Evaluation of Quantiferon TB Gold Test for the Diagnosis of Latent and Active Tuberculosis

Milind S Panchbhai

Biochemistry Research Laboratory

Central India Institute of Medical Sciences, Nagpur-10, India

Tel: 712-223-6441/223-3381   E-mail: milindpanch_ciims@rediffmail.com

Rajpal S Kashyap

Biochemistry Research Laboratory

Central India Institute of Medical Sciences, Nagpur-10, India

Tel: 712-223-6441/223-3381   E-mail: raj_ciims@rediffmail.com

V.S. Agrawal

Biochemistry Research Laboratory,

Central India Institute of Medical Sciences, Nagpur-10, India

Tel: 712-223-6441/223-3381

Hemant J Purohit

Environmental Genomics Unit

National Environmental Engineering Research Institute

Nehru Marg, Nagpur-20, India

Tel: 712-223-6441/223-3381   E-mail: hemantdrd@hotmail.com

Girdhar M Taori

Biochemistry Research Laboratory

Central India Institute of Medical Sciences, Nagpur-10, India

Tel: 712-223-6441/223-3381   E-mail: taori_gm@yahoo.co.in

Hatim F Daginawala (Corresponding author)

Biochemistry Research Laboratory

Central India Institute of Medical Sciences, Nagpur-10, India

Tel: 712-223-6441/223-3381   E-mail: hfd_ciims@rediffmail.com

Abstract

Background: Tuberculosis (TB) is a worldwide public health problem. In the present study we have evaluated the usefulness of Quantiferon TB Gold (QFT-G) test along with tuberculin skin test (TST) in the diagnosis of TB and to demonstrate the prevalence of latent TB in the study population of high TB prevalence area of Nagpur, India. **Materials and methods:** Venous blood samples of 74 study population including 34 control individuals were collected and QFT-G and TST tests were performed. **Results:** QFT-G was more positive than TST in

diagnosing TB infection. The overall specificity of QFT-G & TST was 50% & 65% respectively along with 50% discordant results between QFT-G and TST. **Conclusion:** Diagnosis of tuberculosis is better by QFT-G as compared to TST. However, the detection and prevalence of latent TB infection is much greater when both the tests are combined.

Keywords: QFT, TST, Latent tuberculosis, ESAT-6, CFP-10

1. Introduction

Tuberculosis is a major health problem in India due to the presence of latent tuberculosis infection and inadequacy in diagnosis of tuberculosis (Manabe Y.C 2000). 22 % of the tuberculosis in the world population has been reported from India. Recent health report shows that incident rate for the tuberculosis in India is very high (168/100000) while prevalence rate is 283/100000 (Global tuberculosis control-WHO report 2002, 2008). The early and accurate diagnosis of the tuberculosis infection is therefore essential for the control of tuberculosis.

Acid Fast Bacterium staining and culture are most widely used methods for the diagnosis of the active tuberculosis infection (Global tuberculosis control-WHO report 2009, Perkins M.D 2000). AFB staining is very rapid method but microscopic examination only confirms highly multibacillary samples and its diagnostic performance totally depends on microscopist and in addition it requires multiple specimen which leads to significant drop out of the infectious patients (Foulds J 1998). According to recent WHO report smear microscopy is insensitive and it detects roughly 50% of all the active cases of TB (Global tuberculosis control-WHO report 2002). On the other hand latent tuberculous infection (LTBI) is diagnosed on the basis of tuberculin skin test (TST). TST has many limitations, for example, it has low specificity and gives the cross reactivity with the BCG vaccine, secondly its sensitivity is low in immuno-suppressed patients, who are most susceptible for the tuberculosis (Perkins M.D 2007). Quantiferon TB Gold test require <16 h processing and a centrifugation hence, in-spite of various limitations TST is still used in routine practice for screening of the LTBI (American Thoracic Society 2000).

