AN OBSERVATIONAL STUDY TO DETERMINE THE IMPACT OF GLYCAEMIC CONTROL ON PRESENTATION OF DRUG SENSITIVE AND DRUG RESISTANT PULMONARY TB IN TYPE 2 DIABETES

Tariq Mahmood¹, Arvind Kumar Verma², Kaleem Ahmad³, Sarita Bajaj⁴, Abhinav Chaudhary⁵, Sreenivasa A⁶

¹Professor and Head, Department of Pulmonary Medicine, MLN Medical College, Allahabad, U. P.

²3rd Year Junior Resident, Department of Pulmonary Medicine, MLN Medical College, Allahabad, U. P.

³3rd Year Junior Resident, Department of Pulmonary Medicine, MLN Medical College, Allahabad, U. P.

⁴Professor, Director and Head, Post Graduate Department of Medicine, MLN Medical College, Allahabad, U. P.

⁵Senior Resident, Department of Pulmonary Medicine, SGPGL, Lucknow, U. P.

⁶Senior Resident, Department of Pulmonary Medicine, KMC, Mangalore, Karnataka.

ABSTRACT

BACKGROUND

There is a strong correlation between the two diseases, diabetes and tuberculosis, with impact of one on the other. Poor glycaemic control causes poor outcome of tuberculosis treatment and that can be observed radiologically and microbiologically beside clinical observation.

The aim of the study is to study the impact of glycemic control on presentation (clinical, radiological and microbiological) of drug sensitive and drug resistant pulmonary TB in type 2 diabetes.

MATERIALS AND METHODS

This is an observational cross-sectional study. Patients above 18 years, having PTB with DM over one year were included. PTB with other conditions like HIV, Pregnancy, Connective tissue disorders, Chronic renal failure, Chronic liver disease, Malignancy, on long-term steroid use or cytotoxic drug therapy or on immunosuppressive drugs were not included in this study. Glycemic control was assessed by A1c < 7 as controlled and > 7 as uncontrolled. Clinical, Microbiological and Radiographic parameters of the patients were studied in respect to their glycemic control.

RESULTS

263 PTB patients who were screened for the study, out of which 94 were diabetic. The prevalence of DM in PTB patients was found to be 35.7% (out of 180 drug-sensitive PTB patients 68 were diabetic and out of 83 drug resistant PTB patients 26 were diabetic). The overall mean age was (50 ± 9) years, maximum no. of patients (60%) were in 40 - 60 years' age group, 70% males with mean A1c (8.54 ± 0.03), 81% had uncontrolled glycemic status and 100% had cough with mean A1c (8.47 ± 0.03). 81% were sputum AFB positive with mean A1c (8.64 ± 0.014), 75.5% had lower lung field abnormalities with mean A1c (8.61 ± 0.094), 12.57% upper lung field with mean A1c (7.53 ± 0.012), 9.5% both lung fields with mean A1c (9.19 ± 0.082), 84% had infiltrative lesions with mean A1c (8.45 ± 0.017) and 25.5% had cavities with high mean A1c (10.04 ± 0.029).

CONCLUSION

The association between DM and TB is the most emerging challenge for global TB control. Poor glycemic control has significant effect on sputum smear positivity, more cavity formation and lower lung field involvement with no effect on clinical symptom. Hence, with the help of this study, it can be concluded that screening for DM should be performed routinely in patients with TB that may improve treatment outcomes.

KEYWORDS

Pulmonary Tuberculosis (PTB), Diabetes Mellitus (DM), Glycated Haemoglobin (A1c), Acid Fast Bacilli (AFB).

