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Original Research Article

Fifteen-year case-control study on the interrelationship between pulmonary tuberculosis and diabetes mellitus

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Abstract

Background: This study was conducted to determine the profile and differences in radiological patterns on chest X-rays among diabetic and non-diabetic Drug susceptible (DS) Pulmonary Tuberculosis (PTB) patients.
Materials and Methods: This was a case-control, study conducted from March 2009 to July 2019. The case group included 661 Drug Susceptible PTB (DS-TB) patients with diabetes, and 1318 DS-TB patients without diabetes were enrolled as control groups. Accordingly their radiology and sociodemographic profiles were analyzed.
Results: The participants in this study, encompassing both control and case groups were aged between 20 to 60 years. The mean age was reported as 45.31 years (± 12 years) for the control group and 47.23 years (± 1 year) for the case group. Only 54.54% and 78.40% of the case and control groups, respectively, had a positive tuberculin skin test. About 47.7% of patients in the case group showed lower and middle zone involvement radiologically; they also developed more cavitation compared with the controls (81.1 % vs. 50.8%) and showed multiple lobe involvement with cavitation more frequently than the control group (29.4% vs. 22.7%, p<.001).
Conclusion: Lower zone involvement and cavitory lung lesions in radiology were relatively more common in the case group than in the control group.

Keywords: Atypical Pattern, Cavitation, Diabetes mellitus, Pleural effusion, Pulmonary tuberculosis.

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1. Introduction

Diabetes Mellitus is a worldwide epidemic, and it has been estimated to affect 366 million people by 2030. Most patients reside in low- and middle-income countries where *Mycobacterium Tuberculosis* (MTB) infection is already endemic.[1,2] The combination of DM and tuberculosis (TB) was life-threatening in the pre-antibiotic era when there was no available treatment for both diseases.[3] It is estimated that globally, 1.7 billion people are infected with MTB and, hence, are at risk of developing full-fledged disease.[4] DM is a metabolic disorder that makes our immune system progressively weaker. In diabetic patients, alterations in the bactericidal and phagocytic functions of polymorphonuclear leucocytes play a vital role in the pathogenesis of TB. Immunocompromised patients with TB can exhibit atypical radiological presentation. Multilobar and atypical pulmonary lesions have also been reported among TB patients suffering from DM. Globally, more than 800 million people have diabetes, and 2 million deaths are directly attributed to diabetes every year. In the WHO South-East Asia Region, more than 246 million people aged 30 years and above are estimated to have diabetes.[5]

A recent systemic review on TB and DM suggested that the prevalence of DM among TB patients ranges between 1.9% and 45%, with an overall median worldwide prevalence of 16%. Likewise, the prevalence of TB among DM patients ranges between 0.38% and 14%, and the overall median worldwide prevalence is 4.1%. In countries of Asia, North

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America, and Oceania, the highest prevalence of DM in TB patients were observed, where a substantial proportion of TB patients with DM as a comorbidity were accounted from India.[6] The prevalence of smear-positive PTB was 6.2% among TB-suspected diabetic patients, which is about six times higher than in the general population (0.39%).[7] Deranged blood sugar level also results in delayed smear conversion among PTB patients.[8] PTB has been reported to be five to six times more common with a higher mortality rate, in people with diabetes as compared to people without diabetes. Diabetic patients tend to have a higher absolute neutrophil count than those of non-diabetic controls. Still, their immune functionality seemed impaired because they have a lower capability to phagocytose *M. tuberculosis*.[6,9] Psychological factors, including stress, anxiety, and depression, can significantly impact gene metabolism in patients with tuberculosis (TB) through various mechanisms. These factors play a critical role in determining susceptibility to TB, influencing the progression of the disease, and affecting treatment outcomes.[10] The ongoing morbidity and mortality associated with tuberculosis (TB) are well recognized. Increasing no of cases of drug-resistant TB further exacerbates existing concerns.[11] Various studies have been done on Multi-Drug -Resistance (MDR) Tuberculosis in order to point out the risk factors. Few studies have highlighted the association between low Body- Mass -Index (BMI) and poor treatment response in MDR-TB patients.[12]

