J R Coll Physicians Edinb 2020; 50: 242–6 | doi: 10.4997/JRCPE.2020.306 BRIEF RESEARCH PAPER

# Diabetes mellitus and prediabetes among patients with tuberculosis in a single north Indian tertiary care centre

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**Abstract**

**Background:** Prevalence of diabetes mellitus (DM), though believed to be high among patients with tuberculosis (TB), remains unclear for the want of systematic studies and unequivocal methods of diagnosing DM. This study was done to determine the prevalence of prediabetes and DM in adult patients with TB.

**Methods:** This prospective study of one year's duration, carried out at a tertiary care centre included 313 consecutive adult patients diagnosed (either microbiologically, histologically or based on clinical presentation) with pulmonary or extrapulmonary TB. Those without a history of pre-existing DM were subjected to oral glucose tolerance test (OGTT) with 75 g glucose.

**Results:** In this cohort 85 (27%) patients had pre-existing DM. The remaining 228 patients not diagnosed earlier with DM underwent a 75 g OGTT, of which 63 (28%) were found to have newly detected prediabetes (impaired fasting glucose [IFG] and impaired glucose tolerance [IGT] alone in 36 and 10 patients respectively and both IFG and IGT in a further 17) and DM was diagnosed in 9 (4%) patients (fasting blood glucose [FBG] ≥ 126 mg/dl in 1 and both FBG ≥ 126 mg/dl and 2-h plasma blood glucose [PLBG] ≥ 200 mg/dl in 8 patients). The total prevalence of (newly diagnosed) DM and prediabetes, therefore, was 32% (72 patients); the overall prevalence of DM was 30% (94 patients).

**Conclusions:** This study found high prevalence of prediabetes and diabetes among patients with TB. This underscores the need for a bidirectional screening strategy to improve diagnosis and outcome of both TB and DM.

**Keywords:** oral glucose tolerance test, extrapulmonary tuberculosis, glucose intolerance, impaired fasting glucose, impaired glucose tolerance

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## Introduction

Tuberculosis (TB) infection and diabetes mellitus (DM) are widely prevalent diseases of different aetiologies. Globally, the best estimate is that 10 million people developed TB in 2018, with 1.4 million deaths.[1] India, with its high population density accounts for more than one-quarter (27%) of the world's estimated TB burden.[1] In 2018 it had an estimated 2.6 million cases of TB, accounting for 0.5 million deaths, i.e. one-quarter of the world's TB mortality burden.[1] On the other hand, in 2019 an estimated 463 million were living with DM globally and 4.2 million deaths were related to it.[2] India ranked second with 77 million patients living with DM and 0.9 million related deaths.[2]

People with co-existing DM and TB have a fourfold risk of mortality and an increased risk of TB relapse.[3] The two diseases can worsen each other's course trajectories, which can contribute to their respective mortalities. It is well recognised that people with diabetes are at higher risk of developing TB than those without diabetes, including those transitioning into active TB from its latent form.[3-8] There are some other concerns related to co-management of DM and TB, namely: infection-induced worsening of diabetic control, overlapping pharmacological toxicities, worse clinical course of TB in those with poor glycaemic control and treatment failure.[9,10] In addition, poor glycaemic control in DM, undiagnosed DM, longer duration of DM, and coexisting risk-factors like HIV infection are all likely to worsen the course and outcome of TB.[11] Therefore, the timing and suitability of screening tests for DM in the setting of TB appears to

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be a matter of importance in not only curtailing TB infection and DM rates, but also in reducing the load in an already overburdened healthcare system in India.

The Revised National TB Control Program of India (RNTCP) and National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke of India (NPCDCS) jointly carried out a study which showed a 13% prevalence of DM in patients with TB.[12] But in this study the method of DM screening was a glucometer-based strategy where investigators first used capillary blood glucose (CBG) measured at random and if that was ≥110 mg/dl, a criteria of fasting plasma glucose (FPG )>126 mg/dl was used to diagnose DM. No other criteria were used for diagnosis. In another study involving 1,000 patients with TB from the Indian state of Punjab, 11.6% had coexisting DM and TB, the majority of whom were men (56.5%) in the age group 51 to 60 years and who lived in rural areas (68.4%).[13] This study however, had a retrospective design and patients did not undergo a formal OGTT.