In past few years many researchers working on tuberculosis have developed a number of diagnostic tests, for the diagnosis of the active pulmonary and extra-pulmonary tuberculosis infection (Benjamin R.G1984, Bothamley G. H1998, Chan E. D 2000, Mori T 2004, Rajan A.N 2007, Kashyap R.S2005). But the diagnosis of the Latent tuberculosis is equally important to control tuberculosis infection. Quantiferon-TB Gold test is an in-vitro test based on the IFN-Y production by stimulated T cells in response to antigens that are specific to the *Mycobacterium tuberculosi*s such as ESAT-6, CFP-10, and TB7.7 (Floyd S 2002). ESAT-6 and CFP-10, which elicit strong INF-Y response in T cells from persons infected by *M. tuberculosis* but not from the BCG vaccinated individuals (Andersen P 2000). Earlier many workers have demonstrated the usefulness of the Quantiferon-TB Gold test for the diagnosis of the LTBI.

The objective of the present study is to evaluate usefulness of Quantiferon TB Gold test along with TST in the diagnosis of different types of tuberculosis infection and to demonstrate the prevalence of latent tuberculosis in the unscreened healthy population in high tuberculosis prevalence area of Nagpur.

2. Materials and Methods

2.1 Patients

Seventy four individuals were selected for the study which included 73 individuals from Macca Masjid, Teka Naka area of Nagpur having high prevalence of tuberculosis and 1 individual was enrolled from Central India Institute of Medical Sciences, Nagpur. Written consents were taken from all the individuals. The protocol of the study was approved by Institutional Ethics Committee of Central India Institute of Medical Sciences, Nagpur.

2.2 Diagnostic criteria for the selected individuals

2.2.1 Active TB Group

Active TB was diagnosed on the basis of either sputum AFB positive or culture positive or both as per Revised National Tuberculosis Control Programme (RNTCP) norms. However when both the tests were negative, the individuals were diagnosed by clinical symptoms. Clinical suspicion of tuberculosis was based on minimum of 3 symptoms of the following a) past history of TB b) Fever more than 2–3 weeks c) Progressive unexplained weight loss d) loss of appetite e) night sweats and f) radiographic (chest X-ray) features supporting the clinical diagnosis such as lung parenchymal infiltration mainly involving apical and/or mid zone, miliary shadows and pleural effusion.

2.2.2 Old Pulmonary TB Group

All patients who have received anti-TB drugs (covered under Directly Observed Treatment, Short course) in absence of any other therapy. Daily dosages given as isoniazid 300 mg, rifampicin 450 mg or 600 mg, pyrazinamide 1.5 g or 2.0 g and ethambutol 25 mg/kg for the first 2 months. In the next 2 months rifampicin 450 mg or 600 mg, isoniazid 300 mg and ethambutol given followed by ethambutol, rifampicin 450 mg or 600 mg and isoniazid 300 mg for the next 4 months.. The radiographic features suggestive of healed calcification or consolidation were included in old pulmonary TB Group.

2.2.3 Suspected Pulmonary TB group

The patients having smear negative but adiographic features showing active Koch's lesion in the upper lateral zones and in addition the patients having cough for more than 3 weeks, fever in evening and weight loss were included in suspected pulmonary TB group.

2.2.4 Extra-pulmonary TB group

The patients diagnosed prospectively on the basis of clinical manifestations consistent with TB and cultures of *M. tuberculosis* and completed Anti Koch's treatment.

2.2.5 Suspected extra-pulmonary TB group

Th*e* patients having lymphodenopathy diagnosed on the basis of swollen lymph nodes and one of the following criteria: 1) detection of *M. tuberculosis* in a culture of lymph node tissue or 2) pathological changes consistent with TB and a distinct clinical response to a full course of anti-tuberculosis treatment.

2.2.6 Normal healthy controls

Persons not having past history of TB and no signs of clinical impairment and normal chest X-ray were included as normal healthy controls.

2.2.7 Disease controls

In addition, patients admitted to the hospital for acute or chronic non-TB diseases such as asthma, neurological disorders, non-specific respiratory symptoms, gastrointestinal symptoms, non-specific fever, pneumonia, bronchitis, and lung cancer etc are included as disease controls.

