

Original article**The comparison of tuberculin skin test and quantiferon-tb gold test for the determination of latent tuberculosis infection in healthcare workers in a pulmonary diseases hospital**Derya Yenibertiz¹, Melike Demir², Dilek Kanmaz¹, Esin Tuncay¹

¹Department of Chest Disease, Yedikule Chest Disease and Thoracic Surgery Training and Research Hospital, 34020 Zeytinburnu/Istanbul, Turkey

²Department of Chest Disease, Kecioren Research and Training Hospital, 06380 Kecioren/Ankara, Turkey

Abstract

To evaluate the positivity rate and effectiveness of tuberculin skin test (TST) and Quantiferon-TB Gold test (QFT) in the diagnosis of latent tuberculosis infection in healthcare workers (HCWs) and the parameters that affect the the results of those tests.

Healthcare workers from tertiary care pulmonary diseases hospital were enrolled into the study. BCG scars were evaluated and chest roentgenograms were obtained. TST was applied by the Mantoux method to the participants and the diameters of induration above 15 mm with BCG scars and above 10 mm without BCG scars were considered as positive. On the day of TST, blood sample was taken for QFT which measures interferon gama levels associated with specific antigens such as ESAT-6, CFP-10, and antigen 7.7. The tuberculosis specific antigen-Nil value of $0.35 \geq \text{IU/ml}$ was accepted as positive QFT and $<0.35 \text{ IU/ml}$ was recorded as negative QFT.

Ninety-four HCWs were included. The mean age of the participants was 32.6 ± 9.4 years. Fifty-nine of them were women (62.8%) and 35 were men (37.2%). Thirty (31.9%) of HCWs were doctors, 27 (28.7%) were nurses, and 37 (39.4%) were allied health personal. The positivity of TST and QFT increased significantly with aging ($p:0.026$ and 0.002 , respectively). It was found by univariate analysis that the positivity of QFT was affected from age and working duration but multivariate analysis revealed that the working duration was the only independent risk factor affecting the positivity of QFT ($p:0.018$). A statistically significant correlation was determined between the positivities of TST or QFT and induration diameter ($p < 0.001$). TST and QFT were determined positive in 59 (62.8%) and 51 (54.3%) of the participants, respectively. Low level of agreement was detected between two tests (69.8%, $k:0.391$).

Quantiferon-TB Gold test was found to be more effective and sensitive in relation to TST for the diagnosis of latent infection in the BCG-vaccinated people. We think that

QFT should be used instead of TST for screening latent infection in the HCWs, in the populations with high prevalence of tuberculosis and routine BCG vaccination alike our country.

Key words: *Tuberculin skin test, QuantiFERON-TB Gold test, Latent tuberculosis infection, Healthcare workers*

Corresponding Author:

Melike Demir, Sanatoryum Street. No:25 06380 Kecioren / Ankara, Turkey

melikedoktor@hotmail.com

Introduction

Tuberculosis (TB) is still one of the most common infectious diseases all over the world, especially in African and Asian countries and remains as a public health problem despite the treatment of disease is known for many years (1). Due to close contact with TB patients, the risk of infection is very high in healthcare workers (HCWs) and it continues to be one of the important occupational issues in this population (2,3,4). Thus, it is recommended that HCWs should be screened periodically in terms of tuberculosis infection and disease (5).

Tuberculin skin test (TST), considered as 'gold standard', is the most common screening method for the determination of *Mycobacterium tuberculosis* infection (6). It is an in vivo test by which T-cell response against a single antigen is measured. Although it is used

widely in our country, there are some limitations in the reliability of the test. As previous BCG vaccination and non-tuberculosis mycobacteria exposure cause false positive results, the specificity of the test decreases. There are two other disadvantages associated with TST. Firstly, it is a subjective diagnostic tool because the results vary according to the person evaluating the test and secondly, it requires a second visit for assessment 72 hours after the application (7). Therefore, alternative laboratory tests were needed for the diagnosis of latent tuberculosis infection (LTBI).

These searchings have resulted in discovery of QuantiFERON-TB Gold test (QFT) which is based on the measurement of the level of tuberculosis specific gamma interferon (IFN-gama) released from T cells

following stimulation by specific Mycobacteria antigens (e.g. ESAT-6, CFP-10, and antigen 7.7) within 24 hours by ELISA method (8). The Centers for Disease Control and Prevention (CDC) has recommended the use of QFT for screening the HCWs in order to determine LTBI since 2005 (9).

In this study, the effectiveness of TST and QFT in the diagnosis of latent infection of HCWs was evaluated by determining the positivity rates and their features associated with these rates.