HOW TO CITE THIS ARTICLE: Mahmood T, Verma AK, Ahmad K, et al. An observational study to determine the impact of glycemic control on presentation of drug sensitive and drug resistant pulmonary TB in type 2 diabetes. J. Evolution Med. Dent. Sci. 2018;7(07):904-908, DOI: 10.14260/jemds/2018/206

BACKGROUND

TB is as old as the mankind.¹ TB remains a major global health problem and ranks as the second leading cause of death worldwide, second only to HIV/ AIDS as the greatest killer worldwide due to a single infectious agent.²

An estimated 10.4 million people fell ill with TB in 2016: 90% were adults, 65% were male, 10% were people living with HIV (74% in Africa) and 56% were in five countries: India, Indonesia, China, the Philippines and Pakistan. Drug-resistant TB is a continuing threat to world community. In 2016, there were 6 lakh new cases with resistance to rifampicin, the most effective first-line drug, of which 4.9 lakh had multidrug-resistant TB. Almost half (47%) of these cases were in India, China and the Russian Federation.³

TB is a significant cause of mortality among immune compromised patients and continues to be a significant threat to humans globally.⁴ Diabetes Mellitus (DM) was a known risk factor for TB in the past, but this was mostly neglected during the second half of the 20th century with the advent of widely available treatment for both diseases.⁵ In recent decades with the increasing prevalence of TB, particularly

'Financial or Other Competing Interest': None.
Submission 30-12-2017, Peer Review 27-01-2018,
Acceptance 01-02-2018, Published 12-02-2018.

Corresponding Author:

Dr. Tariq Mahmood,

Professor and HOD,

Department of Pulmonary Medicine,

MLN Medical College,

Allahabad-211001, Uttar Pradesh, India.

E-mail: mlnmctariqmahmood@gmail.com

DOI: 10.14260/jemds/2018/206

multi drug resistant TB and DM cases in the world, the relationship is re-emerging as a significant public health problem and is more challenging. The link of DM and TB is more prominent in developing countries, where TB is endemic and the prevalence of it is rising. Although, DM infection with HIV is considered as the most potent risk factor for TB, the high prevalence of DM in the world and its effect on TB burden is greater than HIV infection in many studies.⁶

Patients with type 2 DM are known to have altered immunity, specifically a chronic inflammatory state in which many cytokines and chemokines are upregulated. These patients are particularly susceptible to bacterial infections, notably *Mycobacterium*, *Staphylococcus aureus*, *Streptococcus pneumonia* and *Pseudomonas aeruginosa*.⁷ The association between TB and DM occur in low- and medium-income countries, where roughly 95% of patients with TB and 70% of patients with DM live.⁸ Patients with DM are at twice the risk of acquiring TB compared to those without DM, and that this association is even stronger in HIV positive subjects.⁹ Moreover, DM patients with smear-positive pulmonary TB have a higher probability of failure of the sputum smear conversion after 2 months of therapy than patients without DM.^{10,11}

DM constitutes a risk factor for active TB and might influence the disease presentation and response to treatment.^{12,13} On the other hand, TB may induce glucose intolerance and aggravate glycemic control in patients with DM.^{14,15} The higher susceptibility of TB in diabetics may be related to a longer duration of disease or due to poor control of glycemic status.¹⁶ Poor glycemic control has been significantly associated with the occurrence of TB.¹⁷ However, at present the mechanisms explaining the association between DM and TB remain unclear. So in this study, we want to see the association of glycemic control with pulmonary TB and to study the impact of glycemic control on clinical, radiographic and microbiological presentation of pulmonary TB in patients with DM.

Aims and Objectives

To study the impact of glycemic control on presentation (clinical, radiological and microbiological) of drug sensitive and drug resistant pulmonary TB in type 2 DM.

MATERIALS AND METHODS

Study Design and Patient Population

It was an observational cross-sectional study, patient presented to Department of Pulmonary Medicine (Indoor Department), MLN Medical College over a period of August 2016 to September 2017. Diagnosis of PTB was confirmed as per the RNTCP criteria.

Inclusion Criteria

1. Patients with PTB confirmed by sputum AFB smear examination as per RNTCP criteria with type 2 DM aged more than 18 years.
2. Patients with sputum AFB smear negative, PTB (diagnosed by physician on clinical and radiological ground) with type 2 DM aged more than 18 years.

Exclusion Criteria

Patients were excluded from the Study if they have any of the following Conditions-

1. Pregnancy.
2. HIV infection.
3. Connective tissue disorders.
4. Chronic renal failure.
5. Chronic liver disease.
6. Malignancies on long-term steroid or cytotoxic drug therapy.
7. Chronic alcoholics.

