Egyptian Journal of Bronchology

Vol. 6, No 2, December, 2012

ORIGINAL ARTICLE

QUANTIFERON TB GOLD TEST IN NON TUBERCULOUS DIABETICS

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Quantiferon represents a significant advance that is expected to replace TST in screening LTBI, and showed a closer correlation with the infection burden than TST. However in groups known to increase the risk of progression of LTBI to active disease like diabetes, the results are not well established. The study performed on 35 subjects (21 diabetics, and 14 healthy control subject age and sex matched) to evaluate of the role of QFT-G in non-tuberculous diabetics. Results showed positive QFT-G in 28.6% (=6) in diabetics, while the TST was positive in 19% (=4) only. The QFT-G positive cases include 50% TST positive, and 50% TST negative. The control group has GFT-G positive in 71.4% TST negative subjects. The overall agreement of both tests in the study population 60%. So in immunocompromized groups, it is wise to use QFT G and TST in assessing LTBI. While in the control group it seems that QFT G test is superior in detecting LTBI especially in tuberculin negative individuals.

Keywords**:** *QFT-G, TST, Diabetes, LTBI.*

INTRODUCTION

Endobronchial obstruction is a common complication of Tuberculosis is caused primarily by mycobacteria tuberculosis (MTB) in humans.[1] It has an estimated 9.3 million new cases and 1.8 million deaths in 2007, mostly in developing countries.[2] About 80% of the population in Asia and Africa test positive in tuberculin skin test (TST).[1] According to WHO, Egypt is considered as one of the high burden countries for tuberculosis.[2]

Latent tuberculosis (LTBI) is the condition where a patient is infected with mycobacterium tuberculosis but does not have active disease.[3] The main risk is that about 10% of these patients will develop active tuberculosis at a later stage.[4,5]Clinical conditions associated with an increased risk of progression of LTBI to active TB are silicosis,[6] diabetes mellitus(DM),[7] chronic renal failure/ hemodialysis,[8] gastrectomy,[9] jejunoileal bypass,[10,11] solid organ transplantation,[12,13] or cancer of head or neck.[14] Clinicians have observed an association between DM and TB since early 20th century, although it was undetermined whether DM is a cause or a result of TB.[15] Although humoral immunity appears to be normal in most diabetics, several types of functional abnormalities have been demonstrated especially uncontrolled diabetics[16] as impaired granulocyte chemotaxis, decreased phagocytosis, macrophage dysfunction, impaired bactericidal activity to infections with intracellular pathogens and superoxide production,[17] besides the effect of angiopathy.[19]

TST remains the test of choice for the diagnosis of LTBI,[20] and identifies persons at high risk who would benefit by treatment of LTBI, if detected[21] The development of T-cell-based interferon-gamma (IFN-γ) assays (IGRAs) for MTB-specific antigens represents a significant advance that is expected to replace the TST in screening for LTBI.[22-24] These IGRAs have demonstrated excellent specificity and shown a closer correlation with the infection burden than the TST.[25-26-27] Comparative genomic studies of mycobacteria identified a genomic region in M. tuberculosis that is not present in BCG strains and in most non-tuberculous mycobacteria,[28] so-called region of difference 1 (RD1) encodes antigens that are highly specific for M. tuberculosis, Early secretory antigenic target 6(ESAT-6) and Culture filtrate protein 10 (CFP10).[20] This test has shown no affection by BCG vaccination due to the absence of these proteins.[29,30]

OBJECTIVES

The study at hand aimed at evaluation of the role of Quantiferon TB Gold in non-tuberculous diabetics.

SUBJECTS AND METHODS

This study was performed in Kasr El-Aini hospital. The study included thirty- five subjects, twenty- one diabetic patients and fourteen subjects as a control group age and sex matched, with negative tuberculin skin test.

Inclusion criteria: DM type I or II, aged above 18 years.

Exclusion criteria: Patients with previous tuberculosis or contacts to tuberculous patients.

Patients receiving immunosuppressive drugs
For each patient, the following was done:

1- Full History taking and clinical examination.

