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Research Article

PREVALENCE OF LATENT TUBERCULOSIS IN DIABETIC AND NON-DIABETIC INDIVIDUALS IN A TERTIARY CARE CENTER: A COMPARATIVE STUDY

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ABSTRACT

Objectives: The aims of this study were as follows: (1) To study the prevalence of latent tuberculosis (TB) in diabetic and non-diabetic population attending the tertiary care hospital. (2) To investigate the association between diabetes mellitus (DM) and latent TB, evaluating the prevalence of positive tuberculin tests and assessing glycemic parameters in diabetic patients with latent TB.

Methods: This was a single-center, hospital-based, observational, and comparative study conducted in the department of general medicine of a tertiary care medical college. One hundred and thirty-six diabetic patients of either gender or 137 healthy individuals acting as control group were included in this study on the basis of a predefined inclusion and exclusion criteria. Patients were evaluated by detailed history and clinical examination. The diagnosis of latent TB was based on a positive tuberculin test without any clinical features of active TB. The prevalence of latent TB infection was compared in both the groups. $p<0.05$ was taken as statistically significant.

Results: Patients in both the groups were found to be comparable in terms of gender distribution and mean age. Predominant patients were found to have type 2 DM. The mean duration of DM was noted to be 91.58±60.68 months. The most common diagnoses of patients in non-diabetes group were COVID-19 (9.49%), neurological diseases (8.76%), infections (7.3%), acute myocardial infarction (6.57%), and iron deficiency anemia (5.84%). About 21.32% of cases in DM group were noted to have latent TB, while the proportion of latent TB was noted to be 7.30% in the non-diabetes group. The mean fasting blood sugar, mean post-prandial blood sugar, as well as mean HbA1c were significantly higher ($p<0.05$) in the subgroup with latent TB versus the subgroup without latent TB.

Conclusion: Individuals with diabetes mellitus were found to have increased risk of latent TB infection. In addition, male gender and elevated glycemic parameters were found to be key factors associated with latent tuberculous infection in diabetes.

Keywords: Diabetes mellitus, Latent tuberculous infection, HbA1c, Tuberculin test.

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INTRODUCTION

Tuberculosis (TB) and diabetes mellitus (DM) represent two formidable global health challenges, each with a significant impact on public health. While the association between active TB and diabetes has been extensively explored, the intersection of latent tuberculosis infection (LTBI) and DM remains a relatively uncharted territory [1]. This paper aims to address this critical gap in our understanding by examining the mechanisms through which individuals with diabetes become more susceptible to the development of LTBI. The coexistence of TB and diabetes poses a dual burden on health-care systems worldwide. The World Health Organization (WHO) estimates that over 10 million people develop active TB each year, and diabetes affects approximately 463 million individuals globally [2]. Despite advances in TB control programs, the incidence of TB remains high, especially in regions where diabetes prevalence is on the rise. Compounding this challenge is the complex interplay between TB and diabetes, leading to increased morbidity and mortality. Recent epidemiological studies have suggested an alarming connection between DM and LTBI, indicating that individuals with diabetes may be more prone to harboring latent TB bacilli [3]. While the link between diabetes and active TB has been extensively studied, the mechanisms underlying the increased susceptibility to LTBI in diabetic individuals remain poorly understood [4].

TB is the leading infectious disease killer in the World and one of the top 10 causes of death worldwide. TB is a disease caused by *Mycobacterium tuberculosis*. It can be an active disease with features of fever with cough and expectoration or latent form in which infection remains in dormant form [5]. The increasing emergence of DM has considerably affected developing countries where TB is endemic. Six of the ten countries projected to have the greatest DM burdens by the year 2035 – China, India, Brazil, Indonesia, Pakistan, and Russia – are classified as high TB burden countries by the WHO [6]. The intersection of DM and TB has substantial public health implications: patients with DM are approximately 3 times more likely to develop active TB than those without DM, and globally, an estimated 15–25% of annual incident TB cases are attributable to DM. The growing evidence of the harmful confluence between DM and TB demonstrates an urgent need to better understand this aspect [7].

While the association between DM and risk of active TB has been well documented, data describing the relationship between pre-DM, DM, and latent tuberculous infection (LTBI) are scarce [8]. LTBI is defined as asymptomatic infection with *M. tuberculosis* in which the bacteria are contained by the host's immune system. Approximately one-third of the world's population has LTBI, and this large reservoir of *M. tuberculosis* is a significant impediment to TB eradication. The lifetime risk of LTBI progressing to active TB is estimated at 10%, with an increased risk among those with immunosuppressive conditions. Although DM increases the risk of active TB disease, it is unclear if the excess disease is due to primary progression to active TB disease, risk of LTBI, reactivation of LTBI to active TB disease, or a combination of these mechanisms [9]. *In vivo* and *in vitro* studies have suggested that DM may affect vulnerability to *M. tuberculosis* infection due to its

effects on innate and adaptive immunity. However, whether the initial immune response to TB exposure and subsequent development of LTBI differs in patients with DM compared to those without DM is unclear. Clarification about the relationship between DM and risk of LTBI is critical for effective disease control and prevention [10].

