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# High glycosylated hemoglobin level as a risk factor of latent tuberculosis infection in patients with uncomplicated type 2 diabetes mellitus

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## ABSTRACT

**BACKGROUND**

Diabetes mellitus (DM) is known to increase the risk of infection including tuberculosis (TB). Some studies also showed that 2-15% of latent TB infection (LTBI) will progress to active TB. This study aimed to obtain the prevalence of LTBI and to determine the risk factors of LTBI in patients with type 2 diabetes mellitus (T2DM).

**METHODS**

This was a cross-sectional study on 242 adult T2DM patients. For LTBI screening we performed the interferon gamma release assay (IGRA) (Quantiferon TB Gold Plus test) and for confirmation of active TB (pulmonary TB) we performed GeneXpert MTB/Rif sputum examination and chest X-ray. Glycosylated hemoglobin (HbA1c) levels, smoking history and BCG scar were collected. Multivariate logistic regression was used to analyze the data.

**RESULTS**

Positive IGRA results were found in 99 of 242 uncomplicated T2DM patients while LTBI was found in 82 patients (33.8%). There were significant differences between T2DM patients with latent TB and T2DM patients without infection in HbA1c and specific IFN-γ levels (TB1 minus nil and TB2 minus nil), i.e. 8.5% and 7.6%, 2.5 IU/mL and 0.06 IU/mL, and 2.6 IU/mL and 0.08 IU/mL, respectively. Multivariate analysis showed that the risk factors for LTBI in T2DM patients were smoking history, HbA1c >7%, and no BCG scar.

**CONCLUSIONS**

Because LTBI is prevalent in T2DM, it is important to screen for it in T2DM patients due to the risk of developing severe active TB. Absence of a BCG scar and high HbA1c levels are strong predictors of LTBI in T2DM patients.
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**Keywords:** Diabetes mellitus, latent tuberculosis infection, pulmonary tuberculosis

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## INTRODUCTION

Tuberculosis (TB) is a global public health emergency. In 2018, Indonesia had an estimated TB incidence of 316 per 100 000 population, or a total of 845,000 cases, and a mortality of 37 per 100 000 population or 98,000 deaths from TB. At the provincial level, in 2018, five provinces contributed to 57% of total new and relapse notifications, i.e. West Java (105,794 cases), East Java (71,791), Central Java (65,014), DKI Jakarta (41,441) and North Sumatra (35,035).[1] The primary *Mycobacterium tuberculosis* infection will develop into TB disease in 5–10% of individuals and in the remaining 90–95% into latent tuberculosis. The latter is important because individuals with latent infection may progress to active TB at any moment, even years after the primary infection.[2] A previous study reported that diabetes mellitus (DM) is known to have a 3 times greater risk of being infected with TB and that the TB rate in DM is higher than in the general population.[3] In the 2017 WHO report on estimated DM-TB burden, Indonesia ranked second as the country with the highest TB burden and fifth as the country with the highest number of DM patients in the world, so the relationship between DM and TB is important in TB endemic countries as well as countries with an increasing prevalence of DM.[4]

Although there is a known association between active TB and type 2 DM (T2DM), it is not clear how high the prevalence of LTBI in T2DM is and whether this T2DM increases the risk of developing LTBI. Identifying latent TB in T2DM patients is an important measure to prevent reactivation of TB into active TB.

A cross-sectional study involving 299 adult T2DM patients showed no significant difference in smoking status, duration of smoking, duration of T2DM, and HbA1c level, between LTBI and non-LTBI subjects.[5] In contrast, a different cohort study in Egypt involving 102 T2DM patients showed that age and HbA1c level are strong predictors of LTBI in T2DM.[6] However, studies investigating the link between DM and LTBI are scarce and heterogeneous.[7] Up until now, there have not been a global consensus or special recommendation in Indonesia on performing latent TB screening in DM patients, making it difficult to find data on prevalence and risk for reactivation and therapeutic recommendations for prevention. Therefore, we conducted this study to determine the risk factors of LTBI in patients with type 2 diabetes mellitus (T2DM).

