Efficacy of DOTS therapy in Pulmonary Tuberculosis with Diabetes Mellitus

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Abstract

Introduction: Diabetic persons are more susceptible to develop tuberculosis than non diabetics. What makes the diagnosis of combination difficult, is the fact that symptoms of complicating disease being masked by coexisting disease. Poor glycemic control helps in proliferation of tuberculosis and tuberculosis itself leads to poor glucose control. Thus both deteriorate each other. Directly Observed Treatment Short course has been found to be equally effective in patients with and without diabetes with pulmonary tuberculosis. **Method:** The patients of either sex with pulmonary tuberculosis and associated diabetes mellitus admitted in medical ward excluding chronic cases. Pulmonary tuberculosis was diagnosed by examination of sputum for AFB and by clinical and radiological assessment. Diabetes mellitus was diagnosed from history, previous records and blood examination as per ADA criteria. **Results:** The cure rate was 82% in diabetic group and 86% in non-diabetic group with failure rate of 6% and 4% in diabetic group and non diabetic group respectively. **Conclusion:** Patients with pulmonary tuberculosis having age more than 40yrs and lower lobe lesions should be subjected to O.G.T. to rule out occult diabetes.

Key word: Diabetes Mellitus, Pulmonary Tuberculosis, Directly Observed Treatment Short course (DOTS)

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Introduction

Diabetes mellitus is one of the oldest known metabolic diseases which affect the young and elderly. It is one of the leading causes of ESRD, non traumatic lower extremity amputations and adult blindness. It is characterized by absolute or relative insulin deficiency. It presents with fatigue, weight loss, polyuria, polydipsia and polyphagia. Confirmation of diagnosis is by elevated blood glucose levels [1].

No other infectious disease, since time immemorial has inflicted upon mankind the misery and suffering in all aspects of life, social, economic and health as TB. It is an infectious disease caused by mycobacterium tuberculosis. Classical presentation of pulmonary tuberculosis is with cough, mucoid expectoration, low grade fever, hemoptysis, dyspnoea and weight loss. Confirmation is done by sputum smear examination and chest x-ray [2]. The coexistence of both diseases is not simply a coincidence. Diabetic persons are more susceptible to develop tuberculosis than non diabetics. What makes the

diagnosis of combination difficult, is the fact that symptoms of complicating disease being masked by coexisting disease. Poor glycemic control helps in proliferation of tuberculosis and tuberculosis itself leads to poor glucose control [3]. Thus both deteriorate each other. Directly Observed Treatment Short course (DOTS) is a strategy to ensure cure by providing the most effective medicine under supervision [2]. Previously development of tuberculosis in diabetics was associated with grave prognosis. Combination of both is like Clash of titans and DOTS has emerged as rising sun for protection of these patients.

Material and Methods

The study was undertaken in Department of Medicine, S.S. Medical College & S.G.M.H., Rewa (M.P.). The patients of either sex with pulmonary tuberculosis and associated diabetes mellitus admitted in medical wards from December 2008 to April 2010. Pulmonary tuberculosis was diagnosed by examination of sputum for AFB and by clinical and radiological assessment. Diabetes mellitus was diagnosed from history, previous records and blood examination as per ADA criteria [4].

Patient age more than 15yrs with clinical features and or radiology consistent with pulmonary tuberculosis and or positive sputum for AFB were included in study and diabetics on insulin or OHA and non-diabetics were compared. Chronic cases (defaulter, relapse, failure) were excluded. The treatment efficacy was gauged by clinical improvement, radiological improvement and sputum conversion in tuberculosis and in diabetics by decreasing insulin requirement and plasma glucose and urine examination.

Results

Our study on 100 diagnosed patients of pulmonary tuberculosis, of which 50 were diagnosed cases of diabetes mellitus. All were registered in DOTS and followed up monthly for sputum conversion, radiological conversion and weight gain.

In the non-diabetic group 40 (80%) cases were in 21-40 years age group, 6 (12%) were in 41-60 years age group and 4 (8%) were in age group 60 years and above. In the diabetic group 16 (32%) cases were in age group of 21-40 years, 16 (32%) 41-60 years and 18 (36%) above 60 years, the result being statistically highly significant (p<0.001). The males predominated study (61%). Occurrence of diabetes in males with TB was more 32 (52.4%) as compared to females with TB 18 (46.1%). Though majority patients were Hindus (58%), the Muslims 18 (56.2%) had more diabetes with TB as compared to Hindus 26(44.8%). Also the rural population outnumbered urbans in TB in diabetes [30(57.6%) v/s 20(42.4%)]. The prevalence of both pulmonary tuberculosis and diabetes associated with pulmonary tuberculosis were more in lower socio economic class (64%).

