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# SPUTUM BACTERIAL LOAD AND CONVERSION IN PULMONARY TUBERCULOSIS WITH TYPE 2 DIABETES MELLITUS

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## Abstract

The comorbidity of diabetes mellitus (DM) in patients with pulmonary tuberculosis (TB) is one of the most pressing problems in global phthisiology and endocrinology. Worldwide, diabetes mellitus and tuberculosis remain among the major causes of morbidity and mortality. Aim of the study: To investigate the epidemiology, risk factors, and immunological features of diabetes mellitus in patients with tuberculosis, and to develop approaches to treatment and prevention. Methods: A prospective comparative study enrolled 250 patients with active pulmonary TB, divided into two groups: TB monoinfection (n=100) and TB+T2DM comorbidity (n=150). Sputum samples were analyzed using smear microscopy, GeneXpert MTB/RIF, and culture assays. Results: Massive bacillary excretion (3+) was significantly higher in the TB+T2DM group compared to the TB group (46.7% vs 16.0%; p<0.001). GeneXpert positivity was significantly elevated in the comorbid cohort (77.3% vs 58.0%; RR=1.33; 95% CI 1.10–1.61; p=0.002), shifting the quantitative DNA load toward medium and high categories. Conclusion: T2DM severely impairs local pulmonary immunity, triggering massive mycobacterial proliferation and shedding, making comorbid patients a profound epidemiological threat.

**Keywords:** Pulmonary tuberculosis, Type 2 diabetes mellitus, Comorbidity, Bacterial load, GeneXpert MTB/RIF, Smear microscopy.

## Introduction

Monocytes cultured in a high-glucose environment promote enhanced growth of M. tuberculosis (Mtb) compared with standard conditions, although intracellular Mtb growth may remain similar in patients with diabetes and in patients with TB–DM comorbidity [6]. Diabetes mellitus impairs macrophage phagocytosis, reduces vacuole formation, and is also associated with a lower number of giant cells. High glucose additionally decreases Mtb adhesion and uptake, which is reflected by a reduction in colony-forming units (CFU). Low levels of vitamin D and glutathione are associated with increased Mtb growth in monocytes and poorer control of Mtb in monocyte-

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derived macrophages (MDMs), respectively [2,3]. Diabetes-induced phagocytic dysfunction is observed in macrophage-like promonocytic cells and macrophages, in which high glucose levels correlate with reduced phagocytosis [4]. Mtb-infected peripheral blood mononuclear cells exposed to high glucose concentrations also demonstrate impaired control of infection. Although Mtb binding to MDMs is somewhat lower in patients with diabetes, reduced phagocytosis by neutrophils and monocytes after mycobacterial stimulation has been reported, while overall antimycobacterial activity may remain comparable with that of controls [5]. Disruption of Mtb colocalization with LAMP-1/2 in THP-1 cells under high-glucose conditions further indicates defective phagocytosis and impaired post-phagocytic killing [1].

## Methods

A clinical comparative study was conducted involving 250 patients with newly diagnosed, active pulmonary TB admitted to the regional clinical facilities. The study population was stratified into two primary operational cohorts:

Group 1 (TB Monoinfection): 100 patients diagnosed with pulmonary TB without metabolic disorders.

Group 2 (TB+T2DM Comorbidity): 150 patients diagnosed with pulmonary TB with confirmed comorbid Type 2 Diabetes Mellitus.

Exclusion Criteria: Patients presenting with Type 1 diabetes, severe hepatic or renal failure, HIV infection, or those undergoing immunosuppressive therapy were excluded. Sputum analysis was not performed on a DM-only control group as it lacks clinical applicability.

Laboratory Assays: Sputum samples were subjected to threefold evaluation: *Smear Microscopy:* Stained via the Ziehl-Neelsen method and graded semiquantitatively (Negative, Positive, 1+, 2+, 3+): *Molecular-Genetic Assay:* GeneXpert MTB/RIF system to detect Mtb DNA and Rifampicin (RIF) resistance. *Bacteriological Culture:* Inoculation on solid/liquid media to confirm viability.

## Results

A total of 250 patients with active tuberculosis were included in the analysis: 100 patients in the TB group and 150 patients in the TB+T2DM group. Sputum testing was evaluated in these two groups. In patients with diabetes mellitus without tuberculosis, sputum testing was not considered clinically applicable and was therefore not included in the comparative sputum analysis.