## METHODS

### Study Design

This was an analytical observational study that was conducted in 2 steps. The first step was to obtain the prevalence of latent TB infection (LTBI) in DM patients and the second was to obtain the risk factors of LTBI in DM patients. The study was performed at the Outpatient Clinic for Endocrinology, Metabolism, and Diabetes at the National General Hospital Dr. Cipto Mangunkusumo (RSCM) and at the Integrated Diabetic Outpatient Clinic, Pulmonary Clinic, Persahabatan Hospital, from December 2017 to January 2019.

### Research subjects

The subjects were adult patients (age >18 years) with type 2 DM (T2DM) and the inclusion criteria were type 2 DM patients without complications who had been diagnosed for >1 year and were willing to participate in the study, as evidenced in writing by signing the informed consent form after receiving the researcher's explanation and reading the explanation sheet about the study. Patients were excluded if they were pregnant and/or lactating, had been diagnosed with cancer, kidney and liver disorders, or were on immune-modulatory medications.

### Sample size determination

The sample size was calculated based on the prevalence of 21.6% previously reported in

a study on LTBI prevalence among diabetic patients in Egypt.[6] Using a precision of 5% at the 5% significance level, a total of 248 subjects was found to be required after assuming a non-response rate of 10%. The sample size was determined using a formula for sample size for prevalence of LTBI in diabetes patients, with an accuracy and type I error of 5%; we found that the total number of patients with T2DM who were to be screened for latent TB was 248. There were 6 patients who were excluded because they did not return to undergo GeneXpert MTB/Rif sputum examination.

**Data collection**

The subjects were taken by consecutive sampling. Subjects who met the inclusion criteria underwent a general physical examination of vital signs and the lungs. After that, the research subjects were interviewed using a study questionnaire that had been prepared to obtain data on persons with T2DM, namely age, gender, length of time with T2DM, glycosylated hemoglobin (HbA1c) levels, levels of fasting plasma glucose (FPG), 2-hour post-prandial plasma glucose (PPPG) and data on risk factors for TB infection, namely history of BCG vaccination, presence of BCG scars, BMI, smoking history, alcohol history, history of contact with active TB patients, and symptoms of active TB. Assessment of nutritional status was carried out by anthropometric examination to assess body mass index (BMI) by measuring weight and height. BMI assessment is by dividing body weight (kg) by height in meters squared. The duration of diabetes diagnosis (years) in this study is based on the TANDEM study which divides the duration of diabetes into three categories, namely less than 5 years, 6-15 years and more than 15 years. TANDEM is a multicenter prospective study with field sites in Peru, Romania, South Africa and Indonesia, countries with diverse healthcare systems and population demographics, but all with a relatively high burden of tuberculosis and an increasing prevalence of DM.[8]

**QuantiFERON blood test**

For examination of latent TB with the QuantiFERON test (QFT), from each of the subjects 4 mL of venous blood was taken and 1 mL was put into each of 4 QFT tubes. The four tubes were then incubated at $37^0$C for 16"24 hours, then centrifuged, and the second stage was by ELISA examination. The QFT-Plus test is said to be positive if the IFN-γ level is <0.35 IU/mL

Furthermore, the subjects were asked to have a chest X-ray and each was given two sputum pots to collect sputum. The sputum used was morning sputum. The sputum pot that had been returned by the subjects was then sent in a bag containing a Blue Ice pack to the laboratory for Xpert MTB/Rif examination. The chest X-ray examination was carried out with the patient in the postero-anterior (PA) thoracic position at the radiology installation of the hospital and the resulting radiograph was read and interpreted by the radiology specialist on duty at that time.

**Test for latent tuberculosis**

The subjects were diagnosed with LTBI if the QFT-Plus test gave a positive result, the Xpert MTB Rif sputum examination was negative, and the chest X-ray was normal. If the QFT-Plus result was positive/negative/indeterminate, the results of the Xpert MTB Rif sputum examination were positive, and the chest X-ray was positive for TB, the study subject was diagnosed as having active TB. If the subjects obtained negative QFT-Plus results and the Xpert MTB/Rif sputum was negative, then the subjects were diagnosed as T2DM without TB infection.

