https://doi.org/10.46389/rjd-2021-1063
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2021; volume 28, issue 4, pages 430–436

Original Research

Impact of type 2 diabetes on manifestations of pulmonary tuberculosis and its treatment outcome

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Received: 6 May 2021 / Accepted: 18 June 2021

Abstract

Objectives: The main objective of the study was to learn about associations between diabetes and TB along with clinical characteristics and outcomes. **Methods:** This was a retrospective observational trial. Between patients with TB who had diabetes and patients with TB who did not have diabetes clinical and radiographic characteristics with outcome were compared. Good outcome was defined as cure and treatment complete whereas a poor outcome as treatment failure, default, or death. **Results:** TB patients who were diabetic remain associated with higher sputum mycobacterial load and chest radiograph abnormalities. More symptoms were observed among diabetic TB patients on presentation. Between patients with and without diabetes, the risk of poor outcome differs after 2 months of anti-TB treatment (RR: 1.1; 95% CI: 0.4–2.6). **Conclusion:** On the outcome of TB treatment uncontrolled diabetes seems to have a negative effect. Each TB patient should be routinely be screened for diabetes and good diabetes control can improve the management of tuberculosis.

Keywords: diabetes mellitus, pulmonary tuberculosis, glycemic control, treatment outcomes.

Introduction

Tuberculosis (TB) is considered as most infectious disease and ranking above HIV and as per WHO report in 2019 it was responsible for 1.2 million death [1]. It has been already established fact that after the initial infection with *Mycobacterium tuberculosis* (bacillus which causes TB) it transfer to a doormat stage while the active stage was developed in only 10% of patients [2]. Immunodeficiency caused by the use of immunosuppressive medication, chronic disease, HIV infection, malnutrition, and diabetes mellitus (DM) is the major factors that triggers the activation of TB disease from the doormat stage [3].

Type 2 diabetes (T2DM) is a metabolic disorder that results as a consequence of varying degrees of increased insulin resistance and relative or absolute insulin deficiency [4]. In both developed and developing countries, prevalence and incidence of diabetes are increasing despite the fact that most of the time it is diagnosed accidentally.

Diabetes has always been considered a well-known risk factor of tuberculosis [5, 6]. Now as the prevalence of diabetes increases in developing countries where TB is already in the epidemic stage [7]. In the recent past several studies had established that almost in a range of 10–30% of patients who were having symptomatic TB are also having associated diabetes [8–12]. Few studies already established that in India the prevalence of new-onset of diabetes among TB is in high stage along with pre-existing diabetes [13–15]. Thus India is facing a double burden of diabetes and tuberculosis which is also considered a serious challenge for the Indian health care system.

Certain clinical findings with atypical chest radiographic features suggested being present in TB patients with DM including fewer cavitary lesions, lower lobe disease, acid-fast bacilli

(AFB) smear positivity and diffuse lung involvement [16–18]. Two recent clinical trials established that inadequate glycemic control which is defined by higher HbA_{1c} level (>6.5%) were associated with the severe radiographic disease along with atypical chest radiographic findings among persons with DM and TB [19, 20]. TB treatment outcomes are affected by the adverse effect of DM i.e. increased risk of relapse, default, and death [21, 22].

The main objective of the study was to learn about associations between diabetes and TB along with clinical characteristics and outcomes.

Materials and methods

Study pattern

This was a retrospective observational trial. As this retrospective study evaluated de-identified data and involved no potential risk to patients, the requirement to obtain written informed consent was waived-off.

Study population

Patients, more than 18 years of age who were presented or admitted with sputum-positive pulmonary tuberculosis confirmed with Chest radiographic findings were included in this retrospective analysis. Exclusion criteria were the use of immunosuppressive therapy or tumor necrosis factor-alpha inhibitor, end-stage renal disease, co-infection with HIV and pregnant or lactating women. From our hospital TB registry, 210 patients were initially identified with TB among which 100 were diagnosed with diabetes and 110 had no diabetes. Within this population, 80 cases were chosen randomly in both cases as it would be sufficient to provide a power of 80% to detect a not more than 15% difference in the event rate of culture conversion with a 2-sided confidence interval of 90%.

Measurements and definitions

Based on sputum acid-fast bacillus (AFB) smear microscopy with culture confirmation, chest radiographic findings and symptoms of pulmonary TB was diagnosed and confirmed by the pulmonary pathology department. All Ziehl-Neelsen–stained sputum slides were examined under microscope sputum mycobacterial load was graded as 1+, 2+, or 3+. TB treatment regimen included rifampicin, isoniazid, ethambutol, and pyrazinamide. Diabetes was concluded if the patients recorded reported with more than 6.5% HbA_{1c}. Patients who were having established T2DM were also received oral anti-DM drugs.

Data collection

Data was collected in a predesigned format. Serological data collected include C-reactive protein level, fasting blood sugar, postprandial blood sugar and HbA_{1c}. Controlled patient data were collected from the registry of the medicine department. Clinical history like the previous history of TB, asthma, smoking habits is also recorded along with demographic details like age, gender, weight, and BMI. Pathological and radiographic reports from patients' clinical records were also used for analysis.