2.3 QuantiFERON-TB Gold test

QuantiFERON-TB Gold test (QFT-G) was done in all samples as per manufacturer instructions (Cellestis Limited, Carnegie, Victoria, Australia). In brief, 1 ml of whole blood was taken in three different heparinized blood collection tubes namely nil tube (without antigen), antigen tube (coated with ESAT6, CFP-10, TB 7.7 antigen), and mitogen control tube (coated with phytohemagglutinin) and incubated for 16 to 18 hrs at 37°C. Approximately 300 µl of plasma supernatant were removed from the incubated tubes and stored at -20°C until used. The second stage of QFT-G test consisted of an enzyme-linked Immunosorbent assay (ELISA). Responsiveness to ESAT-6 or CFP-10 was expressed by number of units of IFN-γ produced after subtracting response to nil control. Results greater than 0.35 IU/ml to either antigen indicated TB infection.

2.4 Tuberculin skin test

Tuberculin skin test was performed wherein 0.1 ml of tuberculin PPD (Serum Institute Pune; equivalent to about five tuberculin units of PPD solution) was injected intradermally into the volar aspect of the forearm, and the transverse induration diameter was measured within 48 to 72 hours. An area of induration of >10 mm in individuals is reported as positive TST.

2.5 Statistical analysis

Comparison of two proportions in the study group was done by the Chi-square test. All statistical analyses were performed using MedCalc statistical software (version 10.1.2.0) with $p < 0.05$ as the cutoff point for statistical significance.

3. Results

A total of 74 individuals participated in the study, none of them was found to be HIV positive. Out of these 55(74%) were BCG vaccinated (from clinical information form) male 36%, female 64%), while 19(26%) were BCG non-vaccinated (male 41%, female 59%). Distribution of the study population according to the different demographic characteristics showed that the major part of the study population lies in the age group of 21 to 40 years (42%), female were predominant in the study population. Similarly the study population was categorised

according to the Body mass index (BMI) wherein most of the females in the study population were underweight (undernourished) and most of them in the direct contact with TB patients (Table 1).

On the basis of diagnostic criteria for different tuberculosis group we found that out of the 74 individuals, 12 (16%) were of confirmed active tuberculosis, 8 (11%) were of suspected pulmonary tuberculosis, 6 (8%) cases of old pulmonary tuberculosis, 2 (3%) cases of confirmed extra pulmonary tuberculosis, 12 (16%) were of suspected extra pulmonary tuberculosis and 34 (46%) cases of healthy and disease control group (Table 2).

The sensitivity of the QFT and TST in different groups was found to be as follows. Out of the 12 active tuberculosis patients 9 (75%) were QFT-G and 3(25%) were TST positive (95% CI 10.1 to 72.8, *P*-value 0.0412). Hence there is significant difference between in the QFT-G and TST in the results in the active TB cases. Out of the 8 suspected PTB Cases 5 (62%) were QFT-G and 7 (87%) were TST positive, out of the 6 cases of the old TB 5 (83 %) were QFT-G and 3 (50%) were TST positive. Similarly in case of the 2 extra pulmonary tuberculosis 1 (50%) was QFT-G positive and out of the 12 Cases of the suspected extra pulmonary tuberculosis 4 (33%) were QFT-G and 2 (16%) were TST positive, among the 34 cases of the healthy and disease controls 13 (38%) were QFT-G and 11 (32%) were TST positive. Thus the overall positivity of the QFT-G and TST in control group was 38% and 33% respectively. (Table 3)

For all discordant results, subjects were more likely to be QFT-G positive/TST negative than TST positive/ QFT-G negative. The highest proportion of discordant results was found among those with Active TB (84%) and Ex-PTB (100%) cases respectively. While the overall discordant in total study population was found to be 50%. (Table 4)

When the participants of all the 6 groups (table 2) were subclassified on the basis of their BMI it was observed 43 (58%) individuals had low BMI index, 26(35%) had normal BMI index and only 5(7%) had high BMI index. 11 (79 %) participants out of 14 healthy control group which are QFT-G and TST Negative were underweight, while only 4 (20%) out of the 20 disease control group were either QFT-G or TST positive had low BMI (Underweight). (Table 5)