We performed a risk factor assessment from the results of the QFT-Plus test. The subjects were divided into 2 groups, namely the positive and negative interferon gamma release assay (IGRA) groups. Then, data were collected regarding risk factors for LTBI including signs and symptoms of TB (cough, coughing up of blood, shortness of breath, chest pain, fever, weight loss, night sweats), history of BCG vaccination, presence of BCG scarring, history of contact with active TB patients, duration of contact, DM

duration, smoking history, alcohol history and for laboratory analysis measurement of HbA1c.

**Statistical Analysis**

The descriptive data in numeric form was presented as mean and standard deviation, whereas the nominal data was given as percentages. Bivariate analyses were performed to compare several variables between the two IGRA groups. Multiple logistic regression analysis was done to obtain adjusted OR (aOR) and 95% confidence interval. Data analysis was performed using Statistical Program for Social Sciences (SPSS) for Windows, version 24.

**Ethical clearance**

The study protocol was approved by the Ethics Committee, Universitas Indonesia, under number 17-07-0649 and ethical clearance number 610/UN2.F1/ETIK/2017.

**RESULTS**

**Study Subjects**

The subjects of the T2DM study consisted of 242 persons, with the majority being of the female sex, namely 147 subjects (60.7%). The largest age group was the age group of 60 years with 115 subjects (47.5%). The highest number of married subjects was 203 (83.9%) and the most frequent occupation was housewife, at 92 persons (38%). All T2DM subjects without a history of TB had had diabetes for an average of 10 years. The duration of diabetes (years) in this study are based on the TANDEM study which divides the duration of diabetes into three categories, namely less than 5 years, 6-15 years, and more than 15 years. Other variables are shown in Table 1.

Latent TB screening was carried out using IGRA QuantiFERON TB Gold Plus examination, Xpert MTB/Rif examination, and chest X-ray to eliminate active TB. From the examinations, we found 99 subjects (40.9%) with positive IGRA. There were 82 subjects with positive IGRA who met the criteria for latent TB, namely no clinical signs and symptoms of TB, negative MTB sputum

Table 1. Sociodemographic characteristics and several risk factors of the subjects (n=242)

| Characteristics | n (%) |
|---|---|
| Sex | |
| Male | 95 (39.3) |
| Female | 147 (60.7) |
| Age (years) | |
| <40 | 13 (5.4) |
| 40–49 | 28 (11.6) |
| 50–59 | 86 (35.5) |
| ≥60 | 115 (47.5) |
| Marital status | |
| Married | 203 (83.9) |
| Widow/widower | 33 (13.6) |
| Unmarried | 6 (2.5) |
| Profession | |
| Unemployed | 13 (5.4) |
| Housewife | 92 (38.0) |
| Employee | 77 (31.8) |
| Retiree | 60 (24.8) |
| History of alcohol consumption | |
| Yes | 3 (1.2) |
| No | 228 (94.2) |
| Ex-drinker | 11 (4.5) |
| History of TB contact | |
| Yes | 28 (11.5) |
| No | 133 (55.0) |
| Unclear | 81 (33.5) |
| History of smoking | |
| Smoker | 24 (9.9) |
| Non-smoker | 173 (71.5) |
| Ex-smoker | 45 (18.6) |
| HBA1c (%) | |
| <7 | 94 (38.8) |
| 7–9.9 | 108 (44.6) |
| ≥10 | 40 (16.6) |
| BCG vaccination | |
| Yes | 40 (16.6) |
| No | 26 (10.7) |
| Unclear | 176 (72.7) |
| BCG scar | |
| Yes | 135 (55.8) |
| No | 107 (44.2) |
| TB symptoms* | |
| Yes | 27 (11.2) |
| No | 215 (88.8) |
| BMI | |
| <18.5 | 5 (2.1) |
| 18.5 –22.9 | 69 (28.5) |
| 23.0 –24.9 | 65 (26.9) |
| ≥25.0 | 103 (42.5) |
| IGRA | |
| Positive | 99 (40.9) |
| Negative | 143 (59.1) |
| IFN-γ | |
| TB1 minus nil | 0.4 (0.0–10.0) |
| TB2 minus nil | 0.18 (0.0–10.0) |
| Xpert MTB/Rif* | |
| MTB detected | 1 (0.4) |

