**Latent tuberculosis infection and pulmonary tuberculosis disease among diabetes mellitus patients in Bandung, Indonesia**

Raspati C. Koesoemadinata\*a, Susan M. McAllisterb, Nanny N.M. Soetedjoc, Dwi Febni Ratnaningsiha, Rovina Ruslamid, Sarah Kerrye, Ayesha J. Verrallb, Lika Apriania, f, Reinout van Crevel g, Bachti Alisjahbanaa,c, Philip C. Hillb.

a TB-HIV Research Centre, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

b Centre for International Health, Department of Preventive and Social Medicine, University of Otago, Dunedin 9054, New Zealand

c Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

d Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

e St George’s, University ofLondon, London SW17 ORE, United Kingdom

f Department of Public Health, Facultyof Medicine Universitas Padjadjaran, Bandung, Indonesia

g Department of Internal Medicine, Radboud University Nijmegen Medical Centre, 6500 HB Nijmegen, The Netherlands

**\*Corresponding author:** Raspati C. Koesoemadinata

Tel: +62 822 18307880, Email: r.c.koesoemadinata@unpad.ac.id

Present address: TB-HIV Research Centre, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

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The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

**ABSTRACT**

**BACKGROUND:** Screening and treatment of latent tuberculosis infection (LTBI) and tuberculosis (TB) disease could reduce diabetes mellitus (DM)-associated TB. We aimed to describe the prevalence of LTBI and pulmonary TB among DM patients in a TB-endemic setting.

**METHODS:** DM patients attending a hospital and community centres in Bandung, Indonesia, underwent LTBI screening using interferon gamma release assay (IGRA). TB was investigated by sputum smear, culture, and x-ray. TB contacts from a parallel study were age- and sex-matched to DM patients to compare LTBI and TB disease prevalence.

**RESULTS:** Of 682 DM patients screened, 651 (95.5%) were eligible. Among ‘TB disease-free’ patients, LTBI prevalence was 38.9% (206/530; 95%CI 34.7-43.2). DM patients were less likely to be IGRA positive than TB contacts (38.6% (54/140); 95%CI 30.5-46.6 vs. 68.6% (96/140); 95%CI 60.9-72.3: p<0.001); but had a higher disease prevalence (4.9% (8/164); 95%CI 1.6-8.2 vs. 1.2% (2/164); 95%CI -0.5-2.9: p=0.054). DM patients in crowded households had increased risk of LTBI (AOR 1.71; 95%CI 1.19-2.45).

**CONCLUSIONS:**

LTBI prevalence in DM patients was lower than in household contacts, but DM patients were more likely to have TB disease. Further studies should explore possible benefits of LTBI screening and preventive therapy in DM patients in TB-endemic settings.

**Key words:** Diabetes, Latent tuberculosis infection, TB disease, Indonesia

**Running title:** Latent TB and TB disease in diabetes patients

**INTRODUCTION**

Globally, the prevalence of diabetes mellitus (DM) in adults was estimated to be 8% of the population (400 million people) in 2015, and to increase by 50% by 2040.1 DM patients are three times more likely to develop tuberculosis (TB),2-4 and have poorer TB treatment outcomes.5-6 Low-resource countries have an increasing prevalence of DM and an ongoing high incidence of TB.1,7-8 Indonesia is both a high DM (6.2%)1 and high TB prevalence country (647 per 100 000).9 In 2010, approximately 9.5% of all TB cases in Indonesia were thought to be attributable to DM, estimated to increase to 14% by 2030.7

While the lower immunity in DM patients and factors related to hyperglycaemia are thought to increase susceptibility to TB disease,2,8,10,11 little is known about the interaction of DM with latent tuberculosis infection (LTBI). In a recently published systematic review and meta-analysis of studies, mostly in high risk populations in developed countries, DM was associated with a small but statistically significant increase in risk for LTBI.12 In studies of DM patients in Singapore (n=220)13 and Mexico (n=605)14 LTBI prevalence in DM patients was 29% and 39%, respectively.

