Family Medicine & Primary Care Review 2021; 23(2): 163–168 https://doi.org/10.5114/fmpcr.2021.105908

ORIGINAL PAPERS

ISSN 1734-3402, eISSN 2449-8580

Screening of latent tuberculosis infection among healthcare students and medical doctors using the tuberculin skin test

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Latent tuberculosis infection (LTBI) is defined as the absence of symptoms of tuberculosis in individuals who have an immune response stimulated by *Mycobacterium tuberculosis* antigens.
Objectives. To estimate the prevalence of LTBI among healthcare students and medical doctors using the tuberculin skin test and to study the associated risk factors.
Material and methods. This cross-sectional study was carried out to review the tuberculin skin test (TST) records of newly hired medical doctors, medical interns and medical students. A review of pre-employment records was done, including results of TST and socio-demographic information, as well as potential factors influencing TST reaction.
Results. Out of 186 enrolled personnel, 43 (23.1%) were positive for TST. A positive TST was significantly associated with high BMI (OR = 1.07, 95% CI: 1.003– 1.142, $p = 0.039$), while it was not significantly associated with male gender (OR = 1.195, 95% CI: 0.530––2.694, $p = 0.668$), age (OR = 0.973, 95% CI: 0.915–1.034, $p = 0.371$), smoking (OR = 0.730, 95% CI: 0.259–2.060, $p = 0.552$), BCG vaccination (OR = 0.785, 95% CI: 0.249–2.481, $p = 0.680$) or chronic disease (OR = 4.828, 95% CI: 0.910–25.608, $p = 0.064$).
Conclusions. Our study population was at a significantly higher risk of LTBI, thus infection control precautions are strongly recommended. Furthermore, more studies are needed to assess the adherence and practices of healthcare workers, especially those who are exposed to tuberculosis patients.
Key words: tuberculosis, infection, mass screening.

Goweda R. Screening of latent tuberculosis infection among healthcare students and medical doctors using the tuberculin skin test. *Fam Med Prim Care Rev* 2021; 23(2): 163–168, doi: https://doi.org/10.5114/fmpcr.2021.105908.

Background

Latent tuberculosis infection (LTBI) is caused by *Mycobacterium tuberculosis*, leading to stimulation of the immune system and a positive tuberculin skin test reaction [1]. A patient with LTBI is asymptomatic and non-infectious to others. However, they have a 5–10% life-time risk of developing active tuberculosis (TB) [2].

In 2016, the World Health Organization [WHO] reported that 1.7 billion people had LTBI worldwide and estimated the prevalence of LTBI to be 23% [3]. International research and research work in Saudi Arabia have indicated an increased risk of tuberculosis as a re-emerging disease, with healthcare workers (HCWs) at particular high risk of exposure to tuberculosis infection. Despite being an old disease, TB continues to be a major public health concern, especially in low- and middle-income settings, such as the Middle East and other developing countries and regions [4].

LTBI screening in high risk individuals is strongly recommended in order to prevent the spread of TB. Accordingly, HCWs have a higher risk of contracting TB than the general population through occupational exposure and should be screened for TB [5]. Routine screening of the general population and not-at-risk groups is not recommended due to the waste of resources, as well as false-positive reactions leading to unnecessary anxiety [6].

TST has traditionally been used as a screening tool for LTBI due to low direct costs and ease of use [7]. Local Saudi guidelines on the management of latent tuberculosis do not recommend using the Interferon Gamma Release Assays (IGRAs) for the diagnosis of active tuberculosis. Interpretation of both tests must be based on the patient's immune status, history of exposure to TB and bacillus Calmette–Guérin [BCG], as well as other risk factors [8].