METHODOLOGY

This study was approved by the Institutional Ethical Committee. After explaining aims and objectives in detail, written consent was obtained. Personal interview was held to collect data including age, gender, symptomatology and relevant information. All patients underwent routine investigations, viral markers, chest radiograph and sputum microscopy for AFB. Glycemic control was assessed by glycated haemoglobin (A1c) using calorimetric method. A1c < 7 was taken as controlled and A1c > 7 as uncontrolled glycemic status. Reading of the chest radiographs was focused on- 1) The type of lung parenchymal lesion as infiltrates, consolidation and cavitation, 2) Location of opacity as upper lung field, lower lung field and diffuse. Upper lung field was defined as lesion involving the upper zone and lower lung field as the involvement of mid and lower zone. The sputum AFB examination was done by Auramine O fluorescent staining. The grade of sputum smear at baseline was defined as: negative - no bacilli in 100 fields; scanty as 10-19 bacilli in 40 fields; 1-10 bacilli per field after examination of 100 fields = 1+; 11 - 100 bacilli per field after examination of 50 fields = 2+; more than 100 bacilli per field after examination of 20 fields = 3+. Demographic profiles, Clinical characteristics, Microbiological and Radiographic parameters of the patients were studied in respect to their glycemic control. Data were described as mean and no. of patients. Student T-tests were used in calculating 'p' values. 'P' value less than 0.05 was considered as statistically significant.

RESULTS

There were 263 TB patients who were presented to Department of Pulmonary Medicine, MLN Medical College, Allahabad, over a period of August 2016 to September 2017. Of them 94 patients were diabetic, diagnosed based on FPG, PPG and A1c values with a prevalence of 35.7%.

In this study, out of 94 patients 70% were males and 30% were females. The mean age was 50 ± 9 years. Most of them, 60% were in the age group of 40 - 60 years.

Demographic Characters	Distribution	No. of Patients	%	Mean A1c $\pm$ SD
Age	<40 years	18	19%	8.65 $\pm$ 0.23
	40 - 60 years	56	60%	8.58 $\pm$ 0.54
	>60 years	20	21%	8.13 $\pm$ 0.14
Sex	Male	66	70%	8.54 $\pm$ 0.67
	Female	28	30%	8.60 $\pm$ 0.019

Table 1. Demographic Feature and Mean AC Correlation

The most common clinical presentation was cough 100% with mean A1c of $8.47 \pm .03$ followed by fever, breathlessness and hemoptysis, but patients with hemoptysis 26.5% had high mean A1c of $(9.12 \pm .023)$. There is no correlation of mean A1c levels with symptomatology.

Clinical Feature	Number of Patients	Percentage	Mean A1c $\pm$ SD
Cough	94	100%	8.47 ± 0.03
Fever	89	94.6%	8.44 ± 0.05
Breathlessness	69	73.4%	8.51 ± 0.12
Hemoptysis	25	26.5%	9.12 ± 0.23
Loss of Appetite	64	68%	8.18 ± 0.04
Weight Loss	23	24.4%	8.55 ± 0.06

Table 2. Clinical Feature and Mean A1c Correlation

In this study regarding sputum status 77 patients were sputum positive with mean A1C of (8.64 ± 0.014) , whereas remaining 17 patients were sputum negative with mean A1C of (7.84 ± 0.005) . On applying T-Test between sputum positive and sputum negative patients, the p-value comes to be 0.003 which is statistically significant.

Sputum Status	No. of Patients	%	Mean A1c $\pm$ SD	P-value
Negative	17	18 %	7.84 ± 0.005	0.0072
Positive	77	82%	8.64 ± 0.014	

Table 3. Sputum Status and Mean A1c Correlation

In this study as per the radiographic presentation (the reporting of the x-ray was done by a Radiologist), out of 94 patients, majority had only lower lung field involvement i.e. 71 patients (75.5%) with mean A1c of (8.61 ± 0.094) ; 12 patients (12.7%) had only upper lung field involvement with mean A1c of (7.53 ± 0.012) and 9 patients (9.5%) had involvement of both lung fields with mean A1c of (9.19 ± 0.082) . On applying T-Test between patients having lower lung field involvement and patients having upper lung field involvement, the p-value comes to be 0.0039 which is statistically significant.

