Utility of tuberculin skin test versus interferon gamma release assay in screening chronic kidney disease patients for latent tuberculosis infection

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Abstract

Latent tuberculosis infection (LTBI) is defined as persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active tuberculosis (TB). Chronic kidney disease patients are immuno compromised and vulnerable for developing active TB.

Early diagnosis of the infection may prevent progression to active disease and the present Programmatic Management of Tuberculosis Preventive Treatment (PMTPT) guidelines suggest offering preventive chemotherapy to people living with HIV (adults and children >12 months), infants <12 months in contact with active TB, household contacts below 5 years, children/adult on immuno suppressive therapy, anti-TNF treatment, dialysis and transplant patients. The current guidelines for latent tuberculosis infection treatment as per PMTPT include 3-month weekly Isoniazid and Rifapentine (3HP) or 6-months daily isoniazid (6H).

LTBI can be diagnosed using Tuberculin skin test (TST) and Interferon Gamma release assay (IGRA). Hence this study was undertaken to determine the utility of tuberculin skin test versus interferon gamma release assay in screening chronic kidney disease patients for latent tuberculosis infection.

This is a prospective observational study which was performed between March 2021 and August 2022, at Respiratory Medicine and Nephrology Departments, Chettinad Hospital and Research Institute. A total of 250 CKD patients in all stages were screened in the study, out of which 20 patients were found to have tuberculosis (pulmonary and extrapulmonary). Among 230 patients, 101 patients were eligible for the study fulfilling the criteria. All participants were tested with TST and QuantiFERON TB Gold in tubes (QFT-GIT). An induration of ≥ 10 mm and IGRA values ≥ 0.35 IU/mL were considered positive for LTBI. Out of the 19 patients who were diagnosed with LTBI, 6 patients were

TST and all 19 patients were IGRA positive. More number of patients were diagnosed with IGRA than TST with a p value of <0.0005. Thus, IGRA seems to more effective tool in detecting LTBI in immuno suppressed like CKD patients.

Keywords: Chronic Kidney Disease, Interferon Gamma Release Assay, Latent Tuberculosis Infection, Tuberculin Skin Test

Introduction

TB is an ancient epidemic disease, infecting quarter of the world population. Twenty-five years ago, due to the high prevalence and incidence of tuberculosis (TB), the WHO declared it a health emergency in 1993.[2] TB has risen to top ten reasons of death.[2] Globally, it is estimated that 10.6 million people fell ill with TB in 2021 and the TB incidence rate increased by 3.6% between 2020 and 2021. Most people who developed TB were in the WHO regions of South-East Asia (45%), Africa (23%) and the Western Pacific (18%), with smaller proportions in the Eastern Mediterranean (8.1%), the Americas (2.9%) and Europe (2.2%). The 30 high TB burden countries accounted for 87% of all estimated incident cases worldwide, and eight of these countries (Fig. 12) accounted for more than two thirds of the global total: India (28%), Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%) and the Democratic Republic of the Congo (2.9%).[1]

According to the National Prevalence Survey for 2019–21, Delhi has the greatest pulmonary TB prevalence at 534/lakh and Kerala has the lowest pulmonary TB prevalence at 115/lakh, well exceeding the 193 anticipated by the World Health Organization (WHO) for 2019. Greater PTB prevalence was seen in older age groups, men, malnourished individuals, smokers, alcoholics, and those with a history of diabetes.[3]

Towards achieving the End TB targets, it is realized unless and until there is an effective vaccination against TB it is important to prevent the emergence of new cases arising from the community from the existing pool of infected (latent TB). LTBI is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB.[4]

The prevalence of LTBI is estimated to be nearly 25% of the global population while in India the prevalence among population aged $\geq$ 15 years is 19.4-23.9%.[3,5] Untreated, the lifetime likelihood of advancement to active TB is 5-10% in immuno competent people, compared to 50-70% in immuno compromised people, as in HIV.[6] Hence, those immuno compromised states like CKD, HIV, chemotherapy, long term steroids, immuno suppressants and malignancy which have potential of progression of LTBI to active TB should be screened for LTBI. To eliminate TB globally by 2050, the occurrence of TB should fall by 20% average yearly from 2015 to 2050.[7] TB preventive therapy (TPT) for LTBI and proper treatment of active tuberculosis are the essential strategies to end TB. Currently TST and IGRA are two available tools to diagnose LTBI.

In India, the prevalence of tuberculosis in patients on dialysis is 10.5%. The risk of tuberculosis in CKD patients being 6.9 to 52.5 times higher than normal people due to impaired immunity caused by CKD.[8] Screening of all CKD subjects for active TB and LTB is essential to prevent morbidity and mortality with CKD. TST and IGRA which are employed for diagnosis of LTBI are associated with specific

advantages and disadvantages with studies showing varying degrees of agreement between the two. The detection of active TB and LTB in CKD remain a challenge because of the atypical presentation and immuno compromised status, so this study was done to determine the utility of tuberculin skin test versus interferon gamma release assay in screening chronic kidney disease patients for latent tuberculosis infection.

