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Prevalence of Latent Tuberculosis Infection in Type 2 Diabetic and Non-Diabetic Individuals

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Abstract
Objective: *To study the prevalence of latent tuberculosis infection (LTBI) between Asian Indian type 2 diabetic and non-diabetic individuals.*
Methods: *Participants with type 2 diabetes (n=98) and age and sex matched controls without diabetes (n=98) were recruited from Institute of Non Communicable diseases, Government Kilpauk medical College, Chennai. LTBI was defined as in duration of ≥10mm after Tuberculin Skin Test (TST) and with no abnormality in Chest X-ray based on WHO 2015 guidelines and Center for Disease control and prevention (CDC, USA) guideline. Type 2 Diabetes Mellitus (T2DM) was defined based on WHO criteria. Biochemical and anthropometric measurements were done using standardized procedures.*
Results: *The 196 participants included 102 women (44.9%). Mean age was 41 ± 9 .4 years and mean body mass index (BMI), 26.32 ± 4 kg/m². The prevalence of LTBI among diabetic and non-diabetic individuals were 35.7% and 12.2 %, respectively (p ≤ 0.001). The mean Tuberculin skin test (TST) In duration values were significantly higher in diabetic, (7.18 ± 3.0 mm) compared to non-diabetic, participants (5.58 ± 3.05 mm, p= 0.002).*
Conclusion: *Prevalence of Latent Tuberculosis Infection is higher among Asian Indian type 2 diabetic subjects compared to age and sex matched non-diabetic participants.*
Keywords: *Diabetes, Latent Tuberculosis, Tuberculin Skin Test, Tuberculosis, Asian Indians, South Asians*
Abbreviations: *LTBI Latent Tuberculosis Infection, T2DM type 2 Diabetes Mellitus, BMI - Body mass index, TST Tuberculin Skin Test.*

Introduction

India is on the threshold of twin epidemics, by Diabetes Mellitus (DM) [1] and by Tuberculosis (TB) [2]. In fact, India holds the global rank-one position in the total estimated cases of TB (3.4 million) [2], and estimated to overtake China in Diabetes [1]. Several studies have suggested that DM increases the risk of TB, for new as well as reactivation of old cases of TB. It also complicates anti-tuberculosis treatment with delayed sputum conversion, increases death or

failure of treatment and increases rate of recurrent TB after successful completion of treatment [3].

Latent tuberculosis infection (LTBI) is a state in which viable Mycobacterium tuberculosis (MTB) bacilli are present in an individual without manifestation of clinical symptoms and signs of active disease [2]. People infected with LTBI are not infectious, but about 5-20% of them progress to active TB and the majority developing TB disease within 2–5 years of the initial infection. So one of the strategies that could be employed is to identify and screen this high risk population before they develop full blown active TB, i.e. in the latent phase.

Few studies have investigated the prevalence of LTBI in healthcare workers, prisons [4-9]. Many research questions regarding association between diabetes and LTBI remains unanswered because of inadequate studies, furthermore none in India have considered diabetic population which is a high risk group. This study is planned to determine the prevalence of LTBI in DM and Nondiabetic population.

Subjects and Methods

This is a cross-sectional study done at Institute of Non-communicable Diseases, Government Royapettah Hospital, Kilpauk Medical College, Chennai. Individuals attending Diabetes clinic and Medicine out-patient department and an equal number of healthy, age and sex matched individuals without diabetes, who attended our hospital out-patient department as attenders were included in the study. Inclusion criteria were patients with Type 2 Diabetes Mellitus above the age of 18, healthy, age and sex matched Individuals without diabetes. Known cases of active Tuberculosis, extra pulmonary TB, Type I diabetes, HIV/ AIDS, patients on steroids, past history of TB, immunosuppressive states like cancer, organ transplants were excluded from the study. The institutional ethics committee of Government Kilpauk Medical College, approved the study and written informed consent of all participants was obtained

Sample Size

Sample size was calculated based on assuming alpha error of 5%, Power of 80, absolute error 10%, Prevalence of Latent Tuberculosis in Type 2 Diabetes is 50%. Thus, a minimum of 95 was required. We recruited 98 diabetic and 98 age, gender matched non-diabetic participants.

