Article

Risk of latent tuberculosis infection among diabetic patients in Azadi Teaching Hospital, Duhok province: a case control study

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Abstract: Diabetes can be linked with impaired host immunity that subsequently increases the rate of various infections including tuberculosis (TB), particularly in developing countries where TB is endemic. The objectives of this case control study were to determine the prevalence and the risk of LTBI among diabetic patients. It is a prospective case control study conducted in Azadi Teaching Hospital from September 2017 until May 2018. The diabetic patients included in this study were randomly selected. The diagnosis of diabetes mellitus (DM) was made according to the American Diabetes Association (ADA). Diabetes mellitus patients and the control participants were offered a voluntary tuberculin skin test (TST). The TST ≥10 mm was considered positive. The results were analyzed by entering the data in SPSS (statistical package for the social sciences, version 16; SPSS Inc., Chicago, Illinois, USA). Two hundred DM patients and 208 control individuals participated in this study. Collectively, 28 patients had positive TST results. Based on the sputum smear microscopy and CXR, none of these patients showed active TB disease. The differences between the DM patients and the control group had no statistical significance apart from previous hospitalization. The prevalence of LTBI was 23.53% in the diabetic group, whereas, it was 9.62% in the control group. The frequency of LTBI in diabetic patients was significantly higher than the control group. When the diabetic group was compared with the control group in terms of diabetic control and the duration of diabetes disease, there was a statistically significant association of diabetes duration ≥ 10 years and TST positivity. In conclusion, the previous hospitalization was a significant risk factor for diabetic patients to acquire TB bacilli. Latent TB infection was more common in diabetics than non diabetics and there was an increased likelihood of having LTBI with the duration of diabetes ≥ 10 years. To avoid the threatening of TB control program, prophylactic treatment of LTBI in diabetic patients is paramount.

Keywords: diabetes mellitus; tuberculin skin test; latent tuberculosis infection

1. Introduction

Like fierce soldiers, diabetes mellitus (DM), which is a common chronic non-communicable disease, invades a large proportion of adults. Globally, it is estimated that the prevalence of diabetes has grown from 4.7% in 1980 to 8.5%, which represents 422 million people in 2014 (WHO, 2016). Diabetes can be linked with impaired host immunity that subsequently increases the rate of various infections including tuberculosis (TB), particularly in developing countries where TB is endemic (Martinez and Kornfeld, 2014). Although, the World Health organization (WHO) has adopted directly observed therapy (DOTS) since 1994 to control TB, its prevalence continues to increase globally, predominantly in low and middle income countries (WHO, 2009). Despite the lack of precise data on the prevalence of TB in Kurdistan, Iraq is a relatively high TB-burden country in the Eastern Mediterranean Region. It is estimated that Iraq has a TB incidence rate of 43/100,000 and a case

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detection rate of 54% (Merza *et al.,* 2016; Merza and Salih, 2012). *Mycobacterium tuberculosis*, the causative agent of TB can persist asymptomatic without tissue damage for years in a human causing latent TB infection (LTBI), which is also known as a state of dormancy (Parrish *et al.,* 1998). Up to 30 percent of the world's population has LTBI and the rate is higher among certain risk groups e.g. immunocompromized and diabetic patients (Kamper-Jorgensen *et al.,* 2015; Parrish *et al.,* 1998). There has been a clear association between DM and TB (Leung *et al.,* 2008). Patients with DM are approximately 3 times more likely to develop TB disease than those without DM. Worldwide, an estimated 15–25% of annual incident TB cases are attributable to DM (Jeon and Murray, 2008; Lonnroth *et al.,* 2014). There are limited studies describing the association between DM and LTBI. Although DM increases the risk of active TB, it is unclear whether the excess in the disease is due to primary progression to TB, risk of LTBI, reactivation of LTBI to active disease, or a combination of these mechanisms (Kuo *et al.,* 2013). Hence, the clarification about the relationship between DM and the risk of LTBI is critical for effective TB prevention and control. The objectives of this case control study were to determine the prevalence and the risk of LTBI among diabetic patients.

2. Patients and Methods
2.1. Setting
The Azadi Teaching hospital (ATH) in Duhok province is a tertiary care referral hospital to manage non communicable diseases such as DM. There is a specialized outpatient diabetes clinic on the ground floor for managing such cases and on the fourth floor, the internal medicine department is allocated to treat inpatients diabetic cases.

