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Investigating Two-stage Tuberculin Skin Test for Screening Latent Tuberculosis Infections in Diabetic Patients: A Regional Study in Khorramabad, Iran

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ABSTRACT

Introduction: latent tuberculosis infections (LTBI) are not detectable by a single-stage tuberculin test and maybe detected after repeating tests 7-21 days later. This phenomenon, called the boosting phenomenon, supports a two-stage test to identify false negatives in a single-stage test. The present study investigates the value of a two-stage tuberculin test in diabetic patients. **Methods**: We performed a tuberculin test for 195 diabetic patients. The patients with induration > 10 mm were subjected to a second tuberculin test 7-21 days later. **Results**: Of 195 patients, 115 came for measuring the tuberculin test induration, which was positive in 3 out of 115 patients (2.61%). Of the remaining 112 patients, 53 patients were subjected to the second test, and 38 patients came back for measuring the induration, which became positive in 4 (10.52%) patients. **Conclusion**: The increased LTBI rate from 2.61% to 10.52% following the second tuberculin test indicates a boosting phenomenon due to a delayed hypersensitivity reaction. Hence, patients with latent tuberculosis who had a false negative test in the first stage were identified.

INTRODUCTION

Although tuberculosis (TB) is a preventable and treatable disease, almost 10 million people are affected with active tuberculosis annually; some 1.5 million people die, making this disease the leading cause of death among infectious diseases worldwide [1]. About 25% of the world's population acquire *Mycobacterium tuberculosis* infection, and 5% to 15% develop active tuberculosis [2]. This disease has become a severe challenge due to the increased immunosuppressive medications and immune-debilitating diseases such as type 2 diabetes [1, 2]. Early diagnosis is a crucial point in the control, treatment, and prevention of tuberculosis, and prophylactic treatment can reduce the risk of active tuberculosis by up to 90% [1-3].

Latent tuberculosis infection (LTBI) means exposure to *M. tuberculosis* without clinical signs and evidence of active tuberculosis in para-clinical examinations, including chest x-rays, sputum cultures, and sputum smears [3]. The bacterium remains inactive in the body and does not cause disease [4]. In these cases, exposure to the causative agent is indicated by the tuberculin skin test (TST) or the level of Interferon-Gamma Release Assay (IGRA) [3-5].

The tuberculin test is performed by injecting 0.1 ml of purified protein derivative (PPD) in the upper 2/3 of the forearm with an insulin syringe. After 48-72 h, the induration (swelling) diameter is measured at the injection site [3-6]. Indurations ≥ 5 mm are considered positive in patients with immunodeficiency and those receiving immunosuppressive drugs [4-6]. Indurations ≥ 10 mm are considered positive in patients with type 2 diabetes mellitus and people exposed to *Mycobacterium*, and indurations ≥ 15 mm are considered positive in all individuals [4-7]. Some people with LTBI have a false-negative tuberculin skin test. This means that once a tuberculin test is performed, an induration < 10 mm occurs, which is regarded as negative in diabetic patients. Repeating the tuberculin test 7-21 days later might result in indurations ≥ 10, indicating a positive tuberculin test for diabetic patients [8, 9]. This phenomenon, known as

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the boosting phenomenon, supports a two-stage tuberculin test to identify false negatives results in the single-stage test. However, even a two-stage TST is insufficient to detect all boosting cases in the elderly [8-10]. To identify the boosting phenomenon in health care workers, a two-stage tuberculin test and follow-up on the occupational risk of tuberculosis are recommended [8-11]. In a study on Canadian health care workers in Manitoba, those who received the BCG vaccine and were born in areas with a higher prevalence of tuberculosis were more likely to become positive in the second tuberculin test. Due to delayed hypersensitivity reaction, a single test may be inadequate to show infection in immunocompromised patients or those having chronic diseases [8-12].

Systematic reviews have also shown that diabetes triples the risk of tuberculosis. In addition, some studies have shown that patients with diabetes are more likely to develop multidrug-resistant tuberculosis, though still there is no explanation for this connection [12-15].

Diabetes can severely affect tuberculosis control, especially in underprivileged areas where tuberculosis is prevalent. One systematic review and meta-analysis published between 1980 and 2010 reported that diabetes was associated with a 69% higher risk of death and an increased risk of recurrence of tuberculosis [16]. Also, since 2010, several extensive cohort studies have reported adverse effects of diabetes on tuberculosis prognosis. Early screening for tuberculosis and diabetes helps physicians improve the outcome of TB treatment [17, 18].

Regarding limited data from Iran, the present study investigated the LTBI prevalence and the value of the two-stage tuberculin test in diabetic patients in Khorramabad, Lorestan Province, from 2018 to 2021.