The purpose of the present study was to examine whether patients with DM were at increased risk of having LTBI.

METHODS

This was a single-center, hospital-based, observational, and comparative study conducted in the Department of General Medicine of a Tertiary Care Medical College. The Institutional Ethical Committee approved the study and informed consent was obtained from all the participants. Diabetic patients of either gender, presenting to the General Medicine outpatient department (OPD), or inpatient department were included in this study on the basis of a predefined inclusion and exclusion criteria. Similarly, a control group of non-diabetic patients were chosen from the general OPD register. The sample size was calculated by formula $n = Z^2 P (1-P)/d^2$ using OPENEPI software version 3 on the basis of pilot studies done on the topic of diabetes patients assuming 90% power and 95% confidence interval (CI), the sample size required was 250 patients. Based on central limit theorem, sample size was determined to be enough if it was more than 250; thus, we included 273 patients in our study. Patients were divided into two groups as following-

- Diabetes group: 136 diabetic patients of either gender
- Non-diabetes group: 137 non-diabetic healthy individuals of either gender.

Demographic details of all the patients were recorded, a detailed history was taken, and a complete systemic examination was done in all the cases. Any relevant past or family history of TB was asked for and noted down. Any history of Koch contact was also enquired and noted. A case pro forma form was used for data collection. Patients were evaluated by detailed history and clinical examination. The diagnosis of latent TB was based on a positive tuberculin test without any clinical features of active TB. Tuberculin test was done by injecting a 0.1 mL of liquid containing 5 TU (tuberculin units) purified protein derivative into the top layers of skin of the forearm. They were called after 48–72 h for the reading. The induration was read, and induration more than 10 mm was taken as positive. At this stage, the person was again evaluated for the active TB. Those not having the active TB were included in the research.

Statistical analysis was done using SPSS version 21.0 software. Quantitative data will be presented as mean and standard deviation. Qualitative data will be presented with incidence and percentage tables. For quantitative data, unpaired t-test will be applied and for qualitative data, Chi-square test was used. $p<0.05$ will be taken as statistically significant.

Inclusion criteria

The following criteria were included in the study:

1. Adult male or female patients
2. Patients above age of 18 years
3. Patients diagnosed with DM (Group D)
4. Patients ready to sign the informed consent document.

Exclusion criteria

The following criteria were excluded from the study:

1. Those who refused consent to be part of study
2. Age of the patients below 18 years
3. Active TB patients
4. Previously diagnosed TB cases
5. Patient not willing to come after 2 day for tuberculin reading
6. All cases having immunosuppression such as leukemia, lymphoma patient on long-term steroids, and HIV-diagnosed patient.

RESULTS

A total of 273 patients were enrolled in the study, 136 in the diabetes group and 137 in the non-diabetes group. The mean age as well as the gender distribution were noted to be statistically comparable ($p>0.05$). The age range was noted to be between 19–90 years in diabetes group and 22–85 years in non-diabetes group (Table 1).

Two of the enrolled cases in the DM group suffered from type 1 DM, while remaining 134 cases suffered from type 2 DM (Figure 1).

The mean fasting blood sugar (FBS) was 163.34±48.15 mg/dL, ranging from 84 mg/dl to 413 mg/dL. The mean post-prandial blood sugar (PPBS) was 238.80±62.77 mg/dL, ranging from 174 mg/dl to 560 mg/dL. The mean HbA1c was noted to be 8.00±0.94 g%, ranging from 6.9 g% to 10 g%. The mean duration of DM was noted to be 91.58±60.68 months, with range of duration being between 1 month and 360 months (30 years) (Table 2).

The most common diagnoses of patients in non-diabetes group were COVID-19 (9.49%), neurological diseases (8.76%), infections (7.3%), acute myocardial infarction (6.57%), and iron deficiency anemia (5.84%) (Table 3).

About 21.32% of cases in DM group were noted to have latent TB, while the proportion of latent TB was noted to be 7.30% in the non-diabetes group. (Table 4).

