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RESEARCH ARTICLE

LATENT TUBERCULOSIS INFECTION: NEED FOR A “GOLD STANDARD” TESTING METHODOLOGY

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Abstract

Tuberculosis (TB) is still a matter of global threat as it is one of the major causes of deaths worldwide. Latent Tuberculosis screening is an important factor in controlling the development of Tuberculosis disease across the globe. This study aims at the importance of Tuberculosis detection at latent stage. It further explores the benefits and drawbacks of testing methodologies used for Latent Tuberculosis diagnosis. The lack of gold standard test significantly impacts the rate for Tuberculosis infection. The study emphasizes on the need of a better testing methodology for developing countries to combat Tuberculosis burden. Existing issues pertaining to the availability of tests in resource-limited settings, cost-efficacy for low-income groups and awareness about the infection at the latent stage of Tuberculosis have been discussed in this literature review. It is important to discuss high risk population, specifically healthcare workers and defining test regularity for them. A study design to track the high-risk population can contribute in keeping a check at Tuberculosis infection. This article focuses on the need for a gold standard test for latent Tuberculosis infection at low cost. The study finds that a new testing methodology has not been introduced in the last ten years which is better than existing ones in terms of accuracy. It is necessary to develop a testing methodology that can differentiate between the Latent Tuberculosis infection and active Tuberculosis with Multi Drug Resistant (MDR) strain. In this exploratory research, secondary data is used as a tool for the study. Electronic databases have been used for the review.

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Introduction:-

TB is found in two forms; active and latent. Symptoms such as cough, weight loss, fatigue, fever are visible in the active phase of TB. On the other hand, no symptoms are visible in latent TB infection (LTBI). Although TB is a communicable disease - a latent TB infection carrier cannot spread the disease and is not considered sick. It is important to address the LTBI burden to achieve the WHO target of TB incidence reduction rate by 90% until 2035 (WHO Report, 2015). To arrest the chances of active TB development, it is critical to diagnose and treat it in its latent stage.

Available testing methods cannot differentiate between latent TB infection and active TB. Multidrug-resistant (MDR)-TB strain is also a matter of concern (Peter Mwaba et al., 2020).

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The scope of this review is to study the available LTBI diagnostic techniques, their accuracy percentage, and the advancement made in the last 5 years to achieve the End TB target set by WHO. The review aims at identifying techniques to define the population at risk of latent TB infection and understand the scope of available tests to diagnose LTBI with MDR strain. It also aims at studying the testing frequency and its efficiency for healthcare workers.

This review will not explore the testing methods specifically used for active TB diagnosis.

The main sources are Google scholar, PubMed and WHO reports.

Available studies conclude that methods in use are available at high cost and prolonged treatment resulting in low completion rate. Researchers have unanimously agreed that ‘‘Gold standard’’ testing for LTBI does not exist.

Available Testing Methods:

The three WHO-approved LTBI testing methods are tuberculin skin test (TST), Interferon-gamma release assay (IGRA) and QuantiFERON (Peter Mwaba et al., 2020). Purified protein derivative (PPD) based TST has been used for centuries whereas IGRA is a decade old test to detect LTBI. However, no test can differentiate between latent TB and active TB strain. The sensitivity range of the Tuberculin skin test lies between 78.7% - 81.6% and specificity range is 52.4%-57.9% (C.C. Leung et. al., 2008). The sensitivity and specificity range of TST is low. Incorrect result estimation percentage is high for TST due to improper injection administration, erroneous induration assessment, and patient unavailability for the reading after 48-72 hours. IGRA has an advantage over TST as revisit is not required. (Neil W. Schluger and Joseph Burzynski, 2010)

Diagnosis is the key step to preclude the spread of TB infection and testing methods with comparatively high accuracy are not available in low resource settings. In high TB burden countries, TB as a disease is well known. However, latent TB infection has low recognition, which adds to the count of active TB cases.

Millions of lives are either lost or are at risk, as the probability of morbidity and mortality is higher in HIV associated TB (Kwan and Ernst, 2011). Approximately 10 million people across the globe were found infected with TB in the year 2018, out of which, 27% population was from India (WHO Report, Global Tuberculosis Report, 2019).

A patient with latent TB infection remains at risk of Active TB development for a lifetime (Neil W. Schluger and Joseph Burzynski, 2010). People with low immunity are at a higher risk of active TB development, if infected with LTBI.

Critical review:

This study has reviewed multiple articles which show the different perspective of latent TB study with respect to its accuracy, cost and risk.

