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Tuberculosis with Diabetes Mellitus: Clinical-Radiological Overlap and Delayed Sputum Conversion Needs Cautious Evaluation-Prospective Cohort Study in Tertiary Care Hospital, India

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Abstract

Background: In India, 15% of pulmonary tuberculosis cases have been estimated to be attributable to DM. Clinical presentation of Tuberculosis and Diabetes is overlapping many times, difficult to differentiate one from other. Although DM has been associated with increased risk of TB treatment failure or relapse, and diminished 2-month and 6-month culture conversion rates, neither international guidelines nor India's Revised National TB Control Programme (RNTCP) currently recommend active screening of TB patients for detection of DM.

Methods: Prospective study conducted at MIMSR Medical College Latur, India during Jan. 2011 to Nov. 2013 included 200 cases of TB with Diabetes Mellitus (DM), compared with 200 cases of TB without DM. Objectives of study were to correlate impact of DM on sputum conversion rate and on clinic-radiological pattern.

Results: PTB was observed in 141 (70.5%) cases with DM as compared to 173 (86.5%) cases without DM, while EPTB was observed in 59 (29.5%) cases with DM as compared to 27 (13.5%) cases without DM ($p<0.0002$). Lower Lung fields involvement in 34 (24.11%) cases with DM and 11 (6.35%) cases without DM cases. Pulmonary Cavities were observed in 55 (39.00%) cases with DM and 49 (28.32%) cases without DM ($p<0.0001$). Sputum conversion at intensive phase completion was observed in 76.53% and 92.70% cases of PTB with and without DM respectively ($p<0.003$). Out of 5.2% cases which were failed to show sputum conversion in diabetic group, 2.8% cases were found to have MDR.

Conclusion: DM affects the clinical, bacteriological and radiological presentation of PTB. Failure of sputum conversion after intensive phase completion should be interpreted cautiously, as many cases were showing sputum conversion after one month therapy of completion of intensive phase and only 2.8% cases found to have MDR.

Keywords: DM; Tuberculosis; DOTS; Sputum conversion

Introduction

Diabetes and pulmonary tuberculosis are the major public health problems in developing countries. The rising prevalence of DM in high TB burden countries may adversely affect TB control [1]. Diabetes Mellitus (DM) almost triples the risk of developing tuberculosis (TB) [2]. A meta-analysis demonstrated that having diabetes was associated with an overall relative risk (RR) of 3.11 for contracting TB [2]. However, neither international guidelines nor India's Revised National TB Control Programme (RNTCP) currently recommend active screening of TB patients for detection of DM.

The estimated prevalence of DM in India in 2010 was 51 million and this is projected to increase to 70 million by 2025 [3]. In India, 15% of pulmonary tuberculosis cases have been estimated to be attributable to DM [4]. A systematic review reporting on the association found 9 studies in which diabetes was estimated to increase the risk of TB infection from 1.5 to 7.8 fold [4]. In order to illustrate the potential public health importance of diabetes as a risk factor for TB, Stevenson et al. [4] estimated the population attributable risk (PAR) for TB from DM within India. They calculated that diabetes could account for approximately 14.8 per cent of incident pulmonary tuberculosis (PTB) in India, and around 20 per cent of sputum positive cases [4].

An analysis of nutrition and DM changes in India also suggests that increased DM prevalence between 1998 and 2008 contributed to an increase in the total number of TB cases in the country which exceeded the rate of population growth in the same time period [5]. These findings highlight the impact of the DM epidemic on TB incidence rates in the country. A study carried out at the Regional Institute of Medical Sciences, Imphal, found the prevalence of pulmonary tuberculosis in people with diabetes to be 27 per cent by radiological diagnosis and 6 per cent by sputum positivity [6]. In a study in Mumbai, tuberculosis was found to be the most commonly occurring concomitant illness in DM patients with 5.9 per cent of individuals in a cohort of over 8000 being co-morbidly affected [7].

