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Latent tuberculosis infection and diagnostic performance of the tuberculin skin test among type 2 diabetics in Sana'a city, Yemen

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Abstract

Background Tuberculosis (TB) is one of the most widespread infectious diseases worldwide, typically persisting in the body as a latent TB infection (LTBI). Patients with type 2 diabetes have an increased risk of LTBI progressing to active TB. Therefore, this study determined the prevalence and predictors of LTBI and assessed the agreement between tuberculin skin test (TST) and interferon-gamma release assay (IGRA) in diagnosing LTBI among type 2 diabetics in Sana'a city, Yemen.

Methods A cross-sectional study was conducted among 150 type 2 diabetics in private health facilities in Sana'a in 2023. Data about demographics, diabetes-related characteristics, and potential risk factors for LTBI were collected using a structured questionnaire. Patients were then screened for LTBI using TST and IGRA. Univariate analysis was used to identify LTBI-associated risk factors, and multivariable binary logistic regression was used to identify independent predictors of LTBI. The agreement between TST and IGRA for diagnosing LTBI was assessed using Cohen's kappa coefficient (κ).

Results LTBI was prevalent among 29.3% of type 2 diabetics using both types of tests (25.3% with IGRA and 21.3% with TST). Male gender was an independent predictor of LTBI (AOR = 4.4, 95% confidence interval: 1.30–15.08; $P = 0.018$). However, being employed (AOR = 0.3, 95% CI: 0.09–0.75; $P = 0.013$) and longer duration since diabetes diagnosis (AOR = 0.3, 95% CI: 0.12–0.98; $P = 0.046$) were identified as predictors of lower LTBI risk. The agreement between TST and IGRA for the diagnosis of LTBI was 88%, with a good and statistically significant agreement between the two test types ($\kappa = 0.670$; $P < 0.001$).

Conclusions LTBI is common among type 2 diabetics seeking medical care in Sana'a city, with about one-third of them possibly being latently infected. A higher LTBI risk can be predicted among males, while a lower risk can be predicted among those employed or being diagnosed with diabetes for at least five years. The TST shows good agreement with IGRA in diagnosing LTBI among type 2 diabetics, supporting its continued use as a cost-effective and easily accessible test for diagnosing LTBI in the country.

Keywords Latent tuberculosis infection, Type 2 diabetics, Tuberculin skin test, Interferon-gamma release assay, Yemen

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Introduction

Tuberculosis (TB) is one of the most common communicable diseases, affecting approximately one-third of the world's population [1]. In 2022, the World Health Organization (WHO) estimated that there were 7.5 million newly diagnosed TB cases worldwide, with an incidence rate of 133 cases per 100,000 people, and designated the disease as the second highest cause of death from a single infectious agent worldwide after coronavirus disease 2019 (COVID-19) [2]. In Yemen, TB is a major public health problem, with an estimated incidence of 48 cases per 100,000 people in 2022 [3]. The prevalence of LTBI among healthcare workers (HCWs) in tertiary care hospitals in Sana'a city was found to be 20% using the interferon-gamma (IFN-γ) release assay (IGRA) but varied from 12.2 to 50.5% using the tuberculin skin test (TST) [4–6], highlighting the high burden of LTBI among at-risk populations in the country. However, the true burden of TB in the country may be underestimated [7]. In Yemen, infants are routinely vaccinated with Bacillus Calmette-Guérin (BCG) shortly after birth as part of the national immunization schedule. However, reported BCG coverage in the country has varied over the years and by geographical area [8]. However, the administrative coverage was only 70% in 2021 compared to 65% in 2010 [8], with the absence of independent third-party survey coverage. Armed conflicts, humanitarian crises and challenging circumstances in the country over the past decade have severely compromised the capacity of the National TB Control Programme and TB centres, resulting in inadequate support and resources. Therefore, extensive efforts are needed to prevent the spread of TB in the country, taking into account the fragile health system infrastructure and the limited resources available.

Latent tuberculosis infection (LTBI) occurs when the immune response to *Mycobacterium tuberculosis* antigens persists without clinically manifesting as an active disease [9]. Therefore, the main goal of LTBI treatment is to prevent progression to active TB, particularly in high-risk populations living in regions with TB burden [10]. While the exact mechanism of TB progression is not yet fully understood, patients with non-communicable diseases (NCDs) that impair their immune systems are more susceptible to LTBI reactivation into active TB [11]. This issue is worrying as the global burden of TB and NCDs increases. The coexistence of LTBI and NCDs can have synergistic negative effects on the health of individuals and the entire population [12]. Although only about 10% of people with LTBI ever experience reactivation, the risk of progression to active TB increases in patients with immunosuppression [13].

Diabetes mellitus (DM) is a chronic metabolic disorder that weakens the immune system and increases susceptibility to infections, including TB. It can increase TB incidence by threefold [14]. The upsurge in the global prevalence of DM, especially in countries with high TB burdens, raises concerns about its potential impact on TB control efforts worldwide [15]. The coexistence of these two diseases stems from the "pandemic" of type 2 diabetes, which is projected to affect 366 million people by 2030 [16]. According to WHO, over 95% of all diabetes cases worldwide are type 2 diabetes [17], and approximately 7.7% of the Yemeni population is estimated to have type 2 diabetes [18]. DM is recognized as a significant but often overlooked risk factor for active TB [19], influencing the clinical presentation, progression and mortality risk associated with TB. Hyperreactive T cells represent one aspect of the defective immune response in diabetics, potentially altering the clinical course of TB in this population [20]. Although a previous study found that DM was significantly associated with IGRA positivity among HCWs in tertiary care hospitals in Sana'a city of Yemen [5], the prevalence and risk factors associated with LTBI among this at-risk population remain unclear.