2.2. Study design and patients
It is a prospective case control study conducted from September 2017 until May 2018. This study was approved by the ethical committee of Kurdistan Board for Medical Specialties. A written informed consent was collected from the diabetic and control group participants. The diabetic patients included in this study were randomly selected. The diagnosis of DM was made according to the American Diabetes Association (ADA) (2017). The study inclusion criteria included: type 2 DM patients and an age $\geq$ 16 years. The exclusion criteria included: Age < 16 years, active TB, previous history of TB treatment, malignancy, chronic kidney disease, persons on immunosuppressive therapy including steroid, and other immunocompromized patients e.g. HIV. Clinico-demographic information was gathered by using a standardized template.

### 2.3. Screening of tuberculosis infection
Diabetes mellitus patients and the control participants were offered a voluntary tuberculin skin test (TST). The TST was made by intra-dermal injection of 5TU/0.1 ml of purified protein derivative (PPD) [manufactured by: BB-NCIPD Ltd. Sofia. Bulgaria] on the volar surface of the forearm. The skin reaction was read after 48 – 72 hrs. The TST $\geq$10 mm was considered positive (Huebner *et al.* 1993). Patients with positive TST were assessed by chest X-ray (CXR) and sputum smear microscopy for acid fast bacilli to exclude active TB disease.

2.4. Statistical analysis
The results were analyzed by entering the data in SPSS (statistical package for the social sciences, version 16; SPSS Inc., Chicago, Illinois, USA). A two-tailed p value < 0.05 was considered statistically significant.

3. Results
During these 9 months, 200 DM patients participated in this study. Figure 1 shows detailed screening of the patients. Collectively, 28 patients had positive TST results. Based on the sputum smear microscopy and CXR, none of these patients showed active TB disease.

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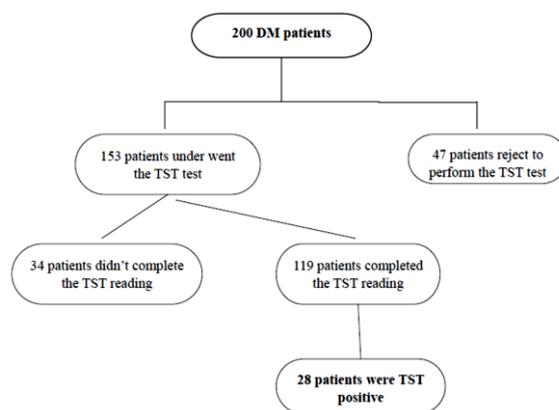
Figure 1. Tuberculin skin tests screening among diabetes patients.

The mean ages of the diabetic and control groups were 54.33±9.30 and 51.34±18.34 years old, respectively. The differences between the DM patients and the control group had no statistical significance apart from previous hospitalization (Table 1).

Table 1. Clinico-demographic profile of the diabetic and control groups.

Variable		Diabtetic patients no (%)	Control group no (%)	OR (95% CI)	P value
Age yr (mean±SD)		54.33±9.30	51.34±18.34	2.99 (-46.7034 to 52.6834)	0.9058
Sex	Male	35 (29.41)	68 (32.69)	1.166 (0.695 to 1.959)	0.621
	Female	84 (70.59)	140 (67.31)		
Smoker	Yes	24 (20.17)	62 (29.81)	0.595 (0.335 to 1.051)	0.068
	No	95 (79.83)	146 (70.19)		
Alcoholic	Yes	7 (5.88)	27 (12.98)	0.419 (0.160 to 1.052)	0.058
	No	112 (94.12)	181 (87.02)		
Previous hospitalization	Yes	74 (62.18)	68 (32.69)	3.386 (2.060 to 5.576)	0.000
	No	45 (37.82)	140 (67.31)		
Hx of BCG	Yes	98 (82.35)	168 (80.77)	1.111 (0.597 to 2.078)	0.770
	No	21 (17.65)	40 (19.23)		
Hx of TB contact	Yes	3 (2.52)	4 (1.92)	1.319 (0.230 to 7.113)	0.708
	No	116 (97.48)	204 (98.08)		

Hx = history; TB = tuberculosis

The prevalence of LTBI was 23.53% in the diabetic group, whereas, it was 9.62% in the control group. The frequency of LTBI in diabetic patients was significantly higher than the control group (Table 2).

Table 2. Results of tuberculin skin test in diabetic and control groups.

Tuberculin Skin Test (TST)	Diabtetic patients no (%)	Control group no (%)	OR (95% CI)	P value
Positive	28 (23.53)	20 (9.62)	2.892 (1.481 to 5.669)	0.001
Negative	91 (76.47)	188 (90.38)		

When the diabetic group was compared with the control group in terms of diabetic control and the duration of diabetes disease, there was a statistically significant association of diabetes duration ≥ 10 years and TST positivity (Table 3).

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Table 3. Comparison of diabetes control and duration of diabetes according to tuberculin skin test positivity.

