Original Article

Burden of diabetes among patients with tuberculosis: 10-year experience from a tertiary care referral teaching hospital in South India

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ABSTRACT

Context: Tuberculosis (TB) and diabetes mellitus (DM) are converging epidemics, each worsening the morbidity of the other. A study of the prevalence of DM in TB patients assumes great importance. **Aims:** The study aims to evaluate the association between DM and TB over a 10-year period in a tertiary care hospital. **Settings and Design:** A retrospective observational study in a southern Indian tertiary care teaching hospital was conducted. **Materials and Methods:** All patients with TB diagnosed and treated during the 10-year study period were identified from the hospital database. All relevant clinical, microbiological, and laboratory results pertaining to diagnosis of DM were collected. The diagnosis of TB and DM was made as per the standard criteria. **Statistical Analysis:** Categorical variables were analyzed using Chi-square test while continuous variables using independent sample *t*-test. **Results:** From 2001 to 2012, we studied 1979 TB patients among whom data on DM were available. The prevalence of DM was 29%, 21%, and 14%, in smear positive, smear negative and extrapulmonary TB respectively (overall 24%). Diabetics were more likely to be men (77.3% vs. 61%; $P = 0.001$); >40 years of age (81.7% vs. 38.9%; $P < 0.001$); heavier (59.96 vs. 50.37; $P = 0.004$); tobacco smokers (16.1% vs. 8.1%; $P < 0.001$); and alcohol consumers (6.8% vs. 4%; $P = 0.02$). They were less likely to be HIV coinfected (1.8% vs. 6.1%; $P < 0.001$). HIV coinfection was seen in 5% of patients and was substantially higher in extrapulmonary TB group (19.4%). Multidrug-resistant TB was lower in DM (11.7%) compared to non-DM (15.9%) ($P = 0.02$). Overall, 48% of the DM patients were diagnosed at the time of TB diagnosis. Over 10 years, no obvious changes in the trend were evident. **Conclusions:** Over a 10-year study period, 24% of the TB patients were diabetic, nearly half were detected at the time of TB diagnosis. There may be a good case for screening all TB patients for DM.

KEY WORDS: Diabetes mellitus, extrapulmonary, prevalence, pulmonary, risk factors, tuberculosis

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INTRODUCTION

The elimination of the global burden of tuberculosis (TB) has been a challenge for national and international agencies for decades.[1] Among the issues that cause concern is the association of diabetes mellitus (DM) and TB.[2]

The global burden of the problems posed by the interaction of DM with TB is well documented.[3] In countries with an epidemiological transition, this interaction is likely to be even bigger.[4] Some low-burden countries such as Denmark seem to have escaped from this problem,[5] while others have not been as fortunate.[6] Dye *et al*., in a study comparing the social and economic transitions in India and Korea, found that the increase of DM in India seems to contribute significantly to the increase in TB, with the converse occurring in Korea.[7]

The "Diabetes Capital" of the world, India[8] is projected to account for 62–80 million DM patients by 2030.[9,10] This along with undernutrition and HIV is the cause for concern with regard to increase in TB burden.[11] Between 1998 and 2008, TB incidence has increased by 28%, attributed to increase in aging population, urbanization, and diabetes. Improvement in nutrition overall is offset by decreasing body mass index (BMI) among rural men.[7]

In a pilot project on more than 8000 TB patients, screening for diabetes found that 8% had known DM and 5% were newly diagnosed at the time of TB diagnosis.[12] This has been studied in the DOTS program in both Northern[13] and Southern India, with data suggesting that approximately 24% of TB patients have DM.[14-16] Screening DM patients for TB has also been attempted in tertiary care centers in India and shown to be feasible.[12] The interaction of HIV in this story has also been evaluated with a suggestion that DM may be more of a risk for TB than HIV.[17] The lessons learned from the HIV-TB coinfection problem should be applied early to stop this unfortunate interaction.[18]

A cohort of TB patients in Tanzania found that 3-month mortality was five times higher among DM patients with HIV and two times higher in the HIV-noninfected group.[19] Data from Brazil have also shown worse outcomes among their DM-TB patients.[20] However, a Thai study[21] did not find such an adverse relationship between DM and poor TB outcomes. Indian data so far have also not shown this association.[16] Any possible adverse interaction, however, may lead to increase in hospitalization needs for TB patients.

More DM patients seem to present with extrapulmonary TB (EPTB).[20,22] This could increase the level of investigative support needed and the cost of diagnosing TB. With these issues in mind, our objective was to evaluate the association between DM and TB over a 10-year period in a tertiary care hospital.