2- Investigation including Chest X-ray, FBS, 2 hours PPBS, creatinin, CD4 T cell % using flow cytometry. Tuberculin skin testing using Mantoux technique, measured after 48-72 hours, level of positivity of tuberculin in diabetics > 10mm induration according to CDC.[31]

3- QuantiFERON® -TB gold test (Cellestis Ltd., Australia) is used. The QFT-G system uses three specialized blood collection tubes that contain antigens representing certain M. tuberculosis proteins (ESAT-6, CFP-10, and TB7.7) as well as positive (Mitogen) and negative (Nil) control,[32] then measurement of IFN-γ by ELISA. A test is considered positive if IFN-γ response to the TB Antigen tube is significantly above the Nil IFN-γ IU/ml value. A positive result suggests that M. tuberculosis infection is likely; a negative result suggests that infection is unlikely.[33]

RESULTS

The study population included 35 subjects. The target group included 21 diabetic patients and 14 healthy individuals in the control group.

The target population included 10 males (47.6%) and 11 females (52.4%), Their mean age was 54.1 + 8.3, with minimum 36 years and maximum 70 years .While the control group included 7 males (50%) and 7 females (50%) , their mean age was 52.1+ 10.2 with max 67. and min 32.

Regarding diabetes in the target group, the mean duration of illness was 10.3 ± 8.3 years. 47.6% was on insulin treatment, 47.6 % on oral hypoglycemics, and 4.8% on both lines of treatment. 90.5% was uncontrolled on the treatment and only 9.5% was controlled. The mean fasting glucose level was 277+80.3, while the mean post prandial level was 390.2+ 119.2. Finally, 81 % of the patients had evident complications of diabetes (peripheral neuritis, cellulitis or gangrene), while only 19% had no evident complications.

As for the CXR findings, there were positive findings in 3 out of 21 CXR in cases with a percentage of 14.3% in the form of apical infiltrates in one case and basal infiltrates in two cases.

Testing the CD4 level showed: The mean CD4 37.8± 10 % with max 53.5% and min 5.2%, while that of the control group was 41.33+ 7.4 % with max 54.4 % and min 38.45% with no statistical significant difference (p= 0.23)

Regarding the tuberculin skin test results in the target group, there were 17 cases out of the total 21 cases with negative TST (81%), while there were 4 cases with positive TST (19%). Knowing that the control group was selected with negative TST, there was no statistical significant difference between the TST in the two groups (p= 0.13)

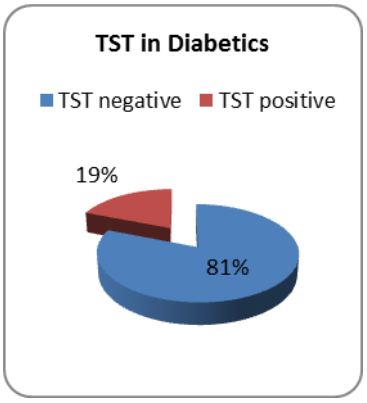

Fig 1. TST in Diabetes Group

Table 1. QFT Results in Cases and Control Groups.

QFT- G	Diabetic patients (n = 21)		Control (n = 14)	
	Frequency	%	Frequency	%
Positive	6	28.6	10	71.4
Negative	15	71.4	4	28.6

Control group showed statistically significant higher prevalence of positive Quantiferon results in the control than diabetic patients with p- value **0.01**

Table 2. Concordance of Both Tests in the Study Population.

		Quantiferon		
		-ve	**+ve**	**Total**
TST	**-ve**	18	13	31
	+ve	1	3	4
	Total	19	16	35

Over all agreement of the TST and Quantiferon equals (18+ 3)/ 35= 60%

Table 3. Tuberculin Versus Quantiferon Cross Tabulation.

Groups				Quantiferon		Total
				-ve	**+ve**	
DM	Tuberculin Test	-ve	Count	14	3	17
			% without Tuberculin Test	82.4%	17.6%	100.0%
			% without Quantiferon	93.3%	50.0%	81.0%
		+ve	Count	1	3	4
			% without Tuberculin Test	25.0%	75.0%	100.0%
			% without Quantiferon	6.7%	50.0%	19.0%
	Total		Count	15	6	21
			% without Tuberculin Test	71.4%	28.6%	100.0%
			% without Quantiferon	100.0%	100.0%	100.0%
Controls	Tuberculin Test	-ve	Count	4	10	14
			% without Tuberculin Test	28.6%	71.4%	100.0%
			% without Quantiferon	100.0%	100.0%	100.0%
	Total		Count	4	10	14
			% without Tuberculin Test	28.6%	71.4%	100.0%
			% without Quantiferon	100.0%	100.0%	100.0%

Groups			Value	Asymp. Std. Error [a]	Approx T [b]	Approx. Sig.
DM	Measurment of Agreement	Kappa	.481	.217	2.285	.022
	N of Valid Cases		21			
Controls	Measurment of Agreement	Kappa	. [c]			
	N of Valid Cases		14			

a. Not assuming the null hypothesis.
b. Using the asymptotic standard error assuming the hypothesis.
c. No statistics are complete because tuberculin test is a constant.