2. Materials and Methods

This was a case-control study, with 661 cases of DM with DS-TB and 1318 controls of DS-TB without DM. Our research includes newly diagnosed cases of DS-TB, visiting the outdoor and indoor patient department of Respiratory Medicine in King George's Medical University, Lucknow, UP, from 2009 to 2019. With the help of inclusion and exclusion criteria, we have selected our study sample. Newly diagnosed cases of DS-TB aged 20 to 60 years of both sexes without any prior history of Anti-tuberculosis treatment (ATT) intake were included in our study. Only those smear-positive acid-fast bacilli (AFB) patients were included in this study. HIV seropositive patients were not included as HIV itself acts as a predisposing factor for atypical radiological presentation. All the survey subjects were given the Anti-tubercular therapy as per the norms of National Guideline.

Following the co-morbid condition of DM, all the patients were segregated into two groups. Those DS-TB patients with DM were designated as cases, and those without DM were selected as controls. Along with that, all patients with confirmed DS-TB were screened for DM. Patients having fasting blood sugar (FBS) levels greater than 126mg/dl, postprandial blood sugar (PPBS) levels more than 200 mg/dl, and random blood sugar (RBS) levels more than 200mg/dl as per WHO (World Health Organization) guidelines were confirmed as a case of DM.

2.1. Ethical consideration

The entire protocol was reviewed by the Institutional Ethics Committee. All patients were informed about the study procedures with both verbal and written information. Written informed consent was obligatorily obtained from each patient willing to participate in the study (Approval Code No-XXXV ECM-B/P5).

Each patient in the study population was evaluated through detailed history and clinical examinations. Data were recorded in the proforma; special emphasis was made on constitutional clinical features such as fever, cough, expectoration, hemoptysis, chest pain, dyspnea, loss of appetite, and significant weight loss.

All patients were subjected to sputum smear examination. Three days of morning sputum examinations for AFB were done by direct smear Ziehl Nelson and auramine O fluorescent staining method. Sputum was graded for AFB as per the WHO criteria (**Table 1**). Bronchoscopic sampling was done in patients with suspected miliary TB or in patients who were unable to expectorate sputum or whose sputum sample AFB smear microscopy came negative. It included bronchial brushings and/or transbronchial biopsy, as the yield from washings is significantly less, and the yield from bronchoalveolar lavage (BAL) is unknown. This intervention was preserved only for those patients where it is essential to provide a quick presumptive diagnosis of tuberculosis. Even post-bronchoscopy sputum specimens were subjected to AFB smear microscopy and mycobacterial cultures.[9] All the patients were subjected to their blood biochemical examination. A blood sample was recruited from all the patients after an overnight fast (about 12 hours) and after a two-hour gap, post prandially. Blood sugar level was estimated using the GOD-POD (glucose oxidase–peroxidase) method. All the patients were subjected to their Glycosylated Hemoglobin Test (HbA1c), which was estimated with the help of the ERBA Kit by Column Chromatography with the Cation-Exchange Resin Method.

2.2. Radiological evaluation

All the patients got their chest X-rays done in a posterior-anterior (PA) view to preserve the radiological record while diagnosing. Atypical localization was defined as middle and lower zone involvement on a PA chest x-ray. The most usual finding on the radiograph was consolidation. Various ancillary findings on chest x-ray were also noted, such as cavity, infiltration, pleural effusion, consolidation, collapse, pneumothorax, hydropneumothorax, miliary patterns, etc (**Figure 1**).

For clinical and research purposes, the National Tuberculosis Association of the USA has provided categorization for classifying the anatomical extent of the disease based on radiology:[13]

1. Minimal: Radiology shows slight to moderate density lesions but should not contain or demonstrate cavitation. They may involve a small part of one or both lungs. Nevertheless, regardless of how it is distributed, the overall extent should not surpass the lung volume on one side, which is limited above by the second chondrosternal joint in the front and by the bodies of the fourth and fifth thoracic vertebrae at the back.
2. Moderately advanced: The lesion may be present on one or both sides, but its total extent should not cross certain limits, as stated below: A widespread lesion with modest density may involve the entire volume of one lung or an equivalent area across both lungs; denser, confluent lesions should be confined to no more than one-third of a single lung's volume; and if a cavity is present, its diameter must be less than 4 cm.
3. Far advanced: Lesion more extensive than the moderately advanced lesion.