MATERIALS AND METHODS

Study design and population

The study was conducted in a 2800-bedded tertiary care university teaching hospital that caters to poor- and middle-class patients. Most patients are from the southern states of Tamil Nadu and Andhra Pradesh, as well as from Northeastern Indian states. This pattern of referral (almost always self-referral by patients) has remained the same over the last 2–3 decades. Patients are mostly seen under general medicine or pulmonary medicine departments. The data in this study are from these two departments.

Regional Prospective Observational Research for TB (RePORT India) is a bilateral, multi-organizational, collaborative research effort, established in 2013 under the Indo-US Vaccine Action Program. The consortium aims to address the threat of TB to the people of India by appropriate research. RePORT has completed the first phase (5 years) recently. In preparation to launch RePORT cohort studies, it became imperative to understand the various risk factors in our TB patients. A retrospective data collection was set in motion. While reviewing the data we had collected, we realized that data on the burden of TB in diabetic patients over a substantial time period is unique, and so, we are sharing the results. This data is not a part of the RePORT prospective data collection.

All patients (inpatients and outpatients) above the age of 16 years who were diagnosed to have TB under the departments of general medicine-unit II and pulmonary medicine from January 1, 2001, to December 31, 2011, were included in the study. Data were obtained from the medical records and microbiology and pathology departments. All suspected TB patients had their clinical data documented in the hospital medical records. Generally, chest radiographs were ordered on all patients. Other radiological tests were ordered as appropriate based on clinical suspicion. The prevailing practice during the study period was that mycobacterial smears were ordered on sputum and other samples collected from patients. Mycobacterial culture and sensitivity to antimycobacterial agents were ordered upfront only when clinical suspicion of drug resistance was suspected. Xpert *Mycobacterium tuberculosis* (MTB)/RIF test had not yet become available for routine patient care. Our pathologists also reviewed the slides of the patients with TB lymphadenitis, diagnosed by histopathology, to see if there was any difference between the DM and the non-DM with regard to the presence of granulomas or presence of acid–fast bacilli (AFB) on smear. We looked at the 10-year pattern of the change in proportion of smear positive TB, smear negative TB, and EPTB among DM and nondiabetic (non-DM) patients.

The following criteria were used for the diagnosis of TB.

Pulmonary tuberculosis

a. Sputum smear positive for AFB and/or culture positive for MTB in the sputum or bronchial lavage sample
b. Sputum smear negative pulmonary TB, but chest X-ray and clinical features suggestive of TB.

Extrapulmonary tuberculosis

a. Tubercular pleural effusion
   i. Pleural fluid AFB smear or MTB culture positive and/or histopathology consistent with the diagnosis of TB
   ii. Lymphocytic exudate with clinical features, suggestive of TB and alternate diagnoses unlikely.

b. Central nervous system TB
   i. Cerebrospinal fluid AFB smear or culture positive
   ii. Tubercular meningitis diagnosed by the treating unit based on Thwaite's diagnostic criteria (score < 4)
   iii. Computed tomography of the brain showing hydrocephalous and/or basal meningeal enhancement and/or space-occupying lesions, suggestive of tuberculoma.

c. Tubercular peritonitis – Histopathology with or without microbiological confirmation
d. Tuberculous lymphadenitis – Histopathology with or without microbiological confirmation
e. Histopathological evidence of granulomatous inflammation on the bone marrow or any tissue other tissue.

We used the standard definitions of DM and impaired fasting and glucose tolerance as suggested by the WHO. In brief, DM was defined as fasting plasma glucose more than 126 mg/dL or postprandial of 200 mg/dL.[23] For outcomes of TB, we used the criteria as suggested by the WHO Global Reporting strategy.[24] A pathologist reviewed at all the lymph node samples that had been reported to have granuloma and consistent with TB, to see of AFB was seen more often in the diabetic patients.

Statistical analysis

All data were collected in predesigned Case Report Forms and entered into Epidata 3.1. The data were exported and analyzed with SPSS for Windows version 16 SPSS 17.0 (Serial No.: 5062851). Categorical values were reported as proportion and percentages and compared using Chi-square test. Continuous variables were reported as mean with standard deviation and compared using independent sample *t*-test. We analyzed the differences between TB patients with and without DM as well as pulmonary TB versus EPTB. The year-wise trend of smear positive TB, smear negative TB, and EPTB was plotted for diabetic and nondiabetic patients in percentages.

Ethics statement

The study was approved by the Institutional Review Board and Ethics Committee of the institution.

RESULTS

In the 10-year study period, there were 2225 patients evaluated with a diagnosis of TB. Among these patients, data on DM were available for 1979 patients. The prevalence of DM was 472/1979 (24%) overall – 281/964 (29%) in smear positive pulmonary TB, 145/696 (21%) in smear negative pulmonary TB and 46/319 (14%) in EPTB.