Table 1:

CKD stage (MDRD criteria) in all patients			CKD stage (MDRD criteria) in LTBI patients	
	Frequency	Percent	Frequency	Percent
1	15	14.9	1	5.2
2	37	36.6	6	31.5
3	11	10.9	0	0
4	23	22.8	6	31.5
5	15	14.9	6	31.5
Total	101	100	19	100

Majority of the participants were in CKD stage 2 (36.6%) and there were 38 patients with severe CKD (Stage 4 and 5). 12 LTBI patients had severe CKD.

Table 2:

On Haemodialysis		
	Frequency	Percent
No	62	61.4
Yes	39	38.6
Total	101	100

This table denotes the number participants with CKD on haemodialysis, accounting for about 38.6%.

Materials and methods

The study was done in Department of Nephrology and Respiratory Medicine, Chettinad Hospital and Research Institute, Kelambakkam, after the approval from Institutional Human Ethics Committee (IHEC) between March 2021 and August 2022.All the CKD patients were screened for active TB after an informed consent. People who fulfilled the requirements and expressed an interest in participating were accepted into the study. All participants were given proforma, clinical examination, Chest X ray, sputum AFB and other tests wherever needed done. All study participants in whom active TB was ruled out were subjected to TST and QuantiFERON TB Gold in tubes (QFT-GIT) tests.0.1 mL of PPD-SI (5 TU) was injected in left volar aspect of forearm intradermally and read in mm between 48 to 72 hours after administration and about 5 ml blood was drawn for estimation IGRA. An induration of ≥ 10 mm according to CDC guidelines and IGRA values ≥ 0.35 IU/mL were considered positive. The participants who turned TST or IGRA positive were considered to have LTBI after excluding active TB.

Results and discussion

After ruling out active TB in our study, total of 101 CKD patients were enrolled and study period was from March 2021 to August 2022. The participants were subjected to both TST and IGRA tests. If either one of the tests turned positive, participant was considered to have latent tuberculosis infection (LTBI). Data entry was done in Microsoft Excel 2020 and analysis was done using SPSS version 23.

In our study, the mean age of 101 CKD patients participated was 52.0±9.4 years (mean ± standard deviation) and 71.3% patients were men. Out of which the mean age of LTBI patients was 49.05 ± 9.7 years and most of them were men (57.8%) while in Chagas ACF et al[9] and C.-H. Wu et al.[10] comparatively had older population (age >60 years) with predominantly men. Out of the 101 CKD patients, 38 patients had severe CKD and were on haemodialysis. Among the LTBI patients, 12 patients had severe CKD and were on renal

haemodialysis while other studies like Chagas ACF et al.[9], C.-H. Wu et al.[10] and H. Al Jahdali et al.[11] had compared patients all on haemodialysis.

In this study, we found that LTBI was detected by TST in 6 (5.9%) and by IGRA in 19 (18.8%) patients. Thus, the percentage of LTBI detected by the IGRA was more than that by the TST. The general accordance between the two tests being 31.5%. Similarly in H. Al Jahdali et al. [11] TST detected LTBI in 26 (13%) and QTF-G test in 65 (32.5%) patients. In the study done by Laura Pass lent et al[12] LTBI, as calculated by the tuberculin test, T-SPOT.TB test, and expert physician panel, was in 12.8%, 35.5, and 26.1 of patients respectively. Comparing TST results and IGRA results in our study, by Fisher's Exact test showed $\chi2=27.530$, p = 0.0005 <0.01 which is highly statistically significant. The sensitivity and specificity of IGRA with TST was 31.6% and 100% respectively, the positive predictive value (PPV) 100 and negative predictive value (NPV) 86.3, accuracy of 87.1%; different from other studies like H. Al Jahdali et al. [11] which had specificity 69.6%, sensitivity 33.1, PPV 78.5 and NPV 23.7. This discrepancy may due small sample size in our study.

Conclusion

In conclusion, screening all CKD patients using the IGRA test instead of the TST may be a better option for diagnosis of LTBI and s hence, to initiate proper chemoprophylaxis or preventive therapy. In addition, other newer tests like C-TB test (TST), as and when available may be compared with IGRA to identify LTBI effectively.

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Abbreviations

WHO	World Health Organization
LTBI	Latent Tuberculosis Infection
TB	Tuberculosis
IGRA	Interferon Gamma Release Assay
3HP	3-month weekly Isoniazid and Rifapentine
6H	6 months daily Isoniazid
CKD	Chronic Kidney Disease
QFT-GIT	QuantiFERON TB Gold in tubes
TPT	Tuberculosis Preventive Therapy
HIV	Human Immuno deficiency Virus
AFB	Acid fast stain
PPD	Purified protein derivative
SSI	Staten Serum Institute