Section: Miscellaneous

Original Research Article

PREVALENCE OF TUBERCULOSIS INFECTION AMONG DIABETIC PATIENTS IN CENTRAL KARNATAKA, INDIA

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ABSTRACT

Background: Diabetes and Tuberculosis are two major prevalent public health challenges in terms of morbidity and mortality in India. Systematic review has shown that, people with diabetes are 2.3times more risk for developing active TB disease compared to people without diabetes. Tuberculosis Infection (TBI) is a condition with persistent immune response to *Mycobacterium tuberculosis* antigen without any clinical symptoms of active TB disease. Individuals with TBI has 5-10% risk of developing active TB disease. The study was conducted with an objective to estimate the prevalence of TBI among diabetics and the factors associated with it.

Materials and Methods: A cross-sectional study was conducted among the 323 diabetics attending outpatient department of tertiary care hospital in central Karnataka, India. Blood samples of the study participants were tested for TBI with Interferon gamma release assay (IGRA) test.

Results: The prevalence of TBI among diabetics was 14.2% (95% CI: 10.6% to 18.5%). TBI did not had any gender or age predominance. People with uncontrolled diabetes had 2.54 (95% CI: 1.11-5.77) times risk of TBI then people with controlled diabetes and this finding was statistically significant.

Conclusion: It is important to diagnose and treat TBI among diabetics, as they are at the risk of developing active TB disease. These findings will guide the policy makers in achieving the TB elimination goal in India.

Keywords: Tuberculosis infection, Diabetics, Interferon gamma release assay, Tuberculosis elimination.

INTRODUCTION

Diabetes Mellitus (DM) and tuberculosis (TB) are two major public health concerns globally. According to International Diabetes Federation (IDF), globally around 537 million people are living with diabetes in 2021 and India contributes to around 101 million (18.8% of the global burden) and 11.4% of the Indians have DM.[1,2] According to global TB report by World Health Organisation (WHO), an estimated 10.6 million people were affected with TB, and 1.3 million people died from the disease in 2022 globally.[3] India being one of the high-burden countries, contributes around 26% of the global TB burden. In 2023, 2.8 million incident TB patients and 0.31 million deaths were estimated from TB in India.[4]

DM is associated with immune dysfunction which alters the immune responses. The hyperglycaemia weakens the inmate immune response by affecting the macrophage, neutrophils, dendritic cells and natural killer cell function. It also disrupts the adaptive immune response. This disruption in the immune response makes individuals with DM susceptible for TB.[5] Systematic review has shown that, people with DM as 2.3times more risk compared to people without DM.[6] As per the WHO data, 15% of TB cases are associated with DM.India accounts for more than 40% of the cases.[7] Considering the risk of TB among DM, the WHO as

developed a framework to address the issues of screening, diagnosis and management of TB and comorbidities including DM.[8]

Tuberculosis Infection (TBI) is a condition, when the individual has a persistent immune response to Mycobacterium tuberculosis antigen without any clinical symptoms of active TB disease.[9] Individuals with TBI carries the lifetime risk of 5-10% for reactivation to disease. Factors like HIV, malnutrition and diabetes increase the risk of reactivation due to compromised immune conditions.[10] Individuals with diabetes face 2-3 fold higher risk of developing TB disease, 2 fold risk of multidrug-resistant TB & mortality during TB treatment, 4 fold risk of TB relapse post-treatment.[11,12] The prevalence of TBI in India ranges between 21-48%.[13] There is no gold standard test to diagnose TBI. Presently, Tuberculin Skin Test (TST) and Interferon gamma release assay (IGRA) test are used to diagnose TBI. Individuals with TBI will be treated with Isoniazid, rifampicin or rifapentine containing regimens.[9]

India has implemented a comprehensive End TB strategy proposed by WHO to eliminate TB by 2025, five years ahead the global plan.[14] The National Strategic Plan (NSP) (2017–2025) is implemented under four broad areas i.e., build, detect, treat and prevent.(15) Prevention of TB is the important strategy to reduce the TB incidence. So, TB preventive treatment has been rolled out among certain high-risk groups individuals like people living with HIV(PLHIV), household contacts of TB patients, individuals on dialysis etc, with TBI to prevent the progression to TB disease.[16]

Although researchers have established the relationship between active TB and diabetes, it is unclear about the prevalence of TBI among diabetics. Early identification and treatment of TBI among the diabetics can help in decreasing the progression to active TB disease and the overall TB burden.[17] So, it is critical to understand the TBI prevalence among the diabetics to End TB in India. This information will help the policy makers in planning strategies to prevent TB among the diabetics. As there are very few studies on TBI among diabetics, the present study was conducted with an aim to estimate the prevalence of TBI among diabetics and the factors associated with it.

Objectives

1. To determine the proportion of latent TB infection among individuals diagnosed with diabetes
2. To assess the factors influencing the proportion of latent TB infection among diabetics.

