



## Original Research Article

## Concomitant presence of diabetes mellitus and tuberculosis: A hospital-based study

Disha Yadav<sup>1</sup>, Shikha Saxena<sup>2,\*</sup>, Rashmi Katyal<sup>3</sup>, Prem C Srivastava<sup>4</sup><sup>1</sup>Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, India<sup>2</sup>Dept. of Biochemistry, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, India<sup>3</sup>Dept. of Community Medicine, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh, India<sup>4</sup>Dept. of Forensic Medicine, Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh India, India

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## ABSTRACT

**Background:** Tuberculosis and diabetes mellitus are major burden in developing countries. Both the co-morbid conditions if present together, can complicate the treatment, decrease cure rates and prognosis for each condition thereby increase morbidity and the tuberculosis burden in the society. This study was undertaken to estimate the concomitant presence of tuberculosis and diabetes mellitus in a tertiary care centre with the objectives to estimate the proportion of diabetes mellitus in diagnosed cases of tuberculosis and to analyse the association of socio-demographic determinants with glucose level in tuberculosis cases.

**Materials and Methods:** The retrospective cross-sectional case record-based study included 148 diagnosed patients of tuberculosis in a tertiary care centre in North India. The proportion of diabetes mellitus and pre-diabetes in tuberculosis patients and its association with socio-demographic determinants was assessed by chi square test and independent association by multinomial logistic regression.

**Results:** The study revealed 31.8% diabetic and 21.6% pre-diabetic patients. Tuberculosis with diabetes mellitus was more prevalent in rural males of 46 - 60 years. Association with this age group was statistically significant ( $p=0.001$ ). The association of smoking and alcoholism in tuberculosis with diabetic and pre-diabetic cases was not statistically significant. A statistically significant association [ $p=0.008$ ] was found between the history of hemoptysis in the tuberculosis patients associated with prediabetes (Odd's Ratio-3.573). Sputum positive tubercular patients had 7.1 times more chance of being diabetic (Odd's Ratio-7.191).

**Conclusion:** The study concluded a high prevalence of diabetics and pre-diabetics in tuberculosis cases in males of older age group between 46-60 years residing in rural areas.

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## 1. Introduction

Tuberculosis (TB) and diabetes mellitus (DM) are individually chronic diseases which together pose significant global public health challenge.<sup>1</sup> Both these diseases have a major burden in developing countries like India. Their association with each other have a significant contribution to the morbidity.<sup>2</sup> World Health Organization (WHO) observed 87% of new TB cases from the 30 high TB burden countries in 2018 out of which eight

countries accounted for two thirds of the total, with India leading the count.<sup>3</sup> According to the National Diabetes and Diabetic Retinopathy Survey report released by the Ministry of Health and Family Welfare, Govt. of India, the prevalence of diabetes in India was at 11.8% in the year 2015-2019.<sup>4</sup> According to India TB Report 2019, Uttar Pradesh is the largest contributor to the TB cases with 20% of the total notifications, accounting for about 4.2 Lakh cases (187 cases/lakh population).<sup>5</sup>

Epidemiological reports have proved a great link between diabetes mellitus and tuberculosis.<sup>6</sup> In a global

\* Corresponding author.

E-mail address: [shikhaprem19@yahoo.co.in](mailto:shikhaprem19@yahoo.co.in) (S. Saxena).

estimate, 15% of all TB cases could be attributable to DM, with 40% of those cases coming from India and China.<sup>7</sup> A person with diabetes mellitus has a higher risk of progressing tuberculosis from latent to active stage.