The odds ratio (OR) of developing latent TB in the diabetes group was 3.44 in comparison to the non-diabetes group (CI: 1.6–7.38, $p=0.001$ considered significant). The mean age was statistically comparable between the subgroups with and without latent TB ($p>0.05$). Number

Table 1: Demographic details in study groups

Parameter assessed	Diabetes group (n=136)	Non-diabetes group (n=137)	p-value
Mean age (years)	51.93±14.24	49.28±15.11	0.21 Not significant
Median age (years)	50	49	-
Minimum age (years)	19	22	-
Maximum age (years)	90	85	-
Number of males	87 (63.97%)	78 (56.93%)	0.28
Number of females	49 (36.03%)	59 (43.07%)	Not significant

Table 2: Glycemic parameters in the diabetes study group

Parameter assessed	Fasting blood sugar (mg/dL)	Post-prandial blood sugar (mg/dL)	HbA1c (g%)
Mean value (±SD)	163.34±48.15	238.80±62.77	8.00±0.94
Median value	160	220.50	7.80
Minimum value	84	174	6.90
Maximum value	413	560	10.00

SD: Standard deviation

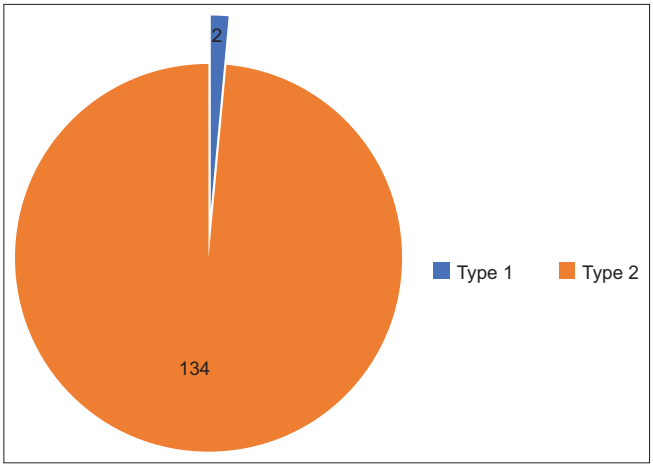

Fig. 1: Type 1 versus type 2 diabetes mellitus

of males in group with latent TB was significantly higher ($p<0.05$) than the number of males in the subgroup without latent TB (Table 5).

The mean FBS, mean PPBS, as well as mean HbA1c were significantly higher ($p<0.05$) in the subgroup with latent TB versus the subgroup without latent TB. Mean duration of diabetes was found to be comparable in patients with latent TB and no latent TB (Table 6).

DISCUSSION

We undertook this study to investigate the prevalence of LTBI in individuals with DM compared to those without diabetes. The OR for developing LTBI in the diabetes group was found to be 3.44 times higher than in the non-diabetes group, indicating a significant association (CI: 1.6–7.38, p=0.001). The prevalence of LTBI varied across different studies with Salindri *et al*. [11] observing 9.2%, and Cohen *et al*. [12] reporting 11.4%.

The factors associated with LTBI in the DM group were explored. While the mean age was comparable between subgroups with and without LTBI, the number of males was significantly higher in the latent TB group, suggesting male gender as a potential influencing factor for LTBI in DM cases. In addition, the mean levels of FBS, PPBS, and HbA1c were significantly higher in the subgroup with LTBI, indicating that uncontrolled DM cases with poor glycemic control were at a higher risk. In comparison to other studies, the findings were consistent with Hensel *et al*. [13] where median HbA1c was higher in patients with LTBI, and the odds of LTBI in those with DM were significantly greater. Lin *et al*. reported an increase in LTBI with age, and the presence of a BCG scar had a protective effect, contrary to the current study. Ping *et al*. [14] found no significant difference in mean ages between patients with and without LTBI, and no significant associations with duration of T2DM, smoking, HbA1c, BCG vaccination, or treatments.

We also explored the link between hyperglycemia and LTBI. Poor glycemic control was associated with macrophage glycation and the defective sentinel hypothesis, suggesting that monocytes in individuals with uncontrolled DM fail to absorb *M. tuberculosis* due to reduced activation in alveolar macrophages. CD271 glycation in mesenchymal stem cells was proposed as a mechanism that may provide a niche for *M. tuberculosis* in LTBI [15]. The differential expression of antimicrobial peptides, such as human β-defensin-2, in patients with DM was suggested to contribute to the increased risk of LTBI and active TB. Furthermore, our study explored the potential role of DM medication in LTBI occurrence. Magee *et al*. found that participants with diabetes not using any diabetes medication had significantly greater odds of tuberculin skin text positivity compared to those using metformin plus two or more other diabetes medications [16]. Similar findings were reported by Sutter A where