The present study, therefore, was undertaken in a tertiary care setting in India with the primary objective of ascertaining the prevalence of glucose intolerance and DM among those diagnosed with TB using the OGTT with 75 g glucose as per the American Diabetes Association (ADA) guidelines.[14] We also analysed other comorbidities in these patients such as human immunodeficiency virus (HIV) infection, obesity and renal impairment.

## Methods

### Patients

This was a prospective study carried out in Christian Medical College & Hospital, Ludhiana, Punjab, India over a period of one year from December 2014 to November 2015. Consecutive adult patients (≥ 18 years of age) diagnosed to have pulmonary and extrapulmonary TB were included in the study after excluding those on glucocorticoid supplementation, pregnant women or critically unwell patients.

Pulmonary tuberculosis (PTB) was defined as any microbiologically, histologically confirmed or clinically diagnosed case of TB involving lung parenchyma or tracheobronchial tree. Extrapulmonary tuberculosis (EPTB) was defined as any microbiologically, histologically confirmed or clinically diagnosed case of TB involving a single site organ other than lungs, e.g. pleura, larynx, lymph nodes, intestine, genitourinary tract, joint and bones, meninges of the brain, etc. Disseminated tuberculosis was defined as any microbiologically, histologically confirmed or clinically diagnosed case of TB involving two or more noncontiguous sites.

### Assessments

Relevant details including those related to demographics, anthropometry and family history of DM was obtained from all patients. Pre-existing diagnosis of DM was carefully ascertained by reviewing their medical records and medications. Details regarding the diagnosis of TB (pulmonary, extrapulmonary or disseminated) and its supporting evidence were noted. Sputum smear status for acid-fast bacilli (AFB – either by Ziehl-Neelsen stain or by auramine-rhodamine stain) and findings of the radiological investigations were also noted.

Tissue biopsy specimens, body fluids and secretions were collected as relevant. Special clinical examinations such as fundus, slit-lamp and dermatological examination were carried out as necessary. FBG and 2-h plasma blood glucose (PLBG), HIV testing, HbA1c, X-ray chest and serum creatinine were done in all patients.

A standard OGTT using 75 g glucose was performed on all patients without DM and the results were interpreted based on ADA guidelines[14] and patients were categorised as being either normal, having prediabetes (IFG, IGT) or DM.

### Statistical analysis

Statistical analysis was carried out using IBM Statistical Package for the Social Sciences (SPSS) Statistics Version 20. Statistical measures such as estimation of mean, proportions and other tools were used to illustrate and compare the data. A p-value of ≤0.05 was considered significant.

The minimum sample size for this observational study was estimated to be 250 using the formula $4pq/d^2$. The study eventually recruited 313 patients in the study period.

### Ethical approval

The Institutional Ethics Committee approved the study (CMC/2725 dated 1/12/2014). All participants gave written informed consent.

## Results

A total of 313 patients diagnosed with TB were enrolled in this study. The demographic and clinical characteristics of the study population are shown in Table 1. There were 159 (51%) patients diagnosed with only PTB. A history of DM was present in 85 (27%) patients, 61 (72%) of who had PTB, 16 (19%) had EPTB and 8 (9%) had disseminated TB. The remaining 228 patients not diagnosed earlier with DM underwent a 75 g OGTT, of which 63 (27%) were found to have newly detected prediabetes (IFG and IGT alone in 36 and 10 patients respectively and both IFG and IGT in a further 17) and DM was diagnosed in 9 (4%) patients (FBG ≥ 126 mg/dl in 1 and both FBG ≥ 126 mg/d and 2-h PLBG ≥ 200 mg/dl in 8 patients). The total prevalence of newly diagnosed of DM and prediabetes, therefore, was 32% (72 patients) and overall prevalence of DM was 30% (94 patients).

An HbA1c of ≥10% indicating poor glycaemic status was present in 41 (43.6%) of the 94 individuals with DM and TB. An HbA1c of ≤7.0% indicating good control was present in only 23/85 (27%) of the patients previously diagnosed with DM. The mean HbA1c among the patients with DM was 9.5%.