Case definition of LTBI

WHO 2015 guidelines for LTBI and Center for Disease control and prevention (CDC, USA) LTBI guidelines recommend using Tuberculin skin test or Interferon Gamma release assays (IGRAs) with Chest X ray. So, we define LTBI as induration of ≥10mm after Tuberculin Skin Test (TST) and with no abnormality in Chest X-ray based on WHO 2015 guidelines and Center for Disease control and prevention (CDC, USA) guidelines [10].

Case definition of DM

Diabetes Mellitus will be defined based on WHO criteria which is diabetic symptoms with random venous glucose ≥ 200, or without symptoms with Fasting plasma glucose ≥ 126, postprandial plasma glucose of ≥ 200, and or Glycated hemoglobin value (HbA1c) >6.5.

Basic Demographics

After obtaining informed written consent, all individuals who meet the inclusion and exclusion criteria were included in the study. A basic demographic details, detailed clinical history, physical examination, and basic investigations were done and entered in the prescribed pro-forma on both diabetic and non-diabetic individuals.

Anthropometry

Anthropometric measurements including weight, height, and waist measurements were obtained using standardized techniques. Body mass index was calculated using the formula, weight in kilograms divided by the square of height in meters. Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mmHg

with mercury sphygmomanometer (Diamond Deluxe BP apparatus; Pune, India). Two readings were taken 5 min apart, and the mean of the two was used.

Tuberculin Skin test

All individuals were then subjected to screen for LTBI using TST and Chest X ray following standard method. In short, the test was carried out by intradermal inoculation of 0.1 ml tuberculin solution containing 5-tuberculin unit (TU) into the volar surface of forearm. The resulting induration would be measured 48-72 hours after the test.

Biochemical parameters

Fasting plasma glucose (FPG) and 2-h post load (75-g) plasma glucose (glucose oxidase-peroxidase method), serum total cholesterol (cholesterol oxidase-peroxidase amidopyrine method) serum triglycerides (glycerol phosphate oxidase-peroxidase amidopyrine method), and HDL cholesterol (direct method, polyethylene glycol pretreated enzymes) were measured using a Roche Autoanalyzer. Glycated haemoglobin (HbA1c) was measured by high performance liquid chromatography method using the Variant machine (BIORAD, Hercules, CA). LDL cholesterol was calculated using the Friedewald equation. The intra- and inter assay coefficients of variation (CVs) for the biochemical assays ranged from 3.1 to 4.6%.

Statistics

The bio-clinical characteristics of the study population were described using frequencies (percent) for categorical level parameters and measures of central tendency (mean and median) and variability (standard deviation and range) for continuous level parameters. Statistically significant differences in bio-clinical characteristics and tuberculin skin test induration were determined using independent samples t test. Difference in proportion of Latent TB infection was determined by chi square test. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using SPSS version 15.0 for windows.

Results

Participants in the study population were 41 ± 9.4 years old with mean BMI of 26.32 ± 4 kg/m². There were 102 women (44.9%). Table 1 presents the bio-clinical features of the non-diabetic and type 2 diabetes study groups. FPG, were significantly higher in diabetic, compared to non-diabetic, participants.

Table 2 shows that mean TST induration value in non-diabetic group was 5.58 ± 3.05 mm while in the diabetic group it was 7.18 ± 3.0 mm (p= 0.002). The prevalence of LTBI was 12.2% and 35.7% in non-diabetic and diabetic population respectively (p = < 0.001). The prevalence is more in male diabetics 50% than in male non-diabetics 20.4 % (p = <0.001) whereas in female diabetics it is 18.2 % vs 2.3 % (p=<0.001) in non-diabetic female population.

