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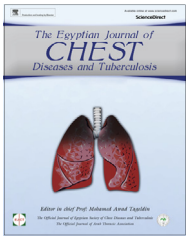

ORIGINAL ARTICLE

Quantiferon vs. tuberculin testing in detection of latent tuberculous infection among chronic renal failure patients

E.A. Abdel-Nabi [a], S.A. Eissa [a], Y.M.A. Soliman [a,*], W.A. Amin [b]

[a] *Faculty of Medicine, Cairo University, Egypt*
[b] *Shebin El-Koum Chest Hospital, Egypt*

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Abstract Latent tuberculous infection (LTBI) lacks a solid gold standard in its diagnosis and many clinicians rely upon tuberculin testing, however there has been an increasing interest in depending on Interferon Gamma Release Assays especially Quantiferon-Gold (QFT-G). Since chronic renal failure (CRF) poses an important health problem in Egypt and taking into consideration the immuno compromisation caused by this condition, LTBI detection emerged as an important health concern in those patients. In this study, the aim was to find which tool was better in the detection of LTBI in CRF patients. Forty patients with chronic renal failure and on hemodialysis, with exclusion of active tuberculosis and other immuno compromisation conditions were tested for LTBI by tuberculin skin test (TST) and QFT-G. 25% of the tested showed LTBI. It was found that although both tests gave comparable results, yet there was a discrepancy between both. TST+/QFT+ group was 10%, TST+/QFT− group was 5%, TST−/QFT+ was 10% and TST−/QFT− group was 75%.

Conclusion: In Chronic renal failure and probably any immuno compromisation setting, it would be better to perform both tuberculin and Quantiferon tests to detect latent tuberculous infection.

Introduction

Tuberculosis (TB) was always considered a communicable infectious disease that had been known for centuries. The causative bacilli were first identified by Robert Koch in the nineteenth century [1].

Tuberculosis remains an important public health problem in Egypt. Egypt is ranked among the mid-level incidence countries [2]. Moreover, the reported prevalence of chronic renal failure is 225 pmp in Egypt [3].

* Corresponding author. Tel.: +20 01117766220.
E-mail address: ymasoliman@yahoo.com (Y.M.A. Soliman).

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About 90% of those infected with *Mycobacterium tuberculosis* are asymptomatic, sometimes called latent TB infection (LTBI), with only a 10% lifetime chance that a latent infection will progress to TB disease [4]. Normal healthy individuals with LTBI have an annual risk of 0.1% (1 per 1000) of developing active TB. However for patients on hemodialysis, the annual risk of disease, if infected, may be 1–2% [5]. Unfortunately until now there is no full proof gold standard in diagnosis of LTBI, however many clinicians rely upon tuberculin testing [6].

CRF is associated with profound immune deficits; involving both the humoral and cellular arms; that predispose to infections [7]. Many studies, have confirmed an increased risk of TB in patients with chronic renal failure and on dialysis in comparison to the general population, varying from 6.9 up to 52.5-fold [8,9].

Aim of study

This study aimed at the evaluation of QFT in the diagnosis of LTBI in CRF patients under hemodialysis.

Methods

The study included 60 adults; 40 of them (patient group) are patients with end-stage renal disease on regular hemodialysis in the National Institute of Urology and Nephrology in EL-Matareyya, Cairo.

All patients with active tuberculosis or other immunosuppressing diseases such as Diabetes Mellitus and AIDS, with liver disease, under corticosteroid treatment for a long period, with immunologic disorders and with hematological disease were excluded.

All were subjected to thorough history taking, full clinical examination, tuberculin skin testing, chest X-ray, sputum analysis for AFB for 3 successive days, serum levels of BUN and Creatinine, ESR and Quantiferon TB-Gold (QFT-G) In-Tube assay.

All the obtained data were collected and statistically analyzed.

Table 1 Association between laboratory investigations and Quantiferon test results in patient group.

Quantiferon Laboratory test	Positive (n = 8)	Negative (n = 32)	P-value
Creatinine (Mean ± SD)	9.9 ± 2.9	11.1 ± 2.4	0.247
BUN (Mean ± SD)	59.8 ± 13.7	65.6 ± 15.4	0.331
ESR 1 (Mean ± SD)	78.1 ± 33.2	77.3 ± 26.9	0.938
ESR 2 (Mean ± SD)	99.1 ± 33.9	105.9 ± 25.7	0.533

Table 3 Association between laboratory investigations and tuberculin test results in patient group.

