**High tuberculosis incidence among people living with diabetes in Indonesia**

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**Abstract**

**Background:**

Data regarding TB incidence among people living with diabetes (PLWD) in TB-endemic settings are scarce. We examined TB incidence among PLWD in Indonesia who had previously been screened for latent TB infection (LTBI) and TB disease.

**Methods:**

PLWD (aged ≥18 years) in an urban setting were examined a mean 3.4 years after they had been screened for active TB and LTBI. Data on subsequent TB diagnosis were collected by interview, and with chest x-ray, sputum smear and *M. tuberculosis* culture. TB incidence rates were stratified for baseline LTBI status, as determined by quantiferon interferon gamma release assay (IGRA).

**Results:**

Of 590 PLWD, 101 had died and 163 could not be contacted or refused. Among 326 re-examined, six (1.8%; 95% CI 0.7-4.0) reported being diagnosed already and a further five were diagnosed with active TB (1.5%; 95% CI 0.50-3.5). The TB incidence rate was 9.85 (95% CI 4.03-15.68) per 1000 person-years. TB incidence was higher among PLWD with baseline LTBI (17.13; 95% CI 5.25-29.00 / 1000 person-years) compared to those without LTBI (4.79; 95% CI -0.63-10.21), with an incidence rate ratio of 3.57 (95% CI 0.86-20.92, p=0.054).

**Conclusion:**

PLWD with LTBI in Indonesia and similar settings are likely to benefit from TB preventive therapy.

**Key words: Diabetes mellitus, Incidence, Tuberculosis**

**Introduction**

People living with diabetes mellitus (PLWD) are approximately three times more likely to develop tuberculosis (TB) than those without diabetes mellitus (DM).1 In low-resource countries where there is an ongoing high incidence of TB2 and an increasing prevalence of DM3 this presents a challenge for TB control.4,5 One option is to consider expanding preventive treatment strategies beyond household contacts of TB cases and HIV positive individuals in TB endemic settings, to include PLWD. In a recent study of PLWD in Bandung City, Indonesia, we found that while the prevalence of latent tuberculosis infection (LTBI) was lower than in household contacts (another high-risk group for TB disease), PLWD were more likely to have TB disease.6 In this respect, they are similar to people living with HIV in whom TB preventive therapy in TB-endemic settings is now regarded as standard practice.7-9 PLWD might, therefore, also benefit from TB preventive therapy.

Mixed results have been reported from the few studies that have investigated the rate of progression from LTBI to TB disease in PLWD. One 5-year cohort of PLWD in Singapore did not find any TB disease10 but the low annual incidence rate of TB in Singapore (40/100,000), the small sample size (n=215) and passive case detection, may have contributed to this. In two cohort studies of PLWD (in Hong Kong11 and Taiwan12), the incidence of TB disease was reported to be higher compared to non-DM patients, however, both these studies relied on cross-matching with either a TB notification registry or a national health insurance database. Lastly, the incidence of TB among PLWD was estimated in Korea but that study was almost 30 years ago and the global situation, particularly in regards to DM has changed considerably.13 Our cohort of PLWD who were tested for LTBI and who were TB disease-free in 2014 in a previous study undertaken by our research team provided an ideal opportunity for follow-up to estimate the incidence rate of TB disease in this population to inform the design of a trial of treatment to prevent TB in PLWD.

**Methods**

***Baseline recruitment, clinical and laboratory examination***

PLWD aged 18 and over were recruited in a cross-sectional study (February 2014 – February 2015) as part of the TANDEM research project14 undertaken in Bandung City, (approximate population 2.5 million), West Java, Indonesia. Recruitment was in the endocrine clinic of a major tertiary referral hospital (Hasan Sadikin Hospital) and from 25 Community Health Clinics (CHCs) throughout the city.6 Study doctors conducted an interview and clinical examination with each participant to collect socio-demographic information, diabetes characteristics (duration of DM, treatment, complications), and enquiry about TB history and symptoms.