Screening and treating high-risk populations for LTBI is a key strategy in TB prevention and control [21]. LTBI screening involves assessing the immune response using TST or IGRA [22]. While TST is commonly used for LTBI screening, its interpretation can be challenging. It may yield false-positive results in people who have received the BCG vaccine or are infected with non-tuberculous mycobacteria (NTM) [23, 24]. False-negative results can also be caused by errors in antigen administration or result reading, as well as poor cold chain maintenance [23, 24]. Moreover, individuals from impoverished and remote communities incur indirect costs associated with revisiting health facilities for test result readings [23, 24]. On the other hand, IGRA is a more specific in vitro test that detects the release of IFN-γ by lymphocytes exposed to specific antigens of *M. tuberculosis*, making it unaffected by BCG vaccination or NTM infection. However, it is more expensive and requires a well-equipped laboratory [25]. The combination of TST with IGRA can increase the sensitivity of LTBI detection in immunocompromised patients [21]. In Yemen, TST is routinely used for LTBI screening in TB centres, as well as in public and private health facilities engaged in TB diagnosis and treatment. Therefore, it is crucial to assess its agreement with IGRA for the diagnosis of LTBI.

Given the rising incidence of type 2 diabetes and the lack of published studies on LTBI among type 2 diabetics in Yemen, this study aimed to determine the prevalence and risk factors associated with LTBI among type 2 diabetics in Sana'a city, Yemen. In addition, the agreement between TST and IGRA in diagnosing LTBI in this population was assessed.

Methods

Study design and population

A cross-sectional study was conducted among type 2 diabetics seeking medical care in private health facilities in Sana'a city from February to June 2023. Adult male and female patients were eligible for inclusion in the study if they provided written informed consent to participate voluntarily. Diabetics with other immunocompromising conditions were excluded from the study.

Sample size and sampling method

Using OpenEpi, version 3.01 (available at www.openepi.com), a minimum sample size of 148 diabetics was determined based on an expected LTBI prevalence of 10.8% in the neighbouring country of Saudi Arabia [26], a confidence level of 95%, an absolute precision of 5%, and a design effect of 1, assuming that the diabetic population is relatively homogeneous and not influenced by clustering. However, 150 patients were recruited for the study. A multi-stage cluster sampling approach was employed to ensure a representative sample, with the city districts serving as study clusters. First, four out of ten districts were randomly selected; namely, Al Wahdah, As Sabain, At Tahrir, and Ma'ain. Second, a list of private health facilities in each selected district was prepared, and four facilities were then randomly selected. Third, all type 2 diabetics attending the selected facilities were invited to participate in the study using a convenience sampling approach until the required sample size was reached.

Data collection

Data on diabetics' demographic and diabetes-related characteristics, along with potential risk factors for LTBI, were collected using a structured questionnaire (Supplementary File 1) through face-to-face interviews. The questionnaire was pilot tested for content and face validity by three experts in the field, as well as for clarity and length among a group of 20 type 2 diabetics who were not included in the data analysis. Based on the feedback received, necessary modifications were made to the final version of the questionnaire used for data collection.

IGRA performance

For the diagnosis of LTBI with IGRA, the commercial kit QuantiFERON-TB Gold (QIAGEN, Hilden, Germany) was used to measure IFN-γ release by enzyme-linked immunosorbent assay (ELISA), as instructed by the manufacturer. Briefly, a trained HCW collected 3 ml of whole blood from each patient into a heparin tube, which was dispensed as 1 ml aliquots into each of the three tubes provided with the kit: one for the assay and the other two for negative and positive controls. The tubes were immediately incubated at 37 °C for 24 h, and the plasma was then separated by centrifugation. Then, IFN-γ was measured in plasma samples using the readwell TOUCH™ automatic ELISA reader (ROBONIK, Thane, India), and the results were interpreted as specified by the manufacturer.

Intradermal TST

The TST was performed and interpreted according to the US Centers for Disease Control and Prevention guidelines [27]. Briefly, 0.1 ml of tuberculin solution (ARKRAY Healthcare, Gujrat, India) was injected intradermally into the inner surface of a forearm. As a negative control, 0.1 ml of sterile normal saline was injected into the other forearm to minimize the potential for misinterpreting non-specific reactions, such as hives or inflammation, as positive TST results. The test result was read 48 to 72 h after injection, and induration of $\geq$10 mm on the test forearm indicated a positive test [27].

Data analysis

Data were analysed using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA) at a significance level of <0.05. Continuous variables were summarized using the mean and standard deviation (SD) for normally distributed data, while the median and interquartile range (IQR) were used for non-normally distributed data. On the other hand, frequencies and proportions were used to describe categorical variables. The prevalence of LTBI among type 2 diabetics was calculated and disaggregated by the results of IGRA and TST, along with the corresponding 95% confidence intervals (CIs).

Univariate analysis using binary logistic regression was used to assess the association between the independent variables and LTBI, along with reporting the odds ratios (ORs) and 95% CIs of the associations. Independent predictors of LTBI were then identified using multivariable binary logistic regression, and their adjusted ORs (AORs) and 95% CIs were also reported. The IGRA results were used in the logistic regression analyses because of the higher specificity of IGRA, which helps reduce misclassification of diabetics with false-positive LTBI. Cohen's kappa coefficient (κ) was used to assess the level of agreement between TST and IGRA for diagnosing LTBI. The level of agreement was classified as poor ($\kappa<0.20$), fair ($\kappa=0.20$–0.40), moderate ($\kappa>0.40$–0.60), good ($\kappa>0.60$–0.80), or very good ($\kappa>0.80$) [28].

Results

Study population characteristics

The mean age of type 2 diabetics in this study was 51.4 ± 12.1 years, ranging from 19 to 85 years, and more than half of them were middle-aged adults (36 to 55 years old). Most diabetics were males (57.3%), urban

residents (74.7%), married (89.3%), literate (72.7%), unemployed (58%), and living in large-sized households with at least five members (78%). The mean percentage of glycated haemoglobin (HbA1c) was 9 ± 2%, with 84.7% of diabetics having an HbA1c percentage of 7% or higher. On the other hand, the median duration since diagnosis of type 2 diabetes was 7 (IQR of 9) years, with 64% of patients having been diagnosed for at least five years and 94.7% reporting antidiabetic medication use (Table 1).

