



PREVALENCE OF LATENT TUBERCULOSIS INFECTION (LTBI) IN PATIENTS WITH DIABETES MELLITUS

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ABSTRACT

Objectives: To determine the prevalence of Latent Tuberculosis Infection (LTBI) in diabetic patients.

Study Design: A descriptive cross - sectional study.

Settings: Pulmonology Department, Fauji Foundation Hospital Rawalpindi

Period: 06 months - 1st Jan 2021 to 1st July 2021.

Material & Methods: After approval by the Ethical Review Committee, Fauji Foundation Hospital Rawalpindi, a cross-sectional study was carried out. Non-probability consecutive sampling technique was used. After obtaining informed consent, around 100 Diabetic patients, both previously and newly diagnosed were enrolled in the study. The study participants were screened for Latent TB infection using chest radiography and the interferon-gamma release assay QuantiFERON-TB Gold In-Tube Test (QFT-GIT) and classified according to CDC (Center for Disease Control and Prevention) guidelines. Data regarding age, gender, HbA1c were also collected.

Results: Out of 100 diabetic patients (mean age: 55.77 ± 12.30 years), of whom majority (93%) were females; 45% of the cases presented with Latent Tuberculosis Infection (LTBI). Chi square test of independence revealed an association of duration of Diabetes Mellitus with Latent TB Infection i.e. 34 (40%) patients who had diabetes for more than 12 months had LTBI; compared to 11 (73.3%) of the patients with DM duration less than 12 months (p - value = 0.025).

Conclusion: A substantial number of LTBI cases were detected in the diabetic population via the QuantiFERON Gold TB test, highlighting the need to integrate TB infection management in diabetes care.

Keywords: Diabetic, Diabetes Mellitus, Latent Tuberculosis Infection, Prevalence, Tuberculosis

INTRODUCTION

Tuberculosis (TB) remains a well-known global health challenge, exacerbated by factors such as socioeconomic issues and lately, the COVID-19 pandemic. It is among the top 10 causes of death worldwide, surpassing even HIV/AIDS in mortality, caused by a single infectious entity *Mycobacterium tuberculosis*. Despite great efforts of the healthcare system globally to abolish TB, a

high global burden is reported. In 2023 alone, around 8.2 million people were newly diagnosed with tuberculosis as per the WHO report on Tuberculosis, surpassing the 7.5 million cases reported in 2022.^{1, 2} This places TB as the leading cause of death due to infectious diseases, even surpassing COVID -19. This is by far the highest number of cases recorded since the inception of WHO global TB monitoring in 1995.

Geographically, the WHO South-East Asia region accounted for 45% of TB cases in 2023; according to the WHO Global Tuberculosis Report 2023. This was by far the highest number of new TB cases of any WHO region. Here it is imperative to note that two – thirds of this global burden is shared by eight countries namely India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa.³ Pakistan is currently rated ‘D’, which means that the burden of disease and the mortality rate, both are very high.