All participants underwent chest x-ray examination. These were classified by the research doctor on the basis of the radiology report as normal; abnormal possible active TB; abnormal probable active TB; abnormal not TB. Those who had a chest x-ray 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 (AFB) smear and *Mycobacterium tuberculosis* (*M. tuberculosis*) culture. Xpert MTB/RIF positive was also done on those suspected of having drug-resistant TB or upon request from a pulmonologist. Participants were classified into four TB categories: 1) Definite TB: *M. tuberculosis* culture or Xpert MTB/RIF positive or on anti-TB medication/already treated for TB; 2) Probable TB: TB symptoms, chest x-ray suggestive of TB and AFB positive but culture negative; 3) Possible TB: TB symptoms and/or chest x-ray suggestive of possible TB, but AFB and culture negative; and 4) No TB: no evidence of TB on a symptom review or investigations. Participants were screened for LTBI by the QuantiFERON-TB Gold In-Tube (QFT) Interferon Gamma Release Assay (IGRA).15

***Follow-up eligibility and procedure***

Eligibleparticipants for follow-up were those who were TB disease-free (n=550) or whose TB disease status was considered ‘possible’ (n=40) at baseline. Follow-up was between August 2017 and August 2018. Eligible participants were contacted by phone, after which they were invited to attend a consultation at the endocrine clinic at Hasan Sadikin Hospital. Participants who were not contactable by phone had a health worker visit them in their home. If the participant was reported by a relative to have died, investigators enquired about the possible cause of death. Participants were reimbursed for their travel costs to the clinic. All follow-up outcomes (death, loss to follow-up, or transferred out of the region) were recorded. Written informed consent was provided by participants at both baseline and follow-up.

***Assessment for tuberculosis at the follow-up examination***

On clinic attendance, study doctors conducted an interview to ask about any TB diagnosis since the baseline examination and any current TB symptoms. For participants who reported being already diagnosed with TB, the date and site of diagnosis, and outcome of the treatment was ascertained from the participant and confirmed, where possible, through the relevant TB clinic and laboratory. All participants were asked to have a chest x-ray that was read by a radiologist independent of the study. Any participant who reported a cough of any duration was asked to provide two sputum samples (morning-spot) for AFB smear and *M. tuberculosis* culture testing. The screening, laboratory and x-ray results of all participants were reviewed by the study doctor and classified into the same categories as at baseline. Any participant found to have TB disease was referred to the relevant TB clinic for treatment according to the National TB Programme guidelines.

***Data analysis and statistics***

All data were entered into a REDCap electronic database. Electronic data were monitored regularly and were cross-checked with the source documents by two researchers. Variables obtained from the baseline dataset included age, sex, ethnicity, education, duration of diabetes, HIV status, body mass index (BMI), Bacillus Calmette-Guerin (BCG), laboratory glycated haemoglobin (HbA1c), chest x-ray result, TB case category, and IGRA result (15).

Statistical analyses were undertaken using STATA 12.1.16 The chi-square test was used to compare groups with respect to non-missing data. Incidence rates and 95% confidence intervals were calculated per 1000 person-years. Person-years was calculated as years from the date of baseline examination to either: a) date of death as reported by the family member; b) date of contact by phone with participant or family for those who had moved from the area or refused to come for follow-up examination; c) date of TB diagnosis for those who had TB diagnosed in another site, or d) date of follow-up examination in the clinic.

**Results**

Of the 590 PLWD who were TB disease-free or TB disease ‘possible’ at baseline, 512 (87%) could be contacted personally, or through their family. Subsequently, 326 had a follow-up examination (Figure 1). Of those who did not have a follow-up examination, 101 (17.1% of the total) were reported to have died, 78 (13.2%) had moved from the area or were unable to be located, and 85 (14.4%) refused to come to the clinic. Excluding those who had died, 66.7% of PLWD had a follow-up examination. The mean time from baseline to follow-up interview was 3.43 years (median 3.45; range: 1.94 to 4.31 years). Compared to participants who had a follow-up examination those who died tended to be older (p=0.03), less educated (p=0.02), had been smokers (0.04), had more poorly controlled HbA1c (p=0.02), more DM complications (p<0.001), had been on insulin (p<0.001) and had been hospitalised in the year before the baseline examination (p<0.001) (Table 1). They were also less likely to have had a normal chest x-ray at baseline (p<0.001), and more than three times as likely to have been classified as possible TB at baseline (p<0.001). Compared to participants who had a follow-up examination, with those who did not were more likely to be males (p=0.03) and to have had a negative IGRA test at baseline (p=0.02) (Table 1).