MATERIALS AND METHODS

A cross-sectional study was conducted in Gadag district, one among the 31 districts of Karnataka State situated in South India. Gadag is a district in central Karnataka with a population of 10.6 million. Gadag district has 7 blocks and 337 villages.[18] Around 74.4% of people live in rural areas and around 65.8% are literate.[19] In the district, 13.2% of men and 12.1% of women are diabetics.[20] Non-communicable disease (NCD) clinics are conducted under the National Programme for Non-Communicable Disease (NP-NCD).[21] Medical officer, staff nurse and lab technologists are providing the services in these clinics in all community health centres (CHC), block level hospitals and district hospital under guidance of the medicine department. Screening and management of diabetes along with other NCDs are done these clinics.[21]

Study was conducted among the adult (>18 years) diabetics attending the NCD clinic under medicine department of Gadag Institute of Medical Sciences, a tertiary care and teaching hospital in Gadag district during December 2023 to May 2024. They were recruited using a simple random sampling method. Individuals with active TB disease, HIV, gestational and juvenile diabetes or on immunosuppressive therapy were excluded from the study.

Sample size: Sample size was calculated based on a previous study that showed the prevalence of TBI among diabetics as 28.1%.[22] Using a precision of 5% with 95% confidence interval and 80% power, the sample size was 323.

After the institutional ethical committee approval and the written informed consent from the study participants, the data on age, gender and the value of random blood glucose level was collected using a pretested structured questionnaire. Venous blood of 5ml was collected under aseptic conditions and subjected for IGRA test.

IGRA is invitro blood test to diagnose TBI. IGRA is done to measure the interferon gamma produced through cell mediated immunity specific for TB antigens. When exposed to Mycobacterium tuberculosis, the body's T-cells release interferon-gamma (IFN-γ). IGRA detects this IFN-γ response, indicating past exposure to TB. IGRA is more specific than tuberculin skin test (TST), as it is less affected by prior Bacille Calmette-Guerin (BCG) vaccine strain that is used routinely in many countries, including India.[23]

Statistical Analysis: Data was entered in Microsoft excel and analysed using Jamovi v2.3.[24] The categorical data is presented as frequency and percentages. The 95% confidence interval is also calculated. The relative risk is calculated for the dependant variables of TBI among diabetics. p-value less than 0.05 are considered statistically significant.

RESULTS

A total of 323 diabetic patients were tested for latent TB infection. The mean (± Standard deviation) age of Study participants was 52.8 (± 13.8) years, 52.2%

were males and 72.4% had random blood sugar levels of above 200mg/dl.

Table 1: Socio-demograghic Risk factors associated with TB infection among Diabetics in Central Karnataka, India

Parameters		TB infection		Total Frequency (Percentage)	p value
		Positive (n=46)	Negative(n=277)		
		Frequency (Percentage)	Frequency (Percentage)		
Gender	Female	23 (15%)	131 (85%)	154(47.8)	0.73
	Male	23 (14%)	146 (86%)	169(52.2)	
Age (years)	<30	2 (11%)	16 (89%)	18(5.7)	0.82
	31-45	13 (7%)	63 (83%)	76(23.5)	
	46-60	19 (14%)	114 (86%)	133(41.2)	
	>60	12 (13%)	84 (88%)	96(29.7)	
RBS (mg/dl)	<140	2 (5%)	39 (95%)	41(12.7)	0.02
	140-200	4 (8%)	44 (92%)	48(14.9)	
	201-300	40 (17%)	194 (83%)	234(72.4)	

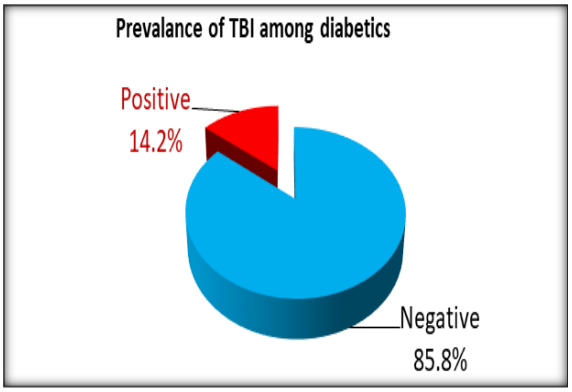

Figure 1: Prevalence of TB infection among Diabetics in Central Karnataka, India

Among 323 diabetics tested with IGRA, 46 were positive for TBI. So, the prevalence of TBI among the diabetics was 14.2% (95% CI: 10.6% to 18.5%). (Figure 1)

Among male diabetic patients 14% had TB Infection whereas 15% of female diabetics had TB infection. According to age 16% of ≤50years and 13% of >50years had TB infection. But gender and age were not statistically associated with prevalence of TBI among diabetics. Whereas 17.1% (RR: 2.54, 95% CI: 1.11-5.77) of the diabetics with uncontrolled DM(RBS>200mg/dl) had TBI compared to 6.7% of the diabetics with controlled DM(RBS≤200mg/dl)and this association was statistically significant (p value= 0.017). (Table 2)

