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Original Article

Prevalence and risk factors for latent tuberculosis among diabetes patients in Taiwan: A cross-sectional study

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Abstract

Introduction: Diabetes mellitus (DM) is a known risk factor for tuberculosis (TB), leading to an approximate three-fold higher risk of developing active TB. However, epidemiological studies on the prevalence of latent TB infection (LTBI) in DM patients are lacking. In this study, we investigated the presence of LTBI and determined risk factors for LTBI in DM patients.

Methodology: We conducted a cross-sectional study at Taipei Medical University-Shuang Ho Hospital in northern Taiwan. The study population comprised DM patients (aged 20-70 years) attending a metabolism outpatient clinic between February 2011 and February 2013, excluding patients who were suspected or confirmed to have active TB. Venous blood samples were drawn from patients to detect LTBI using the QuantiFERON-TB Gold In-Tube (QFT-GIT) method.

Results: We enrolled 1120 patients with DM. The QFT-GIT showed positive results for 241 people (21.5%) and negative results for 879 people (78.5%). The mean age at QFT-GIT positivity was 58.2 years, which was significantly dissimilar to the mean age at QFT-GIT negativity, which was 55.0 years ($p < 0.001$). Multivariate logistic regression indicated that the trend of QFT-GIT positivity increased after the age of 50 years. Effective glycemic control did not differ significantly between QFT-GIT-positive and -negative patients. Moreover, men were predominant were predominant in both QFT-GIT-positive and -negative patients.

Conclusions: More than one-fifth of DM patients have LTBI. Among the DM patients, those older than 50 years may have a higher risk of LTBI. Moreover, effective glycemic control did not differ significantly in patients with LTBI.

Key words: Latent tuberculosis infection; diabetes; interferon gamma release assays (IGRA); QuantiFERON-TB Gold In-Tube method (QFT-GIT).

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Introduction

Every year, 10 million cases of new active tuberculosis (TB) infection are diagnosed, and nearly 1.2 million deaths worldwide are attributed to TB [1]. For many centuries, clinicians have observed an association between diabetes mellitus (DM) and TB [2]. The frequency of TB in DM patients is reported to be three-fold higher than that in patients without DM [3]. Various studies have suggested that approximately 30% of patients with TB may also have DM [4,5]. Most people who are exposed to *Mycobacterium tuberculosis* do not contract active TB but developed latent TB instead. Latent TB infection (LTBI) is a clinical state that has an immunological positive response to *M. tuberculosis* infection without clinical and radiographic evidence of TB-related symptoms and pathology. LTBI may later progress into active TB in some people. The risk of developing active TB increases with the presence of several underlying factors such as old age, human immunodeficiency virus (HIV) coinfection, DM, smoking, malnutrition, and chronic renal failure [6].

The tuberculin skin test (TST) has previously been used for TB screening; however, because of its cross-reaction with nontuberculous mycobacterial species and the Bacillus Calmette–Guérin (BCG) vaccine, the test results are ambiguous, particularly in regions with numerous BCG-vaccinated people or a high TB

incidence [7]. Novel interferon gamma (IFNγ) release assays (IGRA) have been introduced for detecting LTBI, IGRA involves the measurement of IFNγ secreted by the T cells stimulated in vitro with specific *M. tuberculosis* complex antigens, such as early secretary antigenic target-6 (ESAT-6), culture filtrate protein 10 (CFP-10), and Rv2654 (TB7.7) [8,9]. Performing IGRA in BCG-vaccinated populations can improve the diagnostic specificity and facilitate accepting treatment for LTBI [10]. Therefore, the 2010 US Centers for Disease Control and Prevention guidelines recommends IGRA, instead of TST, to diagnose *M. tuberculosis* infections in all circumstances [11].