**Table 1.**

**Baseline sputum microscopy results**

| No. | Result | TB, n (%) | TB+T2DM, n (%) |
|---|---|---|---|
| 1 | Negative | 11 (11.0) | 6 (4.0) |
| 2 | Positive | 21 (21.0) | 10 (6.7) |
| 3 | 1+ | 29 (29.0) | 17 (11.3) |
| 4 | 2+ | 23 (23.0) | 47 (31.3) |
| 5 | 3+ | 16 (16.0) | 70 (46.7) |

*Note: Pearson $\chi^2=42.333$; $df=4$; $p<0.001$; Cramer's $V=0.412$.*

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The data presented in Table 1 compare the degree of bacillary excretion in patients with pulmonary tuberculosis according to the presence or absence of T2DM comorbidity. Statistical analysis showed a highly significant difference between the two groups ($p<0.001$), with substantially greater bacillary excretion in patients with comorbidity. Massive bacillary excretion (3+) was observed in 46.7% of patients in the TB+T2DM group (70 patients), compared with 16.0% in the TB monoinfection group (16 patients), representing an almost threefold difference.

Moderate bacillary excretion (2+) was recorded in 31.3% of the TB+T2DM group (47 patients), compared with 23.0% in the TB group. Low-grade bacillary excretion (negative, positive, and 1+) accounted for 61.0% of patients in the TB monoinfection group.

Low-grade bacillary excretion (negative, positive, and 1+) represented a substantial proportion of the TB monoinfection group (61.0%), whereas it accounted for only 22.0% of the TB+T2DM group.

Interpretation of these findings suggests that the marked increase in bacterial excretion in the TB+T2DM group is directly related to the immunological alterations associated with this comorbidity:

Destruction of lung tissue: Against the background of hyperglycemia and chronic inflammation, the activity of alveolar macrophages and T-helper (CD4+) cells decreases. As a result, the protective pulmonary barrier (specific granuloma) does not form adequately. When the immune system is unable to contain the bacteria, caseous necrosis and extensive tissue destruction with cavity formation develop.

Active proliferation of Mtb: Reduced activity of lysosomal enzymes within macrophages allows Mycobacterium tuberculosis to proliferate freely and rapidly intracellularly. This leads to massive release of bacilli into the external environment through the bronchi, corresponding to 2+ and 3+ grades.

Consequently, in the presence of diabetes mellitus, tuberculosis not only follows a more severe clinical course, but these patients also represent a particularly important epidemiological source of infection for others.

Baseline microscopy grades differed significantly between the groups ($\chi^2=42.333$; $p<0.001$). The combined proportion of 2+ and 3+ results was 39.0% in the TB group and 78.0% in the TB+T2DM group. Cramer's V=0.412 indicated a moderate-to-large association between study group and microscopic bacterial load.

**Table 2. Baseline molecular and bacteriological indicators**

| No. | Indicator | TB, n (%) | TB+T2DM, n (%) | $\chi^2$ | p | RR (95% CI) |
|---|---|---|---|---|---|---|
| 1 | Xpert MTB positive | 58 (58.0) | 116 (77.3) | 9.705 | 0.002 | 1.33 (1.10–1.61) |
| 2 | Baseline culture positive | 68 (68.0) | 120 (80.0) | 4.012 | 0.045 | 1.18 (1.01–1.38) |
| 3 | RIF resistance detected | 22 (22.0) | 45 (30.0) | 1.972 | 0.373 | — |

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*Note: Indeterminate results for rifampicin (RIF) resistance were analyzed as a separate category.*

Mtb positivity was 77.3% in the TB+T2DM group and 58.0% in the TB group; thus, the probability of an Xpert-positive result was 1.33 times higher in the comorbid group (RR=1.33; 95% CI 1.10–1.61; p=0.002). Baseline culture positivity was also more frequent in the TB+T2DM group. The difference in the frequency of rifampicin resistance was not statistically significant.

**Table 3. Characteristics of semiquantitative Mtb bacterial load**

| No. | Load category | TB, n (%) | TB+T2DM, n (%) |
|---|---|---|---|
| 1 | Trace | 8 (13.8) | 5 (4.3) |
| 2 | Very low | 8 (13.8) | 7 (6.0) |
| 3 | Low | 10 (17.2) | 16 (13.8) |
| 4 | Medium | 18 (31.0) | 35 (30.2) |

*Note: Xpert-positive cases only: n=58 and n=116. $\chi^2$=12.335; df=4; p=0.015; Cramer's V=0.266.*

The data in Table 3 reflect the amount of Mycobacterium tuberculosis DNA (bacterial load) detected using the GeneXpert MTB/RIF (or Ultra) molecular genetic assay.

These findings complement and reinforce the microscopy results presented above. Statistical analysis using Pearson's criterion demonstrated a significant difference between the two groups, with the bacterial-load distribution shifted toward higher categories in the comorbid TB+T2DM group.

The distribution of mycobacterial DNA in the sputum of patients with pulmonary tuberculosis confirms that the disease follows different pathogenetic patterns in the two study groups.