The Indonesian National TB Programme recommends screening and treatment for TB disease in family members of a TB positive patient, and screening and treatment for LTBI for HIV patients and children under five years of age, but this is rarely done. There is currently no universal consensus on recommendations for routine screening and treatment for TB disease or LTBI in DM patients15 and there are limited data to inform recommendations on the prevalence of LTBI in DM patients, their rate of progression to active TB, and the benefits of preventive therapy. We therefore conducted a cross-sectional study in DM patients in Indonesia, and compared them to a matched control group of household contacts of TB cases, to gain insight into the prevalence of LTBI and pulmonary TB disease, and to identify any associated risk factors for LTBI.

**METHODS**

*Study setting, participants and eligibility criteria*

The study is part of the TANDEM research program16 conducted in Bandung City (population ~2.5 million), West Java, Indonesia. Eligible patients aged 18 and over with known DM were recruited (February 2014 – 2015) in the endocrine clinic at Hasan Sadikin Hospital, a major referral hospital, and from 25 Community Health Centres (CHCs). Patients provided written informed consent. The study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran (No: 05/UN6.C2.1.2/KEPK/PN/2014), and the Research Ethics Committee, London School of Hygiene and Tropical Medicine (LSHTM ethics ref: 6449, LSHTM amendment no: A473).

A control group comprised non-DM household contacts of TB patients who were recruited in a separate study in Bandung from February 2014 to February 2016. This group was selected for comparison as they are also known to be at high risk of developing TB disease, but most likely due to high rates of LTBI from intense exposure to a TB case rather than through specific immune deficit. Therefore we expected DM patients to have a lower prevalence of LTBI than TB case contacts. The included contacts were aged 25-54 years old, living in the same household as a sputum smear positive index case and had a valid IGRA test result. The control study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran (No: 14/UN6.C2.1.2/KEPK/PN/2014), and the Health and Disability Ethics Committees, New Zealand (13/STH/132).

*Interview, clinical and laboratory examination with DM patients*

Study doctors conducted an interview and clinical examination with each DM patient, covering socio-demographic characteristics and health behaviours. Diabetic history included the duration of disease, medication, and diabetic complications. Self-reported data were cross-checked with medical records. Anthropometric data (weight and height) were measured for calculation of Body Mass Index (BMI) using calibrated digital scales. Blood taken for glycated haemoglobin (HbA1c) was sent to a certified laboratory for measurement.

Patients were asked whether they had a history of TB or were currently taking TB medication. Enquiry about TB symptoms included cough, sputum production, fever, dyspnoea, weight loss, and chest discomfort. All patients underwent a chest x-ray that was read by a radiologist independent of the study. Those who had a chest x-ray result suggestive of pulmonary TB and/or symptoms of cough for two or more weeks were asked to give two sputum samples for acid-fast bacilli smear and *M. tuberculosis* culture. Xpert MTB/RIF positive was also done on those suspected to have drug-resistant TB.

Patients with and without a past history of TB were classified into four categories:

1. Active TB: on anti-TB medication, or *M. tuberculosis* culture or Xpert MTB/RIF positive.
2. Probable TB: TB symptoms, chest x-ray suggestive of TB and smear positive but culture negative.
3. Possible TB: TB symptoms and/or chest x-ray suggestive or possible TB, but smear and culture negative.
4. No TB: no evidence of TB on symptom review or investigations.

Possible TB patients were followed up, on average 10 months after recruitment, with a repeat examination; anyone with an *M. tuberculosis* culture or Xpert MTB/RIF positive result was re-classified as active TB.

All patients underwent screening for LTBI by the QuantiFERON®-TB Gold In-Tube (QFT®) Interferon Gamma Release Assay (IGRA).17 Control group participants were screened for LTBI in the same laboratory, using the same QuantiFERON supplies and collection techniques as for the DM patients.

No routine testing for HIV was done, noting that the HIV prevalence in adults aged 15-49 in Indonesia 0.5%.18

*Matching DM and control patients*

DM patients were stratified by sex, and frequency matched one-to-one to control group participants, in three ten-year age brackets (25-34; 35-44; 45-54) to compare the prevalence of active TB and TB history in the two groups. Where more controls were available in any one bracket, participants were randomly selected using computer-generated list of random numbers in Excel to provide the exact number required. The same process – including only those considered ‘TB-disease free’ – was repeated to compare LTBI prevalence (Supplementary data).