At the time of follow-up, six participants (1.8%; 95% CI 0.7-4.0) reported that they had been diagnosed with TB already: either through the TANDEM research project (n=2), a private hospital (n=2), a private practitioner (n=1), or a public hospital MDR clinic (n=1). Bacteriological confirmation of TB could be established in three participants, two had suggestive chest x-ray lesions and symptoms, and one person without diagnostic information was treated for TB at the time of the follow-up examination (Table 2).

A further five participants were found to have definite (n=4, 1.2%; 95% CI 0.34-3.1) or probable (n=1, 0.3% (95% CI 0.008-1.7) TB at follow-up examination – four with a positive *M. tuberculosis* culture result, and two with positive AFB but negative *M. tuberculosis* culture. Four participants had a chest x-ray suggestive of TB and for one person, the x-ray was abnormal but not thought to be TB. Three patients reported coughing sputum, and two people had no symptoms All of the five participants had a positive baseline IGRA (Table 3). All five participants were referred to their respective community health clinic to start TB treatment.

Based on a total person-time of follow-up of 1116 years and 11 cases diagnosed either through follow-up screening or diagnosed already, the TB incidence was 9.85 (95% CI 4.03-15.68) cases per 1000 person-years. Eight of 138 people with a positive baseline quantiferon result included in the follow-up (5.8%; 95% CI 2.5-11.1) were TB positive (definite, probable or diagnosed at another site), compared to 3 of 181 (1.7%; 95% CI 0.3-4.8) with a negative baseline quantiferon result (Table 4). The incidence rate of TB in those who were IGRA positive at baseline was estimated to be 17.13 cases per 1000 person-years (95% CI 5.25-29.00), compared to 4.79 per 1000 person-years (95% CI -0.63-10.21) in those who were IGRA negative at baseline (incidence rate ratio 3.57; 95% CI 0.86-20.92, p=0.054) (Table 4). Results from a secondary analysis, removing the three cases already diagnosed who were classified as ‘possible’ TB, showed the incidence rate of TB in those who were IGRA positive at baseline was 14.99 per 1000 person-years (95% CI 3.88-26.09) compared to 1.60 per 1000 person-years (95% CI -1.53-4.73) in those who were IGRA negative (incidence rate ratio 9.38; 95% CI 1.21-422.49, p=0.014).

A further 33 people of those followed up were classified as ‘possible TB’ (10.1%; 95% CI 7.1-13.9) (TB symptoms and/or chest x-ray suggestive of possible TB, but AFB and culture negative) at follow-up. Seventeen of these 33 people had a normal chest x-ray at baseline, for six people their chest x-ray was ‘abnormal but not TB’, and for ten the chest x-rays were ‘suggestive of TB’. Of the 16 people classified as ‘possible TB’ at baseline and who were able to be followed-up, one had been diagnosed with TB at another site, ten continued to be classified as possible TB, and five ‘not TB’.

A large number of PLWD examined at baseline had died during the follow-up time (n=101) giving a death rate of 90.50 (95% CI 72.85-108.15) deaths per 1000 person-years. Of the 101 PLWD who died, complications of diabetes was the main reason given by family members (86.1%) (Supplementary Table 1). Of those who died and had a baseline chest x-ray result classified as abnormal-not TB (n=42), the majority (88.1%) had evidence of cardiovascular disease on their x-ray, for example cardiomegaly or atherosclerosis. Two family members reported a reason for death that was respiratory related but it was not possible to confirm whether this was TB-related.

**Discussion**

In this prospective cohort study in PLWD in Bandung, Indonesia the incidence of tuberculosis, as established through history as well as chest x-ray and sputum examination, was 9.85 (95% CI 4.03-15.68) per 1000 person-years with a higher, although not statistically significant, incidence rate in PLWD who had tested positive for LTBI at baseline compared to those who had tested negative.

The incidence rate in our study (985 per 100,000 person-years) was considerably higher than that reported in other cohort studies investigating TB in PLWD. Qui et al.,17 from their large (170,399 PLWD) retrospective cohort study in China with a similar follow-up period to our study, reported an incidence rate of 119.85 (95% CI 111.76-128.54) per 100,000 person-years by identifying TB cases in their mandatory TB surveillance system. In Hong Kong, in a cohort of PLWD aged 65 years and over, Leung et al.11 reported an incidence rate of 295 (95% CI 239-362) per 100,000 person-years. Two separate studies in Taiwan, reported data according to whether PLWD were on Metformin (127 per 100,000 person-years) or not on Metformin (140 per 100,000 person-years),18 or whether they had “good” or “poor” glycaemic control which was defined by a fasting plasma glucose of less than or equal to 130 mg/dl. The respective incidence rates were 65.1 (95% CI 22.6-107.6) and 155.5 (95% CI 114.0-196.9) per 100,000 person-years.19 Each of these studies used a passive TB case finding approach of identifying cases through their national or local TB register which is likely to have underestimated the true number of incident TB cases.