The results of TST should be interpreted cautiously, and the result is individualized according to risk factors. There are three cut off points of TST reaction [5 mm induration, 10 mm induration or 15 mm induration]. A 5 mm or more induration is considered positive in the following: HIV-positive patients, personnel with recent contact with an active TB patient, individuals with nodular or fibrotic changes on chest X-ray, patients with organ transplants and other immuno-incompetent patients. An induration of ≥ 10 mm is considered positive in healthcare workers, recent arrivals (less than five years) from high-prevalence regions, injection drug users, high-risk congregational settings (e.g. prisons, hospitals, homeless, etc.), bacteriology laboratory personnel, along with some medical conditions, such as diabetes mellitus, prolonged corticosteroid therapy, leukemia, renal failure, etc. Finally ≥ 15 mm is considered positive in individuals with no known risk factors for TB [9, 10].

Objectives

To estimate the prevalence of LTBI among healthcare students and medical doctors using the tuberculin skin test and to study the associated risk factors.

Material and methods

Study design and setting

This cross-sectional study was carried out to review the TST records of the newly hired medical doctors in Makkah city, as well as medical interns and medical students of Umm Al-Qura University, Saudi Arabia, between February 2020 and May 2020.

According to Saudi guidelines, newly hired physicians, medical intern and students receiving practical training in hospitals should be tested for LTBI. Additionally, a pre-employment chest X-ray should be carried out as a routine check before being contracted.

Sample size

169 participants were selected based on an LTBI prevalence of 12%; confidence intervals were taken at 95% with a 5% margin of error. We added 10% more to the number in order to accommodate drop-outs or incomplete data. The total sample size consisted of 186 participants.

After oral consent was taken from the study population, all participants who agreed to participate in the study were included. Excluded from the study were pregnant women, nurses, the immunodeficient, administrative staff, technicians, contact with active TB patients within the previous three months and those with changes in their chest X-ray.

Study tools

Saudi guidelines do not recommend using IGRAs for the diagnosis of active tuberculosis and recommend TST for TB screening [8]. This study relies on the results of the TST reaction, and we considered 10 ≥ mm induration as positive in our study [9, 10].

A review of pre-employment records was done, including the results of TST and socio-demographic information, as well as potential factors influencing TST reaction (age, gender, marital status, medications, medical condition, smoking, BMI, BCG vaccination status, history of travel, contact with TB patients and review of chest X-ray).

Data analysis

Data was analyzed using the IBM advanced SPSS statistical package version 20. Qualitative data was presented as frequencies and percentages, and the chi-square test (Fisher's exact test) was used to examine the relation between categorical variables, while continuous variables were presented as means and standard deviations, and the *t*-Test was used for comparison. Binary regression was used to analyze the risk factors. The statistical significance was determined using the 95% CI and $p < 0.05$.

Ethical consideration

This study was approved by the Ethics and Research Review Committee of Umm Al-Qura Faculty of Medicine, and confidentiality was ensured during the study. The participants were approached and made clear of the nature and purpose of the study.

Results

Out of 186 personnel enrolled in this study, 70 (37.6%) were newly hired medical doctors, 67 (36%) medical interns, and 49 (36.3%) were medical students. Approximately half of the study population was female (99 (53.2%)). Most of the study subjects were single (121 (65.1%)), with a minority being married (63 (33.9%)). Most of the study population received BCG vaccination (164 (88.2%)), while a minority of our study population were non-smokers, had no chronic diseases and were not on continuous medication use (25 (13.4%), 28 (15.1%), and 14 (7.5%), respectively). Out of 186 participants tested in our study, 43 (23.1%) were positive for PPD test reaction (≥ 10 mm induration) (Table 1).

Table 1. Baseline characteristics of the 186 participants

		n (%)
Job	medical doctor medical intern medical student	70 (37.6%) 67 (36%) 49 (36.3%)
Gender	male female	99 (53.2%) 87 (46.8%)
Marital status	single married divorced or widowed	121 (65.1%) 63 (33.9%) 2 (1.1)
Chronic disease	no yes	158 (84.9%) 28 (15.1%)
Continuous medication use	no yes	172 (92.5%) 14 (7.5%)
Smoking	no yes	161 (86.6%) 25 (13.4%)
Received BCG vaccination	yes no	164 (88.2%) 22 (11.8%)
Tuberculin skin test	negative positive	143 (76.9%) 43 (23.1%)

Additionally, the prevalence rate of LTBI showed no significant differences across job, gender, marital status, chronic disease, continuous medication use, smoking status, whether having received BCG vaccination, or with respect to age, with *p*-values of 0.543, 0.969, 0.712, 0.091, 0.876, 0.534, 0.963 and 0.376, respectively. On the other hand, the increased prevalence of LTBI in our study population was associated with increased BMI ($p = 0.046$) (Table 2).