*Statistical analysis*

A binomial exact test was used to generate the 95% confidence intervals for prevalence rates. The one-way analysis of variance and Student’s-t-test were used to compare mean values. Characteristics, identified from the literature to be associated with LTBI or TB disease, were analysed using logistic regression in a univariable analysis to generate odds ratios. To determine characteristics associated with IGRA positivity, a multivariable logistic regression model was then constructed to adjust for age, sex and any other variable that reached a p-value of less than 0.20 in the univariable analysis. Mann-Whitney and Kruskal-Wallis tests were used to test associations between quantitative IGRA and indicators of severity of diabetes. Linear regression was used to estimate the correlation coefficient between laboratory HbA1c and TB antigen-induced interferon-gamma (IU/mL). To compare the prevalence of LTBI and active TB between the DM patients and control group, a two-sample test of proportions was used. Study data were managed using REDCap electronic data capture tools.19 Statistical analyses were performed using STATA Version 12.1.20

**RESULTS**

*Study participants*

Of 682 DM patients seen, 654 were eligible and consented. Three patients did not have an IGRA test taken, leaving 651 (95.5%) for analysis. Almost all patients were Type 2 DM (98.9%), the majority were aged over 50 years (85.1%) and about half (51.9%) were on metformin either alone or in combination with another oral anti-DM medication (Table 1). Those recruited through CHCs (48.7%) were more likely to be female (72.9% vs. 60.5%; p=0.001) and were slightly older (mean age 60 years vs. 58 years; p=0.005) than those recruited at the hospital endocrine clinic. A total of 414 TB case contacts aged 25-54 were available for matching.

*Prevalence of LTBI*

The prevalence of LTBI in DM patients who were ‘TB-disease free’ (excluding indeterminate results) was 38.9% (206/530; 95% CI 34.7-43.2). None of these patients had any evidence of TB on symptom review, chest x-ray, smear or culture.

The comparison of ‘TB-disease free’ DM patients and the control group for LTBI prevalence included 140 individuals in each group. The proportion IGRA positive was 38.6% (54/140; 95% CI 30.5-46.6) in the DM group compared to 68.6% (96/140; 95% CI 60.9-72.3) in the control group (p<0.001).

*Active TB*

Of the DM patients who were defined as ‘Not TB-disease free’, 24 had active TB, 40 were possible TB (based on their chest x-ray result), and 35 had a history of TB (Figure 1). There were no patients with probable TB.Of the 24 patients categorised as active TB, 12 were already on TB treatment (smear positive (n=7), extra-pulmonary TB (n=2), smear negative but chest x-ray positive (n=1), no other diagnostic information available (n=2)). Ten further patients were found through TB screening; seven presented with symptoms, three with suggestive chest x-ray lesions, and all had a positive culture or Xpert MTB/RIF result. Two patients were originally classified as ‘possible’ TB but were diagnosed with active TB after follow-up.

The comparison of DM patients with the control group for active TB prevalence included 164 individuals in each group. The proportion with active TB in the DM group was 4.9% (8/164; 95% CI 1.6-8.2) compared to 1.2% (2/164; 95% CI -0.5-2.9) in the control group (p=0.054). The eight DM active TB cases and the two household contacts all had a positive culture. The proportion in both groups with a history of TB was 5.5% (9/164; 95% CI 2.0-9.0) compared to 6.1% (10/164; 95% CI 2.4-9.8), respectively.

*Proportion IGRA positive by TB disease category in DM patients*

The proportion IGRA positive was highest in DM patients with active TB decreasing across the three diagnostic categories (p<0.001). Patients with ‘possible TB’ had the highest proportion with a past history of TB (Figure 2).

*Risk factors for LTBI in ‘TB disease free’ DM patients*

There were no significant associations between sex or age, and IGRA positivity. DM patients in a household with five or more people, had a significantly increased risk of being IGRA positive compared with those in a household with less than five people (OR 1.69; 95% CI 1.18-2.42) (Table 2). This remained significant after adjustment for age, sex, and HbA1c (AOR 1.71; 95% CI 1.19-2.45). No significant differences were observed for any other socio-demographic characteristics. Patients with higher HbA1c, longer duration of DM, and complications of DM appeared to be more likely to be IGRA positive, while patients on DM medication had a reduced risk of being IGRA positive, but none of these results reached statistical significance (Table 2). Analysis of the 14 patients who reported they had received treatment for renal failure (38.5% IGRA positive) also showed no significant result (OR 0.98; 95% CI 0.31-3.03).