The American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America organized a task to review, select, and synthesize relevant evidence. The evidence was used as the basis for recommendations on diagnosing tuberculosis disease and Latent Tubercular Infection (LTBI) in both adults and children. The recommendations were developed, documented, and graded using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method outlined by the American Thoracic Society Criteria, 2017 [14].

2.3. Statistical analysis

All the recorded data were expressed as mean and standard deviation (SD). Statistical analysis was performed using SPSS version 16 (Statistical Package for the Social Sciences, Chicago, IL, USA). Statistically significant p value of < 0.05 was contemplated. A self-supported t-test was used to evaluate the differences between the two study groups. Using the chi-square test, the correlation of two or more variables in the case of frequency distribution was determined.

3. Results

A total of 1979 patients were enrolled in this case-control study. Out of which, 661 patients suffering from DS-TB and DM were enrolled as the case group, while 1318 patients suffering only from pulmonary tuberculosis were enrolled in the control group. The primary demographic profile of the patients, like age, sex, religion, residence, marital status, and socioeconomic status, was considered. Other factors such as history of smoking/tobacco chewing, alcohol intake, family history of PTB, and family history of DM of the two groups (controls and cases) were also utilized in our study. All these above data are summarized in **Table 2**. The age of both controls and cases ranged from 20-60 years with a mean (± SD of) 45.31 ± 1year and 47.23 ± 1year, respectively. Comparing the mean age of the two groups, the t-test revealed similar age between the two groups (45.31 ± 12.92 vs. 47.23 ± 12.55, t=1.41; p=0.160), i.e., did not differ statistically.

Further, in both groups, most of the subjects belonged to the age group of 40-60 years, male preponderance, belonged to the Hindu religion, and resided in urban localities. Most of them were married, belonged to the lower middle class, were non-smokers/tobacco chewers, were non-alcoholic and had no family history of PTB and DM. A comparison of key characteristics between the two groups using the χ^2 test showed no statistically significant differences. In other words, subjects of both groups were socio-demographically (essential characteristics) matched and comparable and thus may not influence the primary and secondary outcome measures.

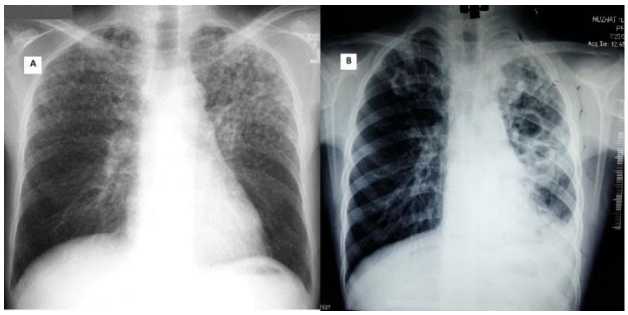

Figure 1: Skiagram of the Chest showing a few of the above-stated ancillary findings. A: Miliary pattern; B- Extensive bilateral cavitation.

Cough was the most typical presenting symptom of PTB in both groups, but the severity of sputum was significantly higher among the case group, with the severity of sputum production *P*<.007. **Table 3** depicts the clinical characteristics; In this study, we found a higher prevalence of hemoptysis, and the severity was significantly high among cases (p=<.0001, odds ratio =4. 215.CI= 2.61-6.8).

The radiological findings, viz. character of the lesion, site of lesion, zone involvement, and extent of lesions of two groups, are summarized in **Table 4**. All the radiological findings differed significantly ($p<0.001$) between the two groups. Chest X-ray patterns of our study population usually showed consolidation with or without satellite nodules, often with cavitary lesions. However, specific ancillary findings were noted on the chest X-ray in the case group, as summarized in **Table 5**.

Cavitary lesion, middle and lower zone involvement, and lower/multiple lobe invasion were significantly ($p<0.001$) higher in cases than controls. In conclusion, atypical radiological findings are significantly associated with PTB and DM.