The baseline variables and risk factors of DM and non-DM are compared in Table 1. DM patients were more likely to be men 364/471 (77.3%) versus 1041/1508 (61%) ($P = 0.001$); >40 years of age 385/471 (81.7%) versus 587/1508 (38.9%) ($P < 0.001$); have higher body weight 59.96 versus 50.37 kg ($P = 0.004$); be tobacco smokers 76/471 (16.1%) versus 192/1508 (8.1%) ($P < 0.001$); and alcohol consumers 32/471 (6.8%) versus 60/1508 (4%) ($P = 0.02$). They were less likely to be HIV coinfected 8/471 (1.8%) versus 92/1508 (6.1%) ($P < 0.001$). While HIV coinfection was seen overall in 5% (100/1979) of patients, this figure was substantially higher in EPTB with 62 of the 319 (19.4%) being coinfected with HIV.

Overall multidrug-resistant (MDR) TB was present in 295/1979 (14.9%) of our patients – lower in DM patients 55/471 (11.7%) compared to non-DM 240/1508 (15.9%) ($P = 0.02$). The important comorbidities, namely chronic liver disease, chronic kidney disease, asthma, chronic obstructive pulmonary disease, and Vitamin D deficiency, were similar in both groups.

We tabulated the weights of the patients as per the RNTCP weight bands [Table 2]. There were significantly more DM patients in the higher weight band 55–69 kg ($P = 0.0008$) and significantly more non-DM patients in the lower weight band 25–39 kg ($P = 0.0008$), suggesting that the DM patients were better nourished than the non-DM. When TB was diagnosed, overall 52% of the DM patients were known to have DM – 53.8% of smear positive, 45.5% of smear negative, and 63.9% of extrapulmonary. The other 48% of the diabetic subjects were diagnosed at the time of TB diagnosis – 46.2% of smear positive, 54.5% of smear negative, and 36.2% of extrapulmonary.

We looked at the discrepant results between smear and culture among the 1597 patients on whom both these tests were done [Table 3]. Smear negative and culture positive results were similar in DM (28, 7.1%) and non-DM (144, 12.2%). Smear positive and culture negative results were high, presumably because a large number of patients had been given empirical anti-TB treatment before reaching our center but were similar – 82 (20.8%) in diabetic and 211 (17.9%) in non-DM.

There were no differences in the AFB smear positivity in the lymph node tissue samples in those with and without DM [Table 4]. Over the 10-year study period, there was no

Table 1: Comparison of baseline variables and risk factors in diabetes and nondiabetes

Variables (*n*)	Unadjusted analysis			Adjusted analysis		
	Diabetes (*n*=471), *n* (%)	No diabetes (*n*=1508), *n* (%)	*P*	OR	95% CI	*P*
Men	364 (25.9)	1041 (74.1)	0.001	1.42	0.85-2.38	0.18
Age >40	385 (39.6)	587 (60.4)	<0.001	5.50	3.44-8.78	<0.001
Weight (kg), mean±SD	59.96±11.46	50.37±11.58	<0.001	1.03	1.01-1.04	0.004
Smokers	76 (38.3)	122 (61.6)	<0.001	1.27	0.71-2.28	0.42
Alcohol consumers	32 (34.3)	60 (65.2)	0.02	1.77	0.78-4.01	0.17
HIV infected	8 (8.0)	92 (92.0)	<0.001	Due to small numbers not included in multivariate		
Chronic liver disease	5 (15.6)	27 (84.4)	0.16			
History of TB	90 (23.9)	287 (76.1)	0.43			
Vitamin-D deficiency	39 (30.5)	89 (69.5)	0.69			
Chronic kidney disease	14 (30.4)	32 (69.6)	0.55			
Asthma	15 (23.8)	48 (76.2)	0.66			
COPD	31 (30.4)	71 (69.6)	0.33			

OR: Odds ratio, CI: Confidence interval, SD: Standard deviation, TB: Tuberculosis, COPD: Chronic obstructive pulmonary disease

Table 2: Revised tuberculosis control program weight band-wise comparison of the diabetes mellitus and nondiabetes mellitus group (*n*=620)

Weight (kg)	DM	Non-DM	*P*
25-39	12 (6.2)	101 (16.3)	0.0006
40-54	98 (50.5)	326 (52.6)	0.67
55-69	82 (42.3)	180 (29)	0.0008
>70	2 (1)	13 (2.1)	0.51

DM: Diabetes mellitus

Table 3: Discrepant smear and culture results in diabetic and nondiabetic pulmonary tuberculosis patients