**Table 1** Demographic and clinical characteristics of the study population

| Characteristics | n | Patients with DM | Patients without DM | p-value |
|---|---|---|---|---|
| Total number of patients (%) | 313 | 94 (30.0) | 219 (70.0) | |
| Age (years)<br>Mean ± SD | 44.14 ± 18.34 | 55.90 ± 13.83 | 39.09 ± 17.74 | < 0.001 |
| Gender<br>Female (%) | 128 (40.9) | 38 (40.4) | 90 (41.1) | 0.912 |
| BMI (kg/m$^2$)<br>>25 (%) | 25 (8.0) | 17 (18.0) | 8 (3.7) | <0.001 |
| Family history of diabetes mellitus in first degree relatives<br>Present (%) | 61 (19.5) | 34 (36.2) | 27 (12.3) | < 0.001 |
| eGFR (by MDRD calculator) (ml/min/1.73 m$^2$) | | | | |
| ≥90 (%) | 194 (62.0) | 44 (46.8) | 150 (68.5) | <0.001 |
| 60 – 89 (%) | 64 (20.4) | 21 (22.3) | 43 (19.6) | 0.586 |
| 30 – 59 (%) | 36 (11.5) | 17 (18.1) | 19 (8.7) | 0.016 |
| 15 – 29 (%) | 10 (3.2) | 6 (6.4) | 4 (1.8) | 0.035 |
| <15 (%) | 9 (2.9) | 6 (6.4) | 3 (1.4) | 0.014 |
| Type of tuberculosis | | | | |
| Pulmonary (%) | 159 (50.8) | 64 (68.1) | 95 (43.4) | 0.001 |
| Extrapulmonary (%) | 118 (37.7) | 21 (22.3) | 97 (44.3) | 0.001 |
| Disseminated (%) | 36 (11.5) | 9 (9.6) | 27 (12.3) | 0.001 |
| Sputum status | | | | |
| Positive (%) | 49 (15.7) | 21 (22.3) | 28 (12.8) | 0.033 |
| HIV status | | | | |
| Positive (%) | 12 (3.8) | 1 (1.0) | 11 (5.0) | 0.031 |
| Type of tuberculosis in HIV patients | | | | |
| Pulmonary (%) | 5 (41.6) | 1 (100) | 4 (36.4) | |
| Extra-Pulmonary (%) | 1 (8.4) | 0 (0) | 1 (9.1) | 0.788 |
| Disseminated (%) | 6 (50) | 0 (0) | 6 (54.5) | |
| Disseminated tuberculosis | | | | |
| With HIV infection (%) | 6 (16.7) | 0 (0) | 6 (22.2) | 0.121 |
| Without HIV infection (%) | 30 (83.3) | 9 (100) | 21 (77.8) | |

HIV: Human Immunodeficiency Virus; SD: standard deviation; BMI: Body Mass Index; eGFR: estimated glomerular filtration rate; MDRD: Modification of diet in renal disease

Among the 94 patients in our study who had DM (9 newly diagnosed and 85 pre-existing) there was no difference in type or frequency of TB depending on the duration of DM. Sputum for AFB was tested in all 313 patients, 49 (15.7%) of whom were detected to be sputum positive. Poor glycaemic control (HbA1c levels of ≥ 10%) was observed in 13 (26.5%) of sputum-positive patients.

Twelve patients were HIV positive, 5 of whom were newly diagnosed. Amongst these 12 patients with HIV and TB co-infection, disseminated TB was present in half (6 patients) and PTB and EPTB in 5 and 1 respectively (Table 1).

Of the 36 patients affected with disseminated TB, DM as a risk factor was noted in 9 and HIV infection in 6 (Table 1). No patient with disseminated TB had both DM and HIV infection.

## Discussion

In this study there were 85 (27%) patients with TB had a pre-existing diagnosis of DM. Following the OGTT, 9/228 (4%) patients were diagnosed to have DM and 63/228 (28%) patients were diagnosed to have prediabetes. The total prevalence of (newly diagnosed) DM and prediabetes was 32% and the overall prevalence of DM was 30%. These figures are much higher than the WHO estimates of 15% worldwide for DM in patients with TB (with India and China accounting for more than 40% of these cases).[15,16]

Our results concur with a recent Indian survey from five randomly selected TB clinics in the state of Tamil Nadu, where around 25% of TB patients had DM of whom a little over 9% were newly detected cases of DM.[17]On the other hand, a

study from the south Indian state of Kerala reported higher prevalence (44%) of DM in patients with TB, of which 21% were newly diagnosed.[18] In a previous study from the same region as ours involving 1,000 patients with TB, 11.6% of the total cases had both DM and TB.[13]