Data analysis and statistics

All data were analyzed with SPSS for Windows version 16 SPSS 17.0. TB patients with DM with those without DM findings were compared. To compare categorical frequencies author used Pearson's $\chi 2$-test and to compare means for normally distributed continuous variables author used the student t-test. p-Value <0.05 was considered as a statistically significant value.

Results

Demographic and other characteristics of patients diagnosed with pulmonary tuberculosis in diabetes and non-diabetes patients were listed in Table 1. It was observed that at the time of diagnosis of TB patients with diabetes were having more BMI and weight as compared to non-diabetic

Table 1: Comparison of demographic and other characteristics of patients diagnosed with pulmonary tuberculosis in diabetes and non-diabetes patients.

Variables	TB without DM (n=80)	TB with DM (n=80)	p-Value
Age (years)	38.6±10.1	51.3±12.4	0.02
Male (N%)	61 (76%)	64 (80%)	0.31
Weight (kg)	62.4±8.7	70.3±12.6	0.03
BMI (kg/m^2)	22.5±2.8	25.4±3.9	0.04
History of TB	17 (21%)	15 (19%)	0.53
Smokers	16 (20%)	18 (23%)	0.89
Asthma	6 (8%)	8 (10%)	0.73
C reactive protein level (mg/dl)	48 (60%)	59 (74%)	0.82
Fasting blood sugar (mg/dl)	158.8±29.6	95.8±4.6	0.001
Post prandial blood sugar (mg/dl)	286.9±61.7	129.5±5.9	0.001
HbA_{1c} (%)	8.9±2.2	5.5±0.2	0.001
Symptoms			
Fever	60 (75%)	66 (83%)	0.39
Cough	62 (75%)	79 (99%)	0.48
Weight loss	64 (80%)	77 (96%)	0.21
Hemoptysis	32 (40%)	34 (43%)	0.11
Dyspnea	51 (64%)	55 (69%)	0.17
Chest radiographic and CT findings			
Right lung disease	29 (36%)	33 (41%)	
Left lung disease	21 (26%)	24 (30%)	0.49
Bilateral disease	30 (38%)	23 (29%)	
Lobar involvement			
Upper lobe lesions	32 (40%)	30 (38%)	0.81
Lower lobe lesions	21 (26%)	25 (31%)	
Diffuse disease (>1 lobe)	27 (34%)	25 (31%)	
Sputum smear grade			
Negative	19 (24%)	21 (26%)	0.23
1 Plus	11 (14%)	2 (3%)	0.06,
2 Plus	7 (9%)	8 (10%)	0.65
3 Plus	43 (54%)	49 (61%)	0.87,

8.9±2.2 was the mean average HbA_{1c} for TB patients having diabetes. Among diabetes patients, 19% were newly diagnosed. About 70% patients were consuming medication for their diabetes among which 12% were on single OHA, 32% were on multiple OHA, 11% were on insulin pls OHA and 11% were only on insulin (Table 2).

patients. In addition among patients without DM, lower lobe involvement was more frequent on chest radiograph than non-diabetic participants. Increased age has also appeared as a risk factor for TB patients associated with T2DM. TB patients who were diabetic remained associated with higher sputum mycobacterial load and chest radiograph abnormalities. Symptoms like cough, fever, weight loss, hemoptysis, and dyspnea were more prominent in diabetic TB patients.

https://doi.org/10.46389/rjd-2021-1063

Between patients with and without diabetes, the risk of poor outcome differs after 2 months of anti-TB treatment (RR: 1.1; 95% CI: 0.4–2.6) (Table 4). Among the 80 patients who had TB with diabetes, 2 patients died within 2 months after initiation of treatment and poor treatment outcome were countered as 16% which was 9% in the case of TB patients without diabetes.

On the basis of patients' reports and pill counts, in the group of patients with TB who did not have DM 91% was the treatment adherence whereas in the group of patients with TB who had DM the treatment adherence was 98%.

Table 2: Hypoglycemic medication details of TB patients who were also having diabetes.

Parameters	TB with DM (n=80)
Newly diagnosed diabetes	15 (19%)
Pre-existing diabetes	65 (81%)
Without any hypoglycemic medication	24 (30%)
On hypoglycemic medication	56 (70%)
Medication details	
On one oral hypoglycemic agent	12 (15%)
On multiple oral hypoglycemic agents	26 (32%)
On insulin only	9 (11%)
On insulin+OHA	9 (11%)

Table 3 depicts the impact of glycemic status on pre-treatment chest CT and sputum smear grade. Diabetes patients for further analysis were divided in three groups [HbA_{1c} >6.5 but ≤7.5% (N=14), HbA_{1c} >7.5 but ≤8.5% (N=23) and HbA_{1c} >8.5% (N=43)]. On pre-treatment chest CT and sputum smear grade there were not many differences among the groups (Table 3).