Table 3: Diagnoses of enrolled cases in the non-diabetes group

Diagnoses	Number of cases	% cases
COVID-19	13	9.49
Neurological diseases	12	8.76
Infection (dengue/giardiasis /mucor/pneumonia)	10	7.30
Acute myocardial infarction	9	6.57
Iron deficiency anemia	8	5.84
Accelerated/portal hypertension	7	5.11
Acute gastroenteritis	7	5.11
Stroke	7	5.11
Liver disease	5	3.65
Fever/febrile seizures	5	3.65
Chronic kidney disease	5	3.65
Snake bite	4	2.92
Megaloblastic anemia	4	2.92
Urinary tract infection/urine retention	4	2.92
Dilated cardiomyopathy	3	2.19
Rheumatic heart disease	3	2.19
Cataract	3	2.19
Migraine	3	2.19
COPD/asthma	3	2.19
Atrial fibrillation	2	1.46
Malignancies	2	1.46
Pleural effusion	2	1.46
Vascular disorder (embolism/DVT)	2	1.46
Poisoning	2	1.46
Acute pyelonephritis	1	0.73
Acute renal failure	1	0.73
Others (Chest pain, hemorrhoids, hyperkalemia, myopathy, pelvic inflammatory disease, arthralgia, peptic ulcer, cardiogenic shock, and thalassemia)	10	7.30

COPD: Chronic obstructive pulmonary disease, DVT: Deep vein thrombosis

Table 4: Prevalence of latent tuberculosis in the study groups

Status of latent TB	Diabetes group (n=136)	Non-diabetes group (n=137)
Present	29 (21.32%)	10 (7.30%)
Absent	107 (78.68%)	127 (92.70%)
p-value	0.001* considered significant by Chi-square test	

TB: Tuberculosis

Table 5: Comparison of demographic characteristics between patient subgroup with and without latent TB in the diabetes group

Parameter assessed	Latent TB subgroup (n=29)	No Latent TB (n=107)	p-value
Mean age (years)	52.43±14.93	50.07±11.35	0.29 Not significant
Number of males	24 (82.76%)	63 (58.88%)	0.001 Significant
Number of females	5 (17.24%)	44 (41.12%)	

TB: Tuberculosis

cases receiving metformin were less likely to have LTBI compared to those not receiving metformin [17].

Zhou *et al*. conducted a study to analyze the association between DM and LTBI through a systematic review and meta-analysis, incorporating 22 studies with 68,256 subjects up to July 19, 2022. Eligible cohort studies, totaling three, yielded a pooled adjusted risk ratio of 1.26 (95% CI: 0.71–2.23). Nineteen cross-sectional studies contributed to a pooled adjusted odds ratio (aOR) of 1.21 (95% CI: 1.14–1.29). The pooled estimate for crude risk ratio from three cohort studies was 1.62 (95% CI: 1.03–2.57), while the crude odds ratio from 16 cross-

Table 6: Comparison of diabetes characteristics between patient subgroup with and without latent TB in the diabetes group

Parameter assessed	Latent TB subgroup (n=29)	No Latent TB (n=107)	p-value
Mean FBS (mg/dL)	178.07±58.96	159.35±44.26	0.01 Significant
Mean PPBS (mg/dL)	261.97±77.41	235.23±58.09	0.001 Significant
Mean Hb A1c (g%)	8.52±1.25	7.88±0.82	0.001 Significant
Mean duration of DM (months)	92.02±59.11	89.97±67.24	0.32 Not significant

TB: Tuberculosis, FBS: Fasting blood sugar, PPBS: Post-prandial blood sugar, DM: Diabetes mellitus

sectional studies was 1.64 (95% CI: 1.36–1.97). Specifically, in the diagnosis of diabetes, the pooled aOR for the HbA1c group surpassed that of the self-reported group (pooled aOR: 1.56, 95% CI: 1.24–1.96 vs. 1.17, 95% CI: 1.06–1.28). The findings from this systematic review and meta-analysis support a positive association between DM and LTBI, indicating that individuals with DM may face an elevated risk of LTBI compared to those without DM. These results underscore the relevance of considering DM as a potential risk factor for LTBI in future research and in shaping public health interventions for managing LTBI within diabetic populations [18]. Similar findings were also reported by the authors such as Lee *et al*. [19] and Lin *et al*. [20].

CONCLUSION

Our study establishes a significant link between DM and increased LTBI prevalence, warranting proactive screening in DM cases. Notably, male gender and elevated glycemic parameters emerged as key factors associated with LTBI in diabetes. These findings advocate for routine LTBI screening in diabetic population, particularly among males and those with higher glycemic levels.

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CONFLICTS OF INTEREST

None.

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