DM is known to cause immune dysfunction and moderate suppression of the immune system [8]. A reduced T-helper1 (Th1)

cytokine response level is also seen amongst diabetic individuals [8]. This immune dysfunction is detrimental to the immune response against TB. Th1 cytokines are vital in the control and inhibition of Mycobacterium tuberculosis bacilli. For example, interferon gamma (IFN-γ) is important for combating microbial infections and both IFN-γ and tumor necrosis factor alpha (TNFα) activate macrophages [8,9]. Activated macrophages release reactive oxygen species (ROS) and free radicals such as nitric oxide which are essential for the control of infection, including TB Not only are macrophages the primary site of TB infection but these cells also instigate the main immune response to TB [9].

Clinical presentation of Tuberculosis and Diabetes is overlapping many times, difficult to differentiate one from other. Loss of weight, loss of appetite and lassitude are common to both the diseases. The association is more common among those above 40 years of age and males appear to be at a somewhat greater risk compared with females. Holden and Hiltz [10] described 106 patients with tuberculosis and diabetes in which diabetes appeared first in 48, while tuberculosis appeared first in 40 and the two conditions were diagnosed simultaneously in 18 patients, as did Sumrova come to similar findings [11].

Concomitant TB and DM is associated with more severe features of TB including increased lung cavitations, increased involvement of lower lung fields and longer periods of smear positivity [12]. Diabetes has been associated with increased risk of TB treatment failure or relapse, [13] and diminished 2-month and 6-month culture conversion rates [14].

In present study, we assessed impact of DM on clinical, microbiological and radiological presenting features of pulmonary tuberculosis, with special emphasis on sputum conversion after completion of intensive phase. We also performed sputum conversion percentage after one month therapy of completion of intensive phase, done evaluation for MDR TB who failed to show sputum conversion.

Materials and Methods

This is a Prospective observational study conducted at Department of Pulmonary Medicine and Tuberculosis, MIMSR Medical College Latur, Maharashtra during Jan. 2011 to Nov. 2013 included 200 cases of TB with Diabetes Mellitus (DM), compared with 200 cases of TB without DM. Objectives of study were to correlate impact of DM on Clinical, Bacteriological and Radiological Presentation of Pulmonary Tuberculosis, and also on sputum conversion at two months DOTS therapy (Category I and Category II of treatment guidelines as per National Tuberculosis control guidelines). Study was approved by Ethical committee of our institute.

Case definitions [15]

1. Pulmonary Tuberculosis, Smear-Positive -TB in a patient with at least one smear-positive for AFB out of the two initial sputum smear examination by direct microscopy.

2. Pulmonary Tuberculosis, Smear Negative- a patient with symptoms suggestive of TB with two smear examination negative for AFB, with evidence of pulmonary TB by microbiological methods (culture positive or by other approved molecular methods) or chest x-ray is classified as having smear negative pulmonary tuberculosis

3. Extra Pulmonary Tuberculosis- Tuberculosis in any organ other than lungs (eg. pleura, lymph nodes, intestine, genitor-urinary tract, joint and bones, meninges of the brain etc.).

Criteria for the diagnosis of diabetes mellitus [16]

Symptoms of diabetes plus casual plasma glucose of >11.1 mmol/L (200 mg/dL) or fasting plasma glucose of >7.0 mmol/L (126 mg/dL) or 2 h plasma glucose of >11.1 mmol/L (200 mg/dL) during an OGTT with 75 g anhydrous glucose.

Inclusion Criteria: The cases satisfying the above said case definition and willing to participate in study were included in the study.

Exclusion Criteria: All those not willing to participate, age < 14 years, pregnant and lactating mothers. Tuberculosis patients with HIV co-infection, patients receiving chemotherapeutic drugs, radiotherapy and immunosuppressive therapy were also excluded.

Methodology: study cases were examined in outdoor of department of pulmonary medicine by consultant three times during the entire DOTS: first one during initiation of intensive phase, second one after completion of intensive phase or at the beginning of the continuation phase and third one at the end of continuation phase.