The fever (80%) was most common presenting symptom in both diabetic and non diabetic group. Symptoms like cough, hemoptysis, swelling in neck were more common in non diabetic group. Dyspnoea and fatigue were more common in the diabetic group and weight loss was almost equally present in both groups [36 (51.4%) non diabetic group v/s 34(48.6%) in diabetic group].

The tobacco (55%) was major addiction in both the groups. Alcohol intake was present in 24 patients 14(58.3%) of which were diabetic and 10 (41.7%) non diabetic.

The most patients had normal body mass index 18.5 – 24.9 (75%) in both groups. The both lean (BMI <18.5)(63.6%) and obese (BMI >30) (75%) were more prevalent in diabetic group. The pallor was the most common sign in both groups (70%), while edema was seen more in diabetic group 8(75%). Increased blood urea was present in 10 patients, 8(80%) of which were diabetic and 2 (20%) non diabetic. The urine albumin was significant in 9 patients, 7 (77.7%) of which were diabetic and 2 (22.3%) non diabetic. The sputum positivity was less in diabetic group 19(38%) compared to non diabetics (46%).

The CXR showed bilateral involvement of lungs, more in diabetics 16 (56.7%) as compared to non diabetics 12(43.3%). Also the diabetics showed predominant lower lobe lesion 15(76%) as compared to non diabetics 4(24%).

Table 1: Distribution of cases according to Radiological changes

| S. No. | Radiology | Pulmonary Tuberculosis | | | | Total |
| | | Diabetes Mellitus | | Non diabetic | | |
		No.	%	No.	%	
C	Consolidation	10	20.0	3	6.0	13
	Infiltration	15	30.0	12	24.0	27
	Fibrosis	4	8.0	3	6.0	7
	Cavitation	5	10.0	4	8.0	9
	Effusion	10	20.0	16	32.0	26
	Pneumothorax	2	4.0	4	8.0	7
	Hydropneumothorax	1	2.0	6	12.0	8
	Miliary TB	1	2.0	2	4.0	3

p<0.05 statistically significant

The most common type of involvement in diabetic group was lung infiltration 15(30%) and pleural effusion 16 (32%) was predominant in non-diabetic group. Also the extra pulmonary involvement was more common in non-diabetic group 26 (65%) in comparison to diabetics 13 (35%).

Table 2: Distribution of cases according to extent of tuberculosis and duration of diabetes

S. No.	Extent of TB	Duration of diabetes		
		<5 yrs	5-10 yrs	>10 yrs
1.	Minimal	10	3	2
2.	Moderately advanced	1	4	1
3.	Far Advanced	2	4	10
Total		**13**	**11**	**13**

p<0.004 Statistically highly significant

Table 3: Distribution of cases according to extent of tuberculosis and fasting blood sugar

S. No.	Extent of TB	Fasting Sugar (mg/dl)			Total
		<100	100-150	>150	
1.	Minimal	8	5	2	15
2.	Moderately advanced	2	3	1	6
3.	Far Advanced	4	5	7	16
Total		**14**	**13**	**10**	**37**

p<0.04 Statistically significant

As the duration of diabetes increases, extent of lesion increases. 8 out of 15 patients with minimal lesion had diabetes of less than 5 years with fasting glucose less than 100mg/dL and 7out of 16 patients with far advanced disease had diabetes for more than 10 years with patients fasting glucose more than 150mg/dL. Thus the increased diabetes duration increased extent of lesion which in turn worsened glycemic control.