In this study the type of lesions were also determined, most of them i.e. 79 patients (84%) had infiltrative lesions with mean A1c of (8.45 ± 0.017) , consolidation with their

mean A1c of (8.46 ± 0.015) and cavitory lesions with their mean A1c of (10.04 ± 0.029) , higher when compared to all other lesions. On applying T-Test between patients having cavity and infiltrative lesions, the p-value comes to be 0.0019 which is statistically significant.

Radiographic Feature	Number of Patients	Percentage	Mean A1c $\pm$ SD
Infiltration	79	84%	8.45 ± 0.017
Cavity	24	25.5%	10.04 ± 0.029
Consolidation	17	18%	8.46 ± 0.015
Bilateral	29	30.8%	8.90 ± 0.014
Upper	12	12.7%	7.53 ± 0.012
Lower	71	75.5%	8.61 ± 0.094
Upper and Lower	9	9.5%	9.19 ± 0.082

Table 4. Radiographic Feature and Mean A1c Correlation

In this study out of 263 patients 180 patients were drug-sensitive pulmonary TB patients, in which 68 drug-sensitive pulmonary TB patients (37.77%) were diabetic and 112 drug sensitive patients (62.22%) were non-diabetic. 83 patients were drug-resistant TB patients, in which 26 drug-resistant TB patients (31%) were diabetic and 57 drug-resistant TB patients (69%) were non-diabetic.

Diabetes Status	Drug-Sensitive Pulmonary TB Patients		Drug-Resistant Pulmonary TB Patients	
	Number of Patients	%	Number of Patients	%
Diabetic	68	37.77%	26	31%
Non-Diabetic	112	62.22%	57	69%

Table 5. Distribution of D Min Drug Sensitive and Drug Resistant Pulmonary TB

In this study, majority 78 patients (83%) had uncontrolled glycemic status with A1c more than 7 and 16 patients (17%) had controlled glycemic status.

A1c	Number of Patients	Percentage
< 7 (Controlled)	16	17%
> 7 (Uncontrolled)	78	83%

Table 6. Glycemic Control in Pulmonary TB-DM Patients

DISCUSSION

In our study, out of 263 patients with pulmonary TB 35.7% had DM. A study done by Hardy Kornfield et al reported 54.1% had associated DM out of 209 pulmonary TB patients from south India.¹⁸ A study by Park et al showed the prevalence of 25.2% of diabetes among pulmonary TB patients.¹⁹ Another study done by Bokam et al reported prevalence of 44% of DM among pulmonary TB patients.²⁰ Compared to previous studies, our study also showed high prevalence (35.7%) of DM among pulmonary TB patients. This explains the increasing prevalence of DM in developing countries like India. A study done by Jagdish Rawat et al, which showed the mean age of the patients pulmonary TB-DM as 53.3 ± 14.06 .²¹ A study done by Bokam et al which showed the mean age of the patients pulmonary TB-DM as 52.13 ± 10.20 . Compared to previous studies, our study also shows higher mean age i.e. 50 ± 9 years with mean A1c of 8.50 ± 0.03 . A study done by Park et al which showed that there were no differences in radiographic findings between controlled diabetics and non-diabetics, but diabetic patients with poor glycemic control had an increased frequency of cavity.¹⁹ A study done by Anand K Patel et al, which showed radiographic presentation of patients of pulmonary TB with DM showed higher involvement of lower lung field 84% when compared to upper lung field and cavitory lesions, more frequently confined to lower lung field.²² A study done by Bokam et al showed that 59% had involvement of only lower lung fields, 29.5% upper lung fields and 11.3% had involvement of both upper and lower lung fields.²⁰ Another study done by Avuthu et al showed that patients with poor glycemic control are likely to have lower lung field involvement and cavitory disease on chest radiograph.⁷ In this study as per the radiographic presentation (observed by a Radiologist), out of 94 patients majority had only lower lung field involvement - 71 (75.5%) with mean A1c of 8.61 ± 0.094 ; 12 patients (12.7%) had only upper lung field involvement with mean A1c of 7.53 ± 0.012 and 9 patients (9.5%) had involvement of both lung fields with mean A1c of 9.19 ± 0.082 . In our study, the types of lesions were also determined, most of them 79 (84%) had infiltrative lesions with mean A1c of 8.45 ± 0.017 , consolidation with their mean A1c (8.46 ± 0.015) and cavitory lesions with their mean A1c of 10.04 ± 0.029 higher when compared to all other lesions. The increased frequency of pulmonary cavitory lesions in diabetic patients with poor glycemic control is probably related to reduced expression of Th1-related cytokines.²³ A study done by Park et al, who reported no differences in clinical symptoms regardless of diabetes control status.¹⁹ Another study done by Bokam et al, which showed most of the patients (93.2%) presented with cough as a common symptom with mean A1c of 9.02 followed by dyspnea and fever, but there is no relation of A1c on clinical symptoms.²⁰ A few other studies have shown that the clinical characteristics of TB do not differ among diabetic and non-diabetic patients.²⁴⁻²⁵ In our study, all of the patients (100%) were presented with cough as a common symptom with mean A1c of 8.47 ± 0.03 followed by fever (94.6%) with mean A1c of 8.44 ± 0.05 , breathlessness (73.4%) with mean A1c of 8.51 ± 0.12 , loss of appetite (68%) with mean A1c of 8.18 ± 0.04 , weight loss (24.4%) with mean A1c of 8.55 ± 0.06 and hemoptysis (26.5%) with mean A1c of 9.12 ± 0.23 . There is no correlation of mean A1c level with symptomatology. A study

