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Original Article

Comparison of Quanti FERON -TB gold and tuberculin skin tests in HIV infected patients in Hamadan, west of Iran

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Abstract

Introduction: Human immunodeficiency virus (HIV) infection increases the susceptibility of patients for latent tuberculosis infection (LTBI) and reactivtion tuberculosis. This study aimed to compare the Quantiferon-TB gold-in tube test (QFT) with tuberculin skin test (TST) in the diagnosis of LTBI in HIV infected patients.

Methodology: This comparative study of 89 patients with HIV in the Behavioral Diseases Counseling Center in Hamadan was carried out from July 2015 to November 2016. After obtaining consent from the patients, all demographic data, clinical manifestations, and laboratory results (CD4 count, TST and QFT) were entered into the questionnaires. The CD4 count is usually routinely performed using flow cytometry at the Behavioral Counselling Center. Quantiferon-TB test was done by using Qiagen – Quantiferon-2 plate kit ELISA.

Results: Totally, 89 HIV infected patients with the mean age of 39.55 ± 10.31 years old were enrolled in the study. Sixty patients (67.42%) were male. The mean duration of HIV infection was 4.44 ± 3.88 years and the mean of CD4 count was 388.65 ± 260.66 cells/µL . Twenty patients had LTBI based on TST. Considering the QFT intermediate results as a positive test, the percent agreement of QFT and TST was 59.55%, which was not statistically significant (P = 0.2387).

Conclusions: According to the results, there was no significant percent agreement between QFT and TST for detecting LTBI in HIV infected patients. However, by decreasing CD4 counts, there was a significant relation between TST positive and LTBI in HIV patients.

Key words: Quantiferon TB-gold test; tuberculin skin test; human immunodeficiency virus; CD4 count.

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Introduction

Human immunodeficiency virus (HIV) HIV is a virus that attacks the immune system and leads to HIV infection and progresses to acquired immune deficiency syndrome (AIDS) [1]. Total of 1.5 million people died from TB in 2018 (including 251,000 people with HIV). Worldwide, TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS) [2]. The World Health Organization (WHO) estimates that, annually, around 8 million people develop active tuberculosis globally, and nearly 2 million people die from the disease [3].

HIV infection increases the risk of tuberculosis due to impairment of immunity, particularly cellular immunity which leads to the activation of latent tuberculosis infection [4-6]. In HIV negative patients, the risk of converting latent tuberculosis infection (LTBI) to disease is 5 to 10% in life, while in HIVpositive patients, the risk is 10 fold, about 30- 50 percent [6-8]. The major risk that these patients may have for society is the increase of multidrug resistance (MDR) tuberculosis; therefore, timely identification and prophylaxis treatment of HIVinfected individuals with TB is one of the most important and useful measures for preventing the occurrence of TB and multi-drug resistant cases [9]. Tuberculin skin test or purified protein derivative (PPD) test is a standard method for diagnosing people with tuberculosis andin HIV positive patients' ≥ 5 mm induration at the inoculation site and 2 mm diameter induration in AIDS patients is considered as a positive test for LTBI [10,11]. In 2005, the Centers for Disease Control and Prevention (CDC) recommended that the Quantiferon-TB test (QFT) and TST is can be used in all cases, but QFT seems to be more specific to *Mycobacterium tuberculosis* than TST. Besides, the predictive value of

QFT results depends on the prevalence of *Mycobacterium tuberculosis* infection in the population and there is no reason to confirm QFT positive by TST [12]. Tuberculosis is one of the most common infections among HIV-positive people worldwide and a major cause of death in these individuals [13,14]. The lifetime risk for active tuberculosis (TB) is estimated to be 5 to 10% for a person with a positive tuberculin skin test (TST), but the risk is much higher in HIV-infected patients, 10% per year [15].

In recent years, two laboratory tests for IFN-γ secretion from T lymphocyte are available in response to stimulation of the highly specific antigen of TB (ESTAT-6 and CFP-10) and QFT is an enzyme-linked immunosorbent assay of total blood for measuring IFN-γ [16]. Quantiferon-TB test is more specific to TST due to less cross-reactivity with BCG and less susceptibility to non-TB mycobacterium. Considering the endemic nature of tuberculosis in Iran and in Hamadan province, and because of the controversial research in terms of the higher specificity of QFT on TST or the lack of superiority to one another, this study was designed to investigate the comparison of QFT and TST in detecting LTBI in HIV infected patients referred to the Behavioral Counseling Center in Hamadan, west of Iran.