After controlling for confounding factors and radiological variables, multivariate logistic analysis showed that PTB patients with diabetes and cavitary lesions had a 5.03 times higher risk (OR=5.03, 95% CI=2.77–9.14;

p<0.001) compared to those without diabetes. Further, patients with bilateral involvement on chest X-ray had 2.86 (OR=2.86, 95% CI=1.63-5.03; p<0.001) fold more risk than unilateral involvement. Similarly, patients with "lower" and "multiple" zone involvement had 6.48 (OR=6.48, 95% CI=2.14-19.66; p=0.001) and 3.07 (OR=3.07, 95% CI=1.54-6.13; p=0.002) fold more risks respectively as compared to those with "upper" zone involvement.

Among the cases, 63.2% (n=418) were treated with insulin for type 2 diabetes mellitus, and the rest, 36.8% (n=243), were on oral hypoglycemic agents. The level of HbA1C was monitored during the treatment period to assess the level of glycemic control, as depicted in **Table 6**.

Table 1: Comparative grading of sputum for acid-fast bacilli.

ZN staining grading	Auramine O fluorescent staining grading	Reporting /Grading
>10 AFB /field after examination of 20 fields	>50 AFB/field after examination of 8 fields	Positive, 3+
1-10 AFB/field after examination of 50 fields	1-49 AFB/field after examination of 20 fields	Positive, 2+
10-99 AFB/100 fields	200-20 AFB/40 fields	Positive, 1+
1-9 AFB/100 fields	1-19 AFB/40 fields	Scanty
No AFB per 100 fields	No AFB per 100 fields	Negative

Footnote**:** - ZN=Ziehl-Neelsen; AFB: Acid Fast Bacilli.

Table 2: Distribution of basic characteristics of two groups at admission

Characteristics	Controls (n=1318) (%)	Cases (n=661) (%)	p value
Age (yrs.):			
20-29yrs	237 (18%)	99 (15%)	0.600
30-39yrs	422 (32%)	231 (35%)	
40-49yrs	329 (25%)	153 (23%)	
50-59yrs	145 (11%)	119 (18%)	
60yrs and above	185 (14%)	9 (9%)	
Sex:			
Females	530 (40.2%)	286 (43.2%)	0.564
Males	788 (59.8%)	375 (56.8%)	
Religion:			
Muslim	455 (34.5%)	248 (37.5%)	0.120
Hindu	843 (64%)	383 (58 %)	
Others	20 (1.5%)	30 (4.5%)	
Residence:			
Rural	620 (47.0%)	295 (44.7%)	0.669
Urban	698 (53.0%)	366 (55.3%)	
Marital status:			
Unmarried	408 (31%)	185 (28%)	0.120
Married	910 (69%)	476 (72%)	
SES:			
Lower	231 (17.5%)	99 (15%)	0.292
Upper lower	385 (29.2%)	156 (23.5%)	
Lower middle	333 (25.3%)	216 (32.7%)	
Upper middle	294 (22.3%)	160 (24.2%)	
Upper	75 (5.7%)	30 (4.5%)	
Family history of PTB:			
Absent	1014 (76.9%)	541 (81.8%)	0.261
Present	304 (23.1%)	120 (18.2%)	
Family history of DM:			
Absent	439 (33.3%)	261 (39.4%)	0.234
Present	879 (66.7%)	400 (60.6%)	

Footnote: - SES: Socioeconomic status; PTB: Pulmonary Tuberculosis; DM: Diabetes Mellitus

Table 3: Frequency distribution of clinical characteristics of two groups

Clinical characteristics	Controls (n=1318) (%)	Cases (n=661) (%)	p-value
Cough:			
Absent	125 (9.5%)	155 (23.5%)	p<0001
Present	1193 (90.5%)	506 (76.5%)	
Sputum production:			
Absent	464 (35.2%)	185 (28.0%)	0.001
Present	854 (64.8%)	476 (72%)	
a) Purulent	315 (23.9%)	101 (15.2%)	
b) Mucopurulent	304 (23.1%)	255 (38.6%)	
c) Mucoid	235 (17.8%)	120 (18.2%)	
The severity of hemoptysis:			
Absent	1014 (76.9%)	310 (47.0%)	p<0001
Present	304 (23.1%)	351 (53.0%)	
a) Streaky	179 (13.6%)	110 (16.7%)	
b) Moderate	90 (6.8%)	151 (22.7%)	
c) Severe	35 (2.7%)	90 (13.6%)	