Table 1: Bio-clinical characteristics between non-diabetic and diabetic study population

Variables	Non diabetic subjects (n =98)	Type 2 diabetic subjects (n = 98)	p value
Age (years)	42 ± 9.6	42.5 ± 9.3	0.745
Gender (male %)	54 (55.3%)	54 (55.3%)	-
Duration of diabetes (years)	-	2 (0-28)	-
Body mass index (kg/m²)	26 ± 3	26 ± 4	0.717
Smoking n (%) Current or past smokers *	23 (23.5)	19 (19.4)	0.482
Contact history of Tuberculosis n (%)*	53 (54.1)	32 (32.7)	0.002
Systolic blood pressure (mm/Hg)	119 ± 14	123 ± 17	0.097
Diastolic blood pressure (mm/Hg)	76 ± 9	79 ± 10	0.084
Fasting plasma glucose (mg/dl)	84 ± 10	167 ± 52	<0.001

Normally distributed shown in mean ± standard deviation, independent samples t test.
*Categorical variable, chi square test was done

Table 2: Mean difference of TST induration and prevalence of Latent Tuberculosis Infection

Variables	Nondiabetic subjects n= 98	Diabetic Subjects n = 98	P value
Tuberculin skin test Induration	5.58 ± 3.05	7.18 ± 3.0	0.002
LTBI prevalence in male * n (%)	11 (20.4)	27 (50)	< 0.001
LTBI prevalence in female * n (%)	1 (2.3)	8 (18.2)	< 0.001
LTBI prevalence in combined population * n (%)	12 (12.2)	35 (35.7)	< 0.001

Normally distributed shown in mean ± standard deviation, independent samples t test
*Categorical variable, chi square test was done

Figure 1 prevalence of LTBI (%) in All individuals combined, male and female in Non-diabetic and Diabetic group

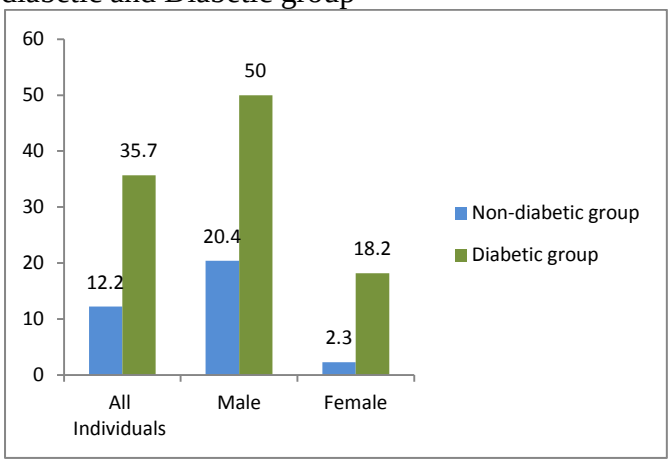

Figure 1 shows that the prevalence of LTBI in nondiabetic and diabetic population, along with prevalence of LTBI in men and women of study participants (p=<0.001).

Discussion

The main findings of the study is as follows

The prevalence of LTBI in diabetic group (35.7%) is more than non-diabetic group (12.2%, p=<0.001). Tuberculosis was a major cause of death in persons with Diabetes Mellitus, before the introduction of insulin. Currently, DM is a major global public health concern. Recent estimates suggests that India is competing with China to emerge as the "diabetes capital of the world ". TB is a major cause of morbidity and mortality in India, which accounts for over 20% of the world TB burden. In spite of global efforts to control it, TB is threating to resurge a global distaster. Although the surge of HIV AIDS contributed to this problem TB epidemic, currently DM could be veiwed as a major contributor. For several decades, though the leathal interaction between diabetes and TB was recognised, it was not systematically studied.

