ORIGINAL ARTICLE

Comparison of tuberculin skin test and quantiferon-TB gold in tube test for diagnosis of latent tuberculosis infection in health care workers: A cross sectional study

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Abstract

Objective: To compare the diagnostic efficacy and agreement of the traditional tuberculin skin test with QuantiFERON-Tuberculosis Gold In-Tube test for latent tuberculosis infection in healthcare workers.

Methods: The cross-sectional analytical study was conducted between March 1 and 31, 2008, at a specialist tuberculosis hospital in Istanbul, Turkey, and comprised healthcare workers who had been employed for at least one year at the hospital and volunteered to take part. Tuberculin skin test and QuantiFERON-Tuberculosis Gold In-Tube test were both performed simultaneously and their results were compared Using SPSS 12.

Results: Out of 34 subjects, 20(58.8%) had a positive tuberculin skin test, and 7(20.6%) had a positive QuantiFERON-Tuberculosis Gold In-Tube test. The two tests agreed in only 15(44.1%) cases and disagreed in 19(55.9%). In 16(47.1%) subjects, the QuantiFERON-Tuberculosis Gold In-Tube test was negative and tuberculin skin testwas positive, while in 3(8.8%) participants QuantiFERON-Tuberculosis Gold In-Tube test was positive and tuberculin skin test was negative. Kappa test revealed discordance between the two tests (κ=-0.13; p=0.92).

Conclusion: Latent tuberculosis infection prevalence was higher based on tuberculin skin test than QuantiFERON-Tuberculosis Gold In-Tube test. The results of the two tests were discordant.

Keywords: Quantiferon, QFT-GIT, Tuberculin skin test, TST, IGRAs, Tuberculosis, Latent tuberculosis infection, LTBI.
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Introduction

Tuberculosis (TB) continues to be a global public health problem. According to the World Health Organisation (WHO) Global TB Report, one-third of the world population is infected with Mycobacterium Tuberculosis.[1] Individuals with latent tuberculosis infection (LTBI) have a 10 per cent risk of developing active TB disease during their lifetime, especially in the first two years.[2,3] Diagnosis of LTBI and its treatment in high-risk populations are considered to be main components of TB control programmes.[1]

Transmission of infection from patients to healthcare workers (HCWs) has been well documented in literature.[4] Independent from the risk in the general population, the risk of TB is higher in HCWs, especially those who are taking care of TB patients. Initial and periodic screening for LTBI is recommended for HCWs who are coming into contact with patients, but the frequency of this is determined by the risk of the setting.[5]

Unfortunately there is no gold standard diagnostic test for LTBI. Traditional tuberculin skin test (TST) has been used for over a hundred years as the diagnostic test, but it has several limitations. TST has low sensitivity and also can be affected by Bacillus Calmette-Guérin (BCG) vaccination, non-tuberculous mycobacteria infections and immunosuppression, which may result in false negative or positive interpretations.[6] All of these contribute to the fact that there is a need for alternative tests.

As a result of studies evaluating M. Tuberculosis organism-specific antigens and recognition of the essential role of interferon gamma (IFN-γ) in specific cellular immune response to these antigens, IFN-γ Release Assays (IGRAs) were developed.[7] IGRAs are measure-specific IFN-γ responses to M. Tuberculosis antigens in ex-vivo mediums. QuantiFERON-Tuberculosis Gold In-Tube (QFT-GIT) test is one of the commercially available IGRAs.[8]

Development of IGRAs has lead to modifications in screening recommendations of HCWs for LTBI. The US Centre of Disease Control and Prevention (CDC) reports that IGRAs can be used in place of, but not together with, TST in all settings.[9] By contrast, the National Institute for

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Health and Clinical Excellence in the United Kingdom recommends dual testing where IGRA is performed only for individuals who have a positive TST result.[10] The Turkish Ministry of Health recommends screening with chest X-rays, sputum acid-fast bacilli (AFB) smears annually. TST is also recommended but frequency of TST is not stated and IGRAs are suggested to be performed as the decisive test when TST result is negative.[11]

The current study was planned to compare the diagnostic efficacy and agreement of traditional TST with QFT-GIT in HCWs who are considered to be an at-risk group for developing LTBI.