Table 1 Characteristics of the study population*

Characteristics	*n*	(%)
Gender		
Male	86	(57.3)
Female	64	(42.7)
Age (years)		
Mean ± SD (range): 51.4 ± 12.1 (19–85)		
19–35	18	(12.0)
36–55	80	(53.3)
≥ 56	52	(34.7)
Residence		
Rural	38	(25.3)
Urban	112	(74.7)
Literacy status		
Literate	109	(72.7)
Illiterate	41	(27.3)
Employment status		
Employed	63	(42.0)
Unemployed	87	(58.0)
Marital status		
Married	134	(89.3)
Unmarried	16	(10.7)
Household size (members)		
Median (IQR): 6 (3)		
Small-to-medium (< 5)	33	(22.0)
Large (≥ 5)	117	(78.0)
HbA1c (%)		
Mean ± SD: 9.0 ± 2.0		
< 7	23	(15.3)
≥ 7	127	(84.7)
Duration of diabetes (years)		
Median (IQR): 7 (9)		
< 5	54	(36.0)
≥ 5	96	(64.0)
Antidiabetic medication use		
Yes	142	(94.7)
No	8	(5.3)

* The total number of diabetics included in the study was 150. SD standard deviation; IQR interquartile range; HbA1c glycated haemoglobin.

Prevalence of LTBI among type 2 diabetics

The overall prevalence of LTBI among type 2 diabetics was 29.3% (95% CI: 23–37). Specifically, 25.3% of cases (95% CI: 18–32) were diagnosed using IGRA, while 21.3% (95% CI: 16–29) were identified using TST (Table 2).

Risk factors for IGRA-based LTBI

Gender was significantly associated with LTBI in univariate analysis, with males being 2.6 times more likely to have an infection compared to females (OR = 2.6, 95% CI: 1.16–5.87; $P = 0.018$). Furthermore, male gender was identified as an independent predictor of LTBI in multivariable analysis (AOR = 4.3, 95% CI: 1.25–14.90; $P = 0.021$). Although employment status (OR = 0.8, 95% CI: 0.35–1.60; $P = 0.456$) and the duration since diabetes diagnosis (OR = 0.7, 95% CI: 0.33–1.50; $P = 0.364$) showed no significant association with LTBI infection in univariate analysis, employment (AOR = 0.3, 95% CI: 0.09–0.75; $P = 0.013$) and longer duration since diabetes diagnosis (AOR = 0.3, 95% CI: 0.12–0.98; $P = 0.046$) were identified as predictors of low LTBI risk by multivariable logistic regression. Nevertheless, LTBI showed no significant association with age, place of residence, literacy status, marital status, household size, glycaemic control, antidiabetic medication use, family history of TB, household contact with TB patient(s), or smoking status (Table 3).

Agreement between IGRA and TST for LTBI diagnosis

The agreement between TST and IGRA in diagnosing LTBI among type 2 diabetics was 88%, with a good and statistically significant level of agreement between the two types of tests ($k = 0.67$; $P = 0.001$) (Table 4).

Discussion

To the best of our knowledge, no previous studies on the prevalence and risk factors associated with LTBI among type 2 diabetics or the diagnostic agreement of TST with QuantiFERON IGRA have been published in Yemen. In this study, the combined use of TST and IGRA revealed

Table 2 Prevalence of LTBI among type 2 diabetics seeking medical care in private health facilities in Sana'a city, Yemen (2023)*

Prevalence of LTBI	*n*	(%)	95% CI
IGRA-based	38	(25.3)	18–32
TST-based	32	(21.3)	16–29
Overall (IGRA and TST)	44	(29.3)	23–37

LTBI latent tuberculosis infection, *CI* confidence interval, *IGRA* interferon-gamma release assay, *TST* tuberculin skin test

* The total number of diabetics was 150. n, number of patients positive with the corresponding test

Table 3 Risk factors associated with IGRA-based LTBI among type 2 diabetics seeking medical care in private health facilities in Sana'a city, Yemen (2023)

