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Evaluation of Active Pulmonary Tuberculosis Among Patients With Diabetes

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Background: According to several studies, diabetes mellitus has been recognized as one of the main risk factors for pulmonary tuberculosis (PTB).

Objectives: The main purpose of this study was to determine the frequency of smear-positive pulmonary tuberculosis (TB) in patients with diabetes.

Materials and Methods: This cross-sectional study was conducted from April 2010 to December 2011 in Ali Asghar Diabetes Center of Zahedan, Iran. Standard chest radiography and sputum smear examination were performed on patients with diabetes who had signs and symptoms of tuberculosis. Cases of active TB were identified and referred to directly observed treatment, short-course (DOTS) centers. In addition, a purified protein derivative (PPD) skin test was done for all patients. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software with chi-square and fisher exact test in cross tabulation.

Results: Of the 400 patients with diabetes, 24 (6%) patients were suspected to have active PTB, yet laboratory paraclinical examinations revealed 4 cases of smear-positive pulmonary TB. The result of the PPD test was negative (induration of 0-4 mm) in 257 (64.25%) patients, intermediate positive (induration of 5-9 mm) in 118 (29.5%) and positive (induration of 10-14 mm) in 25 (6.25%) cases.

Conclusions: The results of this study indicate high frequency of smear-positive TB in patients with diabetes, compared with expected cases in the community and global population. Thus, screening of tuberculosis in patients with diabetes is recommended for the control and successful treatment of the two diseases.

Keywords: Diabetes Mellitus; Tuberculosis; Tuberculin Test

1. Background

Tuberculosis, after AIDS, is the second most common cause of death (1). Almost one-third of the world's population is infected with TB and is at high risk of developing the disease. Annually, over nine million new cases of TB, and almost two million deaths from TB, are estimated to occur around the world. In addition, most of these deaths ($\geq$ 90%) occur in developing countries (2). Nevertheless, in 2010, the incidence of TB was estimated as 2.15 million in Central Asia, which will be tripled by 2030 (3). Meanwhile, since the number of diabetes mellitus (DM) cases has reached 250 million worldwide and it is predicted to double within the next twenty years, TB control is faced with many problems and there is increased rate of TB in such populations (4, 5). A study indicated that the prevalence of diabetes may increase the risk of tuberculosis by approximately 2.5 times (6). Also, another study in Africa reported that the prevalence of diabetes in TB patients was two times greater than non-TB patients (5). This association with type II diabetes was again identified in the 1990s, (7) and diabetes mellitus was introduced as a risk factor for TB in the research literature (8-10). The contribution of diabetes to the burden of TB is not fully understood, but researchers believe that immune response suppression by diabetes mellitus may be influential and also diabetes effect on bactericidal activity of leukocytes may lead to activation of latent mycobacterial infections and disease progression (11). A meta-analysis in 2008 indicated that patients with diabetes are 3.11 times more prone to TB compared to the rest of the population (9). Due to the high incidence of TB in developing countries, the proportion of TB infection in patients with DM is higher in these countries. Swai from Tanzania showed that patients with type 1 DM were at 3-5 times higher risk of developing TB than patients with type II DM (12). There are various studies with different results about the role of TB in DM development. Some studies have demonstrated many cases of glucose intolerance in tuberculosis, (13), however, in various studies, the fraction of TB cases attributable to diabetes has been reported as 15% to 25% (7, 10). Thus, both TB and DM could be considered as a risk

Implication for health policy/practice/research/medical education:
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factor for each other especially in developing countries and this must be taken into consideration in clinical studies. Research has indicated different rates of TB prevalence in patients with diabetes in different countries; 18.4% in India (7) and 19.4% in Kuala Lumpur (14). Tuberculosis treatment in patients with diabetes is associated with higher rate of failure to treatment and thus higher mortality rate (15). Therefore, screening for tuberculosis in patients with diabetes and screening for diabetes in those with tuberculosis seems necessary. In addition, to prevent higher prevalence of patients with diabetes and TB in communities with high prevalence of diabetes, it is often recommended to detect of latent tuberculosis and an appropriate prophylactic treatment. Patients with proper blood sugar control are less likely to be infected with tuberculosis (16, 17).

2. Objectives

With regards to the high prevalence of TB in the Sistan and Baluchistan province (2), this study was carried out to determine the prevalence of smear-positive pulmonary TB in patients with diabetes using tuberculin skin test in the Diabetes Clinic of Zahedan, Iran, during 2010-2011.

3. Materials and Methods

After obtaining the ethics committee approval, this cross-sectional study was conducted at a university-affiliated clinic (Ali Asghar Diabetes Center of Zahedan, Iran), which was a referral for diabetes, from April 2010 to December 2011. An informed consent was obtained from the participating patients.