MATERIAL AND METHODS

Study population. From 2018 to 2021, in a cross-sectional study, 195 patients with type 2 diabetes were referred to Shahid Rahimi Hospital in Khorramabad and were screened for LTBI using a tuberculin skin test. The inclusion criteria included type 2 diabetes and residency in Lorestan Province. The exclusion criteria were having a history of immunodeficiency and active TB and not referring for follow-up.

First TST. The TST was performed by injecting 0.1 ml of PPD in the upper 2/3 area of the forearm. The 5 ml PPD vials (Razi Vaccine and Serum Research Institute, Iran) were provided by Lorestan University of Medical Sciences and stored at 3-5 °C until used. The intradermal injection was performed using an insulin syringe by the standard method [8-11, 18]. A proper intradermal injection caused a swelling with a 6-10 mm diameter at the injection site. After 48-72 h, the skin reaction, i.e., induration (swelling and stiffness with no redness), was measured using a ruler. Induration diameter (stiffness) ≥ 10 mm was considered positive for TST. In diabetic patients, indurations ≥ 10 mm are defined as positive [1-4, 19].

First, the high-risk group was evaluated for TB through a history of fever, sweating, weight loss, cough, hemoptysis, chest pain, shortness of breath, and clinical examination. Those with confirmed TB were excluded. For patients with type 2 diabetes who had no evidence of active tuberculosis, screening was performed by a tuberculin test. If the tuberculin test became positive, a chest x-ray was taken, and if any tuberculosis findings were suspected, the sputum smear and culture were requested for an accurate diagnosis. In the absence of abnormal findings in favor of active TB on chest radiography and negative sputum smear and culture, these patients were classified as having LTBI [1-4, 8-11].

Second TST. Some people with LTBI have a false-negative tuberculin skin test. This means that once a tuberculin test is performed, an induration < 10 mm occurs, and if the tuberculin test is repeated 7-21 days later, an induration ≥ 10 mm may occur, which means a positive tuberculin test. This situation, known as the boosting phenomenon, supports the performance of a two-stage tuberculin test to identify individuals who became negative in the one-stage test [4, 8-11]. Following determining the latent tuberculosis frequency in the first tuberculin test, the second test was performed 7 to 21 days later to evaluate the effect of the boosting phenomenon. To do this, people who tested positive for TST for the first time were considered LTBI. For people whose first-time TST test was negative, after 7-21 days, a second TST was performed in the same standard way. People whose second-stage TST turned positive showed a boosting phenomenon, which meant that the first-time TST result was a false negative. These individuals were also examined for active tuberculosis by chest x-ray, sputum smear, and culture, and due to the lack of evidence of active tuberculosis, they were classified as having LTBI [4, 8-11]. The algorithm for performing the two-stage tuberculin skin test is shown in Figure 1.

The other investigated variables were age, gender, urban residency, duration of diabetes, insulin dependency, cardiovascular disease, lung disease, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and percentage of hemoglobin A1C (HbA1C).

Analysis of data. Descriptive statistics were used to analyze the data including frequencies, percentage of frequencies, means and standard deviations. For analyzing the data, SPSS version 16.0 was run.

Ethical clearance. This study was approved by the ethics committee of Lorestan University of Medical Sciences with registration number IR.LUMS.REC.1400.164.

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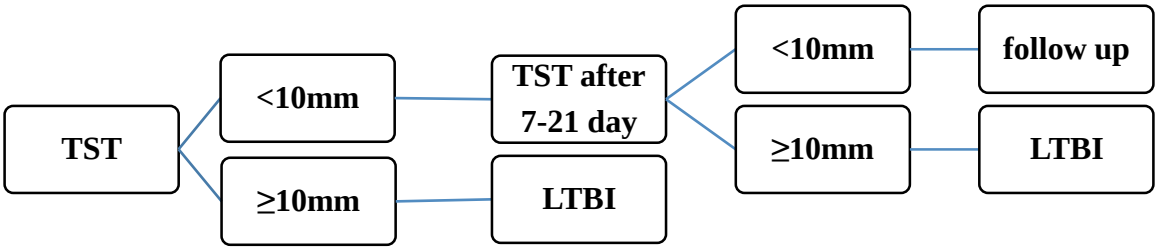

Fig. 1. Algorithm for performing a two-stage tuberculin skin test. TST: tuberculin skin test, LTBI: latent tuberculosis infection. If the first TST is negative, the second TST is performed. The goal of a two-stage TST is to prevent a false-negative response. Suppose tuberculosis infection has occurred in the distant past. In this case, the immune response to *M. tuberculosis* may be reduced. However, an initial TST may boost immune memory, so that a second TST will be positive within 1-3 weeks after the first time (boosting phenomenon) [4, 8-11].