Subjects and Methods

The cross-sectional analytical study was conducted between March 1 and 31, 2008, at a specialist tuberculosis hospital in Istanbul, Turkey, and comprised HCWs who volunteered to take part.

After approval from the institutional ethics committee, those HCWs were enrolled who were employed for at least one year in either the pulmonary division or the microbiology laboratory. A pulmonologist took the history and examined all the participants. Age, gender, occupation subgroup, duration of working at the hospital, BCG vaccination status, past medical history and chest X-ray findings were recorded. Participants who had an immunosuppressive disease, active TB or abnormal radiological findings suggestive of TB were excluded

TST was performed by injecting 0.1ml (5 tuberculin units) of purified protein derivate (PPD) intradermally into the volar part of the forearm. The induration diameter was measured after 72 hours by the pen-point method and was recorded in mm. Positive TST was defined as an induration diameter of ≥15mm for BCG-vaccinated participants and ≥10mm for unvaccinated participants. This was in line with the guidelines of the Turkish Ministry of Health. An induration of ≥10mm was defined as positive regardless of BCG vaccination status only for the purpose of checking the compatibility of the two tests.

QFT-GIT (Cellestis Limited, Carnegie, Australia) test was performed and interpreted as per the manufacturer's instructions in two steps. Prior to the TST being performed, 1ml aliquots of blood were drawn into 3 separate tubes. These tubes contained saline (negative control, nil control); TB-specific antigens (ESAT-6, CFP-10 and TB 7.7); and T-cell mitogen phytohemaglutinin (positive control). The tubes were oscillated 8-10 times in order to ensure that the blood touched the tube surface, and then were incubated with 5% carbon dioxide (CO_2) for 16-24 hours. After incubation, the specimens were centrifuged at 2500 cycles and the separated plasma samples were stored at +4°C.

In the next step, plasma IFN- levels were interpreted using a QFT-GIT enzyme-linked immunosorbent assay (ELISA) kit. An automatic ELISA washer (Bio-Tek Instruments Inc. ELx50, USA) was used for the washing steps. Optic densities of the samples were measured using reference filters of 450 and 620/650nm in an ELISA reader (Bio-Tek Instruments Inc., USA). QFT-GIT Analysis 2.23 programme, provided by the manufacturer, was used to calculate the results. The calculation was based on the value of IFN- release and defined as: positive = TB antigen minus nil control 0.35 IU/ml, or negative = TB antigen minus nil control <0.35 IU/ml; and indeterminate = nil < 8.0 IU/ml and mitogen minus nil control <0.5 IU/ml or nil 8.0 IU/ml. In cases where results were indeterminate, the test was repeated.

A cross-table was created for the diagnostic and epidemiologic parameters of QFT-GIT and TST. Statistical analysis was performed using SPSS 12. The agreement between TST and QFT-GIT was examined using Kappa test.[12] The interpretation of kappa was: $\kappa > 0.75$ excellent agreement; $\kappa = 0.4$-0.75 good agreement; and $\kappa < 0.4$ poor agreement. $P<0.05$ was considered statistically significant.

Results

Of the 34 HCWs, 22(64.7 %) were women and 12(35.3 %) were men. The overall mean age was 33.0±5.8 years (women; 29.9±3.7 years; men: 38.7±4.3 years). The occupational subgroups were physicians (20.6%), nurses (35.2%), laboratory assistants (26.5%), nursing support workers (11.8%) and cleaners (5.9%). The mean duration of working at the TB hospital was 6.7±4.4 years for the whole group: 6.0±5.9 years for physicians, 5.5±2.8 years for nurses, 9.4±4.8 years for laboratory assistants, 6.8±2.4 years for nursing support workers, and 1.5±0.7 years for cleaners. None of the participants had active TB or were immunosuppressed. All had BCG scars except 2(5.9%) participants.