The incidence rate of the reported TB in Taiwan in 2012 was approximately 53 per 100,000 individuals, and the mortality rate was nearly 2.7 per 100,000 individuals [12]. In Taiwan, the BCG vaccine is administered in early childhood, and followed by boosters administered later in life, which limited screening for LTBI through the traditional TST in Taiwan. Therefore, this study investigated the prevalence of LTBI among DM patients by Taiwan by using IGRA to determine risk factors for LTBI in the DM population

Methodology

Study design

We conducted a cross-sectional study at Taipei Medical University-Shuang Ho Hospital, a regional hospital in northern Taiwan. The study population comprised DM patients (age 20-70 years) who visited metabolism outpatient clinic between February 2011 and February 2013. The patients who were being investigated or treated for active TB and patients who had been receiving treatment for suspected or confirmed TB were excluded. The patients with HIV infection, autoimmune diseases using immunomodulator, cancers treated with chemotherapy within the last 3 months, liver cirrhosis, or hepatitis were excluded from this study. The institutional review board of the university approved this study, and all participants provided written informed consent.

Demographic and clinical data were collected from patients' medical records and using a questionnaire. The variables included age, sex, underlying co-morbidities, past TB disease, TB contact history, smoking status, and blood hemoglobin A1c.

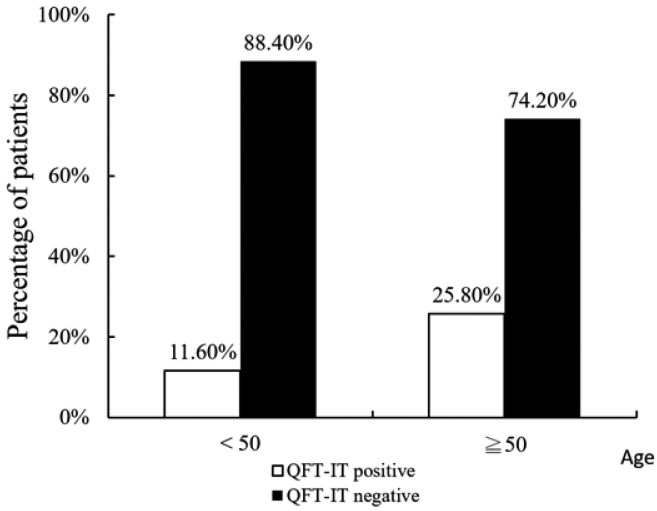
Procedures

Venous blood samples were collected from patients for detecting LTBI based on the QuantiFERON-TB Gold In-Tube (QFT-GIT) method (Cellestis, Australia), which was performed according to the manufacturer's instructions. The interferon-gamma (IFN-γ) concentrations (IU/mL) in plasma were measured using an enzyme-linked immunosorbent assay (ELISA) reader and were calculated using QFT-GIT-analysis Software. IGRA test results were interpreted as negative if the TB antigen minus nil was < 0.35 IU/mL, or if the TB antigen minus nil was ≥ 0.35 IU/mL, but was < 25% of the Nil value; on the contrary, test results were interpreted as positive if the TB antigen minus nil was ≥ 0.35 IU/mL and > 25% of the nil value.

Statistical analysis

Statistical analyses were conducted using SPSS, version 18.0 (Chicago, IL, USA), and data were presented as mean and standard deviation (SD). Univariate analysis of risk factors for positive QFT-GIT results was performed using Student's t-test for numerical variables and the chi-square test for categorical variables. Multivariate analysis of risk factors for positive QFT-GIT results was performed using logistic regression. All potential predictors were included in the stepwise variable selection procedure. A two-sided p value < 0.05 was considered statistically significant.

Figure 1. Association of age with the prevalence of latent TB infection in diabetes patients.



There was a higher QFT-GIT positive rate in patients who had an older age at DM onset, and the mean age at DM onset among patients was significantly higher than that among their negative counterparts (51.38 vs 49.20, p = 0.002). TB: tuberculosis; QFT-GIT: QuantiFERON-TB Gold In-Tube; DM: diabetes mellitus.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and took final responsibility of the decision to submit the manuscript for publication.