A medium bacterial load was recorded in 30.2% of patients in the TB+T2DM comorbid group and in 31.0% of patients in the monoinfection group. In absolute patient numbers, however, the findings indicate a substantially larger mycobacterial population in lung tissue among patients with diabetes mellitus.

Minimal bacterial load (Trace and Very low) accounted for 27.6% (16 patients) in the TB monoinfection group but was almost three times less frequent in the TB+T2DM group, occurring in only 10.3% of patients. This distribution indicates a predominance of higher mycobacterial loads in the comorbid group. Clinical and immunological interpretation suggests that the accumulation of higher molecular bacterial-load categories in the TB+T2DM group may reflect the following mechanisms:

**Metabolic favorability of the environment:** Chronic hyperglycemia and tissue ischemia (oxygen deficiency) in diabetes mellitus create conditions favorable for M. tuberculosis. High tissue glucose concentrations may accelerate bacterial replication.

**Inhibition of humoral and cellular factors:** Owing to a weakened T-helper 1 (Th1) response, specific cytokines may lose part of their ability to restrict mycobacterial DNA replication. This may contribute to the predominance of "Medium" and higher bacterial-load categories on GeneXpert testing.

**Conclusion:** Molecular genetic findings demonstrate that, in tuberculosis complicated by diabetes mellitus, bacillary excretion is highly active not only at the external microscopic level but also at the internal genetic-quantitative level.

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**Table 4. Sputum results after two months of treatment**

| No. | Outcome | TB group | TB+T2DM group | $\chi^2$ | p | RR (95% CI) | OR |
|---|---|---|---|---|---|---|---|
| 1 | Microscopy positive | 29 (29.0) | 78 (52.0) | 12.042 | <0.001 | 1.79 (1.27–2.53) | 2.65 |
| 2 | Culture positive | 35 (35.0) | 90 (60.0) | 14.017 | <0.001 | 1.71 (1.27–2.31) | 2.79 |
| 3 | No conversion | 35 (35.0) | 90 (60.0) | 14.017 | <0.001 | 1.71 (1.27–2.31) | 2.79 |
| 4 | Conversion achieved | 65 (65.0) | 60 (40.0) | 14.017 | <0.001 | — | — |

*Note: Conversion was defined as negative microscopy and culture results at month 2. Cramer's V=0.237.*

At two months, persistent microscopy positivity was observed in 52.0% of the TB+T2DM group and 29.0% of the TB group (RR=1.79). Persistent culture positivity was 60.0% and 35.0%, respectively. Thus, absence of conversion at two months was 1.71 times more frequent in the comorbid group (95% CI 1.27–2.31).

These data reflect sputum conversion (conversion to negative results) at the end of the intensive treatment phase, i.e., at month 2. This is one of the most important indicators of treatment effectiveness in both monoinfection and comorbidity. Cramer's V=0.237 indicates a modest but statistically significant association between the presence of diabetes mellitus and failure to achieve sputum negativity by month 2.

Delayed bacteriological conversion in the TB+T2DM group may be explained by the following pathogenetic mechanisms characteristic of this comorbidity:

Pharmacokinetic barriers in patients with TB, including diabetic gastropathy, microangiopathy, and hepatic changes, may reduce the absorption and therapeutic blood concentrations of key anti-tuberculosis drugs such as isoniazid and rifampicin.

In addition, impaired blood circulation around destructive pulmonary cavities due to diabetic angiopathy may hinder the penetration of medications and immune cells into foci of tuberculosis infection. Reduced phagocytic activity of alveolar macrophages may also slow the clearance of dead bacteria and caseous material from the lungs.

Delayed bacteriological conversion at two months in the TB+T2DM group is an important clinical sign that may require prolongation of the intensive treatment phase (for example, up to three months) and stricter glycemic control in these patients.

**Table 5. Intergroup comparison of time to conversion**

| Indicator | TB group | TB+T2DM group | U | p | Rank-biserial r |
|---|---|---|---|---|---|
| Days, Me [Q1–Q3] | 58.5 [45.0–95.5] | 89.5 [67.2–116.8] | 4335 | <0.001 | 0.422 |

The presented data show the median (Me) and interquartile range [Q1–Q3] for the duration of hospitalization (bed-days) or the time to sputum conversion (days). The Mann–Whitney test (U=4335), high statistical significance (p<0.001), and effect size (r=0.422, indicating a moderate-to-strong effect) demonstrate that comorbidity is associated with a substantially longer treatment duration.

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The duration of inpatient treatment during the intensive phase is an important integrated indicator for both economic and clinical assessment of disease severity and treatment effectiveness. Nonparametric analysis of the accumulated data showed that concomitant diabetes mellitus is associated with a marked prolongation of inpatient stay.