Overall, 20(58.8%) subjects had a positive TST, and 7(20.6%) had a positive QFT-GIT test. Both tests were positive in

Table-1: Comparison of TST and QFT-GIT (Cutoff for TST: 15mm).

n (%)	TST (+)	TST (-)	Total
QFT-GIT (+)	4 (11.8)	3 (8.8)	7 (20.6)
QFT-GIT (-)	16 (47.1)	11 (32.3)	27 (79.4)
Total	20 (58.8)	14 (41.1)	34 (100.0)

*Values of ≥0.35 iu/ml were accepted as positive for QFT-GIT.
†TST induration ≥15 mm for BCG vaccinated participants and ≥10 mm for non-vaccinated participants was defined as positive.
The two tests were discordant (κ=-0.13, p=0.92)
TST: Tuberculin skin test
QFT-GIT: QuantiFERON-Tuberculosis Gold In-Tube test.

Table-2: Comparison of TST and QFT-GIT (Cutoff for TST: 10mm).

n (%)	TST (+)	TST (-)	Total
QFT-GIT (+)	7 (20.6)	- (0)	7 (20.6)
QFT-GIT (-)	21 (61.8)	6 (17.6)	27 (79.4)
Toplam	28 (82.4)	6 (17.6)	34 (100)

*Values of ≥0.35 iu/ml were defined as positive for QFT-GIT.
† TST induration ≥10 mm was defined as positive. BCG vaccination status was ignored.
The two tests were discordant (κ=-0.105, p=0.169)
TST: Tuberculin skin test
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4(11.8%) and negative in 11(32.3%) participants (Table-1). In 16(47.1%) subjects, the TST was positive while the QFT-GIT test was negative. In 3(8.8%) participants, the TST was negative while the QFT-GIT test was positive. There were 27 (79.4%) subjects who had at least one positive test. The two tests were compatible in 15 (44.1%) participants and incompatible in 19 (55.9%). When analyzed with kappa test, they were discordant (κ= -0.13; p=0.92).

Reinterpretation of the data after changing the cutoff value for TST by ignoring previous BCG vaccination, with an induration of ≥10mm defined as positive, increased the number of positive TSTs from 20(58.8%) to 28(82.4%) (Table-2). Both tests were positive or negative in only 13 (38.4%) HCWs. There were no HCWs with a negative TST but a positive QFT-GIT, and the subjects who had a positive TST but negative QFT-GIT increased from 16(47.1%) to 21 (61.8 %). When re-analysed with kappa statistics, the two tests were still discordant (κ=-0.05; p=0.169).

Data from the occupational subgroups was also compared (Table-3). The mean TST induration of the whole group was 14.5 5.6mm; laboratory assistants had the highest (17.6 3.8 mm) induration whereas physicians had the lowest (13.0 2.8 mm). Of the occupational subgroups, 1 (14.3%) and 2 (28.6%) physicians, 8 (66.7%) and 1 (8.3%) nurses, 7 (77.8%) and 2 (22.2%) laboratory assistants, 3 (75%) and 2 (50%) nursing support workers and none of cleaners had TST and QFT-GIT positive respectively. Frequencies of positive and negative results of each test with respect to result of the other one are given in Table-3. The compatibility between the two tests was highest in nursing support workers (n=3; 75%) and lowest in laboratory assistants (n=2; 22.2%). A discordant result consisting of a negative QFT-GIT with a positive TST was seen in 16(47.1%) participants; 13(81%) of them were nurses and laboratory assistants. The other discordant result of having a positive QFT-GIT and negative TST was only seen in 3 (8.8 %) HCWs and 2(66.6%) of them were physicians.