Table 4: Bacteriological and PPD characteristics of two groups

Bacteriological characteristics	Controls (n=1318) (%)	Cases (n=661) (%)	p-value
AFB:			
Scanty	155 (11.7%)	185 (28.0%)	p<0.001
1+	888 (67.4%)	240 (36.4%)	
2+	184 (14.0%)	131 (19.7%)	
3+	91 (6.8%)	105 (15.9%)	
PPD positive:			
No	553 (42.0%)	315 (47.7%)	0.283
Yes	765 (58.0%)	346 (52.3%)	

Footnote: - AFB: Acid Fast Bacilli; PPD- Purified Protein Derivative

Table 5: Frequency distribution of radiological findings of two groups

Radiological findings	Controls (n=1318)	Cases (n=661)	p-value
Pleural effusion	125 (9.5%)	155 (23.5%)	p<0.001
Miliary	35 (2.7%)	105 (15.9%)	0.05
Mediastinal adenopathy	90 (6.8%)	121 (18.3%)	0.003
The character of the lesion:			
Noncavitary	780 (59.2%)	204 (30.9%)	p<0.001
Cavitary:	538 (40.8%)	457 (69.1%)	
Thick-walled	328 (60.9%)	238 (52%)	
Thin-walled	140 (26.1%)	91 (20%)	
Fluid -level	70 (13%)	128 (28%)	
Extent of parenchymal disease:			
Minimal	131 (9.93%)	33 (4.99%)	p<0.001
Moderate	791 (60.01%)	297 (44.9%)	
Far advanced	396 (30.04%)	331 (50.07%)	

Table 6: Distribution of cases according to their mode of glycemic control.

Mode of diabetes control	No of patients	HbA1C level during treatment over a minimum of 6 months		
		Below 5.7% (Normal)	5.7% to 6.4% (Pre diabetic)	6.5% or higher (Diabetic)
Oral hypoglycemic agents	243 (36.76%)	24 (9.9%)	102(42.7%)	117(48.1%)
Insulin therapy	418 (63.23%)	235 (56.2%)	101 (24.2%)	82(19.6%)

Discussion

There is a strong positive association between PTB and DM.[15] DM not only acts as a predisposing factor for new PTB cases but also aids in reactivating dormant PTB. Retrospective data and the original studies suggest that baseline mycobacterial burdens are higher in diabetic patients than in non-diabetics.[16-19] Therefore, the combination of PTB and diabetes may be more infectious at the time of diagnosis and may remain so for a longer duration during treatment.[20] Upper zone involvement and cavitation are typical features of active pulmonary tuberculosis. Radiological images of pulmonary tuberculosis have been described as atypical or unusual in diabetic patients because the presence of lesions and their location were found other than the upper zone.[21-23] In this study, lower zone involvement was seen more frequently among cases, while upper and middle zone involvement was less common. These results are comparable to another study by Perez et al.[24] A higher rate of multiple cavitations was found in cases as compared to only pulmonary tuberculosis, and the same has been reported in many studies.[25,26] Uncontrolled glycemic index in a diabetic patient is a confounding factor for clinical deterioration and atypical radiological pattern of Tuberculosis.[27] Atypical findings of pulmonary tuberculosis had many debating questions for a while. Some authors have reported no significant differences, while others have reported bilateral and multi-lobar involvement. This is important because lower-lobe tuberculosis might be misdiagnosed as community-acquired pneumonia, lung abscess, or cancer. Another similar study by Kim J et al. concluded that bilateral pulmonary involvement, multi-lobar implication, and lymphadenopathy are significantly more common radiological findings in TB patients with DM than in patients without DM.[28] Recommendations have been made for bidirectional screening, but there is little evidence about tuberculosis-specific tests in diabetic patients and vice-versa screening and prophylactic treatment for latent tuberculosis infections in diabetic patients.[29] Studies on PTB patients have shown a direct association between malnutrition and an increased extent of disease and cavitation on CXR.[30] Few studies have findings that highlight the potential role of metformin (compared to sulfonylureas or insulin) in reducing the risk of poor outcomes during and after TB treatment among individuals with RR-TB and diabetes.[31] Comparative studies showed that the proportion of diabetics was higher among patients in the DR-TB group than in the DS-TB group. Another study suggested TB-DM patients had double the risk of developing MDR-TB.[32,33] Impaired immune systems in diabetes mellitus (DM) and specific bacterial genetics may explain primary multidrug-resistant tuberculosis (MDR-TB). Poor glucose control in DM patients can lead to dysfunctions in phagocytosis, reduced reactive oxygen species (ROS) production, and inadequate T-cell responses. MDR strains are generally less virulent due to mutations, making them less likely to cause secondary TB cases compared to drug-sensitive strains. Consequently, these less-fit MDR strains are more likely to thrive in immunocompromised DM patients, resulting in a higher incidence of primary MDR-TB.[34]

