Outcome of Tuberculosis in Patients with Diabetes Mellitus Treated with the Revised National Tuberculosis Control Programme Regimen-A Study from Kerala, South India

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ABSTRACT

Introduction: Multiple studies have shown a clear association between Tuberculosis and Diabetes Mellitus. This study aimed at exploring the outcome of both Pulmonary and Extra Pulmonary Tuberculosis in patients with Diabetes Mellitus treated with the Revised National Tuberculosis Control Programme Regimen

Material and Methods: A prospective study to summarize evidence for the impact of Diabetes Mellitus on Tuberculosis was performed. This study includes 100 patients of Diabetes Mellitus (DM) with newly diagnosed Pulmonary Tuberculosis (PTB) or Extra Pulmonary Tuberculosis (EPTB). Patients included in the study were put on directly observed treatment, short course (DOTS) three times a week as per the Revised National Tuberculosis Control Programme (RNTCP) guidelines.

Results: Sixty four patients had PTB (64%) and 36 patients had EPTB (36%). Of the 61 PTB cases analysed 41 patients were smear positive (67%) and 20 patients were smear negative (33%). Of the EPTB cases, cervical lymphadenitis with 12 cases (33.3%) predominated followed by pleural effusion with 11cases (30.5%).

Of the 41 smear positive PTB patients, 90% converted to sputum negative status at the end of 2 months (except one case of death) The remaining 10% of the patients received an extra month of intensive phase and these were sputum negative at the end of 3 months.

Conclusion: This study shows lower FBS levels in patients with unilateral chest lesions than bilateral lesions. The gain in the body weight and decrease in FBS level during the progression of the treatment is reported. Another important finding of this study is that FBS levels, sputum grading and chest lesions are correlated and the patients with unilateral chest lesions in the X ray had lower FBS levels in comparison to those with bilateral lesions. All these observations indicate that a poor control of DM was associated with more severe forms of PTB.

Keywords: Tuberculosis, Diabetes mellitus, Revised National Tuberculosis Control Programme.

INTRODUCTION

Tuberculosis (TB) still remains a major cause of morbidity and mortality worldwide. Around one third on the world's population is estimated to be infected by the bacillus Mycobacterium tuberculosis, approximately nine million people develop the disease each year, almost two million die annually from the disease.[1,2] The role of Diabetes Mellitus (DM) in the prognosis of Pulmonary Tuberculosis (PTB) and Extra Pulmonary Tuberculosis (EPTB) is a point of interest among various categories of researchers.

Previous studies mostly made in high burden countries have established an important association between DM and PTB. Late diagnosis, improper and inadequate anti tuberculosis therapy (ATT) and immuno deficiency states including DM add insult to the injury.

The global burden of DM is on the rise, the prevalence is estimated to reach 438 million by 2030 and more than 80% of the adult cases will be in the newly developed or developing countries.[3] The dual curse of these two diseases may have an impact on the outcome of treatment. India, among other Asian countries is well known for the prevalence of DM and also TB. The course of TB remains variable especially so when associated with conditions like DM and this study conducted in Kerala, the diabetic capital of India may bring to light the relevance of such co-morbidities.

This study aimed at explaining the outcome of both Pulmonary and Extra Pulmonary Tuberculosis in patients with Diabetes Mellitus. It also intended to study the outcome in relation to duration of DM, age of patients, radiological extent and microbial load and assess the sputum conversion period.

MATERIAL AND METHODS

Jubilee Mission Medical College, a tertiary care referral institute caters to patients from three districts of Kerala, namely – Palakkad, Malapuram and Thrissur. This prospective study included 100 patients of DM with newly diagnosed pulmonary or extra Pulmonary TB. Owing to various reasons 3 cases were excluded from the final analysis. Ethical approval was received from the Institutional Ethics Committee. Written informed consent was obtained from every patient.

Patients included in the study were put on directly observed treatment, short – course (DOTS) three times a week as per the Revised National Tuberculosis Control Programme (RNTCP) guidelines. At the end of the initial intensive phase

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(IP) of treatment, if the sputum smear was positive, the IP was extended by an additional month. Patients with central nervous system and spine involvement were given a total of 9 months of treatment.

Diagnostic and follow up sputum smear examination was done in quality assured designated microscopic centres in the district. All patients were considered to have DM if they reported the disease or a history of intake of anti diabetic drugs, or had a blood glucose value of > 130 mg/dL for fasting blood sugar (FBS) or >200 mg/dL for random blood sugar (RBS) or for post prandial blood sugar (PPBS) during diabetic screening. Blood glucose estimation was done during all visits using the fully automatic biochemical analyser in optimum laboratory conditions with the instruments being periodically calibrated. X-rays were done in all visits for PTB cases and lesions were described as unilateral, bilateral or normal x-rays chest. Sputum for AFB examination was done in relevant cases during all visits. Final outcome of treatment was declared as cured, lost to follow up, treatment failure.