Variable	*N*	IGRA-based LTBI		Univariate analysis		Multivariable analysis	
		n	(%)	OR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
Gender							
Female	64	10	(15.6)	Reference	0.018	Reference	0.021
Male	86	28	(32.6)	2.6 (1.16–5.87)		4.3 (1.25–14.90)	
Age (years)							
19–35	18	3	(16.7)	Reference		Reference	
36–55	80	18	(22.5)	1.5 (0.38–5.58)	0.587	2.3 (0.47–11.16)	0.306
≥ 56	52	17	(32.7)	2.4 (0.62–9.54)	0.204	3.8 (0.65–22.74)	0.140
Residence							
Rural	38	8	(21.1)	Reference	0.483	Reference	0.248
Urban	112	30	(26.8)	1.4 (0.57–3.32)		1.9 (0.65–5.38)	
Literacy status							
Literate	109	32	(29.4)	Reference	0.065	Reference	0.164
Illiterate	41	6	(14.6)	0.4 (0.16–1.08)		0.4 (0.12–1.43)	
Employment status							
Unemployed	87	24	(27.6)	Reference	0.456	Reference	0.013
Employed	63	14	(22.2)	0.8 (0.35–1.60)		0.3 (0.09–0.75)	
Marital status							
Unmarried	16	2	(12.5)	Reference	0.174	Reference	0.767
Married	134	36	(26.9)	2.6 (0.56–11.88)		1.3 (0.24–7.05)	
Household size (members)							
Small-to-medium (< 5)	33	6	(18.2)	Reference	0.285	Reference	0.371
Large (≥ 5)	117	32	(27.4)	1.7 (0.64–4.49)		1.7 (0.54–5.17)	
Duration since diabetes diagnosis (years)							
< 5	54	16	(29.6)	Reference	0.364	Reference	0.046
≥ 5	96	22	(22.9)	0.7 (0.33–1.50)		0.3 (0.12–0.98)	
Glycaemic control (HbA1c %)							
Good (< 7)	23	7	(30.4)	Reference	0.541	Reference	0.846
Poor (≥ 7)	127	31	(24.4)	0.7 (0.28–1.96)		0.9 (0.28–2.85)	
Antidiabetic medication intake							
Yes	142	36	(25.4)	Reference	0.672	Reference	0.745
No	8	2	(25.0)	0.9 (0.19–5.08)		0.7 (0.09–5.43)	
Family history of TB							
No	138	33	(23.9)	Reference	0.156	Reference	0.379
Yes	12	5	(41.7)	2.2 (0.68–7.64)		3.8 (0.20–73.35)	
Household contact with TB patient(s)							
No	140	34	(24.3)	Reference	0.226	Reference	0.600
Yes	10	4	(40.0)	2.1 (0.55–7.80)		0.4 (0.02–10.63)	
Smoking status							
Non-smoker	90	21	(23.3)	Reference		Reference	
Ex-smoker	37	10	(27.0)	1.2 (0.51–2.92)	0.660	0.7 (0.23–2.06)	0.501
Smoker	23	7	(30.4)	1.4 (0.52–3.96)	0.483	1.0 (0.31–3.54)	0.946

N total number examined, *n* number positive by IGRA, *LTBI* latent tuberculosis infection, *OR* odds ratio, *AOR* adjusted odds ratio, *CI* confidence interval, *HbA1c* glycated haemoglobin

that LTBI was prevalent among 29.3% (25.3% using IGRA and 21.3% using TST) of type 2 diabetics seeking medical care in Sana'a city. Gender was an independent predictor of LTBI, being more than four times more likely among males than females, while employment and longer duration since diabetes diagnosis were predictors of reduced

Table 4 Agreement between TST and IGRA in LTBI diagnosis among type 2 diabetics seeking medical care in private health facilities in Sana'a city, Yemen

	IGRA						Agreement (%)[a]	*k*-coefficient	*P*-value
TST	Positive *n* (%)		Negative *n* (%)		Total *n* (%)				
Positive	26	(68.4)	6	(5.4)	32	(21.3)	88.0	0.67	0.001
Negative	12	(31.6)	106	(94.6)	118	(78.7)			
Total	38	(100.0)	112	(100.0)	150	(100.0)			

[a] Calculated as the number of cases in agreement (positive and negative by both techniques)/total number of cases × 100

risk of LTBI. Moreover, 88% of results were concordant between TST and IGRA in screening for LTBI among diabetics in the present study, with good and statistically significant agreement between the two test types.

The IGRA-based prevalence among diabetics in the present study is higher than that (20%) reported for HCWs in tertiary care hospitals in Sana'a [5, 6], while the TST-based prevalence among HCWs in the city ranged from 12.2 to 50.5% [4, 6]. The high prevalence of LTBI among diabetics is concerning because diabetics are more susceptible to infection with *M. tuberculosis* and are at higher risk of developing active TB compared to non-diabetics [29–33]. Therefore, it is crucial to diagnose LTBI in diabetics and early diagnose DM among patients with TB to ensure optimal care for both conditions [34]. As the present study did not include a comparison between diabetics and non-diabetics, further comparative studies are needed to assess the association between type 2 diabetes and LTBI.

The prevalence of LTBI in the present study is comparable to that reported for diabetics in Singapore (28.2%), the United Kingdom (31.5%) and South India (32%), but slightly higher than that reported for diabetics in Taiwan (21.5%) and diabetic Syrian refugees (19.5%) [30, 35–38]. On the other hand, the prevalence is much higher than that among diabetics in Malaysia (4.8–11.4%) and the United States (7.6–11.6%) [11, 32, 39, 40], while it is considerably lower than the reported prevalence among diabetics in Uganda (57.8%), Mexico (51.3%), India (48%), and Indonesia (38.9%) [41–44]. Nevertheless, the prevalence of LTBI among diabetics is likely underestimated in many countries, and differences can arise depending on the epidemiology of TB and the diagnostic method used across different countries. Furthermore, differences in health system infrastructure, access to healthcare services, socioeconomic conditions and diabetes management practices also play a role in the observed variations in the prevalence of LTBI among diabetics across different countries.

The present study found that male gender is an independent predictor of LTBI among type 2 diabetics, which is inconsistent with the significantly higher prevalence of LTBI among female than male HCWs in Sana'a city [5, 6]. This inconsistency indicates that the factors influencing the disproportional distribution of LTBI based on gender may differ between HCWs and other groups in the general population, including diabetics. On the other hand, the finding of the present study agrees with that reported for diabetics in Taiwan [45] but contradicts that observed in Malaysia [11, 13, 40, 46]. The low risk of LTBI among diabetics who were employed or had been diagnosed with diabetes for at least five years may be attributed in part to the possible impact of higher income and better diabetes control in lowering LTBI risk. The lack of significant associations between other demographic characteristics and LTBI among diabetics in the present study is consistent with some previous reports but contradicts others [11, 36, 38, 40–43, 46, 47]. These discrepancies could be attributed, among other reasons, to differences in study designs, sample sizes, and LTBI diagnostic methods employed.