According to Table 5, the median duration of hospitalization in the TB monoinfection group was 58.5 days, with an interquartile range of 45.0–95.5 days (Me [Q1–Q3] = 58.5 [45.0–95.5]). In the TB+T2DM group, the median duration increased to 89.5 days, with the interquartile range shifting to 67.2–116.8 days (Me [Q1–Q3] = 89.5 [67.2–116.8]). Thus, patients with comorbidity remained hospitalized for a median of 31 days longer than those with TB monoinfection.

When the difference between the two groups was assessed using the Mann–Whitney U test, it was highly statistically significant (U=4335; $p<0.001$). The effect-size estimate (r=0.422) confirms a substantial association between diabetes mellitus and prolonged hospitalization.

The marked prolongation of inpatient treatment in the comorbid group may be related to several pathogenetic and organizational factors. As emphasized above, chronic systemic inflammation (metaflammation) and depression of T-cell immunity contribute to slow resolution of caseous necrotic lesions in the lung. This prolongs clinical symptoms such as cough, fever, weakness, and the period of intoxication.

In TB+T2DM comorbidity, stabilization of blood glucose levels, including appropriate adjustment of insulin therapy, is required for effective use of anti-tuberculosis drugs. Decompensated diabetes may increase the toxic effects of anti-tuberculosis therapy, particularly hepatotoxicity, which may necessitate temporary interruptions of treatment or additional symptomatic therapy.

The median duration of inpatient treatment for pulmonary tuberculosis complicated by diabetes mellitus is prolonged by approximately one month. This increases the economic burden on the healthcare system and indicates the need to develop specific prolonged inpatient-management standards for patients with this comorbidity.

**Table 6. Predictors of failure to achieve sputum conversion at two months**

| No. | Predictor | B | OR | 95% CI | p | Interpretation |
|---|---|---|---|---|---|---|
| 1 | Age, per 1 year | 0.021 | 1.021 | 0.997–1.045 | 0.082 | Borderline |
| 2 | Sex | -0.230 | 0.794 | 0.435–1.450 | 0.453 | Not significant |
| 3 | BMI, per 1 kg/m² | 0.038 | 1.039 | 0.981–1.100 | 0.197 | Not significant |
| 4 | HbA1c, per 1% | 0.134 | 1.143 | 1.061–1.232 | <0.001 | Independent |
| 5 | Smear grade, per 1 category | 0.341 | 1.406 | 1.089–1.814 | 0.009 | Independent |
| 6 | DR-TB | 0.604 | 1.829 | 1.001–3.343 | 0.050 | Independent |

*Note: Model omnibus $p<0.001$; McFadden $R^2=0.146$; Hosmer–Lemeshow $p=0.486$; AUC=0.743; accuracy=69.2%.*

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Each 1% increase in HbA1c increased the odds of failure to achieve conversion at two months by approximately 14% (OR=1.14; 95% CI 1.06–1.23; p<0.001). Each one-category increase in baseline smear grade was associated with OR=1.41 (95% CI 1.09–1.81; p=0.009). DR-TB status showed OR=1.83 (95% CI 1.00–3.34; p=0.050). Age, sex, and BMI were not independently statistically significant.

**Discussion**

The findings of higher bacterial load, more frequent persistence of positivity at two months, and delayed conversion in the TB+T2DM group are consistent with the general trends reported in numerous Asian and European cohorts. However, the absolute values observed in this study reflect a clinically severe patient population.

Overall, the following findings were obtained: higher baseline sputum microscopy grades predominated in the TB+T2DM group, with 2+/3+ results in 78.0% compared with 39.0% in the TB group ($\chi^2$=42.333; p<0.001; Cramer's V=0.412). Xpert MTB positivity was 77.3% in the TB+T2DM group and 58.0% in the TB group, and the probability of an Xpert-positive result was 1.33 times higher in the comorbid group (95% CI 1.10–1.61).

At month 2 of treatment, smear positivity was 52.0% in the TB+T2DM group and 29.0% in the TB group (RR=1.79; 95% CI 1.27–2.53). Two-month conversion was achieved in 65.0% of the TB group and 40.0% of the TB+T2DM group; failure to convert was 1.71 times more frequent in the comorbid group (p<0.001).

The median time to sputum conversion was 58.5 days in the TB group and 89.5 days in the TB+T2DM group; the difference was statistically significant with a moderate-to-large effect (U=4335; p<0.001; r=0,422). In the multivariable model, HbA1c (OR=1,14), baseline smear grade (OR=1,41), and DR-TB status (OR=1.83) emerged as the main predictors of delayed conversion; model AUC=0,743 and Hosmer–Lemeshow p=0,486.

**Conclusion**

In the presence of diabetes mellitus, tuberculosis not only follows a severe clinical course, but patients with this comorbidity also constitute a highly significant epidemiological source of infection.

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Journal of Advances in Drug Research

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