In our study, all of the PLWD diagnosed with TB at the time of follow-up and three of the five already diagnosed had a positive baseline IGRA. We also found an increased incidence and higher incidence rate ratio for those who tested positive for LTBI at baseline compared to those who tested negative. This result, however, was not statistically significant and while the secondary analysis, removing the three cases already diagnosed who were classified as ‘possible’ TB, was statistically significant, both incidence rate ratios had wide confidence intervals, in keeping with the small number of cases. Moreover, a large number (n=101; 17%) of PLWD in our study had died, the majority of whom reported complications of their DM at baseline, 22% had been hospitalised in the previous year and of those with an abnormal chest x-ray many had signs of cardiovascular disease. It is therefore likely that their death was related to their DM. However, almost half of those who died had a positive IGRA at baseline and 16% were considered to have possible TB according to their baseline chest x-ray and examination result. While we cannot confirm their exact reason for death, it is possible that some may have had TB which would have potentially increased the incidence rate. Conversely, undertaking active case finding may have led to an over diagnosis of TB and hence a possible overestimate of the incidence rate. After removing from the analysis the three cases who were classified as ‘possible’ TB and could be considered ‘over diagnosis’ the incidence rate decreased, but remained high (7.17 per 1000 person-years, 95% CI 2.20-12.14). Only one other study, to our knowledge, investigated TB incidence on the basis of a baseline LTBI status and reported that none of the LTBI positive patients progressed to active TB over a 6 year follow-up period.10 However, different from our study, only passive case finding was used and the low annual TB incidence rate in Singapore where this study was conducted and the small sample size may have contributed.

Strengths of our study include that we had complete baseline information on a number of variables and we were able to confirm both their LTBI and TB disease status at that time. However, the baseline sample size also restricted the number available for follow-up limiting study power. Our approach of actively following up patients and doing a repeat chest x-ray and examination case finding is also likely to yield more cases than a passive case finding approach of searching medical records. A large proportion of participants (87%) could be contacted personally or their family. It is, however, possible that some TB cases may have been missed amongst those who refused to be followed-up or who were unable to be contacted and, as mentioned above, amongst those who had died. While reasons for death were ascertained from family members, use of a proper verbal autopsy report would have provided greater certainty.

Current WHO guidelines for screening and preventive treatment of people with LTBI are for people living with HIV and infants and children under 5 years of age who are household contacts of pulmonary TB patients.20 To date, there has been an absence of evidence to recommend systematic testing for LTBI in PLWD or the use of preventive therapy of PLWD who are LTBI positive.20 Our earlier study among PLWD in Indonesia showed a lower proportion of LTBI, but a higher proportion of active TB compared to household contacts. Our previous and current study support the need for a randomised controlled trial of TB preventive therapy in PLWD in Indonesia and/or similar settings, and provides important data on incidence and death rates to inform the study design.

**Author contributions**

SM and PH conceived the study. SM, PH, RK and BA designed the study protocol. RvC, PH, RR, JC and BA designed the TANDEM study protocol from which patients were recruited and baseline data obtained. RK, PS, AK, NS and HP carried out the clinical assessment. SM undertook the analysis. SM and PH drafted the manuscript. RvC, JC and RK critically revised the manuscript. All authors read and approved the final manuscript.

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**Competing interests**

None to declare

**Ethical approval**

The baseline study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran (N0: 05/UN6.C2.1.2/KEPK/PN/2014), and the Research Ethics Committee, London School of Hygiene & Tropical Medicine (LSHTM ethics ref: 6449, LSHTM amendment no: A473). The follow-up study was approved by the University of Otago Human Ethics Committee, Dunedin, New Zealand (No. H17/087) and the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran (No. 851/UN6.C.10/PN/2017).

**Figure 1: Flow chart of follow-up of study participants**

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