The prevalence of Tuberculosis (TB) in Pakistan remains alarmingly high, positioning the country as one of the top five nations burdened by this disease globally.⁴ Recent estimates indicate a prevalence of approximately 340 cases per 100,000 population, with significant regional variations and challenges with respect to case detection and treatment.⁵ LTBI constitute hidden pools, feeding new cases. Approximately one-fourth of the world's population is estimated to have Latent TB Infection, presenting a substantial hurdle to TB eradication.⁶ The WHO defines Latent tuberculosis infection (LTBI) as a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active TB. It is characterized by the cellular immune reaction to the mycobacterial antigens, making it a subclinical mycobacterial infection. Following initial exposure to *Mycobacterium tuberculosis*, some individuals who fail to clear all the viable bacilli develop LTBI. In such cases the mycobacteria remain dormant without causing symptoms. The duration of latency is variable, and healthy individuals can harbor LTBI for a lifetime. The likelihood of Latent TB progressing to active form is around 5 to 15% over a lifetime, with even higher risks in immunocompromised individuals.⁷ In Pakistan, the estimated prevalence of Latent Tuberculosis Infection (LTBI) is high, with the rates ranging from 35% in children under five, to 48% in prison populations and up to 40% in healthcare workers. These figures are significant given the lifetime risk of developing active tuberculosis from LTBI.^{8, 9, 10} Diabetes mellitus (DM) is another major global health challenge and ranks among the top 10 causes of death worldwide.¹¹ It is one of the largest global health emergencies of the 21st century. Diabetes Mellitus is responsible for a significant proportion of premature deaths due to non-communicable diseases (NCDs); such as cardiovascular disease, cancer, and respiratory illnesses; and accounts for over 80% of all the premature NCD deaths. Approximately 536.6 million adults, or 10.5% of the global population aged 20-79, have diabetes, with the majority residing in low and middle-income countries. Projections indicate that by 2045, this number could rise to 783.2 million that is 12.2% adults worldwide.¹² Pakistan is projected to experience one of the highest increases in diabetes prevalence, with the number of affected individuals expected to grow from 7.5 million in 2017 to 16.1 million by 2045.¹³ An extremely significant challenge is that a large proportion of people with diabetes remain undiagnosed, a global estimate suggesting around 46 million undiagnosed cases in Pakistan alone, which hampers early intervention and management efforts.¹⁴ Several hypothesis have been proposed to explain the mechanism of hyperglycemia in the pathogenesis of LTBI. Poor glycemic control is associated with macrophage glycation and the defective sentinel hypothesis, in which monocytes fail to absorb *M. tuberculosis* due to reduced activation in alveolar macrophages.¹⁵ Another hypothesis suggests an association of antimicrobial peptide (AMP) gene expression with LTBI, active TB and Diabetes Mellitus.¹⁶

Numerous factors can exacerbate the progression of latent to active TB. The conditions associated with LTBI reactivation are categorized as high, moderate, slightly increased, low and very low risk, depending on their associated risk factors. The high-risk category comprises of patients with chronic renal failure requiring hemodialysis, transplant patients on immune suppressants and patients with silicosis, among others. Moderate risk category includes patients treated with tumor necrosis factor alpha (TNF- α) inhibitors (as for many autoimmune and inflammatory conditions) or glucocorticoids, those with diabetes (all types) and recently infected children under the age of four. Those who abuse alcohol, smoke cigarettes or are underweight or malnourished are at slightly increased risk for LTBI

reactivation. The incidence of TB is higher among these groups as compared to the general population. A commonality among the majority of these conditions leading to increased reactivation risk is suppressed immunity. Here, Diabetes is particularly important as it is observed that the countries with high TB prevalence also have an increasing number of diabetic individuals. Studies show that diabetic patients are more prone to develop TB as compared to individuals without diabetes i.e. around three times more likely.¹⁷ This correlation makes it, all the more, an issue of great concern both for clinical medicine and public health.

By far, no "gold standard" investigation has been developed for detecting Latent TB Infection, but diagnostic tools are helpful.¹⁸ These include the Tuberculin Skin Test (TST) and Interferon Gamma Release Assays (IGRAs including the Quantiferon Gold TB test and T-spot TB test).¹⁹ Since, detection of the actual pathogen is not possible, LTBI is detected by measuring immune responses to *M. tuberculosis* antigens. The TST evaluates cell-mediated immunity and consists of the intradermal injection of a small amount of purified protein derivative from the *M. tuberculosis* bacteria. The test requires two patient visits with a 48–72 hour interval between the administration and reading of the test. It is open to considerable variation in the interpretation of results. On the other hand, IGRA is a whole blood based in- vitro assay that measures the production of interferon-gamma by immune cells in response to *M. tuberculosis* antigen stimulation. The test does not require that the patient return to the lab and can be completed in 24 hours, but it does require greater laboratory infrastructure and technical capacity, which means it is more expensive.

Keeping the pathophysiology of Latent TB in mind, immunological tests are employed not only for diagnosis of the disease but also to monitor the response to drug therapy. Until recently, TST was used for the detection of Latent TB Infection, with a 77% sensitivity and 97% specificity. The specificity further falls to 59%, in the populations previously vaccinated for BCG.²⁰ Presently, the Quantiferon Gold Test has been favored for its higher sensitivity (60 – 90%) and specificity (> 90%), particularly in BCG-vaccinated populations, as it is an in vitro assay of CD4+ T cell-mediated interferon gamma release in response to stimulation by specific *M. tuberculosis* antigens.