In view of the limitations of the aforementioned studies, the present study appears to provide a more accurate estimation of the prevalence of DM in those with TB in our region, at least among patients with TB requiring tertiary level care. The strengths of our study are that we undertook a prospective assessment using the ADA criteria to make the diagnosis of DM, using an OGTT which is still considered the gold standard.[14] However, we did not use HbA1c for the diagnosis of DM as there is still no consensus if the current ADA cut-off of >6.5% is applicable in the Indian setting. In this context, a large multicentric study involving five centres is in progress (GIANT Study - Glucose Intolerance Among New patients with Tuberculosis - Clinical Trial Registry India - CTRI/2019/05/019396). This study incorporates simultaneous OGTT and HbA1c determinations at three different time points to ascertain if HbA1c can replace OGTT in this population.

In the present study, DM was present in 64 (68%), 21 (22%) and 9 (10%) patients with PTB, EPTB and disseminated TB respectively. This finding was similar to a study from Kerala, India of patients with TB and DM, where the prevalence of DM was found to be 38% in PTB and 21% in EPTB.[19] This finding is important as a clear association between DM and PTB has been well recognised, especially when glycaemic control is inadequate. Understandably, disease outcomes, sputum conversion rates and TB drug resistance are worse in this group of patients.

In our study a higher proportion of patients with TB and DM had higher BMI (>25 kg/m$^2$) and low estimated glomerular filtration rate (>30 ml/min/1.73 m$^2$). Both obesity and renal impairment which are seen in patients with DM have potential implications in planning antitubercular regimes in patients. In a study from Indonesia, serum rifampicin concentrations were seen to be lower by 53% in TB patients with DM compared to those without DM.[20] In a recent study from India, TB patients with DM were found to have lower serum concentrations of isoniazid and pyrazinamide compared to those without DM or glucose intolerance and this effect was directly linked to hyperglycaemia.[21] Reduced exposure to anti-TB drugs can be also attributed to the higher body weights observed in patients with concomitant disease. This lower concentration of drugs may contribute to therapeutic failure and acquired drug resistance.[22,23] A significant reduction in dose of up to 50% for ethambutol and pyrazinamide is recommended in patients with reduced renal functions.[24-26] Such inappropriate dosing can jeopardise TB treatment outcomes.[27]

In a Danish study 3% of HIV-infected patients had been diagnosed with DM.[28] The newer agents used in antiretroviral therapy (ART) appear less likely to cause ART-associated DM.[29] In a meta-analysis of postmortem studies by Gupta et al., TB in HIV-infected adults was found to be disseminated in 88%.[30] Alabel et al., in a systematic review, found that the prevalence of DM among HIV-infected TB patients was higher than HIV-uninfected TB patients from sub-Saharan Africa.[31] Hence disease eradication strategies for each of these diseases must focus on and promote early screening for both of these risk factors. In the present study, however, these numbers were too small to derive any meaningful conclusions.

Our study has several important limitations. Firstly, the setting of our study was a tertiary care institute. Patients with TB presenting to such hospitals are likely to be sicker, have more extrapulmonary disease and more likely to have resistant TB. However, the prevalence was as expected and compared well with other parts of India. Secondly, as we only had a one-point assessment for glucose intolerance at the time of diagnosis, we were unable to ascertain whether some of the patients with glucose intolerance reverted back to normoglycaemia once the treatment of TB was completed. Thirdly, confounding factors such as stress-induced hyperglycaemia and hyperglycaemia resulting from intake of ART could not be excluded. Fourthly, as this was not a case-control study, no causative inference of TB and DM or vice versa can be made. Lastly, treatment outcomes, sputum microbial load and sputum conversion period (i.e. time taken to revert from sputum positivity to sputum negativity) and its comparison with glycaemic control were not assessed.

In conclusion, our study found high prevalence of prediabetes and diabetes among patients with TB. Overall, 27% of patients presenting with TB had pre-existing DM. In those without DM, a staggering 28% had prediabetes state and an additional 4% had DM. We therefore believe that a bidirectional screening strategy is important to improve diagnosis and outcome. At present, early detection, strict glycaemic control and regular follow-up remains the cornerstone of managing these patients.

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