Discussion

According to our study, the prevalence of LTBI in HCWs was 58.8% based on the traditional TST, while 20.6% based on QFT-GIT. It increased up to 79.4% based on positivity of either of the two tests. The two tests were compatible in 44.1% participants and incompatible in 55.9%. Statistical agreement analysis revealed that TST and QFT-GIT were discordant in this small group of BCG-vaccinated, high-risk HCWs.

The study population was a high-risk group for LTBI as the subjects were either working at either the pulmonary department or the microbiology laboratory. In literature, population at the highest risk for LTBI are close contacts of TB patients, prison detainees and HCWs respectively.[3,11] Among the HCWs, pulmonary department employees, in particular those taking care of TB patients, are at the highest risk. Centres with annual TB admissions of more than five are assumed to be high-risk centres.[3] Our institution had approximately 400 TB admissions during the year of the study.[13] This is the strength of our study. In situations where there is no gold standard test, such as LTBI, new tests should be evaluated in high-risk populations. It is possible to find misleading results with studies conducted in low-risk populations.

The majority of the participants (94.1%) were BCG-vaccinated and they all had had boosters. In Turkey, BCG

Table-3: Comparison of TST and QFT-GIT by occupational subgroups.

	*Time (year)	TST (mm)	TST + n(%)	QFT + n(%)	TST+, QFT+ (n)	TST+, QFT - (n)	TST-, QFT + (n)	TST-, QFT - (n)	†Coherence (%)
Physician n=7	6.0 5.9	13.0 2.8	1(14.3)	2(28.6)	-	1	2	4	57.1
Nurse n=12	5.5 2.8	14.3 6.4	8(66.7)	12(8.3)	1	7	-	4	41.7
Laboratory assistant n=9	9.4 4.8	17.6 3.8	7(77.8)	2(22.2)	1	6	1	1	22.2
Nursing Support Workers n=4	6.8 2.4	13.3 9.1	3(75.0)	2(50.0)	2	1	-	1	75.0
Cleaners n=2	1.5 0.7	15.0 2.8	1(50.0)	0(0)	-	1	-	1	50.0
Total n=34	6.7 4.4	14.5 5.6	20(58.8)	7(20.6)	4	16	3	11	44.1

*Mean working duration of healthcare workers at the hospital
†The agreement of two tests as percentage
TST: Tuberculin skin test
QFT-GIT: QuantiFERON-Tuberculosis Gold In-Tube test.

vaccination is mandatory; children are vaccinated once at birth and until 2010, children received a booster vaccination during the first and fifth grades of elementary school. High TST positivity is expected in a BCG-vaccinated population because of the false positivity of the test.[14] Still, interpretation of false positivity should be done cautiously as BCG has variable effects on TST, and cross-reactivity wanes over time, especially in people who were remotely vaccinated[14] On the other hand, Tissot et al. determined that an induration diameter of <18mm may have been related to prior BCG vaccination in a previously vaccinated group under 40 years age.[15] Due to the young age of our participants (mean age: 33.0±5.8 years) and the vaccination strategy in Turkey, it can be presumed that false positivity may explain why higher LTBI prevalence with TST compared to QFT-GIT (58.8% vs. 20.6%) was found.

The stated prevalence of LTBI among HCWs in literature varies from 1% to 85.5%, depending on the study population, method and the country in which the study was conducted.[16-19] In some of the studies LTBI is diagnosed based on both a positive IGRA and TST, whereas in others, either one of these tests can be positive for diagnosis. The cutoff values used for both IGRAs and TST differ in studies. Therefore, it is hard to compare our prevalence with most others. When compared with another study from Turkey, prevalence was similar based on TST but lower based on QFT-GIT (58.8 % vs. 53.9 % and 20.6 % vs. 85.5 % respectively).[17]

