PREVALENCE OF LATENT MYCOBACTERIUM TUBERCULOSIS INFECTIONS AMONG DIABETIC PATIENTS ATTENDING SHILAN PRIVATE HOSPITAL, DUHOK CITY

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ABSTRACT

Background

One-third of the world's population is estimated to have latent tuberculosis infection. There is a well-documented association between diabetes mellitus and active tuberculosis, but evidence of the association between diabetes combined with other factors and latent tuberculosis infection remains limited and inconsistent.

Objectives

The study aimed at evaluating the association between diabetes linked to other risk factors with the latent tuberculosis infection.

Patients and Methods

In the present cross-sectional study, 385 diabetic patients were enrolled between the period of May 2016 and May 2017 at Shilan private hospital labs- Duhok city. Of these, 282 patients accepted to participate. The delayed-type hypersensitivity reaction to *Mycobacterium tuberculosis* was evaluated by the tuberculin skin test (TST). This test involved the intradermal injection of 5 tuberculin units per test dose of 0.1 mL of purified protein derivative (Mantoux). Out of the 282 patients, 205 patients completed the TST evaluation and 77 patients did not.

Results

Of the 205 diabetes mellitus patients completed the study, 33 (16.1%) patients showed latent tuberculosis infection, and 2 (0.9%) patients had active tuberculosis (TB) (one pulmonary TB and one TB lymphadenitis). As a result, 203 diabetic patients were included in this study. The majorities of the patients were older than 50 years (66.50%) and they were females (69.95%). Diabetic patients with latent tuberculosis infection were significantly associated with injectable or combination antidiabetic therapy, and also with smoking. No significant association with other variables was found.

Conclusion

The presence of diabetes mellitus did not significantly affect the rate of latent tuberculosis infection on its own. However, when diabetes mellitus was linked with injectable, combined antidiabetic, or smoking, the rate of latent tuberculosis infection has shown to be significantly increased.

Keywords: *LTBI; Diabetes mellitus; TST.*

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INTRODUCTION

Tuberculosis (TB) is regarded as a major global health problem. It is estimated that one-third of the world's population is infected with TB, and every year there are more than 9 million new cases of TB. The pathophysiology of tuberculosis is complex. Acquisition of the infection is primarily dependent on exogenous factors; however, reactivation of disease is largely under the influence of immune sufficiency [1].

The priority for TB elimination is early diagnosis and treatment of pulmonary TB, to reduce transmission. Subsequent steps include screening for clinically asymptomatic LTBI in high-risk populations. In addition to effective active TB control, the post-2015 WHO global TB strategy recognizes that elimination requires a focus on reducing the pool of latently infected individuals from which future TB cases would be generated. It is estimated that one-third of the world's population is latently infected with MTC. However, given the 10% progression rate, clinical and public health services must focus their energies primarily on groups at a higher risk of disease. These include recently infected persons, immunocompromised individuals such as HIV (human immunodeficiency virus) patients, anti-TNF and transplant candidates, and household contacts of pulmonary TB cases. Additionally, health-care workers and migrants from high-incidence countries to low-incidence settings may be tested and given preventive treatment [2]. Despite frequent studies about the link between diabetes mellitus (DM) and active tuberculosis, the effect of DM on the frequency of latent TB has been less investigated.

The few existing reports about a higher prevalence of latent TB infection among diabetics have been confounded by an absence of control groups [3,4]. Results of one study showed the reaction to purified protein derivate (PPD) is significantly correlated to the degree of hyperglycemia [5]. In other studies, the prevalence of TB infection was not affected by the presence of diabetes [6,7], or its effect was removed after adjusting for other variables [8]. Therefore, it appears that diabetic patients are not at greater risk for infection with *M. tuberculosis*. Cell-mediated immunity dysfunction such as in HIV infection is an increasing risk factor of TB development [9].To a lesser extent, impairment of immune function due to moderate-to-high dose steroid treatment is also associated with an increased TB risk [10]. Diabetes mellitus (DM) is a chronic disease that has been associated with impairment of the immune system function. Many studies have shown a significant association between DM and TB [11,12]. In a cohort study from East Asia, it has been found that DM was associated with a modest increase in the risk of active, culture-confirmed, and pulmonary TB with adjusted HRs of 1.8, 1.9, and 1.9, respectively [11]. A study conducted among the UK population published in 2010 found a two time to three-time increase in the risk of TB among diabetic patients [12].

In a meta-analysis of cohort studies conducted in 2008, it has been shown that DM was significantly associated with an increased risk of TB[13]. However, the findings of two of those studies were based on another strong cause of immunosuppression, since the patients included were kidney transplant recipients [14,15]. Another study that included South Korean civil servants also identified an increased risk of TB among people with DM [16]. Most of these case-control studies did not focus properly on other potential major confounders[13], that pay the attention to the validity of the findings that link between the risk of TB and DM. The worldwide increasing prevalence of DM in countries where TB is endemic has raised the wonder whether DM increases the risk of TB infection. It is important to further investigate the relation between DM and other cofounders with the risk of TB,

Aims

To estimate the association between DM and prevalence of latent TB in patients referred to the diabetes clinic in Duhok city.