Results

A total of 1,120 patients were included in this study. The QFT-GIT showed a positive result for 241 people (21.5%) and a negative result for 879 people (78.5%). The mean age at QFT-GIT positivity was 58.2 years (58.20 ± 7.26), which differed significantly from the mean age of QFT-GIT negativity, which was 55.0 years (55.00 ± 8.73, $p < 0.001$) (Table 1) (Figure 1). Mean age at DM onset in QFT-GIT-positive patients was significantly higher than that among their negative counterparts (51.38 ± 8.64 versus 49.20 ± 9.24, $p = 0.002$). No significant differences were observed in body mass index, smoking status, and TB contact history.

We analyzed the correlation between glycemic control and QFT-GIT and determined that neither the average HbA1c value nor the highest HbA1c value recorded over the past three years significantly differed among QFT-GIT-positive and -negative patients (Table 1). Various medications for DM may indicate DM severity; therefore, we analyzed the correlation between the medications of the patients and QFT-GIT, but our results showed no significant correlation (Table 2).

There were no significant differences according to sex between the QFT-GIT-positive and -negative patients (Table 1), wherein men were predominant (58.02% vs 55.01% male patients). However, when we adjusted by age group (20-39, 40-49, 50-59, and 60-69 years), distinctive patterns of male predominance emerged (Figure 2). In the QFT-GIT-negative group, male predominance was observed in the first three age groups (71.4%, 58.8%, and 50.1% male patients, respectively), and female predominance was noted in the 60-70 years' age group (47.6% male patients). Men were predominant in all age groups of the QFT-GIT-positive group (60%, 81.8%, 60%, and 50%,

Table 1. Clinical characteristics of patients with different result of QFT-GIT test.

	QFT-Positive (N = 241, 21.5%)	QFT-negative (N = 879, 78.5%)	p
Age, year, mean ± SD	58.20 ± 7.26	55.00 ± 8.73	< 0.001
Male gender, n (%)	138 (57.3%)	459 (52.2%)	0.164
BMI, Kg/m^2, mean ± SD	26.33 ± 3.57	26.29 ± 4.31	0.904
Age of onset of DM, year, mean ± SD	51.38 ± 8.64	49.20 ± 9.24	0.002
Duration of DM, year, mean ± SD	6.78 ± 6.64	5.73 ± 5.66	0.015
Maximum A1c in recent 3 years (%)	9.31 ± 2.10	9.55 ± 2.23	0.142
Average A1c in recent 3 years (%)	7.73 ± 1.29	7.85 ± 1.32	0.233
Current smoker (%)	73 (30.3%)	207 (23.5%)	0.098
Malignancy (%)	5 (2.1%)	44 (5.0%)	0.051
TB exposure history (%)	15 (6.2%)	55 (6.3%)	0.737

* Student t test for numerical variables, χ^2 test for categorical variables; QFT-GIT: QuantiFERON-TB Gold In-Tube; DM: diabetic mellitus; TB: tuberculosis.

Table 2. Association between medications and GFT-GIT results in diabetic patients.

	QFT-Positive	QFT-negative	$p^{\#}$
Oral Antidiabetic Drugs, n (%)*			0.387
0	8 (4)	40(5.4)	
1	64 (31.7)	239 (32.3)	
2	84 (41.6)	289 (39.1)	
3	37 (18.3)	155 (20.9)	
4	9 (4.5)	17 (2.3)	
Insulin, n (%)	38 (15.8)	132 (15.1)	0.791
Metformin, n (%)	207 (86.2)	741 (85.0)	0.622
Sulfonylureas, n (%)	149 (62.1)	532 (61.0)	0.762
TZD, n (%)	14 (5.8)	30 (3.4)	0.092
DPP4I, n (%)	43 (17.9)	177 (20.3)	0.412
AGI, n (%)	24 (10.0)	69 (7.9)	0.301

* 0 means patients did not take oral antidiabetic drug (OAD), 1 means patients took one OAD, 2 means patients took two kinds of OAD, 3 means patients took three kinds of OAD, 4 means patients took four kinds of OAD; TZD: thiazolidinedione; DPP4I: dipeptidyl peptidase 4 inhibitor; AGI: alpha-glucosidase inhibitor; # χ^2 test.

respectively). A steady decline in the proportion of men was noticeable after the age of 40 years.