Sample size estimation: Sample size was calculated at a population size of 10,000 at 95% confidence level. With 10% error the calculated sample size was 88. Ten percent cases were added for probable lost follow up and the sample size thus obtained was 97.

Inclusion and exclusion
Inclusion Criteria: All newly diagnosed PTB or EPTB patients with Diabetes Mellitus who gave informed consent and were ready for follow up.

Exclusion Criteria: Patients above 80 years of age, who had a past history of TB, pregnant women and patients with decompensated cardiac, hepatic or renal disease were excluded from the study

STATISTICAL ANALYSIS

Data entry, cleaning and storage was done using Microsoft EXCEL 2007 software package. Mean, median and proportions were calculated using SPSS version 20. Chi-square test were used for compared proportions.

RESULTS

A total of 100 patients of TB with DM were included in the study. Only one patient was lost to follow up and two patients had alternate diagnosis while on treatment. Hence 3 cases were excluded and the final analysis was made on 97 cases. These excluded cases were from PTB category. One patient died during the study period. There was only one patient with HIV in the study and hence we have not reported any significance to it.

Out of the total 100 cases of study 67 patients were male and 33 females. Sixty four patients had PTB and 36 patients had EPTB. The age and sex wise distribution of the patients is given in the table 1. Majority of the patients (both PTB and EPTB) were in the age group of 40- 60yrs. Of the 61 PTB cases analysed 41 patients were smear positive (67%) and 20 patients were smear negative (33%). Of the EPTB cases, cervical lymphadenitis with 12 cases (33.3%) predominated followed by pleural effusion with 11cases (30.5%).

Since the study contains only diabetic patients their duration of illness is presented. Nearly quarter of the patients in both categories was on either oral hypoglycemic agents (OHA) or on insulin therapy for more than 5 years (Table 2). However, the majority of the cases were from 1-5 years. Eighty percent of the sputum +ve PTB patients had Hb A_1C levels of between 6 – 12 %. The FBS at the time of presentation was between 130- 300mg/dL in 65% of patients probably indicating that a poor control of DM was associated with more severe forms of PTB. All of them were brought down to normal level of blood glucose during the course of treatment.

Regarding the grading of sputum positive patients 42.5% had a grading of 1+, 27.5% had a grading of 3+, 25% of the patients had a grading of 2+ and only 5% of the patients had scanty bacilli in their sputum (Table 3). Of the 41 smear +ve PTB patients, 90% converted to sputum negative status at the end of 2 months (except one case of death) The remaining 10% of the patients received an extra month of intensive phase and these were sputum negative at the end of 3 months. Out of the 36 cases of EPTB put on analysis 12 had treatment up to 9 months and reported as cured. Of these cases 5 had poor control of diabetes.

The mean weight of the patients at the time of presentation was 55.66 Kg which steadily increased to 60.58 Kg on the third visit. Meanwhile the average FBS was 188.76 mg/dL at the time of presentation and steadily decreased to 125. 74 mg/dL on the respective third visit (Fig 1). Out of the 61 PTB

Age in years	PTB 64 cases		EPTB 36 cases		Total 100	
	Male	Female	Male	Female	Male	Female
<40	5	2	1	2	6	4
40 – 60	26	9	13	6	39	15
> 60	15	7	7	7	22	14
Total	46	18	21	15	67	33
Table-1: The age and sex wise distribution of the patients						

TB type	Duration of Diabetes Mellitus					Total
	< 1yr	1- 5 yrs	5- 10 yrs	10 -15	>15 yrs	
PTB	12	33	8	6	2	61
EPTB	12	14	4	4	2	36
Total	24	47	12	10	4	97
Table-2: Duration of treatment for DM in years						

cases analysed 45 had unilateral lesions in the chest X ray and their average FBS level was 178 mg/dL. The remaining 16 had bilateral lesions in the chest X ray and their average FBS level was 257 mg/dL. When the FBS levels, sputum grading and chest lesions were correlated the patients with unilateral chest lesions in the X ray had lower FBS levels in comparison to those with bilateral lesions (table 4)

DISCUSSION

Different studies[4-6] have shown causal relationship between DM and impaired host immunity to TB. DM diminishes the Th1 response which plays a crucial role in TB. Furthermore, neutrophils in patients with diabetes have reduced chemotaxis and oxidative killing potential than those of non diabetic controls[5], and leucocyte bactericidal activity was reduced in people with diabetes, especially those with poor glucose control taken together, it may be concluded that DM directly impairs the innate and adaptive immune response necessary to counter the proliferation of TB.