‘‘Comparison of T SPOT TB and Tuberculin skin test among silicotic patient’’ by C.C. Leung et.al. – This article compares aforementioned tests on different parameters. This cohort study majorly focuses on silicotic population. The findings of this article based on experiments and statistical analysis supports that T SPOT TB gives better results than tuberculin skin test for latent TB infection. Although tuberculin skin test has been used for centuries to detect LTBI, the actual sensitivity range is unidentified. BCG vaccination also has an impact on test result thereby questioning the test accuracy of tuberculin skin test. T SPOT TB is considered as better for BCG vaccinated population. This article supports the use of T SPOT TB in comparison with tuberculin skin test. However, T SPOT TB test costs higher in comparison to tuberculin skin test. Hence, affordability of T SPOT TB test remains in question for developing countries. There is a scope to address the cost effectiveness of available testing methodology, as it is a major issue for developing countries, at higher infection risk.

The other article ‘HIV and TB: A Deadly Human Syndemic’’ by Kwan and Ernst- focuses on the risk of morbidity and mortality rate of disease in case of HIV associated TB. This article supports the urgent requirement of LTBI diagnostic technique to achieve end TB target. By observational and retrospective study, this article suggests that the rate of TB disease augments when associated with HIV. However, there is a scope to discuss the necessity of TB detection and treatment at latent stage to reduce the chances of HIV- TB alliance. The study states that culture

testing methodology as a gold standard test for TB. However, other articles deny the existence of any gold standard for TB testing.

To check the evolution in testing methodology for latent TB, “Recent Advances in Testing for latent TB” by Neil W. Schluger and Joseph Burzynski has been reviewed. This article gives a fair description of tuberculin skin test with its limitations. It also discusses the latest test - Interferon Gamma Release Assay and its advantages over TST. In this article, IGRA has been considered as significant test for TB with massive advantages. However, the study does not highlight the fact that IGRA cannot differentiate between LTBI and active TB, which is an important aspect.

“Cost analysis of tuberculin skin test and QuantiFERON –TB Gold In- tube test for TB screening in a correctional setting in Dallas, Texas, USA” by Nijhawan et.al. This study compares the cost of TST and IGRA for LTBI testing using a prospective pilot study. This article shows that the IGRA is a better test when compared to TST in terms of accuracy and cost effectiveness. However, several studies state that TST is more cost effective than IGRA. There is a scope for further study to establish cost effectiveness of available tests.

“Advancing new diagnostic tests for latent TB infection due to multidrug-resistant strains of mycobacterium TB- end of the road?” by P. Mwaba et al. describes that no test is ideal for latent TB diagnosis, as no test can detect the multi-drug sensitivity strain. This article raises a serious concern to achieve end TB target by WHO. This article supports the fact that the LTBI testing can preclude the risk of future disease. It also agrees that there is a need of cost effective and convenient test for LTBI. This article highlights that long time has already been invested to find LTBI diagnosis technique. However, this article does not highlight an important fact - No new investigation method has been introduced in the last 10 or more years.

“Comparison of TST and IGRA in diagnosis of latent TB Infection in a high-Burden Setting” by Surendra K Sharma and Richa Vashishtha et al. questions the performance of TST and IGRA for high-burden settings. Using prospective and longitudinal study method, it concludes that TST is better and favored in resource limited settings. However, there is a conflict of thought in determining cost effectiveness. BCG is a mandatory vaccine for every child in India. This article does not highlight the accuracy issue of TST; specifically for BCG vaccinated individuals.

According to WHO report 2015 and 2019, 90% reduction in TB is required till 2035 to achieve the End TB target by 2050. WHO has released a list of thirty countries that are at highest risk of TB disease. India tops the list. Hence, it is a matter of key concern for India to arrest TB at its latent stage.

Research gap:

QFT-GIT is more cost-efficient than TST (Nijhawan et.al., 2016). Whereas, TST is preferred for high burden and resource-limited setting- as per the cost point of view (Surendra K Sharma, 2017). These findings contradict each other. Hence, there is a scope of further study on the cost-effectiveness of available tests.

T.SPOT.TB has higher accuracy in comparison with TST (C.C. Leung et. al., 2008). However, there is no indication of the cost difference between the two. Hence, it needs to be further studied if T.SPOT.TB is suitable for low-income groups with high risk.

IGRA has advantages over TST, as it has better test sensitivity for individuals vaccinated with Bacille Calmette Guerin (BCG). For IGRA- reporting time is less when compared to TST and no revisit is required (Neil W. Schluger and Joseph Burzynski, 2010). Hence, there is a higher probability of getting the results captured. However, IGRA cannot differentiate between latent TB infection and active TB disease.

Conclusion:-

Despite being declared as a major cause of death globally, there is still no gold standard for testing LTBI. It should be cost-effective, as developing countries are primarily impacted by LTBI and can be mounted in resource-limited settings.

Early detection can help in timely treatment and can reduce the morbidity and mortality rate. There is a need to develop a methodology to find out people who are at high risk and have chances to develop TB disease from latent infection. There is still a scope to assess TB infection test frequency for healthcare workers in high burden countries. There is still a need to develop a "gold standard" test for LTBI, which should address accuracy and cost gaps.

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