Table 2: Risk factors associated with TB infection among Diabetics in Central Karnataka, India

Factors		Total diabetics (n=323)	Tuberculosis infection present n=46 (%)		Relative risk (95% CI)	p value
Gender	Male	169	23	13.6%	0.91 (0.53-1.56)	0.733
	Female	154	23	14.9%	1	
Age	>50years	197	26	13.2%	0.83 (0.48-1.42)	0.502
	≤50years	126	20	15.9%	1	
Random blood sugar level	Uncontrolled (>200mg/dl)	**234**	**40**	**17.1%**	**2.54 (1.11-5.77)**	**0.017***
	Controlled (≤200mg/dl)	89	6	6.7%	1	

DISCUSSION

Diabetes and TB are the two public health concerns which affect each other's pathogenesis mechanisms like phagocytosis, monocyte traffic modulation, cytokine production and the altered functions of the innate and adaptive immune cells.[25] Diabetes being the known risk factor for active TB disease and it's known that diabetes worsens the active TB disease condition, leading the negative impact on public health, especially in countries like India where the prevalence of both the diseases is high. Despite this, there are limited efforts in knowing the prevalence of TBI among diabetics. If the TBI is diagnosed and treated then the incidence of TB can be reduced.[26,27]

Tuberculin skin test (TST) and IGRA are presently available in India for diagnosis of TBI. Diagnosis of TBI doesn't have any gold standard test. These tests will indirectly measure the cellular immune response to MTB antigens. It is known from the previous studies that TST will be false positive among the individuals who are BCG vaccinated, infected with nontuberculous mycobacterium (NTM) or other mycobacteria such as M. leprae

infection.[28] IGRA is considered as a better test than TST as it is specific for MTB antigens that are not shared with BCG and NTM. However, it is an expensive test and needs a laboratory infrastructure in comparison with TST.[16] So, in the present study IGRA was considered to diagnose the TBI as we can avoid those false positives in TST.

In the present cross-sectional study conducted among the diabetics attending outpatient department of the tertiary care centre for diabetes management, the prevalence of TBI observed was 14.2% (95% CI: 10.6% to 18.5%). In a cross-sectional study conducted in USA by Barron MM et al,[29] and another study in Malaysia by Ping PA et al,[30] showed the prevalence of TBI among diabetics as 11.6% and 11.2% respectively. A study in Egypt by Agha MA et al,[31] and another study in Singapore by Leow M et al,[22] showed the prevalence of TBI among diabetic population as 21.6% and 28.2% respectively. Extreme high prevalence of TBI among diabetics i.e., 51.3% was seen in another study conducted by Martínez AG et al,[32] in Mexico. TST was used in Indian studies to assess LTBI in diabetics. The prevalence of TBI was 21.32% in DM group & 7.30% in the non-diabetes group in tertiary care hospital, Maharastra.[33] Of the 200 patient without Past or Current TB, who were screened for LTBI, 96(48%) patients were found to have LTBI. Male sex was the only significant risk factor for LTBI (72% VS 59%; P = 0.05).[34]

From the observation in our study, proportion of TBI was not associated with age and gender of the diabetics. Patients with uncontrolled DM (>200mg/dl) had the highest prevalence of TBI of 17.1% as compared to controlled DM of 6.7%. The relative risk of TBI among uncontrolled diabetics 2.54 (95% CI: 1.11-5.77) times higher than the controlled diabetics and this difference was statistically significant. Similar findings of non-association of age and gender and strong association of glycaemic control as risk factors for TBI among diabetics was observed in the study conducted by Torres AV et al in Brazil.[25] If these 14.2% of the diabetics with TBI are untreated then there is risk of these individuals developing into active TB disease, which will be a public health problem and a hurdle in reaching a goal of TB elimination.[14]

There are certain notable strengthens in the study. This is the first study conducted in this region to estimate the TBI prevalence among diabetics. The sample considered in the study is through the scientific way of calculating the sample size, so the outcome observed in the study is robust. As IGRA test was used in comparison with the TST in diagnosing the TBI, the chance false positives were avoided. However, there are certain limitations of the study those needs to be addressed in the future studies. Socio-demographic information's like contact history with TB patients, smoking, alcoholism was not collected. As it was a cross-sectional study, the causality with certainty for TBI can't be made.

CONCLUSION

Among diabetics the prevalence of TBI was 14.2%. It is important to diagnose and treat diabetics with TBI, as they are at the risk of developing active TB disease. These findings will guide the policy makers in achieving the TB elimination goal in India. Further prospective studies are required to investigate the proportion of active TB disease among the diabetics with TBI treated with TB preventive treatment.

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