All patients with diabetes and an active medical record who received monthly follow-up visits and had provided an written informed consent were included in the study. A purified protein derivative (PPD) skin test was done for all patients. They were also examined for the following symptoms, coughing and sputum production for more than two weeks, fever, night sweats, and anorexia and weight loss. Patients who had not provided the consent form were excluded. At the beginning of the study, 400 patients with diabetes filled out a questionnaire containing their demographic and epidemiologic data, history of exposure to tuberculosis and clinical features, history of childhood immunizations and results of tuberculin skin test. A chest X-ray and sputum smear examination were conducted on the patients with diabetes who were suspicious for TB and who did not typically respond to antibiotic treatment. Patients with at least one positive sputum smear (and/or culture), which was also confirmed by the chest X-ray were considered as cases of pulmonary TB with positive sputum smear and were referred to the DOTS (directly observed treatment) centers for treatment. A tuberculin skin test was performed for diagnosis of latent TB infection. This was administered by injecting tuberculin (purified protein derivative: 5 U/0.1 mL per dose) intradermally into the anterior surface of the forearm, and was read 72 hours later. Individuals were considered to have a positive, false positive and negative test results when skin induration was 0-4 mm, 5-9 mm and 10-15 mm, respectively. Statistical analysis was performed using the SPSS software (version 17.0, SPSS Inc., USA). Data were analyzed by the chi-square and Fisher's exact test and $P < 0.05$ was considered significant.

4. Results

A total of 400 patients who had referred to the diabetes center were assessed for TB infection and smear positive pulmonary TB. Of the 400 cases with diabetes, 73 (18.2%) were male and 327 (81.8%) were female. The mean age was 50.96 ± 12.24 (range 7-90) years. Overall, 289 of the participants (72.2%) were uneducated and 305 cases (76.2%) were housewives. Notably, 6 cases (1.5%) reported favorable income, while 224 (56%) and 170 (42.5%) respectively reported low and moderate incomes. Of all the patients with diabetes, 148 (37.0%) had already received BCG vaccine while 175 (43.8%) had no history of vaccination. The remaining 77 (19.3%) patients reported an unknown history of vaccination (Table 1). Regarding type of diabetes, 336 individuals (84.8%) received oral hypoglycemic drugs and 60 (15.2%) were treated with insulin. Four patients had missing data. The results of PPD test was negative (induration of 0-4 mm) in 257 (64.25%) patients, positive (induration of 5-9 mm) in 118 (29.5%) and positive (induration of 10-14 mm) in 25 (6.25%) cases. Chest X-ray and sputum smear and culture test were done for 24 suspected cases who were symptomatic (coughs > 3 weeks, sputum, bloody sputum and fever). Finally, active PTB was confirmed in 4 patients (1 male and 3 females), who belonged to the age group of 45-60 years. Interestingly, these 4 patients had type II diabetes and were treated and controlled with diabetes medications. Statistical analyses showed a significant relationship between smear positive PTB in patients with diabetes and radiological results ($P = 0.001$), TB familial history ($P = 0.005$) and tuberculin test results ($P = 0.008$). However, no significant relationship was detected between sex and history of BCG vaccination. In all confirmed patients with TB, radiological changes showed infiltration in different segments of the chest X-ray. In addition, all cases were Iranian, married and uneducated individuals with low income.

5. Discussion

Our findings revealed that 4 (1%) of 400 patients with diabetes had smear positive PTB. In fact, incidence of PTB in patients with diabetes in the present study was estimated to be 1000 cases per 100000 individuals. There are a few studies on the prevalence of pulmonary tuberculosis in patients with diabetes in Iran. However, TB incidence in the general population is estimated to be 48.5 cases per 100000 individuals in the Sistan and Baluchistan province (2).

Table 1. Frequency Distribution of Patients With Diabetes Suspected of Having Pulmonary Tuberculosis [a]

Results Of Sputum Smear Test Variables	Positive	Negative	Total	P-value
Sex	-	-	-	0.864
Female	3 (75)	17 (85)	20 (83.3)	-
Male	1 (25)	3 (15)	4 (16.7)	-
Tuberculin test result	-	-	24 (100)	0.008[b]
Negative	0 (0)	11 (55)	11 (45.8)	-
Intermediate	1 (25)	9 (45)	10 (41.7)	-
Positive	3 (75)	0 (0)	3 (12.5)	-
History of BCG vaccination	-	-	24 (100)	0.594
Yes	1 (25)	6 (30)	7 (29.3)	-
No	3 (75)	6 (30)	9 (37.5)	-
Unknown	0 (0)	8 (40)	8 (33.3)	-
Familial history of TB	-	-	-	0.005
Yes	4 (100)	3 (15)	7 (29.2)	-
No	0 (0)	17 (85)	17 (70.8)	-
Chest radiologic result	-	-	-	0.001[c]
Positive	4 (100)	0 (100)	4 (16.7)	-
Negative	0 (0)	20 (100)	(83.3)	-