Data presented as n (%) except for IFN-γ [median (min-max); HbA1c: glycosylated hemoglobin; BCG: Bacille Calmette-Guérin; BMI: body mass index; IGRA: interferon-gamma release assay; IFN: interferon gamma; Xpert: Xpert MTB/Rif: *Mycobacterium tuberculosis* and resistance to rifampin

and normal chest X-ray. Only 1 subject (0.4%) was identified with active TB from the result of GeneXpert MTB/Rif sputum examination (MTB positive and no rifampicin resistance). None of the latent TB subjects had clinical symptoms and chest X-ray suggestive of TB or a positive GeneXpert MTB/Rif sputum examination. There were 105 subjects (43.4%) without clinical TB symptoms, who had negative IGRA, negative Xpert MTB/Rif sputum test, and normal chest X-ray.

There was no significant difference in history of TB contact between the two groups (p = 0.535). The presence of a BCG scar was found in different proportions in each group. There was no significant difference in BCG scar presentation between LTBI subjects and subjects without TB infection (p=0.063). The numbers of smokers and ex-smokers in LTBI subjects were greater than in subjects without TB infection. There was a significant difference in history of smoking between the LTBI group and the group without TB infection (p=0.020).

The value of HbA1c also showed an increasing pattern in the non-TB infection and LTBI groups at 7.6% and 8.5%, respectively. The proportion of subjects with HbA1c >10% was found to be significantly greater in latent TB subjects compared to those without TB infection (p=0.002). The subjects with obese BMI but without TB infection had higher BMIs compared to the latent TB group, but there was no significant difference between both groups (p=0.165) (Table 2).

Table 2. Comparison of several risk factors between patients with and without latent tuberculosis

| Variables | Latent TB (n=82) n (%) | Non Latent TB (n= 160) (%) | p value |
|---|---|---|---|
| History of TB contact | | | |
| Yes | 9 (11.0) | 11 (13.4) | 0.535[a] |
| No | 46 (56.1) | 47 (57.3) | |
| Unclear | 27 (32.9) | 24 (29.3) | |
| BCG scar | | | |
| Yes | 41 (50.0) | 53 (64.6) | 0.063[a] |
| No | 41 (50.0) | 29 (35.4) | |
| History of smoking | | | |
| Smoker | 16 (19.5) | 9 (10.9) | 0.020[a] |
| Ex-smoker | 10 (12.1) | 5 (6.2) | |
| Non-smoker | 56 (68.2) | 68 (82.9) | |
| Duration of diabetes (years) | | | |
| ≤5 | 20 (24.3) | 22 (26.8) | 0.831[a] |
| 6−15 | 41 (50.1) | 35 (42.6) | |
| >15 | 21 (25.6) | 25 (30.6) | |
| HbA1c(%) | | | |
| <7 | 22 (26.8) | 35 (42.6) | 0.002[a] |
| 7−9.9 | 43 (52.5) | 37 (45.2) | |
| ≥10 | 17 (20.5) | 10 (12.2) | |
| BMI (kg/m$^2$) | | | |
| <18.5 | 5 (6.1) | 1 (1.2) | 0.165[a] |
| 18.5−22.9 | 21 (25.6) | 23 (28.2) | |
| 23.0−24.9 | 21 (25.6) | 18 (21.9) | |
| ≥25.0 | 35 (42.7) | 40 (48.7) | |
| IFN-γ | | | |
| TB1 minus nil | 2.5±2.4 | 0.06±0.1 | <0.0001 |
| TB2 minus nil | 2.6±2.4 | 0.08±0.1 | <0.0001 |

Data is presented as n (%) except for IFN-γ as mean±SD; [a]: Chi square; [b]: t-test; HbA1c: glycosylated hemoglobin; BCG: Bacille Calmette-Guérin; BMI: body mass index; IFN: interferon gamma