The dual epidemic of tuberculosis and diabetes mellitus complicate the treatment for each condition.<sup>8</sup> Tuberculosis causes impaired glucose tolerance which is a risk factor for developing diabetes mellitus. Even, the chances of deaths and relapse of tuberculosis is significantly higher if the person has diabetes.<sup>7</sup> It is believed that the impairment of immunity in long term diabetics makes the patient more prone to a number of microbial infections including Mycobacterium tuberculosis. The hyperglycemia in diabetes mellitus is believed to favour growth of the tuberculosis bacilli.<sup>2</sup>

TB-DM patients show higher frequencies of fever, haemoptysis, positive acid-fast bacilli sputum smears, consolidation, cavity and lower lung field lesions on chest radiographs, and higher mortality rate.<sup>9</sup> The increased incidence of pulmonary tuberculosis in diabetics could be defect in host defences and immune cell functions.<sup>10</sup>

These comorbid conditions of TB & diabetes could lead to increased morbidity, decreased cure rates & poor prognosis that could increase the TB burden in the society. Therefore, the aim of the study was to estimate the concomitant presence of tuberculosis and diabetes mellitus in the tertiary care centre in North India. The objectives of the study were:

1. To estimate the proportion of diabetes mellitus in diagnosed cases of tuberculosis
2. To analyse the association of socio-demographic determinants with glucose level in tuberculosis cases

## 2. Materials and Methods

The study was carried out in diagnosed patients of tuberculosis admitted in our institute's hospital, a tertiary care centre. This was a retrospective cross-sectional hospital record-based study. Ethical clearance was taken from Institutional Ethics Committee (IEC).

**Inclusion criteria:** The diagnosed tuberculosis patients admitted in the hospital over the period of two years from January 2017 to December 2018 with desired and retrievable complete information were included in the study.

**Exclusion criteria:** The tuberculosis patients with COPD, asthma, heart disease, HIV, long term use of corticosteroids, pregnancy and malignancies were excluded from the study. The permission to review patients' case files and collection of data was taken from appropriate authority of the institute. The privacy and confidentiality of the data was maintained during the study.

The formula  $4PQ/L^2$  was used to calculate the sample size; where P is the estimated prevalence, Q is 100-P and L is the acceptable absolute error.<sup>1</sup>

P= 9%

Q= 100-P i.e. 100-9= 91

L= acceptable absolute error = 5%

$[4 \times 9 \times (100-9)] / (5)^2 = 131$

The sample size was calculated as 131; therefore 148 cases of tuberculosis patients comprised the study population. The diagnosis of these patients for tuberculosis was already done on the basis of history, signs & symptoms, and the investigations i.e. chest X-ray, sputum examination for the acid fast bacilli and bronchoscopy.

The tubercular patients were labelled as diabetic or pre-diabetic on the basis of the following criteria:<sup>11</sup>

### 2.1. Diagnosis of Diabetes Mellitus (DM)

According to American-Diabetes Association, 2019 guidelines, anyone of the following parameters was sufficient to diagnose DM:

1. Fasting blood glucose level  $\geq 126$  mg/dL
2. Postprandial blood glucose level (after 75 gm of glucose load  $\geq 200$  mg/dL
3. Random blood glucose level  $\geq 200$  mg/dL with symptoms of Diabetes Mellitus
4. Haemoglobin A1c/Glycated Hb (HbA1c  $\geq 6.5\%$ )

### 2.2. Impaired Glucose Tolerance (IGT)/Pre-diabetes

IGT was labelled when one or more of the following parameters were present:

1. Fasting blood glucose level = 101 - 126 mg/dL  
Postprandial blood glucose level (after 75 gm of glucose load) = 140 - 200 mg/dL.
2. Postprandial blood glucose level (after 75 gm of glucose load) = 140 - 200 mg/dL.
3. Haemoglobin A1c/Glycated Hb (HbA1c = 5.7 - 6.4%).

The data was analysed using Statistical Package for the Social Sciences (SPSS) software version 23. Chi square test and multinomial logistic regression was applied to observe the statistical significance of the association between various parameters and TB with IGT & DM.