All study cases were subjected to following investigations

Sputum quality was assessed by RNTCP (Revised National Tuberculosis Control Programme) trained lab technician and two sputum samples were examined for AFB by ZN staining at RNTCP accredited Microbiology laboratory of our institute. Sputum examination was done at diagnosis and at two months DOTS treatment follow up in case of category I regimen and at three months treatment in category II regimen as a routine protocol of RNTCP.

Sputum smear examination for AFB was done after one month of therapy of completion of intensive phase in those cases failed to have sputum conversion.

Those cases failed to have sputum conversion at 3 months of therapy, were undergone Liquid culture DST (MGIT-960) for MDR evaluation.

Chest X-ray PA view was done at Radiology department of our institute and Lesions were classified as segmental, nonsegmental, cavitary, miliary, lower lung field, and upper lung field tuberculosis.

BSL random performed in all cases. BSL Fasting and Postprandial level, HBA1c level to assess control of diabetes mellitus.

All 400 study cases either with or without DM received same treatment regimen (DOTS) as per RNTCP (Revised National Tuberculosis control) National guidelines containing four drugs Isoniazid, Rifmapicin, Ethambutol and Pyrazinamide (Category I) for New cases and Streptomycin was added to earlier mentioned four drugs to make Five drug regimen (Category II) for retreatment cases of Tuberculosis.

Statistical analysis: Statistical analysis was done mainly by Chi square test. P value was considered significant if it was below 0.05 and highly significant in case <0.001.

Observation and analysis

There were 200 cases in tuberculosis with Diabetes Mellitus group and 200 cases in tuberculosis without Diabetes Mellitus group. The

mean age of patients in the TB with DM group was 55.4 ± 14.2 years, while in TB without DM was 38.4 ± 11.8 years; the difference was not statistically significant. There were 155 males (77.5%) in TB with DM group and 159 (79.5%) in TB without DM, difference was not statistically significant. Total 149 patients (74.5%) in the TB with DM group had prior diagnosis of DM and in 51 (25.5%) cases diagnosed and treated during hospitalization. Of those 51 cases, 26 patients reported to have DM but were not taking any medication for DM at the time of admission and the remaining 25 were unaware of having DM. 98 cases of total 149 patients who had been diagnosed with DM prior to admission were treated with oral medications for DM and 51 with insulin. During hospital stay, 183 patients (92.5%) were treated with insulin, [17] (8.5%) were on oral medications (oral hypoglycemic agents) (Table 1).

Site of disease	Tuberculosis with DM (n=200)	Tuberculosis without DM (n=200)	P value (CHITEST)
Pulmonary	141 (70.5%)	173 (86.5%)	p<0.0002
Extra-Pulmonary	59 (29.5%)	27 (13.5%)	

Table 1: Pattern of Tuberculosis in study cohort with and without Diabetes Mellitus

Significant difference observed in Pulmonary and Extra-Pulmonary Tuberculosis in study cases with and without Diabetes Mellitus (p<0.0002) (Table 2).

Sputum for AFB smear	Pulmonary Tuberculosis with DM (n=141)	Pulmonary Tuberculosis without DM (n=173)	P value (CHITEST)
Positive	98 (69.5%)	96 (55.49%)	p <0.015
Negative	43 (30.5%)	77 (44.51%)	

Table 2: sputum smear microbiology for AFB in study cases of PTB with and without DM

Sputum AFB microbiology examination has significant correlation in cases with and without DM (p<0.015).

Radiological pattern of Pulmonary Tuberculosis as cavitary, Multilobar, Lower Lung Field (LLF) involvement, was observed more common in cases of PTB with DM as compared to typical Upper Lung field which was most typical pattern in those cases of PTB without DM (p<0.0001) (Tables 3 and 4).