Table 3. Multivariable logistic regression analysis of factors associated with LTBI in the T2DM subjects (n=242)

| Parameter | OR | aOR | 95 % CI | p value |
|---|---|---|---|---|
| Smokers | 0.904 | 2.469 | 1.151 – 5.295 | 0.031 |
| HBA1C >7% | 0.756 | 2.130 | 1.074 – 4.225 | 0.020 |
| No BCG scar | 0.678 | 1.970 | 1.029 – 3.773 | 0.041 |

OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; HBA1C: glycosylated hemoglobin; BCG: Bacille Calmette-Guérin

After multivariate analysis, we found only history of smoking, BCG scar, and HbA1c value as influencing variables for LTBI in T2DM.

Table 3 shows that history of smoking (smokers and ex-smokers) had a significant correlation with risk of LTBI in T2DM patients and was 2.5 times higher (aOR 2.47; CI 95% 1.151 6 5.295). Subjects with HbA1c value of >7% had a 2.1 times risk (aOR 2.13; CI 95% 1.074-4.225), and those lacking a BCG scar had a 2 times higher risk to become active TB (OR1.97; CI 95% 1.029-3.773).

## DISCUSSION

Of 242 T2DM subjects without TB history, 82 subjects had LTBI (33.9%) and 1 subject active TB (0.4%), based on a positive GeneXpert MTB/Rif sputum examination. The obtained prevalence for LTBI in DM was similar to what Koesoemadinata et al.[9] found. Our result was lower than that of a study in Mexico (51%) with an almost similar population, but higher than that of studies in Singapore (28.2%) and Malaysia (28.5%). Only 1 active TB patient was found in the present study, which is similar to that of a study by Leow et al.,[10] which only found 1 active TB patient among 220 patients screened for TB. A systematic review by Workneh et al.[11] mentioned that the TB prevalence in the DM population ranged between 0.38 6 14% with a median of 4.1%. Zheng et al.[12] found that the TB prevalence in the DM population of China ranged from 0.3 6 0.8. The lower prevalence in our study compared to Koesoemadinata et al.[9] may be because of the different study locations. West Java is the province with the highest TB prevalence in Indonesia while Jakarta is only number four. This surely may have affected the TB exposure.

The proportion of LTBI subjects with a smoking history showed that there were more non-smokers than ex-smokers and active smokers, but compared to the non-TB infection group, the LTBI group had more subjects with a history of smoking. We already know that smoking had an obvious relationship with increases in the risk of TB infection, active TB, relapse during TB treatment, and death from TB. Smoking affects the important biological defense mechanism against early TB infection and active TB. This includes abnormalities in airway secretion clearance, lowered function of lung macrophages, and decrease in IFNγ and TNF-α production. Smoking aggravates TB infection and increases the risk for active TB.[13] Some systematic reviews and meta-analyses had reported a correlation of cigarette smoke exposure with TB infection, active TB, and death from TB. Nicotine in cigarettes works through α 6nicotinic receptors which will reduce the production of TNF-α by macrophages to prevent protection against TB and increase the progress of TB infection. Cigarette smoke also will reduce the secretion of IL-12, IFN-γ, and TNF-α to prevent granuloma formation. This will cause an increase in the risk for TB infection which will later on develop into active TB.[13,14] A cross-sectional study in China also showed that smoking is a risk factor for LTBI especially in older smokers and that the risk was correlated with the number of cigarettes, while quitting smoking was closely related to successful LTBI therapy.[15] Detection of LTBI showing false negative IGRA results is more frequent in smokers than in non-smokers. Smoking also causes delayed sputum

conversion which prolongs therapy.[13,14] Exposure to cigarette smoke whether first-hand or second-hand smoking is related to the risk of TB infection and can cause active TB. A study by Bai et al.[16] showed that Taiwan had a relative risk of 5.61 for positive microscopic sputum examination in TB smokers with DM than in TB non-smokers without DM. Therefore TB-DM comorbidity is in general presumably more often found in smokers than in non-smokers.