PATIENTS AND METHODS

Setting

The Shilan Private Tertiary Hospital is a recognized private hospital in Duhok province. It has an additional attachment for the consultation clinic of out-patients' management. There are several outpatients clinic such as infectious diseases, diabetes, pediatrics … etc.

Study design and patients

It is a cross-sectional study conducted between May 2016 and May 2017. All diabetic patients who attended the outpatient diabetes clinic in our center and accepted to participate in this study were included. The patients who were referred to the laboratory were known to be diabetic as they were diagnosed by the specialist physician based on the American Diabetes Association (ADA) recommendations [17]. Patients' information

including demographic and clinical data was collected by using a standardized questionnaire. The inclusion criteria were: DM patients aged≥ 14 years and those who underwent Tuberculin Skin Test with its follow-up. Whereas, the exclusion criteria were: Age <14years, solid and hematological malignancies, chronic kidney disease, patients on immunosuppressive therapy, TB disease, previous history of TB treatment, human immunodeficiency virus (HIV) infection.

Tuberculin skin test (TST)

The delayed-type hypersensitivity reaction to *Mycobacterium tuberculosis* was evaluated by TST with the help of an infectious disease specialist. This test involved the intradermal injection of 5 tuberculin units (TU) per test dose of 0.1 mL of purified protein derivative (PPD) (Mantoux) [Manufactured by Sanofi Pasteur Limited, Toronto Ontario Canada "TUBERSOL®"] into the inner forearm with the palm up with the 1/2" to form a small round bleb wheal. The test result was read after 48 - 72 hours and it was considered positive when TST was ≥10 mm [18]. Patients with positive TST were referred to the infectious disease clinic in our center for further evaluation i.e. to exclude active TB disease.

Statistical analysis

The results were analyzed by entering the data in a Microsoft Excel Spreadsheet. A p-value of less than 0.05 was considered the level of statistical significance.

RESULTS

There were 385 diabetic patients between the period of May 2016 and May 2017. Of these, 282 patients accepted to participate in this study. Out of the 282 patients, 205 patients completed the TST evaluation and 77 patients did not. Of the 205 patients, 33(16.1%) patients showed LTBI, and 2(0.9%) patients had active TB (one pulmonary TB and one TB lymphadenitis). As a result, 203 diabetic patients were included in this study. The majorities of the patients were older than 50 years (66.50%) and they were females (69.95%). Table 1 shows the characteristics of this studied population.

Diabetic patients with LTBI were significantly associated with injectable or combination antidiabetic therapy, and also with smoking. I did not find a significant association with other variables, (Table 2).

Table 1. Characteristics of diabetic patients.

Variable		Number	Percent
Age	**14-50 years**	68	33.50
	>50 years	135	66.50
Sex	**Male**	61	30.05
	Female	142	69.95
Duration of diabetes	**<10 year**	101	49.75
	≥10 year	102	50.25
Type of antidiabetic	**Oral**	154	75.86
	Injectable	19	9.36
	Combination	30	14.78
Smoker	**Yes**	32	15.76
	No	171	84.24
Alcoholic	**Yes**	5	2.46
	No	198	97.54
History of BCG (Presence of scar on the left)	**Yes**	163	80.30
	No	40	19.70
History of TB contact	**Yes**	5	2.46
	No	198	97.54
TST result	**Positive**	37	18.23
	Negative	166	81.77

Table 2. Comparison between diabetic patients according to Tuberculin Skin Test positivity.

Variable		TST positive	TST negative	p-value
Age	**14-50**	14	54	0.566
	> 50	23	112	
Sex	**Male**	12	49	0.698
	Female	25	117	
Duration of diabetes	**<10 year**	19	82	0.827
	≥10 year	18	84	
Type of antidiabetic	**Oral**	33	121	0.036
	Injector combination	4	45	
Smoker	**Yes**	12	20	0.005
	No	25	146	
Alcoholic	**Yes**	1	4	1.000
	No	36	162	
Hx of BCG	**Yes**	33	130	0.172
	No	4	36	
Hx of TB contact	**Yes**	2	3	0.225
	No	35	163	

DISCUSSION

In the current study, DM on its own was not associated significantly with the increase of the risk of LTBI, since only 18.2% of the diabetic patients showed TST positive. However, when linked with other factors, it has been found that smoking in diabetic patients was significantly increasing the risk of LTBI since 37.5% of the smoker diabetic patients showed a positive TST. These findings are comparable with the results found by other researchers; they stated that the presence of DM alone does not justify the screening and treatment of LTBI. However, when combined with other risk factors, the presence of DM may be sufficient to justify screening, and treating LTBI [19-21]. In contrast, Lee *et al*, and Al-Rifai *et al*, in their meta-analyses based on data from different study designs from many populations stated that DM does not only increase the risk of progression to active TB disease but it also increases the risk of LTBI. This controversy could be attributed to the variation of the sample size of studied populations [22,23].