Table 2. Relation between TST results with job, gender, marital status, chronic diseases, continuous medication use, smoking status, BCG vaccination status, age and BMI

		Tuberculin skin test		*p*
		Negative	Positive	
Job	medical doctor	56 (80.0%)	14 (20.0%)	0.543
	medical intern	52 (77.6%)	15 (22.4%)	
	medical student	35 (71.4%)	14 (28.6%)	
Gender	male	67 (77.0%)	20 (23.0%)	0.969
	female	76 (76.8%)	23 (23.2%)	
Marital status	single	92 (76.0%)	29 (24.0%)	0.712
	married	49 (77.8%)	14 (22.2%)	
	divorced or widow	2 (100.0%)	0 (0.0%)	

Table 2. Relation between TST results with job, gender, marital status, chronic diseases, continuous medication use, smoking status, BCG vaccination status, age and BMI

		Tuberculin skin test		*p*
		Negative	Positive	
Chronic disease	no	118 (74.7%)	40 (25.3%)	0.091
	yes	25 (89.3%)	3 (10.7%)	
Continuous medication use	no	132 (76.7%)	40 (23.3%)	0.876
	yes	11 (78.6%)	3 (21.4%)	
Smoking	no	125 (77.6%)	36 (22.4%)	0.534
	yes	18 (72.0%)	7 (28.0%)	
Received BCG vaccination	yes	126 (76.8%)	38 (23.2%)	0.963
	no	17 (77.3%)	5 (22.7%)	
Age		mean ± SD 27.34 ± 7.04	mean ± SD 26.25 ± 7.02	0.376
BMI		mean ± SD 25.24 ± 6.76	mean ± SD 27.46 ± 4.77	**0.046**

Table 3. Binary regression analysis of risk factors for latent tuberculosis infection in healthcare workers

	B	Odds ratio	*p*	95% CI for EXP (B)	
				Lower	Upper
Age	-0.028	0.973	0.371	0.915	1.034
Gender – male	0.178	1.195	0.668	0.530	2.694
Marital status – married	-0.115	0.891	0.812	0.345	2.303
Chronic disease	1.574	4.828	0.064	0.910	25.608
Medications	-1.125	0.325	0.243	0.049	2.147
Smoker	-0.315	0.730	0.552	0.259	2.060
BMI	0.068	1.071	**0.039**	1.003	1.142
BCG vaccination	-0.242	0.785	0.680	0.249	2.481

Binary regression analyses showed that TST+ was significantly associated with BMI (OR = 1.071, 95% CI: 1.003–1.142, $p = 0.039$), while it was not significantly associated with male gender (OR = 1.195, 95% CI: 0.530–2.694, $p = 0.668$), age (OR = 0.973, 95% CI: 0.915–1.034, $p = 0.371$), smoking (OR = 0.730, 95% CI: 0.259–2.060, $p = 0.552$), BCG vaccination (OR = 0.785, 95% CI: 0.249–2.481, $p = 0.680$) or chronic disease (OR = 4.828, 95% CI: 0.910–25.608, $p = 0.064$) (Table 3).

Discussion

Respiratory infections and other infectious diseases, due to close contacts, are a challenging hazard to HCWs. Tuberculosis is still considered a worldwide health problem. It is one of the most important and leading causes of morbidity and mortality in several areas of the world. The last population-based survey studying the epidemiology of tuberculosis infection in Saudi Arabia was published by Balkhy et al. in 2017. Worldwide research, including in Saudi Arabia, shows an increased risk of tuberculosis as a re-emerging disease [11].