A diabetes duration of at least five years was a significant predictor of reduced risk of LTBI. This finding is inconsistent with observations among diabetics in India, Malaysia, and Taiwan [11, 38, 43, 48]. The influence of other factors, including individual variations in immune response and the presence of comorbidities, may play a role in determining the risk of LTBI among diabetics. Therefore, further research is needed to better understand the complex interplay between diabetes, immune function, and LTBI risk. On the other hand, this study did not find a significant association between poorly controlled type 2 diabetes and LTBI. This finding aligns with that observed among diabetics in Kelantan state of Malaysia, India, and Taiwan [[11, 38, 43, 48]. In contrast, poor glycaemic control was identified as a significant risk factor for LTBI among diabetics from Mexico, and the Malaysian state of Terengganu [40, 41].

The absence of a significant association between LTBI among diabetics and household contact with TB patients in this study may be partially explained by the low response rate to this particular questionnaire item, which might have undermined the statistical power to find an association. This low response could be attributed to the possibility of stigmatization experienced by patients who have household cases of TB, leading to a reluctance to

disclose information about their contact history. In contrast, contact with active TB cases was found to be significantly associated with LTBI among HCWs in Sana'a [5]. In contrast to the present study, living with a relative with TB and contact with TB patients were found to be significant risk factors for LTBI among diabetics in Mexico and Terengganu state of Malaysia, respectively [40, 41].

There is a consistent body of evidence to support the notion that smoking is a risk factor associated with poor TB outcomes, including LTBI reactivation, active TB progression, and an increased risk of TB-related mortality [49–51]. Nevertheless, smoking status was not significantly associated with LTBI among patients in the present study. In line with this finding, cigarette smoking was not identified as a risk factor for LTBI among diabetics in Mexico [52], and no significant association was found between smoking status or duration and LTBI among diabetics in Kelantan, Malaysia [11]. In contrast, smoking was identified as a risk factor for LTBI among HCWs in Yemen and diabetics in Malaysia and Taiwan [5, 40, 46, 48]. The conflicting findings on the association between smoking and LTBI across different studies may be attributed to discrepancies in study designs, sample sizes, the type of test used to diagnose LTBI, and the prevalence of smoking in the general population.

There is no gold standard test for the diagnosis of LTBI [1], but both TST and IGRA are recommended by WHO to diagnose it indirectly through immune response detection [9]. In Yemen, TST is routinely used to diagnose LTBI due to its ease of use and affordability. However, this test has several limitations, including its low specificity in BCG-vaccinated individuals, cross-reactivity with NTM, and low sensitivity in immunocompromised patients [23, 24]. These limitations pose a challenge when interpreting TST results, leading to the risk of unnecessary treatments or missed diagnoses with delayed treatment. Given the limitations of TST, this study was the first to assess its diagnostic agreement with the more specific and sensitive IGRA for diagnosing LTBI in type 2 diabetics in Yemen. In this regard, there was a good and statistically significant level of agreement, which contrasts with a previous study that reported a poor agreement between TST and DRG IFN-γ ELISA kit in diagnosing LTBI among HCWs in Sana'a [6], suggesting that the choice of IGRA kits can have an impact on the level of agreement observed between the tests. In agreement with the present study, a significant and substantial level of agreement was observed between IGRA and TST for diagnosing LTBI among Indonesian diabetics undergoing antidiabetic treatment [53]. In contrast, a fair level of agreement was found between IGRA and TST for diagnosing LTBI among diabetics in Singapore and China [30, 54]. The variable agreement between IGRA and TST in various studies can be attributed to several factors, including the specific types of IGRA and TST used, the prevalence of TB in the population under investigation, the presence of other comorbidities, and the immune status of patients [55].

Given the good level of agreement between IGRA and TST in diagnosing LTBI in type 2 diabetics, the continued use of TST in Yemen can be encouraged due to its lower cost and the limited resources in the country. TST remains the widely used test for diagnosing LTBI in developing countries because of its lower cost and ease of use compared to other more specific alternatives, including IGRA [56]. On the other hand, IGRA can be used to confirm suspected false-positive TST results. It is intriguing to note that a previous study, using the same IGRA kit (QuantiFERON-TB Gold) as the present study, found that diabetes does not compromise the sensitivity of IGRA for TB diagnosis [57]. Instead, IGRA sensitivity was found to be significantly higher in TB patients with diabetes compared to those without diabetes [56]. Nevertheless, further research is needed to validate and better understand the interplay between diabetes and the increased sensitivity of IGRA in the context of TB diagnosis.

It is important to consider certain limitations when interpreting the findings of this study. First, the study was conducted among type 2 diabetics who sought medical care in private health facilities, which may affect the generalizability of the findings to the broader diabetic population in the community. In addition, caution should be exercised when extrapolating the study findings to other healthcare settings. Second, selection bias could arise from the convenience sampling of participants, as it was difficult to create a sampling frame for random selection from this type of population. Furthermore, many patients refused to undergo testing with TST and IGRA. However, to mitigate the potential impact of selection bias, the study districts and health facilities were randomly selected. Third, the relatively small size of the study sample might have impacted the statistical power to detect significant associations between certain risk factors and LTBI, even though clearly defined criteria were used for its calculation. Therefore, conducting large-scale studies with larger sample sizes is recommended to obtain more statistically robust results. Furthermore, it is important to acknowledge that the study may not cover the full range of potential risk factors for LTBI. Thus, comparative cross-sectional or case-control studies involving diabetic and non-diabetic populations are warranted to analyse these factors in depth. Finally, due to patient refusals, data on BCG vaccination status could not be collected for the majority of LTBI-positive patients. As a result, this variable had to be excluded from the analysis,

and the potential impact of BCG vaccination on TST results and agreement with IGRA could not be assessed. On the other hand, it was not possible to perform a two-step TST to help reduce the likelihood of false-negative results because diabetics declined to undergo test repetition. Accordingly, further studies incorporating information on BCG vaccination and performing a two-step TST are needed to validate the agreement between the two types of tests in BCG-vaccinated individuals.

