RESEARCH PAPER | Medical science | Volume : 4 | Issue : 10 | October 2014 | ISSN - 2249-555X

Effect of Type II Diabetes Mellitus on Treatment outcomes of Tuberculosis

KEYWORDS: diabetes, TB.

Nilesh Agrawal	Pranay Gandhi	Sunita Sharma
Assistant professor, Dept. of Community Medicine,Travancore medical college, Kollam	Assistant professor, Dept. of Community Medicine, IGGMC, Nagpur	Junior resident-3, Dept. of ENT, SRTR medical college, Ambajogai

ABSTRACT *AIMS: To compare treatment outcomes among TB patients with diabetes with those without diabetes.*

SETTING AND DESIGN: Study was conducted in a tertiary care centre in central India, among patients registered with Revised National TB Control Programme. Prospective observational study design was used.

MATERIALS AND METHODS: Registered TB patients aged 30 and above were invited to participate in the study. Those who were not aware of their diabetic status were diagnosed using oral glucose tolerance test. A total of 89 diabetic and 120 non-diabetic patients were recruited in the study.

RESULTS: Bi-variate (unadjusted) analysis showed similar treatment success rates in the two groups. But adjusted odds ratios for successful treatment among diabetic patients were significantly lower (0.191, 95% CI 0.04-0.90) for pulmonary TB patients and for smear positive pulmonary TB patients (odds ratio 0.099, 0.013-0.761).

CONCLUSIONS: Diabetes increases risk of poor treatment outcomes among pulmonary TB patients

INTRODUCTION

Tuberculosis (TB) still continues to be a major health problem in India. Although the National TB Control Program has helped reduce burden of disease, incidence of disease is unacceptably high. Among the 8.7 million new incident cases of TB in 2009, 2.2 million are said to have occurred in India accounting for a fifth of the global disease burden. [1] Although TB is an infectious disease, previous studies did show increased susceptibility to and increased incidence of TB among those with diabetes.[2] India currently experiences an epidemic of diabetes mellitus (DM) with an estimated 40.9 million diabetics in 2006 and an estimated 70 million in 2025.[3] An epidemiological modelling study reported increased incidence of TB among those with diabetes in India.[4]

Hence, we conducted a prospective study to assess the influence of diabetes on the treatment outcomes of TB under field conditions, among those taking Directly Observed Treatment Short course (DOTS) under Revised National Tuberculosis Control Programme (RNTCP) in a tertiary care hospital in central India.

MATERIALS AND METHODS

A prospective observational study design was used with two sub-groups of TB patients, one with diabetes and other without DM. Since DM has a long latent period and may remain undiagnosed in the absence of screening, an oral glucose tolerance test (OGTT) was chosen for diagnosing DM among patients on treatment of TB. TB patients registered in RNTCP were considered for recruitment in the study.

For estimating sample size for comparison of treatment outcomes among TB patients with and without co-morbid diabetic status, we used the following formula,

$$n = \{z_1\alpha\sqrt{[2P(1-P)]} + z_1\beta\sqrt{[P_1(1-P_1) + P_2(1-P_2)]}\}^2 / (P_1 - P_2)^2$$

where, $P = (P_1 - P_2)/2$

The treatment success rate among the non-diabetic TB patients (P_1) was assumed to be 90% (based on RNTCP accomplishments over the years). And the treatment success rate among the diabetic TB patients (P_2) was assumed to be 75%. With confidence level (α) of 95% and the power ($1 - \beta$) of 90%, the sample size needed to find difference between the two groups was estimated to be 109 in each group.[7]