Sulphonylurea hypoglycemic drugs promote the development of anti-inflammatory M2-like macrophages in vitro and have been proposed as contributors to higher TB risk in DM patients. Data support the hypothesis that TB drives interferon-mediated alteration of hepatic metabolism resulting in reduced gluconeogenesis and drives systemic reduction of insulin sensitivity.[35] In a study, patients receiving combination therapy with Insulin and oral hypoglycemic agents had a greater reduction in HBA1c level than patients treated with oral hypoglycemic agents alone.[36] The rationale for exogenous insulin therapy in patients with type 2 diabetes and active tuberculosis is given below:[37]

1. Severe tuberculosis infection
2. Loss of tissue and function of pancreas
   a. Pancreatic endocrine deficiency
   b. Tuberculous pancreatitis
3. Requirement of high calorie, high protein diet
4. Interactions of antituberculosis drugs with oral antidiabetic drugs
5. Associated hepatic disease prevents use of oral antidiabetic drugs

Oral hypoglycemic agents are contraindicated in severe tuberculosis but may be used with caution once the disease has settled. Rifampicin is a potent hepatic enzyme inducer. It accelerates the metabolism of several oral hypoglycemic agents, especially sulphonylureas and biguanides, and lowers their plasma levels. Therefore, it may cause hyperglycemia in diabetic patients using these drugs. In non-diabetics, it augments the intestinal absorption of glucose and may simulate the symptoms of diabetes.[38] In contrast to rifampicin, Isoniazid inhibits the metabolism of oral hypoglycaemic agents and may increase these drugs' plasma levels. Isoniazid primarily interacts with sulfonylureas by counteracting their effects, leading to poorer glycemic control in diabetic patients using these drugs. It also impairs the release and action of insulin, leading to hyperglycemia even in non-diabetics.[39] Therefore, the insulin dosage should be adjusted while adding and removing these drugs from the patient’s prescriptions. Dipeptidyl protease inhibitors (the gliptins), a comparatively newer class of hypoglycemic agents, have a theoretical possibility of reducing immunocompetence because of their mechanism of action.[40] This effect could worsen the outcome of patients with TB.

4. Conclusion

The lung is one of the primary organs affected by tuberculosis; 79.5% of the newly diagnosed cases had lung involvement. In 2021, an update of the CDC surveillance reports states that 1 out of 5 people with DS-TB disease has diabetes. Radiological findings of tuberculosis in diabetic

patients were found to be different from radiological findings of tuberculosis in non-diabetic patients. In our study, we have seen significant differences in the radiological findings, such as lower lung zone involvement, bilateral involvement, and cavitary lesions, which were relatively more common in diabetic patients than in nondiabetic patients.

5. Declaration of Ethical Approval

The Indian Council of Medical Research Delhi approved this study (IRIS No. 80/606/2008-ECD-I). The patients' proper verbal and written consent was obtained before inclusion in our study.

6. Conflicts of Interest

No conflict of interest by any of the authors.

7. Source of Funding

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