Tuberculin Laboratory test	Positive (n = 6)	Negative (n = 34)	P-value
Creatinine (Mean ± SD)	8.7 ± 2.6	11.2 ± 2.3	0.023*
BUN (Mean ± SD)	56 ± 16.7	65.9 ± 14.5	0.139
ESR 1 (Mean ± SD)	92 ± 12.8	74.9 ± 29	0.166
ESR 2 (Mean ± SD)	118.3 ± 18.1	102.1 ± 28	0.182

* Significant at $P \leqslant 0.05$.

Results

Tables 1–6.

Discussion

The study at hand aimed at the evaluation of QFT in the diagnosis of LTBI in CRF patients undergoing hemodialysis. Firstly, Quantiferon results were not affected by creatinine, BUN, ESR, or duration of hemodialysis as shown in Tables 1 and 2. There was no statistically significant correlation between Quantiferon test results in CRF patients and creatinine (P-value 0.247), BUN (P-value 0.331), ESR (P-value 0.938 for 1st hour and 0.533 for 2nd hour) levels, or duration of hemodialysis (P-value 0.056). This was compatible with a study that revealed that INF-gamma secretion was independent of the duration of HD treatment [10]. It should be mentioned, however, that another study found a significant increase of indeterminate QFT results with an increased HD duration [11].

Secondly, TST results were also not affected by BUN or ESR as shown in Table 3 with no statistically significant association between TST results in CRF patients and BUN (P-value 0.139) or ESR (P-value 0.166 for 1st hour and 0.182 for 2nd hour) levels. But results were significantly affected by creatinine level and duration of hemodialysis as their increase gave a negative TST result. TST negative cases showed a statistically significantly higher creatinine level (P-value 0.023) and mean duration of hemodialysis (P-value 0.021) than TST positive patients as shown in Tables 3 and 4.

This was different from the study which showed no significant correlation between hemodialysis duration and the TST reactivity [12]. However, Ates and coworkers found that there were no associations among the results of TST and QTF-GIT and duration of hemodialysis of the patients [13]. While Shankar et al. found that values of nutritional status markers (hemoglobin, albumin and creatinine) were significantly higher among the tuberculin-reactor ESRD patients [14].

There was a statistically significant association between QFT and TST results in the patient group (P-value 0.002) as mentioned in Table 5. So it might be concluded that Table 5

Table 2 Association between duration of hemodialysis and Quantiferon test results in patient group.

Quantiferon Duration	Positive (n = 8)	Negative (n = 32)	P-value
Duration of hemodialysis in years (Mean ± SD)	2.1 ± 1	4.3 ± 3	0.056

Table 4 Results of the association between duration of hemodialysis and tuberculin test results in patient group.

Tuberculin Duration	Positive (n = 6)	Negative (n = 34)	P-value
Duration of hemodialysis (Mean ± SD)	1.8 ± 1.2	4.2 ± 2.9	0.021*

* Significant at $P \leqslant 0.05$.

Table 5 Association between tuberculin and Quantiferon test results in patient group.

Quantiferon Tuberculin	Positive (n = 8)		Negative (n = 32)		P-value
TST (Frequency, %)					
Positive	4	50	2	6.3	0.002*
Negative	4	50	30	93.8	

* Significant at $P \leqslant 0.05$.

pointed out that QFT and TST were interchangeable in CRF patients. But this could not be true because though TST and QFT tests were immunologically based, TST and QFT did not measure the same components of the immunologic response and were not interchangeable [15]. Moreover, Table 6 in the study at hand showed the following:

* 20% of CRF patients were QFT positive, 6 (15%) were TST positive, 32 (80%) were QFT negative and 34 (85%) were TST negative.
* Only 4 patients had QFT+/TST+, the rest QFT+ were TST− (4 patients) and the rest of TST+ were QFT− (2 patients).

This meant that all patients with a positive result either QFT or TST were 10/40 (25%) of whom 4/10 (40%) were QFT+/TST+, 4/10 (40%) were QFT+/TST− and 2/10 (20%) were QFT−/TST+.

In an immunocompetent population, several studies demonstrate that the combination of TST positive/QTF negative results dominated the discordant results and most of these discordant results were explained by BCG vaccination or non-tuberculous mycobacterial infection (NTM) (e.g., Mycobacterium avium complex) [16]. These cross-reactions tended to result in small reactions to PPD (< 6 mm), but larger reactions might occur [17].