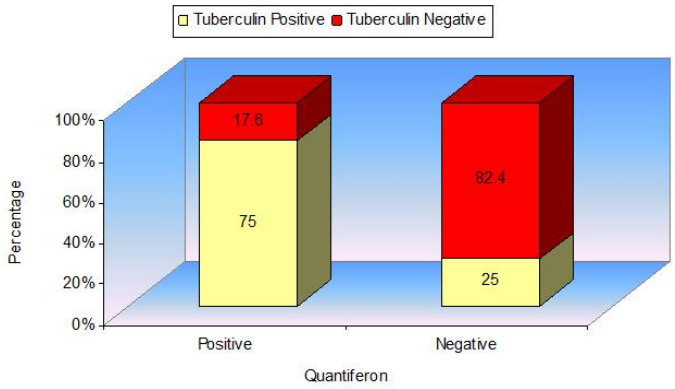

Fig 2. Tuberculin Test Results and Quantiferon Results

Accuracy measures of TST in relation to QFT in diabetics:

- Sensitivity %= true positive / (true positive + false negative) x 100 = 50%
- Specificity %= true negative/ (false positive + true negative) x 100= 93.3%
- Diagnostic accuracy: true positive + true negative / total number x 100= 80.9%
- Accuracy of Quantiferon in relation to TST in diabetics:
- Sensitivity % = 75%
- Specificity %= 82.35%
- Diagnostic accuracy= 80.9 %

Table 4. T-Test.

	Quanitferon	N	Mean	Std. Deviation	P Value
CD4%	-ve	15	38.86000	6.876648	
	+ve	6	35.03333	16.148519	0.45
FBG	-ve	15	264.93	85.553	
	+ve	6	307.33	61.181	0.29
PPBS	-ve	15	366.27	123.360	
	+ve	6	450.00	90.580	0.15
Age	-ve	15	53.20	9.488	
	+ve	6	56.50	3.782	0.43
Onset	-ve	15	10.1333	7.88187	
	+ve	6	10.6805	10.23297	0.89

Table 5. Results in relation to CXR findings LTBI in diabetes

Cases	TST	CXR	QFT
1	Negative	Positive	Positive
1	Negative	Positive	Negative
1	Positive	Positive	Positive

Based on diagnosing LTBI as positive tuberculin skin test and/ or IGRA: In diabetics: 7 out of 21: 33.33% of the diabetics.

DISCUSSION

The study was performed on 35 subjects divided into 21 diabetic patients and 14 healthy individuals, age matched and sex matched. The aim of the study was to evaluate the Quantiferon TB Gold in diabetics. Although the presence of DM alone does not justify screening for LTBI, but in the presence of other risk factors for TB, the presence of DM may be sufficient to justify screening and treatment for LTBI.[34] In addition, the reported MDR TB cases in Egypt is 3-6% which is considered high according to CDC 2011.[35] Also the appearance of XDR according to WHO 2011 is an alarming sign.[36]

CD4% was measured by using flow cytometry. Results showed 41.33+ 7.4% in the control group and in the cases; it was 37.8+10%, with no statistically significant correlation. This indicates no quantitative affection of the cell mediated immunity. The idea is that the ability to respond to TST correlates with the degree of cell-mediated immunity and decreases as the CD4 cell count.[37]

Quantiferon TB Gold showed positive results in 6 / 21 patients with a percentage 28.6% (Table 1), relative to the positive tuberculin 4 / 21 with a percentage of 19% (Fig 1). However in control group QFT was positive in 10/ 14 by a percentage 71.4% (Table 1) in completely negative TST patients. Results showed overall agreement of both TST and QFT-G test in study population as a whole equals 60% as shown in (Table 2). While the cross tabulation of the tests in each subgroup, showed good concordance with no statistical significant Kappa 0.022 (Table 2).