4. Discussion

In the present study blood sample of individuals in different tuberculosis groups and controls were analyzed by 3rd generation Quantiferon TB Gold test and Tuberculin skin test for the diagnosis of TB infection. These test demonstrated the prevalence of latent tuberculosis in the unscreened healthy population in high tuberculosis prevalence area of the Nagpur. Quantiferon TB Gold test uses Mycobacterium tuberculosis specific antigen peptide of ESAT-6, CFP-10 and TB 7.7. (Pai M 2005). The positivity of QFT-G in active tuberculosis disease is found to be 75%. The positive QFT-G is due to presence of activated T-cells. The results are in agreement with previous published reports (Menzies R.I 2000). While the QFT–G is useful in detecting LTBI, it has been reported that is not very useful in detecting active tuberculosis (Rieder H.L 1999).

The Positivity of QFT-G in suspected pulmonary tuberculosis is less as compared to active tuberculosis. The less activity of interferon gamma may be due to intrinsic limitations of test. Secondly the suspected PTB patients may have memory T cells which are producing IL-2 but no interferon gamma so that effector T cells are not generated. Other possibility may that effector memory T cell population is maintained, by continuing exposure to environmental mycobacteria expressing cross-reactive ESAT-6 or CFP-10 homologues(Pai M 2005, Harari A 2005, Aiken A. M, Dheda K 2005). Most of subjects included in this group shows initiation of clinical symptoms. The RBC count in suspected tuberculosis (10.84mil/cu. mm) is high as compared to control (healthy and disease control) (4.55mil/cu.mm) groups which may indicates that *M. tuberculosis* required more oxygen for growth. The previous study shows that oxygen is required for multiplying *M. tuberculosis* (Zahrt T.C 2000)

As per previously published report that in EPTB patients, the secretion of IFN-gamma by blood cells in response to *M. tuberculosis* antigens is poorer than the PTB patients and have shows only 16% sensitivity for QFT-G in EPTB(Hussain R 2002, Lee J.Y 2006, Dewan P.K 2007). Our result shows 33.33% QFT-G positivity which may be considered as intermediate positivity as earlier published data(Yoshihiro K 2009, Oznur A.K 2009). In this group 11 cases had early stage of lymphodenopathy which may be responsible for low positivity of QFT-G. The one subject with suspected pleural effusion did show high QFT-G positivity.

The old tuberculosis cases had completed their AKT treatment. The radiographic findings are suggestive of healed and consolidated lesion in lungs. This group has highest QFT-G activity. The high positivity of QFT-G may be due to persistence of circulating T cells for several weeks after the infection is cleared, or may be due to survival of infected organisms, or due to presence of the different specific strain $H_{37}R_V$ mycobacterium infection which activated effectors T-cells (Radhakrishna S 2003), or viable intracellular mycobacteria may persist in

some of healed and consolidated sites, and may subsequently re-activate causing post primary (reactivation) TB (Haque A. K 1990).

The comparative relationship between QFT-G activity and TST shows that TST activity in suspected pulmonary tuberculosis is more than other tuberculosis groups included in the study. This might shows that TST response is significantly associated with development of active tuberculosis (Kunimoto D 2009).

In the absence of any gold standard test, TST is the test of choice for the detection of the latent tuberculosis infection, however the sensitivity reported by many workers show large variability between 30 to 60 % in their results. In our study we found the sensitivity of the TST to be 33% in healthy population. The TST positive results show indurations of >15 mm are more likely to be the result of TB infection than of BCG vaccination (Wang L 2002). In recent years new promising test based on IFN-Y release assay by sensitized T cell (test) is used for the detection of the latent TB infection (Yoshihiro K 2009). Sensitivity of QFT-G test is also recommended for the diagnosis of the latent tuberculosis. In our study we observed 38.% positivity of QFT-G test in the control (healthy and disease) group which is in agreement with previous studies (Pai M 2005, Menzies R.I 2000).