Despite the above limitations, this study still provides important insights into the high prevalence of LTBI in this particular population. It also serves as a critical foundation for conducting future studies in various community and healthcare settings, enabling more comprehensive investigations into the burden of LTBI and associated factors. Meanwhile, this study informs physicians and policymakers in the country about the agreement of TST with QuantiFERON IGRA for the diagnosis of LTBI among diabetics, highlighting the practicality of the continued use of TST.

Conclusions

LTBI is common among type 2 diabetics seeking medical care in Sana'a city, with about one-third of them potentially latently infected based on the combined use of TST and IGRA. As a result, it is crucial to conduct longitudinal studies to investigate the possible progression of LTBI to active disease among this at-risk population. Furthermore, gender serves as an independent predictor of LTBI among type 2 diabetics, consistently showing higher infection rates in males compared to females. However, employment and a longer time since diabetes diagnosis may predict a lower risk of infection. The TST shows good agreement with IGRA in diagnosing LTBI among type 2 diabetics, supporting its continued use as a cost-effective and easily accessible test for diagnosing LTBI in the country. However, for patients who may have received false-positive results with the TST, the use of IGRA may provide a better alternative for LTBI diagnosis.

Abbreviations

AOR	Adjusted odds ratio
BCG	Bacillus Calmette-Guérin
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DM	Diabetes mellitus
ELISA	Enzyme-linked immunosorbent assay
HbA1c	Glycated haemoglobin
HCW	Healthcare worker
IFN-γ	Interferon gamma
IGRA	Interferon-gamma release assay
IQR	Interquartile range
LTBI	Latent tuberculosis infection
NCD	Non-communicable disease
NTM	Non-tuberculous mycobacteria
OR	Odds ratio
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
TST	Tuberculin skin test
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

RA and AA designed the study and prepared the application for the study grant. AA, NA, SSA, and NFN collected data and performed the TST and IGRA. RA, AA, and NA analysed the data and interpreted the results. RA, AA, and NA drafted the manuscript. AAA and SSA revised the manuscript. All authors read and approved the final version of the manuscript submitted for publication.

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Availability of data and materials