done by Bokam et al, which showed people with very poor glycemic control had high sputum positivity rates with mean A1c of 9.46, while A1c of 8 in case of sputum negative patients.²⁰ With regard to the rate of positive smears at the time of diagnosis, results are conflicting. Although, some authors reported a higher frequency of negative sputum smears among TB-DM cases,²⁶ others found DM as an independent risk factor for numerous acid-fast bacilli on the sputum smear examination²⁴ and some showed no association between DM and patient's bacteriology results. Conflicting results might be due to the control status of DM.¹⁹ In our study 82% patients were sputum positive with mean A1c of 8.64 ± 0.14 , whereas remaining 18% were sputum negative with mean A1c of 7.84 ± 0.005 . People with very poor glycemic control had high sputum positivity rates with mean A1c of 8.64 ± 0.014 , while A1c of 7.84 ± 0.005 in case of sputum negative patients. A study done by Chen-Yuan Chiang et al which showed 88.8% had A1c more than 7 and 11.2% had A1c less than 7.²⁷ A study done by Payam Tabarsi et al reported 40% of their study population had normal glycemic control of less than 7.²⁸ Another study done by Bokam et al, which showed 93.20% had A1c more than 7 and remaining 6.80% had A1c less than 7.²⁰ In our study, 83% patients had uncontrolled glycemic status ($A1c > 7$) and only 17% patients had controlled glycemic status ($A1c < 7$). High prevalence of diabetes, illiteracy, unawareness and low socioeconomic status of the patients may be the causes for improper control of glycemic status in our study.

CONCLUSION

Prevalence of DM among pulmonary TB is on the rise with uncontrolled diabetics predominantly affected. Poor glycemic control has significant effect on sputum smear positive rates, cavity formation and lower lung field involvement with no effect on clinical symptoms. Therefore, diabetic patients especially those with poor glycemic control should be screened regularly for TB as new cases of DM are increasing in TB patients. Hence, TB patients should also be investigated routinely for diabetes, so that both the diseases can be detected early and treated promptly. Further studies may be needed to investigate and confirm above findings.

REFERENCES

- [1] Mohan A, Sharma SK. Epidemiology. In: Sharma SK, Mohan A. eds. TB. New Delhi: Jaypee Brothers Medical Publishers 2001; p. 14-29.
- [2] World Health Organization. TB factsheet.
- [3] <http://www.who.int/gtb/publications/factsheet/ind ex.htm>.
- [4] Patel AK, Rami KC, Ghanchi FD. Radiological presentation of patients of pulmonary TB with diabetes mellitus. Lung India 2011;28(1):70.
- [5] WHO global TB report 2017.
- [6] www.ssajm.org/article.asp?issn=23845147;yea2015;v olume=2;issue...Avuthu.
- [7] Ruslami R, Aarnoutse RE, Alisjahbana B, et al. Implications of the global increase of diabetes for TB control and patient care. Trop Med Int Health 2010;15(11):1289-99.
- [8] Schaible UE, Kaufmann SH. Malnutrition and infection: complex mechanisms and global impacts. PLoS Med 2007;4(5):e115.