MATERIAL AND METHODS

The HCWs employed in Yedikule Chest Diseases and Surgery Education and Research Hospital which is a specialized institution in the treatment of tuberculosis were included into this study. The workers with active tuberculosis disease, immune deficiency, and malnutrition were excluded. The age, gender, occupation, working duration, previous history of tuberculosis of all participants were recorded. BCG scars were evaluated and chest roentgenograms were obtained.

In TST, tuberculin solution containing 0.1 ml 5TU RT 234 TWEEN 80 was

performed intradermally with Mantoux method to the left volar side of the forearm. The test results were interpreted and recorded by the person who applied after 72 hours. A diameter of induration greater than 15 mm in BCG-vaccinated person or greater than 10 mm in unvaccinated individuals was considered as positive TST.

On the day of TST, 5 ml blood sample was taken from all the participants who had TST into the lithium heparinized tubes. The QFT was performed and interpreted within two hours in accordance with the instructions of the manufacturer of the QFT kit (Cellestis Ltd, Carnegie, Victoria, Australia). A determined QFT IFN-gama level associated with TB specific antigens of $0.35 \geq \text{IU/ml}$ was considered as QFT positive and $<0.35 \text{ IU/ml}$ was defined as QFT negative.

The analysis of data was carried out by using SPSS 11.5 statistical package programme (SPSS Inc., Chicago, Illinois, USA). Descriptive data were shown as mean \pm standard deviation for continuous variables and as the number of cases and/or frequency for nominal variables. The comparisons between two continuous variables were performed by Student t test. Nominal variables were compared with Pearson's

chi-square or Fisher's chi-square tests. Med calc program was used for Kappa test, Spearman's rho test, and the calculation of cut-off values. The effects of the variables on TST and QFT were evaluated by multivariate analysis. The results were assessed with 95% confidence interval and the significance was set at a p value of <0.05 .

RESULTS

Ninety-four HCWs whose mean age was 32.6 ± 9.4 were participated into our study. Fifty-nine of them were women (62.8%), 35 of them were men (37.2%). Thirty (31.9%) of HCWs were doctors, 27 (28.7%) of them were nurses, and the remainder were allied health personnel.

TST and QFT were determined positive in 59 (62.8%) and 51 (54.3%) of the participants, respectively (Table 1). Although no difference was determined between the TST positive and negative group by average working duration, it was detected that the working duration of QFT positive HCWs was significantly longer than QFT negative group ($p:0.013$). The mean working duration of QFT positive and negative HCWs were 7.8 ± 6.7 and 4.7 ± 4.9 years, respectively. The average age of workers with positive TST was

34.3 ± 9.5 years and with negative TST was 29.9 ± 8.7 years. The difference between those groups was statistically significant ($p:0.026$). Similarly, there was significant difference between the average ages of the workers with positive and negative QFT (35.4 ± 9.8 vs. 29.4 ± 7.9 years, $p:0.002$) (Table 2). There was no significant relation between the TST or QFT positive and negative groups according to gender and occupational subgroups of the HCWs.

Univariate analysis revealed that the positivity of QFT was affected from age and working duration. However, the working duration was determined as the only independent risk factor for the positivity of QFT by multivariate analysis.

Statistically significant correlations were found between the positivities of QFT or TST and induration diameter ($p < 0.001$ for both the tests and r values were 0.353 and 0.363, respectively). It was determined that the positivity of QFT was significantly more common in the workers with TST of ≥ 15 mm ($p:0.003$). The rate of QFT positivity was found as 72.5% in the cases with a TST diameter of ≥ 15 mm (Table 3).

When the agreement between QFT and TST was assessed by Kappa test, a low level agreement was found (69.8%, k:0.391). The specificity and sensitivity

of QFT according to TST were calculated as 71% and 69%, respectively (Table 1).

Table 1. The frequency of TST and QFT positivity and the agreement of these tests

		TST			K:0.391
		Negative	Positive	Total	
QFT	Negative	25 (26.6%)	18 (19.1%)	43 (45.7%)	
	Positive	10 (10.6%)	41 (43.6%)	51 (54.3%)	
	Total	35 (37.2%)	59 (62.8%)	94 (100%)	

Table 2. The comparisons between TST and QFT positive and negative groups according to mean working duration and age

Category	Positive TST	Negative TST	p	Positive QFT	Negative QFT	p
Working time (years)	7.1 ± 6.3	5.3 ± 5.6	p:0.184	7.8 ± 6.7	4.7 ± 4.9	p:0.013
Age (years)	34.3 ± 9.5	29.9 ± 8.7	p:0.026	35.4 ± 9.8	29.4 ± 7.9	p:0.002