Data related to sensitivity or specificity of IGRAs and about the agreement of IGRAs with each other or with TST results is available in literature. Results again vary or are controversial. The current study revealed poor agreement between TST and QFT-GIT similar to our previous study with 58 TB patients and 38 healthy controls in which we found discordance between TST and QFT-GIT; that the QFT-GIT was more sensitive and specific.[20] Supporting our findings are studies by He et al. from Mongolia and Zwerling et al. from Canada, who also found poor agreement between these two tests.[21,22] In contrast, Mirtskhulava et al. found good agreement between these tests in HCWs with unknown BCG vaccination status.[19] In another study, Alvarez et al. found good agreement in negative results and poor agreement in positive results between the two tests.[23] However, in this study the LTBI prevalence was very low, even when using either of the two tests as positive (11.2%), leading us to question the TB risk of the study population. For a new test, to determine whether positive results are compatible, the test should be performed in a population with a high-risk of TB, while on the other hand, the accuracy of negative results should be tested in a low-risk population.

We compared the prevalence of LTBI and the agreement between the tests in different subgroups. Even though the numbers in the subgroups were not enough to analyse statistically, it still gave us important information. The laboratory assistants had the longest working duration (9.4±4.8 years), the highest mean TST induration (17.6±3.8 mm) and the highest prevalence of LTBI. Eight (88.9%) of them had positive results in at least one test. This finding is consistent with studies that reveal an association between work duration and TST positivity.[19] Among the other subgroups, even though the mean working duration was not longer, nursing support workers had higher prevalence of LTBI (42.8%, 66.7% and 75%; respectively in physicians, nurses and nursing-support workers). This can be explained with the longer time periods spent with patients and their possible disregard for protective precautions.

Since there is no gold standard for testing LTBI, diagnostic values of the tests, such as sensitivity, specificity and negative predictive value (NPV), cannot be correctly assessed. The only exact measure of LTBI can be made when the risk for active TB associated with a particular test result has been defined. This can be established by long-term cohort studies in which untreated populations with positive results at baseline are followed up. Such studies are expensive and complex and ethically impossible in most of the countries where the standard of care is to offer treatment to such persons.[24] However, diagnostic values of the LTBI test can be estimated from epidemiological studies. Menzies et al. estimated sensitivity of IGRAs from studies of patients with active TB; persons in contact with patients with active TB who were categorised into gradients of exposure; and concordance of IGRA and the TST. They also estimated specificity from studies of healthy persons with a very low likelihood of exposure.[24]

Compatible with our results, Menzies et al. presented important data on the diagnostic value, clinical importance and interpretation of IGRAs results in their meta-analysis. They analyzed 14 studies for sensitivity and 8 studies for specificity of IGRAs. They concluded that there is discordance between TST and IGRAs in both patient and at-risk groups; TST has different interpretation cutoffs for different countries and regions which means diagnosing LTBI only with TST is difficult; the sensitivity and specificity of the IGRAs increase with the increased number of antigens used in the tests; new tests have better diagnostic value in countries where BCG vaccination is performed routinely; the limitation of the efficacy studies of IGRAs is the lack of a gold standard diagnostic test for LTBI; and in the studies where TB patients were compared, IGRAs were found to have higher sensitivity and specificity than TST.[24]

According to our results and the current literature, any of the test is not superior to the other, but new tests (IGRAs)

are promising and have good specificity. Especially in BCG-vaccinated populations, the performance of IGRAs is expected better. The CDC has recommended that IGRAs shall replace TST, but the UK National Institute for Clinical Excellence has suggested that IGRAs are useful adjuncts to TST.[9]

There are some limitations of our study. Our study population was small and therefore we could neither compare the occupational subgroups nor the age subgroups. It was a single-centre study, and the prevalence rates may not represent the HCWs in the whole of Turkey and may be affected by our centre's infection control policy. Finally, the lack of a gold standard diagnostic test for LTBI was, like in other studies, a limitation in determining the accuracy of the new test. These limitations diminish external validity and generalisability of our results, but they are compatible with literature.

Conclusion

TST and QFT-GIT tests were discordant and any of the test was not superior to the other. LTBI prevalence was higher based on TST than the prevalence based on QFT-GIT. Further studies are required before using the QFT-GIT test routinely in LTBI diagnosis.

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