The WHO reported the prevalence of TB in Saudi Arabia to be 86 per 100,000, 55 per 100,000, 10.6 per 100,000 and 10 per 100,000 in 1990, 2004, 2015 and 2017, respectively, compared to the worldwide average of 133 per 100,000 [11, 12].

The current study reviewed the results of PPD testing in 186 persons, including newly hired doctors, medical interns and medical students, with a positive PPD finding in 43 (23.1%) of the participants.

Local studies in Saudi Arabia showed a wide range of LTBI prevalence [11]. In a tertiary hospital in Riyadh, Hajoj et al. screened all newly hired HCWs from 2012 to 2015 and found that 31.5% of the included HCWs were positive [13]. This higher rate could be due to the TB endemic region of the enrolled HCWs. El-Helaly et al. reviewed the health records of new HCWs from 2009 to 2011, which revealed that 29.8% had a positive PPD [14]. A recent study in 2020 found 6,090 out of 6,404 HCWs (95.1%) tested utilizing TST had a negative PPD, while 314 (4.9%) had a positive PPD [15]. Another study in Saudi Arabia using both TST and QFT GIT among healthcare workers working during the Hajj pilgrimage season found that the LTBI rate was 10.8% [16]. From Muhayil city, another study was carried out in the same context using TST testing 208 HCWs and found that 47 (22.5%) tested positive [17]. Murad et al. found that out of 296 students, 35 undergraduate female students of health sciences (12%) had a positive PPD reaction [18].

A study in two Moroccan cities reported the prevalence of LTBI among 631 HCWs to be varied between 40.7% with QFT--GIT to 52% based on TST [19]. Additionally, Al-Sokkary et al. conducted a study on HCWs in a chest hospital in Zagazig city, Egypt, finding that the prevalence of LTBI identified by QFT-GIT and by TST was 28.8% and 59.1%, respectively [20].

In the current study, we observed that out of 67 medical intern, 15 (22.4%) had a positive TST, which is nearly similar to a report from a study carried out in Tunisia that found that the prevalence of LTBI was 26.6% among medical interns [21].

Cohen et al., in 2019, systematically reviewed 88 studies from 36 countries and found that with a 10 mm cut-off, the total prevalence of LTBI was 24.8% based on IGRA, whereas it was 21.2% based on TST. They concluded that with significant regional differences, the international prevalence of LTBI no longer amounts to a third of the world population but is closer to one-fourth [22]. Another systematic review done by Alele et al. screened 21 studies and found that the median prevalence of LTBI among HCWs was 62% [23].

LTBI prevalence in our study is less than reported by Chen et al., who concluded that a 33.9% of HCWs in chest hospitals had positive PPD; these higher results may be due to increased exposure of HCWs to TB bacilli inside the chest hospitals [24]. Furthermore, a work from India by Janagond et al. reported

higher positive PPD results (36.8%) [25]; this higher rate may be due to India being ranked by WHO as one of the top eight countries having a high incidence of TB [26]. These values are compatible with the prevalence reported from high TB burden countries such as Brazil (37%), China (54%) and India (43%) [27].

On the other hand, the study by Li et al. reviewed the UK occupational TB HCWs screening database from 2010 to 2017 and reported a 4% positive PPD rate among new HCWs. This lower rate than our study finding may be explained by UK being one of the low incidence TB countries [28]. Similarly, the results of a retrospective study in Italy by Olivieri et al., which screened 2,136 HCWs, found 144 (6.7%) were PPD positive, which is less than our findings [29].

Uden et al. reported the prevalence of LTBI among healthcare workers [HCWs] of 37% [30]. Additionally, Parks, in South Korea, documented that the prevalence of LTBI was higher among HCWs compared to the general population [31]. Keshavarz et al., in 2019, reported that the LTBI prevalence among HCWs in the Children's Care Hospital in Iran to be 27.13% based on TST [32]. Apriani et al., in 2019, searched multiple databases, such as Embase, Medline and Web of Science, for publications on LTBI among HCWs from 2015 to 2017 and concluded that prevalence of a positive TST was 14–98% [33]. A study from Côte D'Ivoire in Africa by Kassim et al. reported a very high LTBI prevalence; out of the 512 enrolled HCWs, 405 (79%) had a positive PPD reaction [34].