*Quantitative IGRA results in DM patients*

The TB antigen-induced interferon gamma production did not vary significantly across any of the four indicators of DM severity (Table 3 and Figure 3).

*Indeterminate IGRA results*

All indeterminate results in DM patients were due to a low mitogen result. The overall proportion of indeterminate results was 4.9% (32/651; 95% CI 3.4-6.9), and 4.0% (22/552; 95% CI 2.0-5.9) in ‘TB-disease free’ patients. The characteristics of ‘TB-disease free’ patients with indeterminate results are shown in Table 2. There was a significantly increased risk of having an indeterminate result for those who had an HbA1c ≥10% compared to those with an HbA1c <10% (OR 3.22; 95% CI 1.36–7.61). There were no significant findings with respect to other characteristics. The proportion of indeterminate results in the age and sex-matched groups was 3.6% (95% CI 1.2-8.1) in the DM group and 1.4% (95% CI 0.2-5.0) in the control group.

**DISCUSSION**

The prevalence of LTBI was 38.9% (95% CI 34.7-43.2) in our study population of patients with DM. In the age- and sex-matched comparison, the prevalence in DM patients (38.6%; 95% CI 30.5-46.6) was 30% lower than contacts of persons with TB (68.6%; 95% CI 60.9-72.3), while the prevalence of active pulmonary TB was higher in DM patients (4.9% vs. 1.2%).

Our overall LTBI prevalence estimate was lower than that reported in a similar DM population in Mexico (51%),14 but higher than in Singapore (29%).13 Both these studies, however, used TST for LTBI diagnosis and the Mexican study used a ≥5 mm cut-off for positivity; when using the recommended ≥10 mm cut-off (the same as in Indonesia) the prevalence was 39% – similar to our study. No population LTBI estimates are available to provide a context for these studies but in one large population-based study using IGRA in China (n=21,022) LTBI rates were between 13-20%.21 Also using IGRA, an American study among a refugee population reported a LTBI prevalence of 43% in those with DM (n=54) and 39% in those with pre-DM (n=235), both of which were higher than the 26% in refugees without DM.22 The DM refugee sample was small and they were from a diverse range of countries with different underlying TB prevalence; therefore it is difficult to compare with our study. In a recent meta-analysis, the authors estimated that if the prevalence of LTBI is 30% in the non-DM population, the expected prevalence in the DM population would be 33.6%.12

The lower LTBI prevalence in our matched DM patients compared to those in the control group is not surprising given that the controls were from households of a known TB positive patient.23 Other possible control groups are non-DM patients recruited from clinics, or individuals in the community. The selection of controls from either source, however, would need to be carefully done to ensure a robust comparison. A comparison with case contacts provides insight into the relative benefits of preventive therapy. A lower prevalence of LTBI and higher prevalence of TB disease suggests that DM patients would benefit even more from preventive therapy than case contacts.

The prevalence of active TB in our study of DM patients was 3.7% (95% CI 2.2-5.2) and 6.1% (95% CI 4.3-7.9) were categorized as possible TB. There was a higher prevalence of active TB in the matched DM group (4.9%) than the control group (1.2%), although this difference was of borderline significance (p=0.054) and the proportion with a history of TB was similar in both groups (5.5% vs. 6.1%). Given the higher prevalence of active TB in the DM group, despite lower LTBI prevalence, the increased susceptibility to TB in DM patients is unlikely to be primarily driven by relatively increased LTBI rates and DM patients are similar to HIV patients in this regard.24-26

A relatively high proportion of ‘possible TB’ DM cases had a past history of TB, in keeping with the high likelihood that cured TB patients have residual persistent changes on their x-rays such as that caused by fibrosis. While the IGRA was not used as a screening test to guide TB investigations in this study, we note that the one active TB patient with a negative IGRA presented with a productive cough of more than three weeks, mandating sputum testing regardless of any x-ray result. Each of the three active TB patients with indeterminate IGRA results were already on anti-TB medication at the time of recruitment. All of the patients in our study had a chest x-ray. However, if the chest x-ray had been restricted to only those with a positive IGRA, no TB cases would have been missed, but 349 x-rays avoided. A formal feasibility and cost-benefit analysis would be needed to show whether IGRA is preferred over x-ray for initial screening. Furthermore, it would be useful to conduct a formal comparison with TST.