Different studies on different groups of patients showed wide range of results. A study done on 40 chronic renal failure patients and 20 control group, QFT-G was positive in only 8/40 patients (20%), While TST was positive in 6/40 (15%). QFT-G was positive in 5/20 of the totally tuberculin negative control group by a percentage of 25%.[38]

Another study screening 153 patients were screened for LTBI with both QFT-G test and TST prior organ transplantation, 37 (24.2%) had a positive TST and 34 (22.2%) had a positive QFT-G. Overall agreement between tests was 85.1% (κ= 0.60).[39]

In another study done on 336 HIV – infected persons, 7 (2.1%) had a positive tuberculin test, 9 (2.7%) had positive QFT-G test.[40]

There may be suboptimal response of QFT-2G to exposure to tuberculosis antigens namely ESAT-6 and CFP-10 in the Quantiferon Gold test, which may lead to false negative results in the diabetic group. There are two patterns by which false negative results are shown on QFT-2G tests; one pattern involves the decrease of interferon-gamma production due to advanced patient age or lymphocytopenia, and in the other lymphocytes cannot produce interferon-gamma for Mycobacterium tuberculosis-specific antigen in young patients without underlying disease.[41]

On the other side the number of QFT-G positive in control group 10/ 14 by a percentage 71.4% (Table 1) in patients with negative TST. This disconcordance was demonstrated in other studies performed on the immunocompetent group.[42] Another study of LTBI involved 652 apparently healthy adult pastoralists was undertaken in a known endemic area (Ethiopia), QFT G was positive in 363/ 570 (63.7%) while tuberculin was positive in 183/587 (31.2 %) with cutoff point 10 mm induration. There was poor agreement between the results of the tests (k = 0.098, 95% CI, 0.08 - 0.13).[43] While on the current study kappa could not be measured due to negativity of the tuberculin skin test in the control group.

This high positive results in the control group may be explained by considering Egypt as one of the high risk areas (the incidence or the prevalence is above 20/ 100000 population) for tuberculosis in the WHO's Eastern Mediterranean region for a very long time till 2010 which was the first time to decrease less than 20 and reaches 18/100000.[44]

It was stated that IGRAs allow a more accurate diagnosis of LTBI in immunocompetent patients.[45] There was a discrepancy in the results between the TST and QFT G may be explained by high specificity of QFT for the M. tuberculosis infection. Or the two-step TST was not performed which would have maximized the TST sensitivity.[46] The high number of negative TST results emphasizes the probable superiority of IGRAs because these tests eliminate both technical difficulties in performing a TST and subjectivity involved in TST interpretation.[47]

In the current study, accuracy measures of TST in relation to QFT in diabetics: Sensitivity = 50%, Specificity = 93.3% and diagnostic accuracy= 80.9%. While the accuracy of Quantiferon in relation to TST in diabetics: Sensitivity=75%, Specificity = 82.35% and, diagnostic accuracy= 80.9%.

On the contrary to our results: QuantiFERON-TB Gold is stated to have higher specificity than the tuberculin skin test. Rates of positivity provide different results in routine clinical practice. The pooled sensitivity was 78% (73% to 82%) for QuantiFERON-TB Gold.[48]

The results of sensitivity, specificity and diagnostic accuracy of Quantiferon test in relation to TST showed good sensitivity (66.7%), very high specificity (88.2%) and

very high diagnostic accuracy (85%). The results of sensitivity, specificity and diagnostic accuracy of TST in relation to QFT showed moderate sensitivity (50%), very high specificity (93.7%) and very high diagnostic accuracy (85%).[38]

Another study revealed that the sensitivity of TST was 77% and the specificity was 97% while the pooled sensitivity in QFT-G-IT was 78% and the specificity was 96%.[49] However the other mentioned QFT is more sensitive than the TST in detecting TB disease (78% vs. 50%, respectively).[41] Triverio et al, 2009 stated that QFT was the only test with a significance of having LTBI; because among 5 patients with definite prior TB, TST was positive in 1 and QFT in 2.[49] The CDC, 2005 stated that the specificity of QFT-G is more than TST, while the sensitivity of QFT-G for TB disease equals that of the TST.[50]

Quantiferon was found to be unaffected by CD4 level, FBS, PPBS, AGE as referred to table 4. This is compatible with Hoffmann et al, 2010 study which revealed that INF-gamma secretion was independent of age.[47]

The high prevalence of QFT positivity may have several explanations such as endemic area for TB, their frequent contacts, their old age, and immunological defect.[51]

CONCLUSION

In immunocompromized group of patients due to any reason, it is wise to use both tests QFT G and TST in assessing LTBI. While in the control group it seems that QFT G test is superior in detecting LTBI especially in tuberculin negative individuals. However it is recommended to study the Quantiferon G test in normal individuals in details, whether tuberculin positive or negative according to the normal incidence of the population.

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