The current study demonstrated that the prevalence rate of LTBI showed no significant differences across job, gender, marital status, chronic disease, continuous medication use, smoking, whether having received BCG vaccination and with respect to age, with *p*-values of 0.543, 0.969, 0.712, 0.091, 0.876, 0.534, 0.963 and 0.376, respectively. On the other hand, the increased prevalence of LTBI in our study population was associated with increased BMI ($p = 0.046$).

Out of 49 undergraduate medical students enrolled in the current study, 14 (28.6%) had a positive TST, which was much higher than an Italian study showing that among 2,082 undergraduates, 23 (1.1%) had a positive TST [35]. Additionally 14 (20%) of our medical doctors and 22.4% of our medical interns had a positive TST, which is much higher than the same Italian study, which revealed that among 864 postgraduates , 24 (2.78%) had a positive TST. LTBI was statistically significant when comparing postgraduates to undergraduates in the Italian study, while our study showed no significance. The Italian study found that the number of previously vaccinated individuals was more than non-vaccinated ($p = 0.001$) in the postgraduate group, while our study found no significant difference.

In our study, we found that LTBI was 23% among males and 23.2% among females, with no statistically significant difference. A similar result was reported by Nabil et al., with 22% in males and 23% in females [36]. Schablon et al. reported no significant difference – 7.2% in males and 7.1% in females [37]. Additionally, the previously mentioned Italian study found that there was no significant statistical gender difference regarding the incidence of LTBI [35]. On the other hand, further studies showed that the male gender is at risk for active TB infection due to more exposure, as well as the biological differences between the sexes [38, 39]. Some studies documented Asian and African ethnicities, female gender and younger age groups as associated TB risk factors [40, 41]. Similarly, a study by Mirtskhulava et al. reported that women had a higher prevalence of LTBI than men [42].

Our study showed no difference between smokers and non-smokers having LTBI; however, other studies reported that smokers had a higher risk of LTBI when assessed by TST [43, 44].

This study found no association between age and LTBI, while other studies reported an increased risk of LTBI prevalence at an elderly age [45, 46]. Nienhaus et al., in 2007, documented that the prevalence rate of LTBI increased from 4.6% in participants younger than 30 years to 69.2% in those older than 60 years [47].

Marital status in our study was not a risk factor for LTBI, but other studies showed that divorced/widowed individuals had the highest prevalence, while single individuals had the lowest prevalence (30.3% vs 4.2%) [11].

Body mass index (BMI) has been shown to be linked to an individual's susceptibility to numerous infections and conditions. However, the association between BMI and the risk of TB infection has been poorly studied; our current study demonstrated that the increased prevalence of LTBI is associated with increased BMI ($p = 0.046$). The results of a systematic review done by Saag et al. found that underweight individuals are not at increased risk of LTBI [48]. Another study from a rural area in China revealed that BMI ≥ 28.0 kg/m^2 was found to be independently associated with an individual's susceptibility to TB infection [49].

The link between BMI and TB infection is not widely understood, despite years of research on its association with active TB [50, 51]. It is thought that increased adipose tissue negatively affects immune function and decrease host defense in obese persons [52]. Additionally, the accumulated adiposity could decrease the pulmonary defense via metabolic disturbances [53].

Conclusions

The prevalence of LTBI in our study was considered high. For this reason, strong infection control precautions are strongly recommended to prevent TB infection. Furthermore, more studies are needed to assess the adherence and practices of healthcare workers, especially those who are exposed to TB patients. There was a positive relationship between obesity and LTBI. Accordingly, more studies are recommended to study the relation between LTBI and active TB, and we suggest adding obesity to the high risk group for TB. Family physicians and primary healthcare providers play an important role in early diagnosis of LTBI and in health education.

Source of funding: This work was funded from the authors' own resources.
Conflicts of interest: The authors declare no conflicts of interest.

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Tables: 3
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Received: 18.07.2020
Reviewed: 31.07.2020
Accepted: 8.03.2021

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