This study aims to utilize the Quantiferon Gold TB test to assess LTBI prevalence in a diabetic population, providing better insights into the TB burden among Diabetic patients. Given the limited data on routine LTBI screening for DM patients and the lack of consensus on prophylactic treatment, this study underscores the need to integrate TB infection management into diabetes care to enhance public health outcomes.

METHODOLOGY

The research was conducted after approval by the institutional review board (IRB), Fauji Foundation Hospital, (ERC number 807/RC/FFH/RWP). A descriptive cross-sectional study was carried out at Pulmonology Department, FFH Rawalpindi over 6 months i.e. 1st Jan 2021 to 1st July 2021. The sample size of approximately 100 cases was calculated employing WHO sample size calculator, using an anticipated population proportion of 43.4%, with a 95% confidence interval, and an absolute precision of 10%.²¹ Non-probability consecutive sampling was used. The inclusion criteria entailed age of 20-80 years, both genders (male, female) and Type 2 diabetic patients. All the patients who had Active TB; past history of TB infection or treatment (successful or failure); radiological features of old or healed tuberculosis such as calcified nodules, non-calcified nodules, pleural thickening, bronchiectasis with volume loss and fibro - nodular scarring; chronic pulmonary disease; chronic hepatic or renal disease; pregnancy; HIV infection; any type of malignancy and undergoing chemotherapy; immune system disease, receiving corticosteroid or immunosuppressive therapy - were excluded from the study.²² Diabetic patients, both previously and newly diagnosed, presenting at the diabetic clinic of Fauji Foundation Hospital were enrolled in the study after informed consent was obtained.

Operational definitions: Latent TB Infection is considered if Quantiferon Gold Test (QFT) is positive and the chest radiograph is negative for active features of tuberculosis (such as consolidation,

cavity, military infiltrates, hilar, para - tracheal, mediastinal lymph node enlargement, atelectasis and pleural effusion).

The result of the QFT is calculated by measuring the IFN- γ levels in the tubes containing TB antigens {tuberculosis-specific antigens (TB1, TB2)}, minus the IFN- γ levels in the negative control tube (containing heparin alone).

Results are classified as positive, negative, and indeterminate.

- Positive result = Level of TB antigen minus Nil ≥ 0.35 IU/mL and $\geq 25\%$ of the Nil tube
- Indeterminate result = Level of mitogen minus Nil < 0.5 IU/ml or the Nil > 8 IU/ml
- Negative result = TB antigen < 0.35 IU/ml and mitogen control ≥ 0.5 IU/ml

For Diabetes, diagnostic criteria according to American Diabetes Association (ADA) was employed, i.e.

- Fasting plasma glucose (FPG) level ≥ 126 mg/dL (7.0 mmol/L) OR
- Random plasma glucose (RPG) level ≥ 200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia OR
- HbA1C $\geq 6.5\%$ (48 mmol/mol)

Data Collection Procedure: Diabetic patients (both previously diagnosed and newly diagnosed) presenting in diabetic clinic at Fauji Foundation hospital were enrolled in the study. Patients underwent detailed clinical evaluation and blood sugar checks, for induction of cases. All patients were screened for latent TB infection using chest radiography and the Quantiferon-TB Gold In-Tube Test (QFT-GIT), as per CDC guidelines.

In Quantiferon-TB Gold In-Tube Test (QFT-GIT); for each case, four heparinized blood collection tubes are used. The first tube contains heparin alone (Nil tube, negative control), the second tube contains the T cell mitogen (mitogen tube, positive control), and the third and fourth tube contain tuberculosis-specific antigens (TB antigens tube TB1, TB2). One-milliliter aliquots of blood are drawn directly into each tube and incubated at 37 °C for 24 hours, and then centrifuged and stored at 4 °C. The result of the IFN- γ assay i.e. TB response (TB antigen minus nil) is determined by measuring the IFN- γ in the TB antigen minus that in the negative control tube. When the level of TB antigen (TB1 or TB2)-Nil is ≥ 0.35 IU/mL and $\geq 25\%$ of the Nil tube, result is considered as positive. If the mitogen-Nil is 8 IU/ml, result is considered as indeterminate. If the TB antigen is < 0.35 IU/ml and mitogen control is ≥ 0.5 IU/ml, the test is considered as negative. For negative, positive, and indeterminate results, the probability of Mycobacterium tuberculosis infection is not likely, likely, and uncertain, respectively.