The Present study, showed that in Diabteics 35.7% were positive for Latent Tuberculosis Infection (LTBI) and 12.2 % in non-diabetics were positive for LTBI. When compared with the studies from Mexico (50%), [11] Spain (42.2%) [12], Puerto Rico (42.4%), this study revealed a lower prevalence in Diabetics; however, when compared to study from Asia pacific region the prevalence were higher to a Singaporean study (28.2%) [13]. This could be due to differences in the various cut-off values for TST that have been used, for example the Mexicans used 5mm as cut-off, whereas we used 10 mm based on WHO criteria. It is shown that almost over one quarter of patients with T2DM harbor LTBI. It is very well known that DM changes the immunity by impairing chemotaxis, phago- and monocyte activity, and also increasing T-cell activity. All these alterations are present during acute hyperglycemia. In addition, in patients with T2DM, a decrease in circulating levels of Interferon gamma (IFg), interleukin 2 (IL-2), tumor necrosis factor a (TNF-a), and IL-17F (all of these implicated in the immune control of TB) have been reported [14]. So these changes in immunity could have had led to subjects with DM accuquiring LTBI and may predispose a individual to greater risk for TB reactivation

In our study, contact history was significantly different particularly in diabetics than in non-diabetics (p=0.002). Furthermore the prevalence of LTBI was higher in Diabetes. So, diabetes and contact H/O could be synergistic for Latent TB infection. This finding was in agreement with studies done in Uganda, Thailand, and China which have reported more transmission at home due to household contact exposure[15-19]. However, other studies have shown that more transmission happens outside home especially in work places like healthcare settings due to nosocomial transmission [9,20,21,22]. Others demonstrate higher

transmission among students in the healthcare settings, prisoners and gold miners [9,23,24,25] which are higher risk populations. To the best of our knowledge, our study is among the first to show that the risk of LTBI is higher among those who are Diabetic and have a contact history of TB in the population.

The risk of Diabetes was lower when compared to other risk group like prisoners, illicit drug users, homeless people and health care workers, HIV /AIDS, patients on TNF alpha inhibitors, hemodialysis, nevertheless these are data from the low prevalent TB countries. Various studies have shown that employment categories at highest risk include healthcare workers and gold miners [9,25,26]; participants in our study worked in diverse settings but none were in the known high-risk categories. Our findings and those from previous studies suggest a potential need for periodic LTBI screening coupled with preventive treatment programs at workplaces but the cost-effectiveness of such an intervention should be evaluated.

The strength of this study is that it provides a relative precise snap shot of the prevalence of LTBI in T2DM and non- diabetics, in an urban Asian Indian setting as it was a population-based study conducted in an urban community in a relatively young age group. Another unique feature of this study is that it demonstrates the risk of LTBI being higher in those with Diabetes Mellitus than in general population, furthermore the risk even higher in a diabetic group with the history of contact of Tuberculosis. There are some limitations in our study. Our study, being a cross-sectional one, was not designed to address the effect of glycemic control on the prevalence of LTBI. Although we have shown a relationship between diabetes status and LTBI, it does not confirm causality, and the role of confounders cannot be excluded; this would need a well-planned prospective study. Furthermore, the limited sensitivity of tuberculin skin test may have underestimation of the true prevalence of LTBI. However; we believe that this is a valuable addition where the studies are limited in LTBI / TB in Asian Indians with or without T2DM.

In spite of global efforts to control it, TB is threatening to resurge as a global disaster. The significance of collision of the epidemics is evident. Atypical presentation of TB in Diabetics, like paucity of fever and constitutional symptoms are common, so it is imperative to create awareness about TB. All the more the search for LTBI in Diabetes as well as in high risk group population [27] should be done to ensure every measure has been addressed to prevent, identify, or control the spread of TB.

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KVR is the guide for this study, contributed to the manuscript. VPA conceived, did the statistical analysis, interpreted the study, and wrote the first manuscript. Both the authors vouch for the data and integrity of the study.