- [9] Sen T, Joshi SR, Udwadia ZF. Tuberculosis and diabetes mellitus: merging epidemics. *J Assoc Physicians India* 2009;57:399-404.
- [10] Faurholt-Jepsen D, Range N, Praygod G, et al. Diabetes is a risk factor for pulmonary TB: a case-control study from Mwanza, Tanzania. *PLoS One* 2011;6(8):e24215.
- [11] Mi F, Tan S, Liang L, et al. DM and TB: pattern of TB, two-month smear conversion and treatment outcomes in Guangzhou, China. *Trop Med Int Health* 2013;18(11):1379-85.
- [12] Alisjahbana B, Sahiratmadja E, Nelwan FJ, et al. The effect of type 2 DM on the presentation and treatment response of pulmonary TB. *Clin Infect Dis* 2007;45(4):428-35.
- [13] Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on TB treatment outcomes: a systematic review. *BMC Med* 2011;9:81.
- [14] Jeon CY, Murray MB. DM increases the risk of active TB: a systematic review of 13 observational studies. *PLoS Med* 2008;5(7):e152.
- [15] Dooley KE, Chaisson RE. TB and DM: convergence of two epidemics. *Lancet Infect Dis* 2009;9(12):737-46.
- [16] Fisher-Hoch SP, Mathews CE, McCormick JB. Obesity, diabetes and pneumonia: the menacing interface of non-communicable and infectious diseases. *Trop Med Int Health* 2013;18(12):1510-9.
- [17] Olmos P, Donoso J, Rojas N, et al. TB and DM: a longitudinal-retrospective study in a teaching hospital. *Rev Med Chil* 1989;117(9):979-83.
- [18] Bokam BR, Thota P. Effect of glycemic control on pulmonary TB in diabetics. *Indian Journal of Basic and Applied Medical Research* 2016;5(3):198-207.
- [19] Kornfeld H, West K, Kane K, et al. High prevalence and heterogeneity of diabetes in patients with TB in south India: a report from the Effects of Diabetes on Tuberculosis Severity (EDOTS) Study. *Chest* 2016;149(6):1501-8.
- [20] Leung CC, Lam TH, Chan WM, et al. Diabetic control and risk of TB: a cohort study. *Am J Epidemiol* 2008;167(12):1486-94.
- [21] Park SW, Shin JW, Kim JY, et al. The effect of diabetic control status on the clinical features of pulmonary TB. *Eur J Clin Microbiol Infect Dis* 2012;31(7):1305-10.
- [22] Bacakoglu F, Basoglu OK, Cok G, et al. Pulmonary TB in patients with DM. *Respiration* 2001;68(6):595-600.
- [23] Tabarsi P, Baghaei P, Marjani M, et al. Changes in glycosylated haemoglobin and treatment outcomes in patients with TB in Iran: a cohort study. *Journal of Diabetes Metab Disord* 2014;13(1):123.
- [24] Chang JY, Dou HY, Yen CL, et al. Effect of type 2 diabetes mellitus on the clinical severity and treatment outcome in patients with pulmonary TB: a potential role in the emergence of multidrug resistance. *J Formos Med Assoc* 2011;110(6):372-81.
- [25] Singla R, Khan N, Al-Sharif N, et al. Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. *Int J Tuberc Lung Dis* 2006;10(1):74-9.
- [26] Tatar D, Senol G, Alptekin S, et al. TB in diabetics: features in an endemic area. *Jpn J Infect Dis* 2009;62(6):423-7.
- [27] Rawat J, Sindhwani G, Biswas D. Effect of age on presentation with diabetes: comparison of non-diabetic patients with new smear-positive pulmonary TB patients. *Lung India* 2011;28(3):187-90.
- [28] Chiang CC, Lee JJ, Chien ST, et al. Glycemic control and radiographic manifestations of TB in diabetic patients. *PLoS One* 2014;9(4):e93397.