Discussion

In urban India, the prevalence of diabetes was in the range of 5.6–12.4% [23]. Gupta et al had already established that in India diabetes was more co-existing with TB than with HIV (31.8% vs. 8.9%) [24]. This high prevalence of diabetes leads a great challenge for clinicians to treat TB patients.

Several studies already confirmed in line with our study that symptoms of TB among diabetic patients such as fever, cough, hemoptysis, with loss were more prominent at presentation compared to non-diabetic TB patients [25, 26]. Several earlier studies have established the fact that uncontrolled diabetes increases the risk of developing active TB [27, 28], but how severity and outcome of TB are influenced by blood glucose level is still not documented. The main reason for

Table 3: Impact of glycemic status on pretreatment chest CT and sputum smear grade.

Parameters	HbA_{1c} >6.5 but ≤7.5% (n=14)	HbA_{1c} >7.5 but ≤8.5% (n=23)	HbA_{1c} >8.5% (n=43)	p-Value
Chest CT				
Right lung disease	6 (43%)	9 (39%)	17 (40%)	
Left lung disease	3 (21%)	6 (26%)	16 (37%)	0.19
Bilateral disease	5 (36%)	8 (35%)	10 (23%)	
Lobar involvement				
Upper lobe lesions	5 (36%)	9 (39%)	23 (53%)	0.21
Atypical, lower lobe, and diffuse	9 (64%)	14 (61%)	20 (47%)	
Sputum smear grade				
Negative	4 (29%)	7 (30%)	11 (26%)	
1 Plus	1 (7%)	3 (13%)	1 (2%)	0.08
2 & 3 Plus	9 (64%)	13 (57%)	31 (72%)	

Table 4: Association between diabetes and tuberculosis treatment outcomes.

Patients type	Poor outcome				Success			Relative risk (95% CI)
	Treatment failure n (%)	Default n (%)	Died n (%)	Total	Cure n (%)	Treatment complete n (%)	Total	
Patients with diabetes (N=80)	5 (6%)	6 (8%)	2 (3%)	13 (16%)	35 (44%)	32 (40%)	67 (84%)	1.1 (0.4–2.6)
Patients without diabetes (N=80)	2 (3%)	4 (5%)	0	6 (9%)	33 (41%)	41 (50%)	74 (91%)	Ref

this may be, in developing countries like India, many factors influence the presentation of TB patients including both diabetic and non-diabetic patients such as accessibility to health care, awareness of the disease, gender, age, nutritional status, comorbidity, adherence to the treatment, etc. When TB patients were associated with uncontrolled diabetes situation becomes more critical as diabetes itself triggers the severity of TB symptoms. In line with the few earlier studies present studies also documented that among patients without DM lower lobe involvement was more frequent on chest radiograph than non-diabetic participants [29–31]. TB patients who were diabetic remained associated with higher sputum mycobacterial load and chest radiograph abnormalities [32, 33]. Increased age has also appeared as a risk factor for TB patients associated with T2DM in our study and this has also confirmed in previous documentation [34, 35].

In the current study the impact of diabetes on TB treatment outcome after 2 months was also evaluated. Among the 80 patients who had TB with diabetes, 2 patients died within 2 months after initiation of treatment and poor treatment outcome was countered as 16% which was 9% in the case of TB patients without diabetes. Conflicting results were reported in previous studies, as few studies fails to establish the effect of DM on TB cure rates [36, 37] whereas others established a strong relationship [39–41]. To assess the patient's response during anti-TB treatment therapy monitoring of sputum cultures and smears was important. The success of anti-TB treatment depended on the time until the conversion of cultures to negative [42]. In a current study among patients with TB and DM, a higher initial sputum smear grade was observed and after 2 months of anti-TB treatment delayed sputum culture conversion occurred more frequently in patients with diabetic TB patients.

In the current study, it was also documented that a large number of the TB patients were not on any medication and there was a difference in treatment adherence between the two groups. Thus treating diabetes with proper anti-diabetic drugs is most important and achieving near-normal blood glucose levels can change the treatment outcome. More awareness regarding diabetes care and outcome among the TB patients who had diabetes or were in the pre-diabetes stage need to be the primary focus of clinicians.

There are a few limitations with this study which include its small sample size and retrospective nature. However, the samples side was enough to draw a clinically meaningful conclusion and there was an absolute accuracy of DM and TB-related data as it was recorded from the hospital clinical database.

Conclusion

On the outcome of TB treatment, uncontrolled diabetes seems to have a negative effect. Each TB patient should be routinely be screened for diabetes and good diabetes control can improve the management of tuberculosis.

https://doi.org/10.46389/rjd-2021-1063

Conflict of interest

The authors have no financial disclosure of conflicts to report.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and in accordance with the Declaration of Helsinki of 1964 and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants involved in the study.

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 https://doi.org/10.46389/rjd-2021-1063