Methodology

This comparative study was conducted on 89 HIV positive patients at Behavioral Counselling Center in Hamadan from July 2015 to November 2016. After receiving written consent from HIV infected patients, demographic information (age, sex, occupation, residence), clinical manifestations (cough and sputum), length of HIV, stage of AIDS (CD4 count < 200 cells/μL) , receiving antiretroviral therapy (ART), TB prophylaxis, CD4 count, Quantiferon-TB test (QFT), and TST results, sputum smear and culture and chest X-ray reports were entered on the checklist. The CD4 count is usually routinely performed using flow cytometry at the Behavioral Counselling Center.

For each HIV infected patients, a tuberculin skin test (TST) or Mantoux test using 0.1 mL (5 international units) of purified protein derivative (PPD) (Razi Vaccine & Serum Research Institute, Tehran, Iran) was intradermally injected on the forearm and then 72 hours later, the diameter of induration was measured. A positive TST was defined as an induration ≥ 5 mm in HIV infected patients. In the patients with clinical signs of coughing and sputum, a three-time sputum specimen for smear and culture was sent to Hamadan Health Center laboratory as well as chest radiography for all patients. In addition, from all patients, 5 mL blood samples for QFT were taken and transferred to Arad laboratory in Hamadan.

The QFT was performed in 12 hours after blood sample collection. QFT was done by using Qiagen – Quantiferon-2 plate kit ELISA and manufacturer instructions (Cellestis company of Australia, with code: J05990301). Each Qiagen-Quantiferon test contained: A negative control; that had only blood sample of the patient. A positive control; in addition to blood samples it contained a phytohemagglutinin to stimulate the production of the interferon. The test tube; that had blood and some specific antigens of *Mycobacterium tuberculosis* (such as CFP-10 and ESAT- 6). The test was considered positive if the levels of interferon γ were more than 0.35 IU/mL provided that the negative tube levels were less than 0.35 IU/mL and positive control was equal or more than 0.5 IU/ml. However, the test sample with interferon level less than 0.35 IU/mL level and a positive control level of less than 0.5 IU/mL was considered borderline or intermediate. This data was analyzed to measure correlations of two tests (TST and QFT) and other variables in Stata Version 14 software by Chi-square, Fisher exact test, and independent t-test. Kappa statistics for agreement between QFT test and TST were used. The positive and negative predictive value of QFT and TST tests was performed. The significance level in all statistical tests was less than 0.05.

This study was approved by the Ethics Committee in Hamadan University of Medical Sciences with code: IR.UMSHA.REC.1394.9.

Results

Totally, 89 HIV infected patients with the mean age of 39.55 ± 10.31 (range: 8-70) years old were enrolled in the study. The mean duration of HIV infection was 4.44 ± 3.88 (range: 0-15) years and the mean of CD4 count was 388.65 ± 260.66 cells/μL (range: 9-1008). In addition, the most of patients lived in urban areas (92.13%) and 67.42% were male (Table 1).

However, there was no positive sputum culture for mycobacterium tuberculosis.

In Table 2, the results of QFT and TST based on positive and negative sputum smear show that there was no statistically significant relationship between these tests ($P \geq 0.05$).

Table 3 shows that the relationship between the mean of CD4 count with two tests. Negative TST result was significantly associated with higher CD4 count ($P = 0.0448$), but for QFT, this relationship was not significant ($P = 0.4317$).

In Table 4: compares negative, intermediate or borderline, and positive QFT results with TST, and there was no statistically significant relationship between these tests (P = 0.772).

Furthermore, in comparison between QFT and TST results in HIV infected patients: with considering QFT borderline results as positive results, the percent agreement of two tests was 59.55% (Kappa = 0.0702); there was no statistically significant difference (P = 0.2387); however, with considering QFT borderline results as negative results, the percent agreement of two tests was 73.03% (Kappa = 0.0166). There was no statistically significant difference (P = 0.4287).