The greater rate of positive results reported with TST than with QFT in persons with and without recognized risks for *M. tuberculosis* infection might be explained by either greater specificity with QFT, greater sensitivity with TST, or both [18].

Studies found no association between LTBI and having a positive TST, but found a strong association between prior BCG vaccination and having a positive TST. Especially that QFT was not affected by prior BCG vaccination and less influenced by previous infection with NTM; however, TST was variably affected by these factors [19,20].

In comparison to healthy controls, TST reactivity rates were lower and anergy rates higher in ESRD patients [13,14,21–23]. These findings of false TST negativity might be due to uremic immunosuppression, particularly in BCG vaccinated population. Also in vitro assays would be able to detect the very first steps in the immune activation cascade, less influenced by the uraemic immune suppression than the TST, which depended on the integrity of the whole immune activation cascade resulting in a cutaneous induration in vivo [10].

It was shown that HD patients were still able to produce IFN-gamma ex vivo upon PPD-stimulation, although they were TST negative; suggesting an immune dysfunction at a later stage of the activation cascade resulting in cutaneous anergy [24].

Uremia was found to partly inhibit cellular immunity leading to false negative skin tests [25]. This finding was proved by the finding of a decreased T-cell response, marked by anergy rate of 32–40% to the intracutaneously administered antigens in uremic patients [22,26].

In another study, TB diagnosis tended to be hampered by a negative TST in uremic patients, which was found in some reports in 40–100% of the cases [27]. The anergy was attributed to uremia and/or dialysis induced defect in the co-stimulatory function of antigen-presenting cells and a persistent inflammatory state of monocytes [28].

High prevalence of QFT positivity may have several explanations such as endemic area for TB, their frequent hospital contacts, their old age, and uremic immunological defect. HD patients might have a higher rate of previous tuberculosis infection. However, when patients over, equal to and under 65 years of age were compared, there were no significant differences with respect to both TST and QFT positivity [29].

Regarding the TST negative/QTF positive discordant subjects it might be speculated that TST missed these LTBI diagnoses because of the high specificity of QFT for the M. tuberculosis infection. Although a two-step TST was not performed and this would have maximized the TST sensitivity

Table 6 Comparison between positivity and negativity in both tuberculin tested and Quantiferon tested patients.

Test	Number of patients	% Of all + (patients 10)	% Of all (patients 40)
QFT+/TST	4	40	10
−QFT+/TST	4	40	10
QFT−/TST	2	20	5
All	10	100	25
−QFT−/TST -The rest	30		75

[30,31]. However a booster effect could not be ruled out in this situation and a boosted reaction on a subsequent TST might be misinterpreted as a newly acquired infection, compared with the false negative result from the initial TST [32]. It should also be mentioned that repeating TST was time consuming, subject to variability between different readers, and did not improve specificity [19,30,31].

In a recent study the absolute number of peripheral blood lymphocyte and mitogen-stimulated IFN-γ response were found to be closely associated with antigen-stimulated IFN-γ production in whole blood assay in immunologically unselected TB patients [33].

In the present study the overall concordance between TST and QFT was 85% in ESRD patients; 10% TST and QFT positive and 75% TST and QFT negative. A finding substantiated by other studies [13,34].

T-cell assays identified significantly more patients with LTBI than did the TST and diagnostic agreement varied across groups [35]. Although, IGRAs and TST were shown to be similar in their diagnostic performance for LTBI with approximately 10% sensitivity benefit for using TST and an IGRA in combination with a slightly greater specificity loss [36]. But IGRAs were regarded by some studies as more accurate in the diagnosis of LTBI in immunocompetent patients than TST. [37,38].

Lee and his co-researchers compared QFT, ELISPOT, and TST in ESRD patients on hemodialysis and demonstrated a high prevalence of LTBI in this population and that QFT was the most accurate method for identifying those truly infected with *M. tuberculosis*, even in BCG-vaccinated individuals [39].

Conclusion

In Chronic renal failure patients, it is recommended to perform tuberculin testing and Quantiferon to have a better chance of detecting LTBI. This is because each test depends on a different immunological pathway. Taking into consideration that LTBI may bear devastating consequences for those patients, if it progressed to TB, LTBI must be detected.

Conflict of interest statement

None declared.

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