All relevant data are included in the manuscript, and the datasets for the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki regarding research on human subjects. The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, University of Science and Technology, Sana'a, Yemen (MECA No.: EAC/UST216). In addition, written informed consent was obtained from all participants after providing them with a clear explanation of the objectives of the study. Participants were assured that they had the right to withdraw from the study at any time without providing a reason. The privacy of participants and the confidentiality of their data were ensured.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: WHO; 2018. WHO/CDS/TB/2018.4.
2. World Health Organization. Global tuberculosis report 2023. Geneva: WHO; 2023.
3. World Health Organization. Tuberculosis profile. Yemen; 2022. https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&iso2=%22YE%22&lan=%22EN%22. Accessed 4 Mar 2024.
4. Askar F, Alaghbari K, Bamashmus M, Alselwi A. Prevalence of latent tuberculosis infection (LTBI) among health care workers at Al-Thawrah Modern General Hospital, Sanaa - Yemen 2016. Nurs Health Care. 2019;4(1):1–5. https://doi.org/10.33805/2573-3877.128.
5. Al-Khamesy KSA, Al-Shehari MM, Al-Moyed KA-KA, Atf-allah JYY, Al-Shamahy HA, Al-Hadad AM. Prevalence and risk factors of latent tuberculosis among healthcare workers in Sana'a city, Yemen using whole blood interferon-γ release assay. Univers J Pharm Res. 2022;7(5):1–7.
6. El-Aghbary DA, Atf-allah JY, Al-Robasi ABA. Interferon-gamma release assay *versus* tuberculin test in diagnosis of latent tuberculosis infection among healthcare workers, Sana'a city Yemen. Sana'a Univ J Med Sci. 2023;2(1):23–31.
7. Anaam MS, Alrasheedy AA, Alsahali S, Alfadly SO, Aldhubhani AH. Rate and risk factors of recurrent tuberculosis in Yemen: a 5-year prospective study. Infect Dis (Lond). 2020;52(3):161–9. https://doi.org/10.1080/23744235.2019.1690162.
8. World Health Organization, United Nations Children's Fund. Yemen: WHO and UNICEF estimates of national immunization coverage – 2021 revision. 2022. https://data.unicef.org/wp-content/uploads/2022/07/yem.pdf. Accessed 23 Aug 2024.
9. World Health Organization. Guidelines on the management of latent tuberculosis infection. Geneva: WHO; 2015. WHO/HTM/TB/2015.01.
10. Ai JW, Ruan QL, Liu QH, Zhang WH. Updates on the risk factors for latent tuberculosis reactivation and their managements. Emerg Microbes Infect. 2016;5(2): e10. https://doi.org/10.1038/emi.2016.10.
11. Ping PA, Zakaria R, Islam MA, Yaacob LH, Muhamad R, Wan Mohamad WMZ, et al. Prevalence and risk factors of latent tuberculosis infection (LTBI) in patients with type 2 diabetes mellitus (T2DM). Int J Environ Res Public Health. 2021;18(1):305. https://doi.org/10.3390/ijerph18010305.
12. Ugarte-Gil C, Carrillo-Larco RM, Kirwan DE. Latent tuberculosis infection and non-infectious co-morbidities: diabetes mellitus type 2, chronic kidney disease and rheumatoid arthritis. Int J Infect Dis. 2019;80S:S29-31. https://doi.org/10.1016/j.ijid.2019.02.018.
13. Agha MA, Yousif M, Shehab-Eldin W, El-Helbawy NG, Moustafa RG, Sweed EM. Latent tuberculosis infection among patients with type 2 diabetes mellitus. Egypt J Chest Dis Tuberc. 2020;69(2):277–83. https://doi.org/10.4103/ejcdt.ejcdt_85_19.
14. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008;5(7):e152. https://doi.org/10.1371/journal.pmed.0050152.
15. Lee MR, Huang YP, Kuo YT, Luo CH, Shih YJ, Shu CC, et al. Diabetes mellitus and latent tuberculosis infection: a systemic review and meta-analysis. Clin Infect Dis. 2017;64(6):719–27. https://doi.org/10.1093/cid/ciw836.
16. Restrepo BI, Schlesinger LS. Host-pathogen interactions in tuberculosis patients with type 2 diabetes mellitus. Tuberculosis (Edinb). 2013;93(Suppl0):S10-4. https://doi.org/10.1016/S1472-9792(13)70004-0.
17. World Health Organization. Diabetes: key facts. 2023. https://www.who.int/news-room/fact-sheets/detail/diabetes. Accessed 3 Mar 2024.
18. World Health Organization. Diabetes Yemen 2016 country profile. 2016. https://www.who.int/publications/m/item/diabetes-yem-country-profile-yemen-2016. Accessed 3 Mar 2024.
19. Jeon CY, Harries AD, Baker MA, Hart JE, Kapur A, Lonnroth K, et al. Bi-directional screening for tuberculosis and diabetes: a systematic review. Trop Med Int Health. 2010;15(11):1300–14. https://doi.org/10.1111/j.1365-3156.2010.02632.x.
20. Kumar Nathella P, Babu S. Influence of diabetes mellitus on immunity to human tuberculosis. Immunol. 2017;152(1):13–24. https://doi.org/10.1111/imm.12762.
21. Cole B, Nilsen DM, Will L, Etkind SC, Burgos M, Chorba T. Essential components of a public health tuberculosis prevention, control, and elimination program: recommendations of the Advisory Council for the elimination of tuberculosis and the National Tuberculosis Controllers Association. MMWR Recomm Rep. 2020;69(7):1–27. https://doi.org/10.15585/mmwr.rr6907a1.
22. Muñoz L, Stagg HR, Abubakar I. Diagnosis and management of latent tuberculosis infection. Cold Spring Harb Perspect Med. 2015;5(11):a017830. https://doi.org/10.1101/cshperspect.a017830.
23. Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. Am J Respir Crit Care Med. 1999;159(1):15–21. https://doi.org/10.1164/ajrccm.159.1.9801120.
24. Rehman MU, Bibi S, Imran, Khan Z, Khan AS, Hussain Gilani SY, et al. Role of tuberculin test as a diagnostic tool for tuberculosis. J Ayub Med Coll Abbottabad. 2018;30(4):529–33.
25. Machingaidze S, Wiysonge CS, Gonzalez-Angulo Y, Hatherill M, Moyo S, Hanekom W, et al. The utility of an interferon gamma release assay for diagnosis of latent tuberculosis infection and disease in children: a systematic review and meta-analysis. Pediatr Infect Dis J. 2011;30(8):694–700. https://doi.org/10.1097/INF.0b013e318214b915.
26. Bukhary ZA, Amer SM, Emara MM, Abdalla ME, Ali SA. Screening of latent tuberculosis infection among health care workers working in Hajj pilgrimage area in Saudi Arabia, using interferon gamma release assay and tuberculin skin test. Ann Saudi Med. 2018;38(2):90–6. https://doi.org/10.5144/0256-4947.2018.90.
27. Centers for Disease Control and Prevention. Tuberculin skin testing. 2020. https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm. Accessed 3 Mar 2024.
28. Altman GA. Ractical statistics for Medical Research. London: Chapman and Hall; 1992.
29. Ruslami R, Aarnoutse RE, Alisjahbana B, van der Ven AJ, van Crevel R. Implications of the global increase of diabetes for tuberculosis control and patient care. Trop Med Int Health. 2010;15(11):1289–99. https://doi.org/10.1111/j.1365-3156.2010.02625.x.
30. Leow M, Dalan R, Chee CBE, Earnest A, Chew D, Tan A, et al. Latent tuberculosis in patients with diabetes mellitus: prevalence, progression and public health implications. Exp Clin Endocrinol Diabetes. 2014;528–32. https://doi.org/10.1055/s-0034-1377044.
31. Hensel RL, Kempker RR, Tapia J, Oladele A, Blumberg HM, Magee MJ. Increased risk of latent tuberculous infection among persons with prediabetes and diabetes mellitus. Int J Tuberc Lung Dis. 2016;20(1):71–8. https://doi.org/10.5588/ijtld.15.0457.
32. Barron MM, Shaw KM, Bullard KM, Ali MK, Magee MJ. Diabetes is associated with increased prevalence of latent tuberculosis infection: findings from the National Health and Nutrition Examination Survey, 2011–2012. Diabetes Res Clin Pract. 2018;139:366–79. https://doi.org/10.1016/j.diabres.2018.03.022.
33. Bisht MK, Dahiya P, Ghosh S, Mukhopadhyay S. The cause-effect relation of tuberculosis on incidence of diabetes mellitus. Front Cell Infect Microbiol. 2023;13:1134036. https://doi.org/10.3389/fcimb.2023.1134036.
34. World Health Organization. Collaborative framework for care and control of tuberculosis and diabetes. Geneva: World Health Organization; 2011.
35. Jackson C, Southern J, Lalvani A, Drobniewski F, Griffiths CJ, Lipman M, et al. Diabetes mellitus and latent tuberculosis infection: baseline analysis of a large UK cohort. Thorax. 2019;74(1):91–4. https://doi.org/10.1136/thoraxjnl-2017-211124.
36. Ismail MB, Nour D, Raad G, Osman M, Rafei R, Mallat H, et al. First data on latent tuberculosis infection in Syrian refugees with diabetes in Lebanon. Public Health. 2020;189:97–100. https://doi.org/10.1016/j.puhe.2020.09.021.
37. Aravindhan V, Bobhate A, Sathishkumar K, Patil A, Kumpatla S, Viswanathan V. Unique reciprocal association seen between latent tuberculosis infection and diabetes is due to immunoendocrine modulation (DM-LTB-1). Front Microbiol. 2022;13: 884374. https://doi.org/10.3389/fmicb.2022.884374.
38. Chang A, Wu CZ, Lin JD, Lee CN, Tsai KY, Wu PH, et al. Prevalence and risk factors for latent tuberculosis among diabetes patients in Taiwan: a