RESULTS

Patient characteristics: Review of records from TB registers of the two TB units identified a total of 584 patients aged 30 years and above registered from 1st November 2011 to 31st May 2012. A total of 233 TB patients consented to participate in the study. Fifty of these 233 patients were known diabetics and their diabetes status was confirmed with review of medical records. Remaining 183 participants were screened for DM with OGTT test. Of these 183 patients, 120 had normal glucose levels, 24 showed impaired glucose tolerance and 39 were found to be diabetic. The patients with impaired glucose tolerance were excluded from study. Fifty patients who were known diabetics and 39 patients diagnosed by OGTT were included into the TB with the DM group (n = 89). The comparison group included 120 who had normal glucose levels on OGTT. Table 1 provides details of patient characteristics. Out of the total 209 patients in the study, three-fourths were males (76.1%) and one-fourth were females (23.9%) whereas 31.1% were illiterate. Majority (55%) were daily wage labourers and most (76.6%) had monthly income less than Rs. 5000/- per month. 44.5% (n = 93) were smokers and 55.5% (n = 116) were consuming alcohol among the study group and considerable overlap was seen. The diabetic and non-diabetic groups were not statistically different with respect to smoking or alcohol use. The average weight at treatment initiation was 51.09 kg for a diabetic and 45.01 kg for a non-

Volume : 4 | Issue : 10 | October 2014 | ISSN - 2249-555X

diabetic. Among the known cases of diabetes (n = 50), two (4%) were not taking any treatment and one (2%) was diagnosed as a diabetic just 1 week prior to the interview. The rest (n = 47) were taking allopathic treatment from a registered allopathic practitioner either from the government sector or from private practitioners. Nearly one-third (32%) of these 50 known diabetics had missed at least one dose during 2 weeks prior to the interview. There was no evidence of diabetic nephropathy or renal failure in these patients.

Table 1:

	Diabetic group (n=89) no (%)	Non-diabetic group (n=120) no (%)
Age, median years	50 yrs	48 yrs
Sex: male	72 (80.9)	87 (72.5)
Female	17 (19.1)	33 (27.5)
Smoker	40 (44.9)	53 (44.2)
Alcohol user	50 (56.2)	66 (55.0)
Body weight at initiation of treatment	51.09 kg	45.01 kg
Type of TB:		
New smear positive TB	40 (44.9)	37 (30.8)
New smear negative and new extrapulmonary TB	36 (40.4)	64 (53.3)
Retreatment TB	13 (14.6)	19 (15.8)

Characteristics of tuberculosis patients who had diabetes mellitus and of TB patients who did not have DM

It is seen from Table 1 that among new TB patients, more diabetics had sputum smears positive before initiation of treatment compared to the non-diabetics. Combining the new and retreatment cases, pre-treatment sputum positivity among diabetics (59.6%) was higher (but not significantly higher with p = 0.5) than among non-diabetics (45.8%).

Diabetes and TB treatment Outcomes:

Initial response to TB treatment was good. Out of 109 smear positive TB patients, 106 converted to smear negative status by end of intensive phase (IP). Sputum smears for the remaining three patients (all new smear positive patients) were positive at end of IP; of these three, two were diabetics and one was non-diabetic. It is seen from Table 2 that the success rate of TB treatment was 89.9% (n = 80) among those with diabetes and 95.8% (n = 115) among those without diabetes. The success rate was not associated with diabetes in univariate analysis or after adjustment with age, sex, smoking, alcohol use and adherence to treatment. Treatment success rates among pulmonary patients among non-diabetics were higher although not significantly higher in univariate analysis. After adjusting for age, sex, smoking, alcohol use and adherence to treatment and sputum smear result at end of IP, diabetics had less likelihood of successful treatment. Limiting analysis to sputum smear positive pulmonary TB patients also showed that diabetics had less likelihood to be successful compared with non-diabetics. However, the success rates in the two groups were very similar for new smear positive (NSP) patients, 90% for diabetics and 91.9% for non-diabetics. No relation was seen between the presence of diabetes and successful treatment among NSP in univariate or multivariate analysis. All sputum smear negative and extrapulmonary TB patients successfully completed their treatment. Only one among the extra-pulmonary patients was a diabetic. The treatment outcomes of 14 patients were not successful. Among them nine (64.3%) were diabetics and five were non-diabetics. The adverse treatment outcomes included failure (7), default (5) and death (2) as a whole. Among the five patients who defaulted, four were new sputum positives and one was retreatment with history of default previously. Only one among the five defaulters was a diabetic. Overall, the adherence to treatment was found to be better in the diabetic group. Nearly 75% of non-diabetics were not regular in treatment missing at least three doses during treatment, thereby extending treatment duration by at least 1 week; this proportion was less for diabetics (57%). Mean delay in completing treatment was significantly smaller for diabetics (13.2 days) compared to non-diabetics (18.5 days). Two patients, one male and one female died during the course of the study.