Patients with poor glycemic control as suggested by high Hb A_1C and FBS levels at the time of inclusion in the study had more severe forms of PTB. This study shows lower FBS levels in patients with unilateral chest lesions than bilateral lesions. In a similar study from India[6] also reported this association of poor glycemic control and severity of PTB (Table 3) The gain in the body weight and decrease in FBS level during the progression of the treatment as reported in this study is clearly in accordance with the above reports and confirms that better glycemic control is essential for the effective control of TB. Another important finding of this study is that FBS levels, sputum grading and chest lesions are correlated and the patients with unilateral chest lesions in the X ray had lower FBS levels in comparison to those with bilateral lesions. All these observations show a clear association between TB and DM.

This study was carried out in India which has a high burden of both TB and DM. Kerala is considered to be the diabetic capital of India. The prevalence of DM in TB patients in Kerala is 44%.[7] This is a unique study as it includes patients from peripheral health facilities incorporated into the RNTCP programme. This study had certain limitations. The patients were not followed up after completion of their treatment for a long period. Hence the relapse rates were not known. Other co-morbidities like COPD, smoking etc were not taken into account which could have influenced the outcome of the treatment.

Certain actions need to be taken to strengthen the diabetic care at peripheries also in managing the TB patients. We need to strengthen our care to tackle this dual curse. In 2011, the World Health Organization and the International Union against tuberculosis and lung disease reported the association between TB and diabetes and calling for increased collaboration between TB and diabetes control efforts.

Diabetes and TB represent a critical intersection between communicable and non communicable diseases in some of the world's present countries. As the prevalence of non communicable diseases (NCD) continues to rise, the effects of NCD's on the prevention and treatment of infectious diseases will likely become more evident.[8] Diabetic patients should

Glycemic control	PTB sputum grading			
	Scanty	1+	2+	3+
DM in years				
<1	1	3	5	6
1-5	0	10	3	1
5-10	1	4	2	4
10-15	0	0	1	0
>15	0	0	0	0
DM control method				
Diet	0	0	1	0
OHA	2	10	8	8
Insulin	0	5	2	3
Insulin + OHA	0	2	0	0
DM - FBS level				
<130 mg/dL	0	3	3	4
130-300 mg/dL	2	11	8	5
300-500 mg/dL	0	2	0	2
>500 mg/dL	0	1	0	0
DM - HbA_1C in percent				
<6	0	1	1	2
6-12	2	14	9	9
>12	0	2	1	0

Table-3: Range of glycemic control and PTB sputum grading

Sputum grading	Lesion in chest X ray	DM-FBS average level	
		130-300 mg/dL	300-500 mg/dL
Scanty	Unilateral	215 mg/dL	-
	Bilateral	199 mg/dL	-
1 +	Unilateral	192 mg/dL	-
	Bilateral	-	353 mg/dL
2 +	Unilateral	149 mg/dL	-
	Bilateral	154 mg/dL	-
3 +	Unilateral	171 mg/dL	-
	Bilateral	201 mg/dL	-

Table-4: Correlation of FBS levels, sputum grading and chest lesions
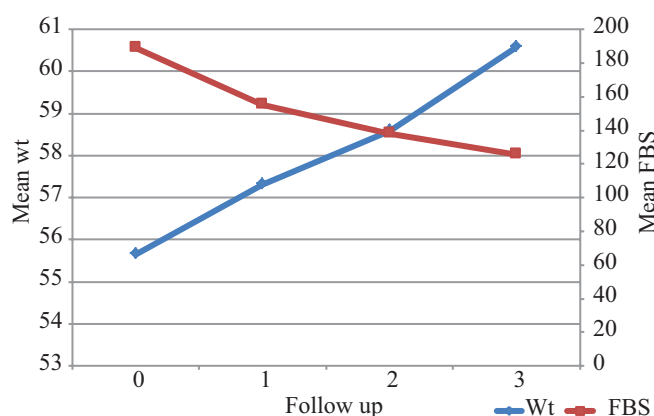

Figure-1: Glycemic control and body weight

remain part of the DOTS structure after completion of TB treatment to ensure optimal follow up and rapid detection of possible relapses. The programme regimen should develop educational materials for patient education especially so amongst diabetics explaining them their risk of developing active TB. Symptoms of cough for more than 2 weeks, fever, anorexia, weight loss should be clearly highlighted to such

patients so that they can seek early TB screening.

Recent reports on DM and TB indicate a global interest on this dual curse. However, in developing countries, the outcome of TB in patients with DM cannot be overlooked. Hence, probably better awareness among patients and integrated programme care should be aimed at in order to cure this deadly dual combo.

CONCLUSION

Patients with TB should be screened for Diabetes Mellitus. Similarly patients with Diabetes Mellitus should be regularly screened with X ray chest and sputum AFB whenever clinically indicated. DOTS programme should incorporate free treatment strategies for comorbid diseases especially DM because of the strong correlation between the two. As patients with poorly controlled DM had more severe forms of PTB stringent measures to control blood sugars should be advocated. A high degree of patient awareness and integrated health care programmes would be effective in combating this dual curse.

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