cross-sectional study. J Infect Dev Ctries. 2022;16(04):644–9. https://doi.org/10.3855/jidc.15839.
39. Martinez L, Zhu L, Castellanos ME, Liu Q, Chen C, Hallowell BD, et al. Glycemic control and the prevalence of tuberculosis infection: a population-based observational study. Clin Infect Dis. 2017;65(12):2060–8. https://doi.org/10.1093/cid/cix632.
40. Husain NF, Yusoff HM, Hassan NM, Aziz AA. Prevalence of latent tuberculosis infection and its associated factors among diabetic patients availing primary health care in Terengganu state, Malaysia. Oman Med J. 2023;38(5):e546. https://doi.org/10.5001/omj.2023.97.
41. Martínez-Aguilar G, Serrano CJ, Castañeda-Delgado JE, Macías-Segura N, Hernández-Delgadillo N, Enciso-Moreno L, et al. Associated risk factors for latent tuberculosis infection in subjects with diabetes. Arch Med Res. 2015;46(3):221–7. https://doi.org/10.1016/j.arcmed.2015.03.009.
42. Koesoemadinata RC, McAllister SM, Soetedjo NNM, Febni Ratnaningsih D, Ruslami R, Kerry S, et al. Latent TB infection and pulmonary TB disease among patients with diabetes mellitus in Bandung, Indonesia. Trans R Soc Trop Med Hyg. 2017;111(2):81–9. https://doi.org/10.1093/trstmh/trx015.
43. Dabhi PA, Thangakunam B, Gupta R, James P, Thomas N, Naik D, et al. Screening for prevalence of current TB disease and latent TB infection in type 2 diabetes mellitus patients attending a diabetic clinic in an Indian tertiary care hospital. PLoS ONE. 2020;15(6): e0233385. https://doi.org/10.1371/journal.pone.0233385.
44. Kazibwe A, Kyazze AP, Ssekamatte P, Mutebi EI, Kibirige D, Kaddumukasa M, et al. TB infection in adults with diabetes mellitus in Uganda. Int J Tuberc Lung Dis. 2023;27(4):308–14. https://doi.org/10.5588/ijtld.22.0614.
45. Ting WY, Huang SF, Lee MC, Lin YY, Lee YC, Feng JY, et al. Gender disparities in latent tuberculosis infection in high-risk individuals: a cross-sectional study. PLoS ONE. 2014;9(11): e110104. https://doi.org/10.1371/journal.pone.0110104.
46. Swarna Nantha Y, Puri A, Mohamad Ali SZ, Suppiah P, Che Ali SA, Ramasamy B, et al. Epidemiology of latent tuberculosis infection among patients with and without diabetes mellitus. Fam Pract. 2017;34(5):532–8. https://doi.org/10.1093/fampra/cmx017.
47. Abbas U, Masood KI, Khan A, Irfan M, Saifullah N, Jamil B, et al. Tuberculosis and diabetes mellitus: relating immune impact of co-morbidity with challenges in disease management in high burden countries. J Clin Tuberc Other Mycobact Dis. 2022;29: 100343. https://doi.org/10.1016/j.jctube.2022.100343.
48. Lin CH, Kuo SC, Hsieh MC, Ho SY, Su IJ, Lin SH, et al. Effect of diabetes mellitus on risk of latent TB infection in a high TB incidence area: a community-based study in Taiwan. BMJ Open. 2019;9(10): e029948. https://doi.org/10.1136/bmjopen-2019-029948.
49. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. Arch Intern Med. 2007;167(4):335–42. https://doi.org/10.1001/archinte.167.4.335.
50. Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLoS Med. 2007;4(1): e20. https://doi.org/10.1371/journal.pmed.0040020.
51. Slama K, Chiang CY, Enarson DA, Hassmiller K, Fanning A, Gupta P, et al. Tobacco and Tuberculosis: a qualitative systematic review and meta-analysis. Int J Tuberc Lung Dis. 2007;11(10):1049–61.
52. Reichler MR, Khan A, Sterling TR, Zhao H, Moran J, McAuley J, et al. Risk and timing of tuberculosis among close contacts of persons with infectious tuberculosis. J Infect Dis. 2018;218(6):1000–8. https://doi.org/10.1093/infdis/jiy265.
53. Reviono R, Sutanto YS, Harsini H, Saptawati L, Marwoto M, Suryawati B, et al. The agreement of immunoglobulin gamma release assay (IGRA)/T-SPOT tuberculosis and tuberculin skin test to detect latent TB infection in diabetes mellitus patients. Indones J Med. 2021;6(3):298–306.
54. He Y, Cao X, Guo T, He Y, Du Y, Zhang H, et al. Serial testing of latent tuberculosis infection in patients with diabetes mellitus using interferon-gamma release assay, tuberculin skin test, and creation tuberculin skin test. Front Public Health. 2022;10:1025550. https://doi.org/10.3389/fpubh.2022.1025550.
55. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med. 2008;149(3):177–84. https://doi.org/10.7326/0003-4819-149-3-200808050-00241.
56. Al-Orainey IO. Diagnosis of latent tuberculosis: can we do better? Ann Thorac Med. 2009;4(1):5–9. https://doi.org/10.4103/1817-1737.44778.
57. Walsh MC, Camerlin AJ, Miles R, Pino P, Martinez P, Mora-Guzmán F, et al. The sensitivity of interferon-gamma release assays is not compromised in tuberculosis patients with diabetes. Int J Tuberc Lung Dis. 2011;15(2):179–84 i-iii.

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