	Variable	Positive	Negative	OR (95% CI)	P value
Diabetes control	Good (55, 46.22%)	10	45	1.761 (0.677 to 4.636)	0.279
	Poor (64, 53.78%)	18	46		
Duration of diabetes	<10 years (60, 50.42%)	9	51	2.692 (1.016 to 7.267)	0.032
	≥10 years (59, 49.58%)	19	40		

4. Discussion

Generally, the risk of LTBI can be influenced by DM especially with patients who have poor controlled diabetes. It is well known that patients with DM retain TB infection and disease more than the general populations (Kim *et al.,* 1995). To our knowledge, this is the first study in Iraqi Kurdistan to compare and assess the prevalence and certain risk factors between diabetic and non-diabetic patients.

In this study, considering the comparative variables between diabetic patients and the control group, a significant association was not found except for the previous hospitalization (p value = 0.000). The Center for Disease Control and Prevention (CDC) stated that people who reside in institutional settings e.g. hospitals are at high risk to develop LTBI (CDC, 2000). It is clear that patients with diabetes especially those who are poorly controlled are frequently visiting the hospital or demanding hospital admission, which exposes them more to TB bacilli.

A number of cohort studies documented an association between DM and TB with regards to variables such as smoking and alcohol consumption (Leung *et al.,* 2008; Pealing *et al.,* 2015); however, we did not find a significant association in this study. The main reason behind this might be related to the underreporting of smoking and alcohol drinking due to social stigma.

In this current study, the prevalence of LTBI in the diabetic group was significantly higher than the non diabetic group (OR, 2.892; 95% CI, 1.481 to 5.669; p = 0.001). The prevalence rate of LTBI in the diabetic was thrice as non diabetic patients. This was in accordance with studies reported by other researchers from different locations (Barron *et al.,* 2018; Hensel *et al.,* 2016; Lee *et al.,* 2017). A study on adults from the United States showed a statistically significant association and documented that the prevalence of LTBI among diabetes was more than twice the prevalence of those without DM (Barron *et al.,* 2018). Similarly, Hensel *et al.* conducted a cross sectional study during 2013 and 2014, which revealed refugees with DM or pre-DM from high TB burden countries were more likely to have LTBI (Hensel *et al.,* 2016). In a systematic review Lee and his colleagues concluded significant increased odds of LTBI among patients with diabetes compared to patients without diabetes (Lee *et al.,* 2017). On the contrary, other studies did not find a significant association with diabetes e.g. LTBI was not a significant risk in diabetic patients using the standard 10 mm PPD cut off value according to the Malaysian case control study (Swarna Nantha *et al.,* 2017). In our study, the high prevalence rate of LTBI in diabetic patients urges our health policy maker to encourage screening this vulnerable group, especially considering that Iraq is a highly endemic area for TB. It is also important to encourage prophylactic treatment of LTBI in diabetic patients. An important key message from the WHO to countries with a high burden of TB and DM is to recommend intergraded management of such conditions, because of their frequent coexistence (WHO, 2016).

In this study, we found a significant association between the duration of diabetes ≥ 10 years and LTBI (OR, 2.692; 95% CI, 1.016 to 7.267; p = 0.032). Likewise, a cross-sectional study from AL-Hilla Teaching Hospital in Babylon Province of Iraq (Khalil, 2011), and another case control study from Turkey (Tatar *et al.,* 2009) reported the clinical importance of the duration of DM and TB disease. The reason behind this can be related to patients who demand health care and hospitalization as they have a longer duration of diabetes. Inversely, a study based on 15 years of follow-up of the entire Danish population did not find association between the duration of DM and incidence of TB (Kamper-Jorgensen *et al.,* 2015).

In contrast to the AL-Hilla study from Iraq (Khalil, 2011), our study did not find association between poor diabetic control and LTBI. Several studies documented the association between poor glycemic control and LTBI (Niazi and Kalra, 2012; Cousins, 2017).

Although the precise explanation of this finding is unclear, it might be due to the random selection of patients. Hence, we recommend further studies with a larger sample size to follow this association in the best way.

The main limitations in this study were a small sample size and a single center study. Also, the misclassification bias might reduce the positive association of certain variables with DM e.g. smoking status, and alcohol

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consumption; because of the underreporting by the participants themselves in this study. Additionally, the loss of follow up of the TST in 34 patients was another limitation.

5. Conclusions

Previous hospitalization was a significant risk factor for diabetic patients to acquire TB bacilli. Latent TB infection was more common in diabetics than non diabetics and there was an increased likelihood of having LTBI with the duration of diabetes ≥ 10 years. To avoid the threatening of TB control program, prophylactic treatment of LTBI in diabetic patients is paramount.

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Conflict of interest

None to declare.

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