## 3. Results

In this retrospective record-based hospital study, we analysed 148 patients who were already diagnosed with tuberculosis in the year 2017-18. Out of 148 tubercular patients, we found that 47 patients (31.8%) had frank diabetes mellitus while 32 patients (21.6%) had impaired glucose tolerance (IGT) or pre-diabetes and the rest 69 patients (46.6%) were normoglycemic [Figure 1]. The mean age of diabetic TB patients and pre-diabetic TB patients was  $50.68 \pm 10.93$  and  $51.15 \pm 16.63$  years while the mean age of normoglycemic TB patients was  $41.47 \pm 17.74$  years. A significant association between age and tuberculosis

patients with IGT & DM was found. The maximum number of tuberculosis patients (n=50) were noted in the age group of 46-60 years. Notably, the highest percentage of diabetics (46.8%) and pre-diabetics (40.6%) was also present among this age group. We also analysed that in this age group of 46-60 years, we had more number of diabetic patients as compared to normoglycemic tubercular patients which was statistically significant ( $p=0.001$ ). Overall we had maximum number of diabetic tubercular patients in the age group of 31-45 years (31.9%) and 46-60 years (46.8%). We had least number of patients in the age group >75 years [Table 1]. There was overall male predominance (M:F=2.29:1) in tubercular patients and similarly male predominance was found in TB patients with DM & IGT category. Out of 103 tubercular male patients, 34(33.0%) had frank diabetes mellitus and 26 (25.2%) had IGT while there were only 13 females (28.9%) in diabetic category and 6(13.3%) in IGT category out of 45 tubercular female patients [Figure 2]. The socio-demographic determinants were also assessed in relation to glycemic status [Table 2]. Tuberculosis patients from rural areas were more (60.1%) as compared to those of the urban areas (39.9%). The percentage of diabetics TB cases in rural area was about 31.5% while in urban area was 32.2%. In IGT TB category, 19.1% patients belonged to rural areas whereas 25.4% patients to urban areas. In terms of smoking or tobacco abuse, there were 28.4% diabetics and 25.4% pre-diabetics whereas 46.3% were in normoglycemic category. Similarly, among alcoholic tubercular cases, 26.5% were diabetics and 29.4% had IGT, but these differences were statistically non-significant.

The Tables 3 and 4 show the results of multinomial logistic regression on the various factors which are associated with the presence of diabetes mellitus and IGT in the confirmed cases of tuberculosis, the significant variables in table IV were found to be age group between 15-30 years [p value: 0.006] and the presence of hemoptysis. [pvalue:0.008]. The O.R. values suggest that the individuals with age between 31-45 years have a much higher chance of getting diabetes mellitus as well as IGT that is about 2.300 times and 0.521 times respectively. The presence of hemoptysis in tubercular patients have 1.778 more chances to develop diabetes mellitus while 3.573 times more chances to develop IGT than the patients who do not have the history of hemoptysis. As far as the case of sputum positivity for tubercular bacilli is concerned, the people have about 7.191 times more chances of developing diabetes as compared to the chance of developing IGT being only 0.496.

#### 4. Discussion

The present retrospective study analysed 148 admitted patients of diagnosed tuberculosis from the record during the year 2017-2018, for the concomitant presence of diabetes mellitus and tuberculosis. We noted prevalence of DM & Pre-diabetes among TB patients to be 31.8%