RESULTS

Primary findings. In this study, the tuberculin test was performed on 195 diabetic patients. 115 out of 195 patients were referred for measurement of the tuberculin test result, which was positive in 3 out of 115 patients (2.61%). The 112 patients with a negative test in the first stage were called for the second tuberculin test 7-21 days later. Of 112 people, 53 came for the second test, and 38 showed up to measure the second result. In 4 out of 38 patients (10.52%), the second test result was positive (indurations ≥ 10mm). Therefore, the latent tuberculosis infection prevalence increased from 2.61% (3 out of 115) to 10.52% (4 out of 38) after the second tuberculin test, indicating the boosting phenomenon effect due to the delayed hypersensitivity reaction.

Demographic information. Among the 115 patients studied, 75 patients (65.22%) were female, and 40 patients (34.78%) were male. The mean age for men was 54.35 (±12.03) years, for women 56.8 (±12.60) years, and for the whole study, the population was 55.95 (±12.41) years. Among 115 patients, 107 (93.04%) lived in cities, and 8 (6.96%) were in villages. On average, patients had a 9 (±7.37) years history of diabetes, 9.99 (±7.50) years in women, and 7.25 (±6.86) years in men. Forty-two patients (36.52%) were under treatment with insulin, and 73 (63.48%) with oral medications. Forty-five patients (39.13%) had cardiovascular disease, and 24 (20.87%) had lung disease. Retinopathy was diagnosed in 54 patients (46.96%), nephropathy in 54 (46.96%), and neuropathy in 51 (44.35%). None of the patients provided a history of congenital or acquired immunodeficiency. Only 22 (19.13%) of the patients had HbA1C less than 8.5%, and 93 (80.8%) had HbA1C ≥ 8.5%, a sign of poor diabetes control.

Follow-ups. In immunocompetent diabetic patients, indurations with a diameter ≥ 10 mm are defined as positive. Hence in the first test, only 3 (2.61%) exhibited LTBI. Chest x-rays were taken from these three patients, and sputum culture and smear were performed, which were normal and showed no evidence of active tuberculosis. These people were defined as having latent tuberculosis and were referred to the city health center to treat latent tuberculosis infection. However, the second tuberculin test was performed for 53 patients who were referred for the second tuberculin test 7-21 days after PPD injection. Of 38 individuals who came to measure the second test result, 4 (10.52%) showed indurations ≥ 10 mm, indicating a boosting phenomenon due to a delayed hypersensitivity reaction. Normal chest x-rays and negative sputum cultures ruled out active tuberculosis in these patients. Patients with latent tuberculosis were referred to the city health center for treatment.

DISCUSSION

The present study demonstrated the role of boosting phenomenon in diagnosing LTBI in diabetic patients. Accordingly, the prevalence of LTBI increased from 2.61% to 10.52%.

From 1994 to 1998, a prospective observational cohort study was performed to evaluate the TST among 5,773 health care workers at a municipal hospital in an area with a high prevalence of tuberculosis. This study showed the probability of an increased positive tuberculin test in the second stage, more evident in the older adult with low income and people with a history of BCG vaccination [9]. In a prospective cohort study in Germany, LTBI cases were identified by TST and IGRA. In some people, a positive TST was associated with a negative IGRA test. This means those who tested positive for TST, may have a false negative IGRA test. This finding highlights the importance of a two-step tuberculin test [10].

In patients with immunodeficiency or chronic disease, a single tuberculin test may be insufficient due to a delayed hypersensitivity reaction. In a study on 187 dialysis patients in one of the endemic areas for TB in Turkey, the positivity for the first and second tuberculin tests were 55% and 68.4%. The increased positivity was pronounced in males and those with a history of tuberculosis exposure and lower serum ferritin levels [20].

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Patients with diabetes are at greater risk for converting LTBI to active TB. Developing diabetes also increases the risk of progression from primary infection to active tuberculosis. Case studies have shown that the odds ratio of TB patients with diabetes is 2.44 to 8.33 times higher than healthy individuals [21-25]. The reported prevalence of diabetes among TB patients varies from 1.9% to 45.0% worldwide; the prevalence of TB reported among patients with diabetes varies from 0.38% to 14.0%, and the average prevalence is 4.1% [26]. The World Health Organization (WHO) currently recommends dual screening; diabetes screening in all patients with tuberculosis and vice versa [27].

The limitations in our study were the sensitivity and specificity of TST in patients with type 2 diabetes. We selected a more significant cutoff point (10 mm) to overcome false-positive results (BCG-vaccinated countries regard this cutoff point). To overcome false-negative results, we designed a two-stage method.

In this study, the prevalence of latent tuberculosis increased from 2.61% (3 of 115) to 10.52% (4 of 38) following the second tuberculin test, indicating the boosting phenomenon due to the delayed hypersensitivity reaction. Like similar studies, this study showed that the effect of the boosting phenomenon was more important in patients with a form of immunodeficiency. This emphasizes the value of performing a two-stage tuberculin test in these patients.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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