All chest radiographs were reviewed and reported by a qualified radiologist, blinded to the Quantiferon-TB Gold In Tube test results. Data on age, gender, fasting blood glucose levels, random plasma glucose levels, duration of DM, HbA1c results and Quantiferon-TB Gold test results were collected on a designated proforma.

Data Analysis Plan: SPSS version 19.0 was used for data entry and analysis. For qualitative data as the gender of patients, LTBI, new and previously diagnosed diabetic patients, frequencies and percentages were calculated. As for quantitative data such as age, Fasting Plasma Glucose (FPG), Random Plasma Glucose (RPG) and HbA1c, means and standard deviations were calculated. Effect modifiers like age, gender, and duration of diabetes mellitus were stratified. Chi-square test of independence was employed for post-stratification analysis with a p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Descriptive Statistics: Out of the 100 patients included in the study, 93% were females. The mean age of the patients was 55.77 ± 12.30 years, with a range from 20 to 80 years. A majority (85%) of the patients were previously diagnosed diabetics. The descriptive statistics of Fasting Plasma Glucose (FPG), Random Plasma Glucose (RPG) and HbA1c were 175.04 ± 55.80 , 17.44 ± 4.96 and 9.52 ± 2.24 respectively. (Table 1)

The objective of the study was to determine the frequency of Latent Tuberculosis Infection in Diabetic patients. Latent TB Infection was detected in 45% of diabetic patients. Effect Modifiers such as age, gender, and duration of diabetes mellitus were stratified and compared with frequency of LTBI in diabetic patients. The results of chi - square test of independence yielded that 35 (77.8%) of the 51-80 years old patients had LTBI in comparison to 10 (22.2%) of the patients aged 20-50 years who tested positive for LTBI ($p = 0.321$). Of the male patients, 5 (11.1%) had LTBI; whereas 40 (88.9%) female patients had LTBI ($p = 0.144$). For the patients who had diabetes for more than 12 months (i.e. previously diagnosed), 34 (40.0%) had LTBI; whereas Latent TB was positive in 11 (73.3%) of the patients with DM duration less than 12 months (i.e. newly diagnosed) ($p = 0.025$). (Table 2)

Table 1: Descriptive statistics of patients

Sr. No.	Variables		n	Mean $\pm$ Standard Deviation
1	Age		100	55.77 $\pm$ 12.30
2	Gender	Male	7 (7%)	
		Female	93 (93%)	
3	Fasting Plasma Glucose (mg/dl)		100	175.04 $\pm$ 55.80
4	Random Plasma Glucose (mmol/L)		100	17.44 $\pm$ 4.96
5	HbA1c		100	9.52 $\pm$ 2.24
6	Diabetic Patients	Newly diagnosed (<12 months)	15 (15%)	
		Previously diagnosed (>12 months)	85 (85%)	
7	Latent TB Infection	Positive	45 (45%)	
		Negative	55 (55%)	

Table 2: Post Stratification Chi Square Test Analysis for assessing the impact of effect modifiers on Latent TB infection

Sr. No.	Effect Modifiers		Latent TB Infection		Total	p-value*
			Positive	Negative		
1	Age in years	20-50	10 (22.2%)	8 (14.5%)	18 (18%)	0.321
		51-80	35 (77.8%)	47 (85.5%)	82 (82%)	
2	Gender	Male	5 (11.1%)	2 (3.6%)	7 (7%)	0.144
		Female	40 (88.9%)	53 (96.4%)	93 (93%)	
3	Duration of DM	>12 months	34 (40.0%)	51 (60.0%)	85 (85%)	*0.025
		$\leq$ 12 months	11 (73.3%)	4 (26.6%)	15 (15%)	
		Total	45	55	100	

* p – value of ≤ 0.05 is considered statically significant.