In our study the discordance of TST and QFT-G was found to be 41%, but when positivity of both test were considered, we found more QFT-G positive cases compared to TST(table 4). Although QFT-G positivity may not hampered from BCG vaccination status, but TST status shows large variation in positivity mostly due to BCG vaccination status (Andersen P 2000, Ewer K 2003, Pai M 2004, Menzies D 2007), cross reactivity of environmental non-tuberculous mycobacterium antigen with PPD antigen (Black G.F 2003), malnourishment (Liebeschuetz S 2004) and/or due to high prevalence area of tuberculosis which leads to a shift of immune response away from a Th1 type (Floyd S 2002). Despite that both TST and QFT-G must be performed simultaneously for the diagnosis of the latent tuberculosis infection in healthy population. The positivity of latent tuberculosis by using both tests was found to be 56%. These results include cases of QFT-G negative but TST positive along QFT positive and TST negative. (Table 4)

5. Conclusion

The QFT G is the better test as compared to TST in diagnosis different tuberculosis group. The diagnosis of latent tuberculosis infection by QFT-G is better as compared to TST. However, the detection and prevalence of latent tuberculosis infection is much greater when both the tests are combined.

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Table 1. Distribution of the study population according to the different demographic characteristics of the study participants (n=74)

Characteristics	n	Male (%)	Female (%)	P-value
Age (Years)				
1 to 20 Years	30(39)	9(30)	21(70)	0.0045*
21 to 40Years	31(42)	13(42)	18(58)	0.31
41 to 60Years	11(15)	5(45)	6(55)	0.9660
More than 60 years	3(4)	2(67)	1(33)	0.9870
Body Mass index				
Normal	25(35)	11(42)	15(58)	0.3808
Underweight	45(61)	15(33)	30(67)	0.0026*
Obese	3(4)	2(67)	1(33)	0.9870
BCG vaccination				
Present	42	15(36)	27(64)	0.0189*
Absent	32	13(41)	19(59)	0.2340
History of direct contact with TB patients				
Yes	23	5(22)	18(78)	0.0005*
No	51	23(45)	28(55)	0.4168
TST				
Positive	26	5(19)	18(81)	0.0001*
Negative	48	23(48)	25(52)	0.8510
QFT				
Positive	37	15 (40)	22(60)	0.136
Negative	37	13(35)	24(65)	0.0189

Table 2. Distribution of the study population based on the diagnosis criteria (n=74)

Characteristics	Number of Patients
Active PTB	12
Suspected PTB	08
Old PTB	06
Extra-PTB	02
Suspected Extra-PTB	12
Healthy control	34
Total	74

Table 3. Results of the QFT and TST in the different tuberculosis and healthy control group (n=74)

Characteristics (n)	QFT Positive n (%)	TST Positive n (%)	Difference	95% CI	Chi-square value	Significance P-value
Active PTB (12)	09(75)	03(25)	50%	10.1% to72.8%	4.167	0.0412*
Suspected PTB (8)	05(62)	07(87)	25%	-17.1% to 58.5%	0.329	0.5663
Old-PTB (6)	05(83)	03(50)	33%	17.1% to 67.2%	0.359	0.5489
Ex-PTB (2)	01(50)	01(50)	0.0%	-57.3% to57.3%	1	0.3173
Suspected Ex-PTB (12)	04(33)	02(16)	17%	-17.1% to 47%	0.244	0.6216
Control (34)	13(38)	11(33)	5%	-17.1% to 26.4%	0.0310	0.8592
Total (74)	37(50)	27(36)	14%	-1.9% to 28.9%	2.415	0.1202

Chi square test for the comparison of two proportions, *** P<0.05**

Table 4. Distribution of percentage of concordant and discordant results for QFT and TST (n=74)

Characteristics (n)	No. of discordance /Total no.(%)	Subjects that were :			
		QFT^+/TST^+ n (%)	QFT^-/TST^- n (%)	QFT^+/TST^- n (%)	QFT^-/TST^+ n (%)
Active PTB	10/12(84%)	1(8)	1(8)	8(67)	2(16)
Suspected PTB	1/8(12.5%)	5(62)	2(25)	0	1(12)
Old-PTB	4/6(66.67%)	2(33)	0	3(50)	1(17)
Ex-PTB	2/2(100%)	0	0	1(50)	1(50)
Suspected Ex-PTB	6/12(50%)	0	6(50)	4(33)	2(17)
Control	14/34(41.17%)	5(15)	15(44)	8(24)	6(18)
Total	37/74(50%)	13(18)	24(32)	24(32)	13(18)