Table 2

Treatment outcomes	Diabetics no. (%)	Not diabetics no (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95 % CI)
All patients				
Cured				
Completed				
Failure	41 (46.1)	43 (35.8)		
Default	39 (43.8)	72 (60.0)		
Death	7 (7.9)	0 (0.0)		
Successful treatment (all patients)	1 (1.1)	4 (3.3)		
	1 (1.1)	1 (0.8)	0.386(0.125-1.196)	0.170(0.017-1.662)
Successful treatment (pulmonary TB) n=182	80 (89.9)	115 (95.8)	0.448(0.144-1.394)	0.191*(0.040-0.900)
	75 (89.3)	93 (94.9)	0.479(0.149-1.537)	0.099*(0.013-0.761)
Successful treatment (smear positive TB) n=109	44 (83.0)	51 (91.1)		

Treatment outcomes of tuberculosis among patients with and without diabetes

Determinants of failure:

A total of seven patients continued to remain sputum positive in spite of taking full course of anti-tubercular drugs. At the beginning of therapy, they were registered as relapse (three cases), failure (two cases) and new smear positive (two cases). All the seven were cases of diabetes. Of the seven patients, six were lost to follow up and samples could not be sent for drug sensitivity testing. One patient could be followed up was diagnosed as a case of multiple-drug resistant TB and was initiated on category IV regimen under RNTCP. Table 3 shows univariate association between independent variables and sputum result at the end of treatment. Diabetes and positive sputum at the end of

Volume : 4 | Issue : 10 | October 2014 | ISSN - 2249-555X

intensive phase were factors found to be associated with positive sputum at the end of treatment.

Table 3:
Predictors of sputum positivity at end of treatment

Variable	Patients with positive sputum at end of treatment no (%)	Patients with negative sputum at end of treatment no (%)	P value
No. of patients	7	85	
Diabetics*	7 (100.0)	41 (48.2)	0.013
Male sex*	6 (85.7)	77 (90.6)	0.526
Non-serocoversion at the end of intensive phase*	2 (28.6)	1 (1.2)	0.014
Smoker*	4 (57.1)	54 (63.5)	0.707
Alcohol user*	4 (57.1)	58 (68.2)	0.679
Interruption of treatment (median days)**	10 days	11 days	0.631
Age (median years)**	54 years	49 years	0.274

DISCUSSION

In the present study, only three new smear-positive patients failed to convert at the end of intensive phase. The smear conversion rate was lower among diabetics but data was not sufficient to draw meaningful conclusions. A previous Indian study[6] showed no difference in both smear and culture conversion results at the end of 2 months among new pulmonary TB patients. However, many studies in rest of the world showed that smear and culture conversion rates were poor among diabetics.[5] Two such studies did not find difference at the end of intensive phase but reported some delay in conversion in the diabetic group. [8,9]

In this study, the treatment success rates were similar in the diabetic and non-diabetic groups. However, after adjusting for some confounders we found that diabetes is associated with poor outcomes among pulmonary TB patients. A systematic review on this issue also found that patients with DM receiving TB therapy are at risk for poor outcomes, but not controlling for confounders may underestimate the negative impact of DM in TB patients.[5] Better adherence to treatment among diabetics, as observed in the study was one such confounder.

The study had certain limitations. First, success of treatment was based upon sputum smear results and smear cultures were not obtained. Secondly, none of these patients were tested for the presence of drug resistance before beginning of the study and only one patient could be tested at the end of treatment. More than a third were diagnosed during course of TB treatment and were not on hypoglycemic agents throughout TB treatment and glycemic control was not measured among these patients. Serum levels of rifampicin or other drugs were not measured. Although we attempted adjusting for some confounders, we could not adjust for some like severity of chest radiograph findings, glycemic control and susceptibility to drugs.