[a] Data are presented in No. (%)
[b] Chi-Square Test and Fisher Exact Test
[c] $P < 0.05$ significant

According to the present study, the rate of tuberculosis in patients with diabetes is significantly higher than the general population in various regions of Iran and also higher than the latest global statistics of 140 per 100000 individuals (4). Another study in Iran reported this rate as 682 in every 100000 individuals, which is higher than the general population in various regions of Iran and also the latest global statistics for PTB prevalence (18). In a study by Metanat et al. 14% of patients with diabetes who were admitted to an infectious diseases ward in Zahedan, had PTB (19). Another study in India showed that diabetes accounts for 14.8% of pulmonary tuberculosis and 20.2% of smear-positive TB; (7) while, another study reported this rate as 6.3% (20). There are many studies which have addressed both diabetes and PTB and introduced diabetes as a risk factor for development of active TB through promoting the progression of latent TB infection to active disease (18). A five-year retrospective study of TB patients in Semnan city of Iran reported this rate as 27% (21). In our study, symptoms of pulmonary TB patients with diabetes (in terms of radiological and clinical findings) were similar to those without diabetes, while another study in Semnan, showed a significant relationship between radiological results and smear positive PTB in patients with diabetes. Patients with diabetes presented atypical radiological presentation of pulmonary TB. In these patients, lower lung lesion and cavitations are found in all age groups (21). In our study, all patients with active TB had type II diabetes, while in a study in Tanzania TB was accompanied by type I diabetes (12). In Korea, a three-year longitudinal survey involving 800 000 civil servants showed that the risk ratio of TB in patients with diabetes versus controls (without diabetes) was 3.47 (95% CI 2.98–4.03). In a study on 4690 elderly patients with diabetes in Hong Kong, patients with haemoglobin A1c greater than 7% were at risk of active TB three times more than those with haemoglobin A1c of less than 7%. These data suggest that poor glycaemic control is a risk factor for tuberculosis. As the tuberculin test has the greatest availability and cost effectiveness in developing countries, it is still the most practical diagnostic test for latent tuberculosis infection even in patients with diabetes. Negative results of the tuberculin test in a quarter of these patients indicated that considering clinical signs of the disease has an important role in early diagnosis of patients. In our study, 29.5% (118 individuals) of patients with diabetes had border line PPD (5-9 mm) and 6.25% showed more than 10 mm of reaction, which was less than that of the study in Qazvin (12.3%) (18). In our study, cases with borderline skin test were more than that of the study by Asefzadeh (15.1%) (18), which can be due to the high incidence of TB in the province of Sistan and Baluchestan.

According to our study, neither the more common side effects of PPD test including self-limited necrosis, lymphadenitis, lymphangitis and infection at the injection site, nor the rare side effects such as anaphylaxis, urticaria and

angioedema were detected. Although in the present study, 64.25% of patients with diabetes showed negative reaction to PPD test, Assefzadeh reported this rate to be 72.7%. Furthermore, 38.2% of our cases had received the BCG vaccine. Although many studies have implied the concomitant of diabetes and PTB, they could not specify which one occurs prior to the other. In other words, they failed to determine whether diabetes causes PTB or vice versa. The mechanisms can be directly related to hyperglycaemia as well as indirect effects on macrophage and lymphocyte function, leading to diminished ability to contain the organism. It seems that diabetes might adversely affect T-cell production of interferon γ, and T-cell growth, function, and proliferation. On the other hand, impairment of glucose metabolism probably preceded tuberculosis in these patients. In conclusion, the results of this study indicate a high prevalence of smear-positive TB in patients with diabetes, compared with expected cases in the community and the global population. Thus, screening of tuberculosis in patients with diabetes is recommended for the control and successful treatment of the two diseases. Further cohort studies are warranted to investigate the prevalence of PTB among patients with and without diabetes. The design and conduct of a cohort study is also recommended to assess the prognosis of patients with tuberculosis.

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Authors' Contribution

Fatihe Kerman-saravi: concept, design, definition of intellectual content, technical and material support and sample collection. Maliheh Metanat: design, literature search, manuscript preparation, manuscript edition and material support; Batool Sharifi-mood: manuscript preparation, literature search and sample collection.

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