The way the researchers depend on the classification of diabetic patients when they rely on laboratory testing as the basis for the diagnosis of DM the higher rate for TB or LTBI is more probable than those that used self-reporting or medical records as diabetics. These speculations are supported by the observation reported by Leung et al when they found that patients with poor recent glycaemic control as evidenced by a hemoglobin HbA1c 7% had a significantly increased risk of TB [24].

Extensive studies are done to investigate the association between smoking and active TB, but reports on the smoking impact on LTBI are relatively few [25,26]. In the present study, smoking prevalence among diabetic patients was 15.8%, more likely to men and the majority of them were older-aged (66.5%), and it was significantly associated with LTBI (37.5%)($p<0.005$). These results are consistent with the data reported by others, Jia-Yih *et al* and David *et al* in their study identified smoking as an independent risk factor for LTBI, both in ex-smokers and current smokers [27,28].

Experimental studies have shown that the adverse effects of tobacco smoke in pulmonary immunity might contribute to the increased incidence of LTBI and the progression to active TB [29]. On the other hand, uncertainty could be raised with the results of these studies since some clinical studies speculate that the smoke effect on impairment of the immunity might

lower the sensitivity of TST and IGRA test and in turn lowering the positive rates of active TB and LTBI [30].

The other factor that has been associated significantly with LTBI rate in diabetic patients in the present study is injectable or combination (injectable and oral) antidiabetic therapy (8.1%) when compared with those taking the antidiabetic treatment orally, this finding is consistent with the data reported by Dobler CC *et al* when stated that the risk for developing TB is greater among those treated with (injectable) insulin for diabetes [20]. However, in the current study, as I did not have clear data on the duration of DM people with type I diabetes, the doses they take per day and the duration of taking the insulin and all were based on patient self-reporting, it remains unclear whether injectable insulin is an independent risk factor for LTBI. Furthermore, in this study, I did not find any other variable that modifies the effect of DM on the risk of LTBI like age and sex. Two published studies have demonstrated stronger associations of DM with TB among people aged less than 40 years compared with older people [31,32].

Another study did not show the same trend for age on DM patients diagnosed based on medical records [33]. Certain limitations in the present study have to be addressed. In the current study, the relatively low proportion of TST positive (20.2%) among the 163 BCG vaccinated studies individuals which were incomparable with some other studies is due to that in the current study only 10 mm and more indurations were taken into account as a standard for the LTBI inspection. The proportion of BCG-vaccinated people who have a positive tuberculin skin test (TST) has been reported to vary from 0% to 90%. These wide differences may depend on the dose, the manufacturer of the vaccine, age, and the interval between vaccination and testing.

Variation in the cutoff for positivity used during TST testing also explains some of the observed variations. Nevertheless, a positive reaction of >15 mm in someone who was vaccinated >15 years before is unlikely to be related to BCG vaccination and would likely reflect the presence of TB infection [2]. The 2006 National Institute for Health and Care Excellence (NICE) guidance also suggested using different TST cut-offs for children who had previously been vaccinated with BCG (15 mm induration) and those who had not been (6 mm induration). The rationale for this was that a prior BCG immunization might lead to false-positive results and impaired specificity of the TST. However, it was felt that the size of the induration would differentiate between BCG and TB infection—the larger the induration, the greater the probability that the response was due to TB infection [33]. Also in another in a survey study in Taiwan, the researchers suggest that a positive TST represents either active or latent TB infection rather than past BCG vaccination. Therefore, high BCG vaccination coverage in this region does not appear to limit the usefulness of the TST as a tool for diagnosing TB [34].

Also, the results of the current study are supported by the data reported by Menzies *et al*., 2000, in their study, they nicely demonstrate that in those who had received one vaccination early in life, a 10-mm cutoff was predictive of TB, also, the study suggests possibly using a cutoff greater than 10 mm for decisions about treatment of LTBI among individuals who have received more than one BCG vaccination [35]. In the present study, the patient self-reporting of smoking status might have been recognized as biased by a certain extent of social impact which may have underestimated the precise prevalence of smoking which in turn could affect risk estimates, and also uncertainty in reporting the potential of BCG vaccination, duration the DM been diagnosed and insulin therapy. One of the weaknesses of the current study is the use of a single test (TST) which could affect the limit of the significance of the results in the study. In future works, we recommend including the IGRA and the T- spot test rather than the comparison with the TST.

In conclusion**,** the presence of DM did not significantly affect the rate of LTBI on its own. However, when DM is linked with injectable, combined antidiabetics, or smoking, the rate of LTBI has shown to be significantly increased.

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Conflict of interests

The author declares that there was no competing interest in this study.

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