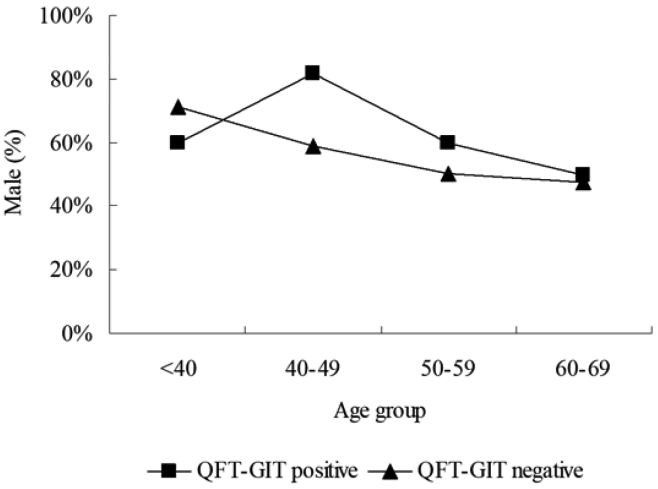
Multivariate logistic regression indicated an increasing trend after the age of 50 years (Table 3). No significant difference was observed in the age of initial DM diagnosis and DM duration. We used 50 years of age as the cut-off point and determined that patients older than 50 years had a significantly higher prevalence than did patients younger than 50 years (11.6% vs 25.8%, $p < 0.001$).

Discussion

This study showed that there is a high prevalence (21.5%) of LTBI among DM patients in a country with intermediate burden of TB as determined using the IGRA test, which is in line with the findings of other studies. A study performed in Taiwan reported a 21.1% positive rate of LTBI among DM patients, which is similar to the finding noted in our study [13]. Higher prevalence was reported in several studies worldwide: 38.9% (Indonesia) [14], 43.4% (Atlanta) [15], and 51.3% (Mexico) [16]. A systematic review and meta-analysis of 13 studies, concluded that DM increases the risk of LTBI [17]. Two other studies conducted in Taiwan and Atlanta also revealed a higher incidence of LTBI in DM patients than in those without DM [13,15].

Age is the most common risk factor for TB development in DM patients. A study conducted in southern Mexico determined that the prevalence of DM-related active TB infection was higher in the 45-to 64-year-old age group [18], a finding that may also apply to LTBI patients. A study on health care workers in Germany reported that age was a putative risk factor for LTBI, and that workers older than 55 years (odds ratio [OR] 14.7, 95% confidence interval [CI] 5.1-42.1) exhibit higher positive IGRA results, than those younger than 25 years [19]; these results corresponded to those of the current study. Another study, conducted in Malaysia, showed that health care workers older than 35 years had higher LTBI rates than those younger than 24 years (OR 9.49, 95% CI 2.22-40.50) [20]. In summary, active TB or LTBI occurred more frequently among people older than 35 years. In our study, age older than 50 years has a higher incidence of LTBI than younger age (OR 2.974, 1.149-7.698, $p = 0.025$). A study on recently arrived refugees in Atlanta revealed that patients with LTBI tended to be older [21].

Figure 2. Association of age and gender with the prevalence of latent TB infection in diabetes patients.