#### Distribution of TB cases

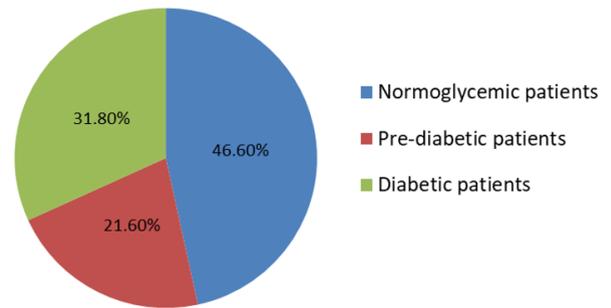


Fig. 1: Distribution of TB Patients according to the glycemic index

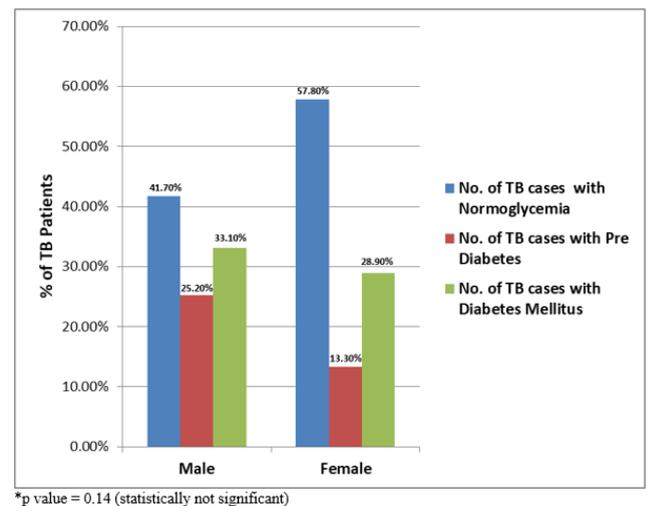


Fig. 2: Distribution of TB cases according to the glycemic index with gender as a determinant

and 21.6% respectively. Overall, we found almost 53.45% of TB cases had hyperglycemia. Similar findings were reported by Viswanathan et al<sup>12</sup> in their cross-sectional study done in South India. They reported the prevalence of diabetes mellitus and pre-diabetes among TB patients to be 25.3% and 24.5% respectively, and almost 50% of TB patients had some form of hyperglycemia. Raghuraman et al<sup>13</sup> also conducted a cross-sectional study and noticed the prevalence of diabetes to be 29% among TB patients. Balakrishnan et al<sup>14</sup> reported prevalence of DM as 44% among TB patients using glycosylated haemoglobin (HbA1c) as a diagnostic tool. Gupta et al<sup>15</sup> found DM as the most frequent risk factor for pulmonary TB in India. Our neighbouring country Pakistan also reported ten times higher prevalence of DM in TB patients compared to normal population.<sup>16</sup> In another country like Zambia with a very high TB burden, TB co-morbidity was significantly associated with DM (OR = 6.5, 95% CI 1.7–25.3).<sup>17,18</sup> Conversely, in low TB burden countries such as Australia,

**Table 1:** Distribution of TB cases according to the glyceemic index with age group as a determinant

| Age Group (Years) | No. of TB cases with Normoglycemia | No. of TB cases with Pre Diabetes | No. of TB cases with Diabetes Mellitus | Total      |
|-------------------|------------------------------------|-----------------------------------|--|------------|
| 15-30             | 23(74.1%)                          | 6(19.4%)                          | 2(6.5%)                                | 31(100.0%) |
| 31-45             | 18(51.4%)                          | 2(5.7%)                           | 15(42.9%)                              | 35(100.0%) |
| 46-60             | 15(30.0%)                          | 13(26.0%)                         | 22*(44.0%)                             | 50(100.0%) |
| 61-75             | 12(38.7%)                          | 11(35.5%)                         | 8(25.8%)                               | 31(100.0%) |
| >75               | 1(100.0%)                          | 0(0.0%)                           | 0(0.0%)                                | 1(100.0%)  |
| Total             | 69                                 | 32                                | 47                                     | 148        |

\*p value = 0.001 (statistically significant)