Table 3. QFT status according to the diameter of TST

		Diameter of TST (mm)					Total
			0-4	5-9	10-15	Above 15	
			n	%	%	%	
QUANTIFERON	Negative	n	14	4	9	16	43
		%	32.6%	9.3%	20.9%	37.2%	100%
	Positive	n	6	1	7	37	51
		%	11.8%	2%	13.7%	72.5%	100%

p:0.003

DISCUSSION

Tuberculosis still continues to be an important health problem for our country together with wide geography of the world (10). The TB infection is more frequent in HCWs than general population due to high rate of exposure by droplet infection or direct contact (11). Any individual is considered to have latent tuberculosis infection when exposed to TB bacilli, have a positive TST but have no clinical and radiological findings. LTBI among HCWs is influenced by factors such as age, working duration, and BCG vaccination (12). Tuberculosis can be controlled in a society by determining the cases with LTBI and taking necessary precautions in order to prevent the conversion of latent infection to the tuberculosis disease and the spreading to other individuals (13).

Despite TST is frequently used in the screening of the risk of TB infection, because of its high false positivity rate in vaccinated individuals and low sensitivity in the immunocompromised people, children, and elders, alternative diagnostic methods are needed (14,15). QFT which measures the levels of IFN-gama released from T lymphocytes in

response to specific antigens and is a specific test in the diagnosis of Mycobacterium tuberculosis infection one of the modalities discovered as a consequence of this requirement (16). Currently, the screening of all HCWs with TST and QFT at the initial employment and periodically during the entire working duration afterwards is recommended (9).

The previous studies found that the positivity of QFT increased parallelly with the increasing age and working duration of HCWs (17,18,19). Mirtskhulava et al (17) showed in their study among HCWs that the working duration over 5 years increased the positivity of TST and QFT and being over 30 years old was associated with increased positivity of QFT. In one of the studies that evaluated the concomitant positivity of TST and QFT, it was found that the positivity of TST was associated with age and the positivity of QFT was associated with working time (20). Another study found a relationship only between the positivity of QFT and age (6). In our study, it was found that the positivity of TST and QFT increased with age. However, the working duration solely affected the positivity of QFT. Despite

the positivities of TST and QFT decrease by age in the general population due to weakened immune system, the positivities of those tests are seen more frequently in the HCWs because of longer duration of exposure by age. Although QFT positivity was associated both with age and working duration by univariate analysis in the current study, multivariate analysis showed that the only independent variable that affected the QFT positivity was working duration and the age was dependent on the duration of exposure. As significantly higher increase in the QFT positivity in relation to TST positivity was observed parallel with duration of exposure, it was thought that QFT was more sensitive in the diagnosis of latent infection.

Another factor that affects LTBI in the HCWs is BCG vaccination. In our study, it was observed that the positivity of TST increased with the rising number of the BCG scars but the positivity of QFT was not affected from such vaccination. Lee et al (21) denoted in their study that TST was not a useful test for detection of LTBI in the countries with moderate TB prevalence as it was influenced from the number of BCG vaccinations. Another study

indicated that QFT results did not change with previous BCG vaccination (22). In a study conducted in Germany, it was reported that TST and QFT had similar sensitivity in the diagnosis of LTBI in unvaccinated individuals. However, as QFT was not affected from previous vaccination, it was more specific than TST in those vaccinated with BCG (23). Parallel with these studies, it was found in our study that QFT was more accurate for detection of LTBI in the countries with routine BCG vaccination program. CDC have already suggested QFT as a screening test for HCWs (9).

In consistent with similar previous studies (23,24), as the diameter of TST induration increased over 15 mm, the positivity rate of QFT also increased in the current study. Some investigations asserted that the agreement between TST and QFT was not very high because of the increased TST positivity related with BCG vaccination or higher prevalence of infection in certain populations. Low level agreement might also be resulted from the elderly participants in those studies who often had decreased TST positivity (4,25,26). In parallel with those reports, high level of agreement between the results of

TST and QFT was established in the unvaccinated individuals and the populations with lower prevalence of tuberculosis (4,26). The agreement between TST and QFT in HCWs employed in our institution was determined to be low ($k:0.391$). Similarly, we think that this was resulted from the higher prevalence of TB and high rate of BCG vaccination in our country.

In conclusion, QFT is more sensitive and effective in relation to TST for screening of LTBI in the people with BCG vaccination. Therefore, we think that QFT should be used instead of TST for scanning LTBI in the HCWs living in the populations with routine BCG vaccination and high prevalence of TB alike in our country.

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