Considering the intermediate or borderline results of QFT as a positive outcome, there was no significant relationship between QFT and TST (P = 0.477).

Predictive value at a best scenario (Table 5): That is, all cases of quantitative intermediate QFT results should be considered as positive. The positive predictive value of TST is 45% and the implication is that only 45% of people with TST positive, also have positive QFT and the negative predictive value of TST is 63.77% and the implication is that only 63.77% of people who have a negative TST are also negative QFT.

Predictive value in worst scenario (Table 6): All results of the quantitative intermediate QFT should be considered as negative. The positive predictive value of TST is 10% which means only 10% of people with TST positive, also have positive QFT and the negative predictive value of TST is 91.3%; it means only 91.3% of patients with a negative TST, also have a negative QFT.

Consequently, the positive predictive value of TST in the best and worst scenario was 45% and 10%, respectively, and the negative predictive value of TST in the best and worst scenario was 63.77% and 91.3%, respectively.

Discussion

Acquired immunodeficiency syndrome (AIDS) is a disease caused by HIV and associated with severe cellular and humoral immunity deficiencies that weaken the host defense system; hence, resulting in susceptibility to infections such as pneumococcal pneumonia, pulmonary tuberculosis, toxoplasmosis infections, and fungal infections [17]. The peresent study was done on 89 HIV patients with a mean age of 39.55 ± 10.31 years old. In addition, the mean duration of HIV and CD4 count were 4.44 ± 3.88 years and 388.65 ± 260.66 cells/μL, respectively.

The level of agreement between TST and QFT in the diagnosis of LTBI in HIV positive patients considering QFT intermediate results as positive was 59.55%, and considering QFT intermediate results as negative was 73.03% which none were statistically significant.

In this study, TST and QFT had similar results in latent TB diagnosis and no statistically significant difference was funded. Some studies, such as Howley *et al*. [18], Vaziri *et al*. [19] and Khawcharoenporn *et al*. [20] showed that TST is more appropriate for latent TB screening in HIV infected patients.

However, Ramos *et al*. [21] reported that that the dual and sequential TST and QFT methods could be useful in identifying in latent TB screening in HIV patients.

On the contrary, the studies of Souza *et al*. [22] and Jones *et al*. [23] showed that in HIVinfected patients, QFT may be more useful and valuable than the TST test for diagnosis of LTBI .

Table1. Demographic and clinical characteristics in 89 HIV infected patients.

Variables	N (%)
Gender	
Male	60 (67.42)
Female	29 (32.58)
Habitat	
Urban	82 (92.13)
Rural	7 (7.87)
Occupation	
Un-employee	39 (43.82)
Employee	1 (1.12)
Free job	49 (55.06)
AIDS stage	
Yes	12 (13.48)
No	77(86.52)
History of anti-HIV treatment	
Yes	69 (77.53)
No	20 (22.47)
History of Anti-TB prophylaxis	
Yes	13 (14.61)
No	76 (85.39)
History of anti-TB treatment	
Yes	7 (7.87)
No	82 (92.13)
TST	
Positive	20 (22.47)
Negative	69 (77.53)
QFT	
Positive	8 (8.99)
Borderline	26 (29.21)
Negative	55 (61.80)
Sputum smear (TB)	
Positive	1 (1.12)
Negative	88 (98.88)

Table 2. Comparison of TST and QFT results based on sputum smear for mycobacterium tuberculosis (MTB) in 89 HIV infected patients.

Variables		Sputum smear (MTB)		P value *
		Negative	Positive	
PPD	Negative	68	1	0.775
	Positive	20	-	
QFT	Negative	55	-	0.382
	Borderline	25	1	
	Positive	8	-	

* Using Fisher exact test.

Table 3. Comparison of TST and QFT results based on CD4 counts in 89 HIV infected patients.

Variables		CD4 count (cells/µl) Mean ± SD	P value *
PPD	Negative	418.41 ± 260.05	0.0448
	Positive	286.00 ± 241.59	
QFT	Negative	416.95 ± 260.62	0.4317
	Borderline	340.92 ± 276.40	
	Positive	349.25 ± 276.40	

* Using independent t-test.