To summarize, we found poor treatment outcomes among diabetic TB patients compared those without DM. There is need to review policy of similar treatment regimen for DM-TB co-morbid patients. Lack of sputum culture at the end of treatment and other limitations discussed earlier affects the strength of evidence in this study and similar studies are needed to provide evidence for the policy decision.

REFERENCE

1. Global Tuberculosis Report 2012. [Last accessed on 2013 July 18]. Available from: http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf . | 2. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies. PLoS Med. 2008;5:e152. | 3. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res. 2007;125:217–30. | 4. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, et al. Diabetes and tuberculosis: The impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health. 2007;7:234. | 5. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: A systematic review. BMC Med. 2011;9:81. | 6. BanuRekha VV, Balasubramanian R, Swaminathan S, Ramachandran R, Rahman F, Sundaram V, et al. Sputum conversion at the end of intensive phase of Category-1 regimen in the treatment of pulmonary tuberculosis patients with diabetes mellitus or HIV infection: An analysis of risk factors. Indian J Med Res. 2007;126:452–8. | 7. Lwanga SK, Lemeshow S. Sample size determination in health studies: A practical manual. Geneva: World Health Organization; 1991. | 8. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff TH, et al. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clin Infect Dis. 2007;45:428–35. | 9. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg. 2009;80:634–9. | 10. Ruslami R, Nijland HM, Adhiarta IG, Kariadi SH, Alisjahbana B, Aarnoutse RE, et al. Pharmacokinetics *of antituberculosis drugs in pulmonary tuberculosis patients with type 2 diabetes. Antimicrob Agents Chemother. 2010;54:1068–74. | 11. India Tuberculosis-Diabetes Study Group. Screening of patients with tuberculosis for diabetes mellitus in India. Trop Med Int Health. 2013;18:636–45. | 12. Oluboyo PO, Erasmus RT. The significance of glucose intolerance in pulmonary tuberculosis. Tubercle. 1990;71:135–8. | 1. Global Tuberculosis Report 2012. [Last accessed on 2013 July 18]. Available from: http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf . | 2. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies. PLoS Med. 2008;5:e152. | 3. Mohan V, Sandeep S, Deepa R, Shah B, Varghese C. Epidemiology of type 2 diabetes: Indian scenario. Indian J Med Res. 2007;125:217–30. | 4. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, et al. Diabetes and tuberculosis: The impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health. 2007;7:234. | 5. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, et al. The impact of diabetes on tuberculosis treatment outcomes: A systematic review. BMC Med. 2011;9:81. | 6. BanuRekha VV, Balasubramanian R, Swaminathan S, Ramachandran R, Rahman F, Sundaram V, et al. Sputum conversion at the end of intensive phase of Category-1 regimen in the treatment of pulmonary tuberculosis patients with diabetes mellitus or HIV infection: An analysis of risk factors. Indian J Med Res. 2007;126:452–8. | 7. Lwanga SK, Lemeshow S. Sample size determination in health studies: A practical manual. Geneva: World Health Organization; 1991. | 8. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff TH, et al. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clin Infect Dis. 2007;45:428–35. | 9. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg. 2009;80:634–9. | 10. Ruslami R, Nijland HM, Adhiarta IG, Kariadi SH, Alisjahbana B, Aarnoutse RE, et al. Pharmacokinetics *of antituberculosis drugs in pulmonary tuberculosis patients with type 2 diabetes. Antimicrob Agents Chemother. 2010;54:1068–74. | 11. India Tuberculosis-Diabetes Study Group. Screening of patients with tuberculosis for diabetes mellitus in India. Trop Med Int Health. 2013;18:636–45. | 12. Oluboyo PO, Erasmus RT. The significance of glucose intolerance in pulmonary tuberculosis. Tubercle. 1990;71:135–8. |