Hemoglobin A1c is a product of glucose binding to hemoglobin (Hb) in erythrocytes. Examination of this parameter is a gold standard examination to evaluate control of blood glucose. Generally, the half-life of Hb is approximately 3-4 months so the value of HbA1c reflects the control of blood glucose over a long period of time. Based on the American Diabetes Association Complete Guide to Diabetes,[17] HbA1c has been approved as the glycemic control measurement parameter in DM patients. The level of diabetic control in our study as measured by HbA1c showed uncontrollable diabetes in LTBI subjects. Martinez et al.[18] in their study found the mean of HbA1c in TB diabetic subjects to be 7.5, which is lower than the 8.5% in our study, which shows that an HbA1c value of >7% is correlated with the incidence of LTBI in DM patients. Our study is in line with a meta-analysis by Chen et al.[19] who concluded that the TB prevalence will increase by 2.05 times in patients with an HbA1c of >7% compared to patients with an HbA1c of <7%. An epidemiological study in America also showed that patients with poor glycemic control had a 2.2 times higher risk of latent TB infection than had patients without diabetes. The high HbA1c level shows poor glycemic control and is correlated with an increased risk of diabetic complications which further increases the risk for TB infection. The effect of the increase in HbA1c level on the natural and adaptive immune system has been known from some studies. HbA1c is related to a receptor for advanced glycation end product (RAGE). Among the functions of RAGE is participating in the control of T cell activation and differentiation. One study showed that an elevated HbA1c level might be a factor contributing to Hb structural modifications in diabetics, which may have deleterious effects linked to the pathological complications of type 2 diabetes mellitus. [20] Reaching glycemic control in countries with a high diabetic burden in Asia is quite difficult due to the lack of optimum health facilities, poor education, and great economic disparity. A 5-year survey of 11,799 diabetes patients, among whom 5,888 were from Asia, showed that only 20–30% had an HbA1c of <7%.[21] The Diabcare-Asia project performed a cross-sectional study and reported that among 24,317 diabetic patients from Bangladesh, China, Indonesia, Malaysia, Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, and Vietnam, 55% had an HbA1c value of >8%.[11] Poor glycemic control in Asian diabetes patients, including those from Indonesia, is an important factor in the development of LTBI and also the reactivation of latent TB in patients with DM. Gomez et al.[22] in their study showed that attachment to and ingestion of *M. tuberculosis* by monocytes in DM subjects were lower compared to non-DM subjects. Multivariate analysis showed poor glycemic control as measured by HbA1c and FBG as predictive factors for the low interaction between *M. tuberculosis* and monocytes.

Our study showed that the absence of a BCG scar affected the incidence of latent TB in type 2 DM. This result is in line with the study by Lin et al.[23] which reported that the presence of a BCG scar protected T2DM patients against LTBI. The study by Chen et al.[24] also showed that BCG vaccination is a protective factor against latent TB. Some studies showed similar results and found that the effectivity of BCG vaccine protectivity towards TB infection was 59%.[25]

The present study has some limitations including the fact that some misleading factors such as uncontrollable socioeconomic and environmental factors which might be correlated with DM affect the measurement of LTBI risk. However, the present study used the Quantiferon TB Gold Plus test which is the latest generation

of IGRA for measuring IFN-γ not only from CD4 but also from CD8, so that the reduced sensitivity in T2DM can be managed. The clinical implication of our study is the increased awareness of T2DM patients in the future, because they have a high risk of LTBI. A longitudinal study is therefore required to identify the predictive value of HbA1c for progression to active TB in patients with DM.

## CONCLUSION

This study demonstrated that a high HbA1c level is a risk factor of LTBI in patients with T2DM from a geographic area that has a high incidence of TB. It is important to perform TB screening in DM patients due to the high risk for LTBI and progression to active TB.

## CONFLICT OF INTEREST

The authors have no financial or personal conflicts of interest in the present study.

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## CONTRIBUTORS

YA contributed to the conception of the study, data collection and final approval of the version to be published. DB contributed to data analysis and interpretation. D contributed to drafting the manuscript. All authors have read and approved the final manuscript.

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