Table 4. Comparison of TST and QFT results in 89 HIV infected patients.

Variables	TST		P value *
QFT	Negative	Positive	
Negative	44 (63.77)	11 (55)	0.772
Borderline	19 (27.54)	7 (35)	
Positive	6 (8.7)	2 (10)	

* Using chi-square test.

Table 5. Comparison of TST and QFT results in 89 HIV infected patients with considering QFT borderline results as positive results.

Variables	TST		P value *
QFT	Positive	Negative	
Positive	9 (45%)	25 (36.23%)	0.477
Negative	11 (55%)	44 (63.77%)	

* Using chi-square test.

Table 6. Comparison of TST and QFT results in 89 HIV infected patients with considering QFT borderline results as negative results.

Variables	TST		P value *
QFT	Positive	Negative	
Positive	2 (10%)	6 (8.70%)	0.857
Negative	18 (90%)	63 (91.3%)	

* Using chi-square test.

Therefore, such a discrepancy may be due to demographic factors and health differences between the study population and the incidence of TB and HIV in Hamadan.

In this study, the relationship between the mean CD4 count and TST showed that negative TST results were significantly associated with higher CD4 count, but for QFT, that was not significant. Contrariwise, in the study of Cheallaigh *et al*. [24] there was a significant relationship between CD4 count and QFT results, and because of the low prevalence of tuberculosis, they found QFT appropriate for screening HIVinfected patients.

In the peresent study, there was a significant relationship between positive TST results and a decrease in CD4 count which illustrates the effect of CD4 count on the results of TST, so it is better to use QFT in screening of LTBI in HIV patients with reduced CD4 count.

On the contrary, in Kabeer *et al*.'s study, reported that the positive TST at the 5-mm cut-off point (19%) was significantly lower than QFT (38%) and indeterminate results for QFT was more common in patients with CD4 < 100 cells/μL than in those with > 100 cells/μL [25].

The findings of the study indicate the efficacy of the TST result on CD4 cell count decreases with the progression of HIV disease, and it has an important role in selecting the appropriate method for screening LTBI. It is recommended in this group of patients, which are most at risk of developing tuberculosis, QFT should be used to screen for latent tuberculosis. Moreover, QFT has no reminder effect in the patient, and it has repeatability in a short time.

In the peresent study, in comparison between QFT and TST results in HIV infected patients: with considering QFT borderline results as positive, the percent agreement of two tests was 59.55% ; however, with considering QFT borderline results as negative, the percent agreement of two tests was 73.03. There was no statistically significant difference in both conditions.

However, in the study of Luetkemeyer's *et al*. [26] concordance between QFT and TST was 89.3% and in the study of Souza *et al*. [22] an agreement between TST and QFT was 96% which resulted QFT is better than TST for detecting LTBI in HIV infected patients.

Furthermore, in this study, the positive predictive value of TST in the best and worst scenario was 45% and 10%, respectively and the negative predictive value of TST in the best and worst scenario was 63.77% and 91.3%, respectively. In the other words, this difference may be affected by various populations, environment and health factors and the incidence of HIV and TB in two different populations. The findings of the study showed that disagreement between two tests in identifying LTBI in HIV infected patients, but there was no statistically significant difference; it means there was no priority for each test in recognizing LTBI.

The limitation of this study was, we do not repeat QFT for borderline or intermediate results in HIV patients; however, by considering statistical analysis of positive and negative conditions of the test separately, this issue has been controlled.

Conclusion

According to the findings, there was no significant percent agreement between QFT and TST for detecting LTBI in HIV infected patients and no preferences for diagnosing LTBI by these tests. However, by decreasing CD4 count, there was a significant relation between TST and LTBI in HIV infected patients. Concerning decreasing CD4 cells with progressing HIV disease that is very crucial to select a proper method for screening LTBI in HIV patients. Therefore, it is recommended to use QFT as a screening test for identifying LTBI in high risk patients.

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Authors' Contribution

All authors have approved the manuscript and had a substantial contribution in data gathering, sampling, manuscript drafting, interpretation and critical revision of manuscript and data analysis.

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