**Table 2:** Distribution of TB cases according to glyceemic index with socio-demographic determinants

| Parameters     | No. of TB cases with Normoglycemia | No. of TB cases with Pre Diabetes | No. of TB cases with Diabetes Mellitus | Total     | p-value   |        |
|----------------|------------------------------------|-----------------------------------|--|-----------|-----------|--------|
| Residence area | Rural                              | 44(49.4%)                         | 17(19.1%)                              | 28(31.5%) | 89(100%)  | 0.594  |
|                | Urban                              | 25(42.4%)                         | 15(25.4%)                              | 19(32.2%) |           |        |
| Smoking        | Present                            | 31(46.2%)                         | 17(25.4%)                              | 19(28.4%) | 67(100%)  | 0.537  |
|                | Absent                             | 38(46.9%)                         | 15(18.5%)                              | 28(34.6%) |           |        |
| Alcohol        | Present                            | 15(44.1%)                         | 10(29.4%)                              | 9(26.5%)  | 34(100%)  | 0.430  |
|                | Absent                             | 54(47.4%)                         | 22(19.3%)                              | 38(33.3%) |           |        |
| Hemoptysis     | Present                            | 17(35.4%)                         | 16(33.3%)                              | 15(31.3%) | 48(100%)  | 0.040* |
|                | Absent                             | 52(52.0%)                         | 16(16.0%)                              | 32(32.0%) |           |        |
| Sputum         | Present                            | 59(45.0%)                         | 26(19.8%)                              | 46(35.1%) | 131(100%) | 0.042* |
|                | Absent                             | 10(58.8%)                         | 6(35.3%)                               | 1(5.9%)   |           |        |

\*p value&lt;0.05 (statistically significant)

**Table 3:** Multiple logistic regression on various factors in tubercular patients with diabetes

| Variables         | O.R.* (Odd's Ratio) | 95% C.I. (Confidence Interval) | p-value |
|-------------------|---------------------|--------------------------------|---------|
| <b>Age</b>        |                     |                                |         |
| 15-30             | 0.230               | 0.071 - 0.747                  | 0.14    |
| 31-45             | 2.300               | 0.917 - 5.765                  | 0.76    |
| 46-60             | .                   | .                              | .       |
| <b>Hemoptysis</b> |                     |                                |         |
| Present           | 1.778               | 0.712 - 4.437                  | 0.218   |
| Absent            | .                   | .                              | .       |
| <b>Sputum</b>     |                     |                                |         |
| Present           | 7.191               | 0.828 - 62.448                 | 0.074*  |
| Absent            | .                   | .                              | .       |

\* Adjusted for all other variables, \*p value&lt;0.05 (statistically significant)

**Table 4:** Multiple logistic regression on various factors in tubercular patients with IGT

| Variables         | O.R.* (Odd's Ratio) | 95% C.I. (Confidence Interval) | p-value |
|-------------------|---------------------|--------------------------------|---------|
| <b>Age</b>        |                     |                                |         |
| 15-30             | 0.208               | 0.067 - 0.639                  | 0.006** |
| 31-45             | 0.521               | 0.173 - 1.567                  | 0.246   |
| 46-60             | .                   | .                              | .       |
| <b>Hemoptysis</b> |                     |                                |         |
| Present           | 3.573               | 1.396 - 9.150                  | 0.008** |
| Absent            | .                   | .                              | .       |
| <b>Sputum</b>     |                     |                                |         |
| Present           | 0.496               | 0.146 - 1.690                  | 0.262   |
| Absent            | .                   | .                              | .       |

\* Adjusted for all other variables, \*\*p-value&lt;0.05 (statistically significant).

TB risk in diabetic patients was increased only moderately (relative risk RR = 1.48, 95% CI 1.04–2.10).<sup>19</sup> In a cohort study from Hong Kong, patients with well-controlled DM had lower risk for TB.<sup>20</sup> These findings suggested that hyperglycemia and tuberculosis are risk factors for each other. Diabetes mellitus impairs both innate and adaptive immune responses to mycobacterium tuberculosis and cytokines are reported to be upregulated in TB patients. Several studies also reported that TB patients who have DM, present with a higher bacillary load in sputum, delayed mycobacterial clearance and higher rates of multi-drug resistance (MDR) infection.<sup>21,22</sup> Though some of the anti-tubercular drugs like rifampicin was reported to increase the blood glucose level but not to that extent of pre-diabetes and DM.<sup>23</sup>

The present study also revealed that there was overall male predominance in tuberculosis as well as TB with pre-diabetes and DM. Similar findings were noted in study in a tertiary care hospital in North India and other parts of India, Japan and Ethiopia.<sup>2,24–27</sup> Contrary, female predominance was found in Iran.<sup>28</sup> This can possibly be explained as the male patients have greater involvement in outdoor activities, and are frequently exposed to external environment. Moreover greater stresses in life may lead to over-eating in males which may cause fluctuated blood sugar levels.