DISCUSSION

The rise of diabetes mellitus (DM) has significantly impacted developing nations where tuberculosis (TB) remains prevalent.²³ According to the World Health Organization (WHO), six out of the ten countries expected to bear the highest DM burdens by 2035—China, India, Brazil, Indonesia, Pakistan, and Russia—also face high TB prevalence. This overlap between Diabetes and Tuberculosis has profound implications on public health, as individuals with DM are around two to four times more

likely to develop active TB compared to those without Diabetes. Globally, it is estimated that DM accounts for around 30% of new TB cases each year.^{24, 25} Though there is a well-established association between DM and active Tuberculosis, there is a scarcity of data reflecting the linkage between pre Diabetes, Diabetes, and latent TB.²⁶

In our study, we found that 45.0% of diabetic patients had LTBI; a prevalence rate similar to the 43.4% reported by a study conducted at Emory University's School of Medicine.²¹ The mean age of our participants was 55.77 ± 12.30 , with a majority (93%) being females. This demographic distribution differs from the WHO report, which recorded an average age of 46 ± 37 years and a more balanced gender distribution – 45.1% males and 54.2% females.

A study conducted in the USA depicted a 5.9% (95%CI, 4.9-7.0%) prevalence of LTBI and the odds of latent TB were higher among individuals with diabetes (OR 1.15, 95% CI 0.90-1.47) compared to those who did not have diabetes, after adjusting for factors such as history of active TB, sex, age, smoking status.²⁷ Also, the odds of latent TB in adults with pre-diabetes were similar to those without diabetes (OR 1.15, 95% CI 0.90-1.47). This suggests a prominent linkage between diabetes and LTBI. Numerous studies have highlighted a high prevalence of Latent TB among Diabetics. A study conducted in 2014 in Atlanta USA, among refugees showed that the prevalence of Latent TB was higher among patients with DM (43.4%) and pre-DM (39.1%) compared to those without DM (25.9%) ($p < 0.01$). The patients were also screened for DM using HbA_{1c}, and for LTBI using the QFT test. Among 702 patients, 54 (7.8%) had DM and 235 (33.8%) had pre-DM. LTBI was prevalent in 31.3% of the refugees. In our study, LTBI was prevalent in 45% of the diabetic patients.

Another study conducted in Brazil in 2022, established the link between Diabetes and Latent TB. In this study, healthy controls were employed i.e. non-DM volunteers. All participants (553 in total) were screened for DM and for LTBI employing HbA_{1c} and QFT-GIT tests respectively. Among the study participants, QFT-GIT tested positive in 88 (15.9%) of the individuals, of whom 18 (20.5%) were non-diabetics, 30 (34.1%) had Type 1 Diabetes and 40 (45.4%) had Type 2 Diabetes.²⁸ In our study, we only recruited diabetic individuals – a limitation.

These findings elucidate that latent tuberculosis infection is more common in people with diabetes than non-diabetics. The presence of DM may weaken the immune defenses necessary to prevent Mycobacterium tuberculosis infection, underscoring the importance of comprehensive management strategies for DM and LTBI. Therefore, the treatment of latent TB infection in diabetics will be a step forward towards control of Tuberculosis.

There are certain limitations to our study as well, such as limited time frame and small sample size. A larger sample size would make the findings more generalizable. Another limitation is the recruitment of diabetic patients only. In certain studies, both diabetic and non-diabetic controls have been recruited. In this study, the association of diabetes alone with LTBI has been taken into account. Further studies can explore other factors affecting immunity of the patient such as nutrition, serum vitamin D levels and serum iron levels; smoking and presence of other co - morbidities. A further limitation is the type of study as ours was a cross sectional study. In order to ascertain causality, a prevalence study may be undertaken in future.

The World Health Organization's "end TB strategy" aims to lower the incidence of tuberculosis by 90% and TB deaths by 95% by 2035. In order to achieve these targets, a multipronged strategy is required; on one hand to detect and treat active TB cases and on the other to reduce the reservoir of latent TB cases.

CONCLUSIONS

In summary, this study identified a significant number of LTBI cases in the diabetic population using the Quantiferon Gold TB test i.e. 45%. Furthermore, the results of our study indicate that individuals with the shorter duration of diabetes (<12 months) are more prone to develop Latent TB infection compared to those with the longer duration (>12 months). Prompt implementation of LTBI screening programs and preventive treatment is the key to reduce the risk of TB disease and transmission in Pakistan.

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