Number	Smear−culture + (%)	Smear+culture −(%)
DM (394)	28 (7.1)	82 (20.8)
Non-DM (1179)	144 (12.2)	211 (17.9)
Total (1573)	172 (10.9)	293 (18.6)

DM: Diabetes mellitus

Table 4: Comparison of lymph node histology of tuberculosis patients with and without diabetes mellitus

Lymph node biopsy	Diabetic (*n*=132), *n* (%)	Nondiabetic (*n*=495), *n* (%)	*P*
Granulomatous inflammation with acid-fast bacilli (*n*=91)	18 (13.64)	73 (14.75)	0.84
Granulomatous inflammation without acid-fast bacilli (*n*=536)	114 (86.36)	422 (85.24)	

subjective change in the pattern of pulmonary TB (sputum smear positive and negative) and EPTB among our patients [Figure 1]. Therefore, no further trend analysis was done.

DISCUSSION

We have endeavored to study the burden of DM-TB in an Indian referral hospital. Most studies reported a mean age around 40 years and have similar smoking and alcohol usage. As reported by us, Gupta *et al*. in a study among rural South Indians report higher prevalence of coexisting DM than HIV (31.8% vs. 8.9%).[17] However, among our EPTB patients, the pattern was reversed with the prevalence of DM being 14.4%, while HIV coinfection

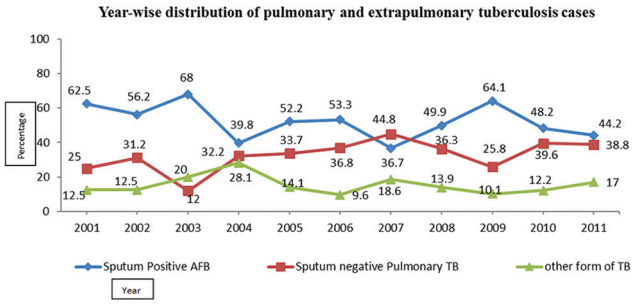

Figure 1: Time trend in the type of tuberculosis among the study patients

was higher 19.4% and seemed to be a more important risk factor.

Co-existing DM varies in different studies from India, and there seems to be a rural–urban difference. Rates of co-existent DM was 12.6% in the North,[13] 24% in Kerala,[16] and 25% in RNTCP centers in Tamil Nadu.[14] In addition, a study from the RNTCP centers reported finding an additional 24.5% to have pre-DM; thus, almost 50% of TB patients showed evidence of an abnormal glucose metabolism. Kumpatla *et al*.[15] found that newly diagnosed DM was 10.5% among TB patients with DM; however, our study found that to be close to 48%. It seems imperative to screen all TB patients for DM. The India DM-TB study found 642–956 cases of newly diagnosed TB patients for every 100,000 DM patients screened.[12] This study as well as that by Viswanathan *et al*.[14] would suggest that we should also screen all DM patients for TB.

The RePORT consortium[25] performs observational biomarker studies in selected Indian centers and two of the cohorts reported prevalence data of TB-DM. The JIPMER, Puducherry team, reported a prevalence of 35.2% of DM in their TB patients.[26] The EDOTS study of TB patients from Chennai reported very high DM prevalence with 54.1% of the patients being classified as diabetic, 21.0% as impaired glucose tolerance, and only 24.9% as normoglycemic.[27] The use of oral glucose tolerance test for the diagnosis of

DM, which they found to be superior to HbA1c may be one of the factors that led to the high rate of detection of DM in the TB cohort.

Our study showed that smoking, alcohol consumption, and HIV coinfection were lower in the DM–TB patients. The DM patients were also heavier and possibly better nourished. Conversely, more non-DM patients could have been undernourished or malnourished. Since patient's height had not been measured, we were unable to corroborate this using BMI measurement.

Nearly 15% of our patients had MDR TB; this is to be expected given that the study was done in a tertiary care center.

Limitations

Our study was a retrospective analysis, which has its limitations. However, DM and TB related data were accurate and mostly available from the hospital electronic database of all laboratory tests. HIV testing was not mandatory in the period covering the early part of our data, and so, it was done at the discretion of the clinician. Mycobacterial cultures are not routinely done for all cases, and treatment in some was based on smear microscopy alone.

CONCLUSIONS

We report data of the burden of DM in a cohort of TB patients in a tertiary care teaching hospital in Southern India. Our study is an endorsement of the plan to screen all TB patients under the RNTCP for DM. This could facilitate optimal treatment of DM, which in turn could improve TB outcomes. More studies are required to see if reduction of the burden of DM could help reverse the TB burden in India.

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Conflicts of interest

There are no conflicts of interest.

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