We categorized the QFT-GIT-positive and -negative male patients into four groups (20-39, 40-49, 50-59, and 60-69 years). In the QFT-GIT-negative group, male predominance was observed in the first three age groups (71.4%, 58.8% and 50.1% of male patients, respectively). Men were predominant in all age groups of the QFT-GIT-positive group (60%, 81.8%, 60%, and 50%, respectively). A steady decline in the proportion of men was noticeable after the age of 40 years. TB: tuberculosis; QFT-GIT: QuantiFERON-TB Gold In-Tube; DM: diabetes mellitus.

Table 3. Factors associated with latent TB infection diagnosed by QFT-GIT in multivariate logistic regression.

Risk Factors	Multivariate	
	OR (95% CI)	p
Age, years		
< 40	1.00	
40-49	1.305 (0.464-3.673)	0.614
50-59	2.974 (1.149-7.698)	0.025
60-69	3.429 (1.325-8.873)	0.011
Duration of DM, years		
< 1	1.00	
1-9	1.322 (0.855-2.045)	0.209
≥ 10	1.558 (0.855-2.840)	0.148
Age of onset of DM, years		
< 40	1.00	
40-49	1.476 (0.740-2.945)	0.892
50-59	1.574 (0.701-3.533)	0.352
60-69	1.830 (0.670-4.999)	0.385

QFT-GIT: QuantiFERON-TB Gold In-Tube; DM: diabetic mellitus; TB: tuberculosis.

Currently, the World Health Organization guideline does not recommend screening for LTBI in DM patients. However, screening for LTBI among DM patients older than 50 years may be justified. Further study of the benefits of this kind of limited LTBI screening is needed.

In the current study, we observed a steady decline in the proportion of men with increasing age in both the QFT-GIT-positive and -negative groups. It is known that DM is more prevalent among women than among men, and in this study, the prevalence increases as age increases. Numerous studies have reported male predominance among non-DM pulmonary TB patients. The female-to-male ratio was < 1, and it decreased with increasing age [22]. In a study conducted by Perez-Guzman *et al.*, male DM patients had pulmonary TB; however, a steady decline was observed in the proportion of men with increasing age, and this differed from non-DM patients [23]. A commonly accepted explanation for the higher number of men with TB is that men are more socially active than women, which predisposes them to a higher transmission rate of *M. tuberculosis.* However, this theory cannot explain the results among DM patients.

Questions regarding whether effective glycemic control affects both immunity and LTBI incidence have been posited. One study showed that IFNγ production was impaired under high-glucose conditions [24]. A study conducted in Hong Kong that examined 4690 elderly DM patients indicated that people who had an HbA1c value greater than 7% had a three-fold risk of active TB, a risk that was higher than that in people with an HbA1c value of less than 7% [25]. These data suggested that poor glycemic control was a risk factor for TB. Our study showed that neither HbA1c values nor the highest HbA1c value recorded over the past three years significantly differed among QFT-GIT-positive and –negative patients. A study performed in Taiwan also concluded that glycemic control is not related to the risk of LTBI. However, one study drew a conclusion contrary to that of our study. A study in Mexico showed that poorly-controlled DM patients (HbA1c > 7%) have a higher risk of developing LTBI. The relationship between glycemic control and LTBI is not established.

Conclusions

A high prevalence of LTBI among DM patients (21.5%) was observed in this study. Among DM patients, those older than 50 years may belong to the higher-risk group for LTBI. In addition, effective glycemic control did not show significant variances in the presence of LTBI. However, some aspects remain to be investigated, such as cost-effectiveness of the approach used in screening for LTBI among DM patients older than 50-years, and the possible benefit of preventive treatment of LTBI in DM patients.

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Authors' Contributions

CNL and ATH provided the initial idea for the study. ATH and KYT developed the protocol. AC, ATH, CZW, JDL, KYT, and PHW introduced the study to the patients and invited them to join this study. All authors analyzed and interpreted the data. AC and ATH wrote the first draft of the manuscript. All authors contributed to the preparation of subsequent versions of the manuscript and approved the final version for publication. ATH is the guarantor.

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