Radiological Pattern	Pulmonary Tuberculosis with DM (n=141)	Pulmonary Tuberculosis without DM (n=173)	P value (CHITEST)
Upper Lung field	11 (7.80%)	85 (49.13%)	p < 0.0001
Cavitary Pattern	55 (39.00%)	49 (28.32%)	
Multilobar Pattern	41 (29.07%)	28 (16.18%)	
Lower Lung Field	34 (24.11%)	11 (6.35%)	

Table 3: Radiological Patterns of Pulmonary Tuberculosis in study cases with and without Diabetes Mellitus

Extra-Pulmonary site	Tuberculosis with DM (n=59)	Tuberculosis without DM (n=27)	P value (CHITEST)
Lymph nodes	29 (49.15%)	14 (51.85%)	p > 0.8
Pleural	55 (39.00%)	8 (29.62%)	
Meninges	2 (3.38 %)	2 (7.40%)	
Peritoneal	3 (5.08%)	1 (3.70%)	
Others	8 (13.5%)	2 (7.40%)	

Table 4: Extra-Pulmonary Tuberculosis manifestations in with and without DM

Extra-pulmonary Tuberculosis Manifestations was comparable and found to be insignificant difference between cases with and without Diabetes mellitus (p>0.8).

Sputum conversion percentage was found significantly lesser in PTB with DM as compared to those without DM (p<0.003) (Table 5).

Sputum conversion after Completion of Intensive Phase	Sputum Positive AFB Pulmonary Tuberculosis with DM (n=98)	Sputum Positive AFB Pulmonary Tuberculosis without DM (n=96)	P value (CHITEST)
Present	75 (76.53%)	89 (92.70%)	p <0.003
Absent	23 (23.47%)	7 (7.30%)	

Table 5: Sputum Conversion Status after completion of Intensive phase follow-up of Pulmonary Tuberculosis in Study cases

Discussion

Type of tuberculosis and bacteriological profile in cases with and without DM

In our study, we observed highly significant association between Pulmonary (PTB) and Extra-Pulmonary Tuberculosis (EPTB) in cases with and without Diabetes Mellitus ($p<0.0002$). PTB was observed in 141 (70.5%) cases with DM as compared to 173 (86.5%) cases without DM, while EPTB was observed in 59 (29.5%) cases with DM as compared to 27 (13.5%) cases without DM. Former observation were supported by studies conducted by Perez Guzman et al. [17], Kim et al. [18]. Contradictory to mentioned fact, studies by Nissapatorn et al. [19], Yamagishi et al. [20], Nakamoto and Saito et al. [21], Borgdorff et al. [22] shown pulmonary tuberculosis was considered the most common form found in diabetic patients and it showed a much higher proportion than cases without DM.

Sputum smear examination for AFB was observed positive in 98 (69.5%) cases in PTB DM group as compared to 96 (55.49%) cases in PTB without DM. Yield of sputum smear examination for AFB was found to significant in both groups ($p<0.015$).Reason for large proportion of sputum positivity in DM group would be because of more cavitary type pulmonary TB and also multilobar involvement with soft exudative type lesions in these cases. Study done by Kim et al 18 in Korea showed that positive sputum smear for AFB was 68% in diabetic patients. In contrast, Bacakogolu et al. [23] found that fewer diabetic patients were smear positive compared to non-diabetic patients without any clear explanation for their finding.

This indicates that the presence of diabetes mellitus continues to play an important role in the development of pulmonary tuberculosis as well as more bacterial yield in sputum examination.

Radiological patterns of pulmonary tuberculosis in study cases with and without diabetes mellitus

Radiological pattern of Pulmonary Tuberculosis as cavitary, Multilobar, Lower Lung Field (LLF) involvement, was observed more common in cases of PTB with DM as compared to typical Upper Lung field (ULF) which was most typical pattern in those cases of PTB without DM. ($p<0.0001$). Observation supported by studies by Bacakoglu et al. [23], Morris et al. [24], but contrary to present observations in radiological features were observed by Al-wabal et al. [25], Bashar et al. [26], documented predominant upper lung field involvement in their study.