We found maximum number of tuberculosis patients in the age group of 46-60 years. Moreover, this age group had the highest percentage of pre-diabetics and diabetics in TB patients. a significant association [p-value: 0.006] was also found between the tuberculosis patients and the pre-diabetics in the age group between 15-30 years [OR:0.208; CI 0.067-0.639]. In a study from North India, the mean age in the tuberculosis-diabetes mellitus patients was found to be  $56.67 \pm 12.24$  years while in cases of tuberculosis only, it was  $41.60 \pm 18.66$  years which is similar to our study.<sup>2</sup> The studies conducted in Iran<sup>29</sup> and Ethiopia<sup>30</sup> also had similar results. A study done in Japan also revealed high prevalence of diabetes in cases of active tuberculosis in males above 40 and 50 years of age.<sup>26</sup> This can also be explained as in advancing age, there is decreased immunity and general decline of physical health. Moreover, there is lesser ability to reach the health care centres. It is also reported that age above 46 years was associated with poor treatment results.<sup>31</sup> In fact, there is also increased involvement of work with poor debility in the age group of 40-60 years, as a result there is poor adherence with treatment.<sup>32</sup>

In this study we recorded most cases from the rural areas in each category. Among tubercular cases from rural areas, there were more cases of DM (31.5%) as compared to pre-diabetes (19.1%) but overall normoglycemics were more in both urban and rural areas. Our findings were in corroboration with a study done by Singh et al in North India<sup>2</sup> while contradictory findings were noted by Sen et

al in India<sup>33</sup> and Sulaiman et al in Malaysia.<sup>32</sup> Most of our Indian population belongs to rural areas. Moreover, there is delay in seeking medical care as well as poor compliance of the treatment that lead to greater incidence of morbidity among rural population in this region of India.

A significant association [p value: 0.008] was found between the history of hemoptysis in the tuberculosis patients associated with the condition of IGT. [OR-3.573; CI 1.396-9.150] but in the case of the tuberculosis with DM, association was not found to be significant [OR-1.778; CI 0.712- 4.437]. In a study by Restrepo et al, in Mexico-Texas border showed a higher rate of fever and hemoptysis among diabetic patients.<sup>33</sup> No association was found in the presence of sputum positive culture in these patients but it was found that the sputum positive tubercular patients had 7.191 times more chances of being diabetic [OR-7.191; CI 0.828- 62.448] while looking towards the results in the pre diabetics, this chance was found to be quite lower, [OR-0.496; CI 0.146- 1.690]. Similarly, in another study conducted by Kurbatova et al on TB patients from five countries, also reported a lower but not significant rate (OR 0.76, 95% CI 0.54–1.06) of sputum culture conversion among patients with DM.<sup>34</sup>

Although no significant association of smoking or alcohol with pre-diabetic & diabetic TB patients was found but a study by Sinurova et al conducted in Puducherry demonstrated significant association between alcohol consumption and prevalence of DM.<sup>12</sup> Stress along with the alcohol consumption decrease the immune response of the host and also alter the various metabolism including glucose homeostasis.<sup>35</sup>

## 5. Conclusions

In the indexed study, it was observed that there was a high prevalence of diabetes mellitus and impaired glucose tolerance in tuberculosis patients. As both the diseases complicate the treatment of each other and lead to greater morbidity, therefore, we concluded that early screening for diabetes mellitus and pre-diabetes in TB patients and individualised treatment of these co-morbid conditions could lead to better outcome and prognosis. In India, we have an effective RNTCP program which could be further improved to diagnose and monitor such a coexistence of TB & DM that could help in decreasing the morbidity load in Tuberculosis.

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## 7. Conflict of Interest

The authors declare they have no conflict of interest.

## 8. Source of Funding

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**Shikha Saxena**, Associate Professor

**Rashmi Katyal**, Professor

**Prem C Srivastava**, Professor

### Author biography

**Disha Yadav**, Student

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