In our study, the only significantly associated risk factor for LTBI in DM patients was being in a household with a greater number of household members. Data were not collected on whether household members included someone with current or past history of TB. However, household crowding is a recognized risk factor for TB.27,28 The lack of significant findings with any of the other DM-specific characteristics such as use of DM medication or level of HbA1c, which have been reported to be associated with both active TB3,5,29 and LTBI13,14 is notable. In Singapore, the use of metformin was negatively associated with LTBI in a multivariate model,13 yet no such association was seen in our study. For HbA1c, the odds ratios for patients with an HbA1c between 7.0-9.9% and ≥10% were both increased but neither of these results were significant. A similar lack of any statistically significant relationship between cytokines and HbA1c levels in people with LTBI and DM (n=30) or pre-DM (n=30) has been previously reported.11

Investigation of the quantitative IGRA results found that no indicators of severity of diabetes were related to level of TB antigen-nil. This was different to results presented from a Tanzanian study that found lower TB antigen specific interferon gamma release in diabetes patients, regardless of their TB status. However, the diabetes patients were all newly diagnosed and not yet on treatment.30

The overall proportion of indeterminate results in our DM study (4.9%) was higher than the rate of indeterminate results observed in the younger age- and sex-matched groups (DM 3.6%; Control 1.4%), and in Indonesian children (3%).31 The proportion of indeterminate results in adults is estimated to be between 4% to 6% although in studies of immunosuppressed people this can range from 3% to 27%.17,32 The proportion found in our study therefore appears to be acceptable. The increasing odds of an indeterminate result with HbA1c ≥10% (OR 3.22; 95% CI 1.36–7.61) suggests DM is associated with impaired T-cell responses.

To our knowledge, this is the first study to report LTBI prevalence using IGRA in DM patients in Indonesia, and to have a comparison control group. It is a relatively large study with recruitment of patients both from a referral hospital and CHCs. The main limitation is that the study was cross-sectional so we have no ability to provide a timeline for the acquisition of *M. tuberculosis* infection or to estimate the progression from LTBI to TB disease. A further limitation is that the estimation of patients with a history of TB, and those on current TB treatment, was self-reported and confirmation of their diagnosis was not available. Furthermore, in the control group, their age and sex was not available and were imputed based on assumptions (Supplementary data). Finally, this study was focused on pulmonary TB and we may have missed some cases of sub-clinical extrapulmonary TB.

We have shown that LTBI is reasonably common among DM patients in our study population of patients with DM, as is undiagnosed TB disease. Comparison with TB case contacts indicates that DM patients should be considered a potential high priority group for preventive therapy. However, it would be important to consider the age of the patients and the risk of adverse reactions and drug-drug interactions.33 Noting the benefits of prophylactic treatment in HIV patients, further studies are needed to quantify the risks and benefits of such an approach in the growing group of people with LTBI and DM in TB-endemic settings.

**AUTHORS’ DISCLAIMER**

The authors declare no conflicts of interest.

**AUTHORS’ CONTRIBUTIONS**

RvC, PCH, BA, RR conceived the study and designed the study protocol; RCK and NNS carried out the clinical assessments; AJV and DFR carried out the IGRA tests and analysis; AJV and LA designed and implemented the control group study.

RCK, SMM and SK analysed the data; RCK and SM drafted the manuscript; PCH critically revised the manuscript. All authors reviewed a final draft of the manuscript. RCK and SMM are guarantors of the paper.

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**Figure legends:**

**Figure 1:** Flow chart of diabetes study participants and their tuberculosis (TB) and Interferon Gamma Release Assay (IGRA) status

**Figure 2.** Proportion of diabetes patients Interferon Gamma Release Assay (IGRA) positive according to tuberculosis (TB) case definition\*, and proportion of patients within each TB case definition category who had a history of TB

\* p<0.001

**Figure 3:** Laboratory HbA1c and tuberculosis (TB) antigen-induced interferon-gamma (IU/mL) defined as antigen-nil, and the trend for diabetes patients who were ‘TB disease free’ and had a positive IGRA result\*

\* Correlation co-efficient=0.007; p=0.92