Lower Lung fields involvement in 34 (24.11%) cases with DM and 11 (6.35%) cases without DM cases. According to lung field involvement, Hernandez et al. [27] observed 48% patients affected with lower lung fields, Aktogu et al. [28] found a higher rate of LLF TB among diabetics as compared with nondiabetics (11% and 5.3%, respectively). Singla et al. [12] observed in their study that isolated LLF lesions were significantly more common in diabetic than in nondiabetic patients (23.5% vs 2.4%). Pérez-Guzmán et al. [17] showed in their study that the TB DM group had a significantly higher rate of LLF lesions in comparison with the TB group (19% vs 7%).

Pulmonary Cavities were observed in 55 (39.00%) cases with DM and 49 (28.32%) cases without DM. These findings were similar to Shaikh et al. [29] and Bacakoglu et al. [23] found 50% and 59% of patients with PTB DM affected with cavitatory lung involvement respectively.

Extra-Pulmonary (EPTB) Tuberculosis manifestations in study cases with and without diabetes mellitus

Extra-pulmonary Tuberculosis (EPTB) was observed in 29.5% and 13.5% cases with and without DM respectively. Observation between both groups is statistically highly significant ($p<0.0002$). Explanation for high frequency of extra-pulmonary manifestations in diabetic patients can be related to some degree of generalized and localized immunosuppression induced by DM.17 S. Carreira et al. [30] observed the higher rate of extra-pulmonary manifestations in diabetic patients than in nondiabetic cases.

Although EPTB was observed frequently in cases with DM as compared to cases without DM, organ involvement was similar irrespective of DM, and not having significant association ($p>0.8$). Lymph node TB is common form of EPTB followed by Pleural, Meningeal, and Peritoneal in both the groups.

Sputum conversion status in PTB after completion of Intensive phase follow up

Sputum conversion percentage was found significantly lesser in study cases with DM as compared to cases without DM i.e. 76.53% versus 92.70% respectively. This difference is statistically highly significant ($p<0.003$). Jiménez-Corona et al. [31] made observation regarding delayed sputum conversion at 60 days and agrees with most studies [32], although the timing of delayed conversion has been shown to vary.

Prevalence of MDR TB in cases with DM who failed sputum conversion

Sputum conversion was observed to be delayed in diabetic cases and after subsequent one month follow up of treatment, 94.8% cases were documented sputum smear conversion. Out of 5.2% cases which were failed to show sputum conversion in diabetic group, subjected to MDR evaluation on liquid culture DST (MGIT-960) and 2.8% cases were found to have Multidrug resistant Tuberculosis.

Prevalence of multidrug resistance tuberculosis (MDR TB) in cases with DM showing delayed sputum conversion found to be similar as in cases without DM and doesn't have any significant association when both groups compared.

We preferred Insulin therapy for all study cases of TB with DM because

The rationale for exogenous insulin therapy in patients with type 2 diabetes and active tuberculosis is:

Severe tuberculosis infection and less reliable dosing, frequency and bioavalibility of oral hypoglycemic agents.

Interactions of antituberculosis drugs with oral antidiabetic drugs.

Associated hepatic disease prevents use of oral antidiabetic drugs.

Loss of tissue and function of pancreas either because of pancreatic endocrine deficiency due to pancreatic calcification or tuberculous pancreatitis.

Conclusion

DM affects the clinical, bacteriological and radiological presentation of PTB. High index of suspicion required especially when clinical

presenting features are overlapping and radiological pattern is atypical. Sputum conversion at the end of Intensive phase is delayed in DM cases. Failure of sputum conversion should be interpreted cautiously, and many cases were showing sputum conversion after one month treatment of completion of intensive phase.

DOTS has similar outcome in form of treatment success irrespective of diabetes mellitus. Although MDR evaluation is mandatory in those cases not showing sputum conversion at the end of intensive phase in cases without DM, it should be done cautiously in DM cases. We observed that sputum conversion was observed in proportionate number of cases after one month treatment of completion of intensive phase, and it would decrease cost of MDR evaluation in those cases of TB with DM especially in high burden countries like India.

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