Female	151 (27.3%)	110 (19.9%)	143 (25.8%)	150 (27.1%)	
Age	30-50 years	60 (32.3%)	33 (17.7%)	45 (24.2%)	48 (25.8%)	0.155
	51-70 years	108 (25%)	88 (20.4%)	119 (27.5%)	117 (27.1%)	
	71-90 years	18 (20.7%)	21 (24.1%)	17 (19.5%)	31 (35.6%)	
Education level	Illiterate	134 (27.1%)	110 (22.3%)	122 (24.7%)	128 (25.9%)	0.16
	Elementary/middle school certificate	43 (23.9%)	25 (15.6%)	49 (27.2%)	60 (33.3%)	
	High school diploma	6 (24%)	4 (16%)	10 (40%)	5 (20%)	
	University degree	3 (6%)	0 (0%)	0 (0%)	2 (40%)	
Addiction	Yes	8 (24.2%)	4 (12.1%)	12 (36.4%)	9 (27.3%)	0.482
	No	177 (26.4%)	138 (20.6%)	169 (25.2%)	187 (27.9%)	
Underlying condition	Yes	31 (17.4%)	36 (20.2%)	48 (27%)	63 (35.4%)	0.001
	No	165 (31.3%)	133 (25.2%)	106 (20.1%)	123 (23.3%)	
Duration of disease	Less than 1 year	16 (28.1%)	17 (29.8%)	11 (19.3%)	13 (22.8%)	0.005
	1-3 years	57 (22%)	51 (19.7%)	60 (23.2%)	91 (35.1%)	
	4 years and more	82 (21.1%)	80 (20.6%)	104 (26.7%)	123 (31.6%)	
Coughing	Yes	16 (19%)	18 (21.4%)	21 (25%)	29 (34.5%)	0.309
	No	170 (27.4%)	124 (20%)	160 (25.8%)	167 (26.9%)	
Fever	Yes	7 (17.5%)	14 (35%)	11 (27.5%)	8 (20%)	0.075
	No	179 (26.9%)	128 (19.2%)	170 (25.6%)	188 (28.3%)	
Night sweats	Yes	10 (11.1%)	24 (26.7%)	37 (30%)	29 (32.2%)	0.005
	No	176 (28.6%)	118 (19.2%)	154 (25%)	167 (27.2%)	
Weight loss	Yes	15 (27.8%)	9 (16.7%)	11 (20.4%)	19 (35.2%)	0.020
	No	171 (26.3%)	187 (28.7%)	170 (26.1%)	123 (18.9%)	
Appetite loss	Yes	6 (14.3%)	13 (31%)	12 (28.6%)	11 (26.2%)	0.154
	No	180 (27.1%)	129 (19.5%)	169 (25.5%)	185 (27.9%)	
Chronic Coughing of sputum	Yes	11 (17.7%)	16 (25.8%)	19 (30.6%)	16 (25.8%)	0.118
	No	175 (27.2%)	126 (19.6%)	162 (25.2%)	180 (28%)	
Bloody sputum	Yes	1 (12.5%)	4 (50%)	2 (25%)	1 (12.5%)	0.515
	No	185 (26.5%)	138 (19.8%)	179 (25.7%)	195 (28%)	
diabetes control condition	Controlled with medication	152 (31.7%)	100 (20.8%)	116 (24.2%)	112 (23.3%)	0.001
	Controlled without medication	8 (24.2%)	9 (27.3%)	6 (18.2%)	10 (30.3%)	
	Uncontrolled	26 (13.5%)	33 (17.2%)	59 (30.7%)	74 (38.5%)	