Table 4: Distribution of cases according to duration for sputum conversion

S. No.	Category	Avg. duration for sputum conversion (Months)		Statistical significance (p)
A	Non diabetics	1.4		significant (p<0.05).
	Diabetics	2.0		
B	Type I DM	2.1		insignificant (p>0.05).
	Type II DM	1.9		
C	Insulin	1.6		significant (p<0.05).
	OHA	1.9		
D	Radiological	Diabetic	Non diabetic	significant (p<0.01).
	Grade- **I**	1.8	1.6	
	Grade- **II**	2	1.8	
	Grade- **III**	2.6	2.2	

Average duration for sputum conversion in diabetics (2 months) was more than non diabetics (1.4 months) with longer sputum conversion duration in type 1 diabetics (2.1 months) as compared to type 2 diabetics (1.9 months). Patients on OHA required longer duration (1.9 months) than those on insulin (1.6 months).
The average weight gain in non-diabetics (5.5kg) was more than diabetics (4.9kg). Patients with type 2 diabetics (5.1 kg) had more gain than type 1 diabetics (4.2kg). Similarly patients on insulin treatment gain weight more weight (4.8kg) than patients on OHA (4.2kg).

The effective DOTS treatment results in decreased Insulin /OHA requirement in 68% diabetics. As the grade of radiological lesion increased the amount of insulin /OHA requirement decreased less.

Hepatitis (3) and peripheral neuropathy (4) occurred more in diabetic group. Withdrawal of therapy was not required in any patient. Thus DOTS was well tolerated in both groups.

Table 5: Distribution of cases according to duration for radiological conversion

S. No.	Category	Average duration for Radiological conversion (Months)		Statistical significance (p)
A	Non diabetics	2.3		Significant (p<0.05).
	Diabetics	2.7		
B	Type I DM	2.9		Insignificant (p>0.05).
	Type II DM	2.4		
C	Insulin	2.4		Significant (p<0.05).
	OHA	2.8		
D	Radiological	Diabetic	Non diabetic	Significant (p<0.01).
	Grade- I	2.4	2.2	
	Grade- II	2.6	2.4	
	Grade- III	3.6	3.1	

It is evident from table that if grade of radiological lesion increases duration for sputum conversion also increases, more so in diabetics (2.7months) was than non diabetics (2.3months) with average radiological conversion duration of 2.9 months in type 1 diabetics and 2.4 months in type 2 diabetics.

Table 6: Distribution of cases according to outcome

S. No.	Category	Pulmonary Tuberculosis				Total	Statistical significance (p)
		Diabetes Mellitus		Non diabetic			
		Total	%	No.	%		
1.	Cured	41	82.0	43	86.0	84	insignificant p>0.05
2.	Failure	3	6.0	2	4.0	5	insignificant p>0.05
3.	Defaulter	2	4.0	3	6.0	5	insignificant p>0.05
4.	Death	4	8.0	2	4.0	6	significant p<0.05
Total		**50**		**50**		**100**	

The cure rate was 82% in diabetic group and 86% in non-diabetic group with failure rate of 6% and 4% in diabetic group and non diabetic group respectively. The defaulter rate was 4% in diabetic group and 6% in non diabetic group. The mortality rate was 8% in diabetic group and 2% in non diabetic group.

Discussion

The number of cases of pulmonary tuberculosis decreased with increasing age and the prevalence of diabetes with pulmonary TB increased with age with male predominance which could be because male patients in the study similar to the study by Oluboyo PO et al and Lin S et al [5,6]. This is also supported by Fernandes study (2004) [7]. The above findings therefore highlight the importance of oral GTT in male tubercular patients, specially the elderly.

The study revealed higher prevalence of PTB with diabetes mellitus in muslim patients, which was supported by Jawed et al study in Pakistan (1995) on 100 patient found 49% prevalence of PTB with diabetes mellitus [8]. The higher prevalence of impaired glucose tolerance in Muslim tuberculous patients may be due to their peculiar dietary habits, rich in animal fats and cholesterol, poverty and illiteracy.

In our study prevalence of diabetes with TB in rural areas was more than urban areas similar to the Deshmukh et al study in 1996 which showed 42% prevalence in rural areas [9]. This may be attributed to increased contribution of rural population to total cases, where awareness of disease and level of literacy is low. Our study revealed not only the greater prevalence of tuberculosis in the lower socioeconomic class but also of DM with TB as well. This may well be explained by the common factor of malnutrition and poor access to medical facilities leading to mal-nutrition related diabetes.

The tobacco chewing and smoking not only predispose to pulmonary tuberculosis but also to the precipitation of latent diabetes in such patients. It may also lead to the early detection of pulmonary tuberculosis in patients presenting with cough secondary to these addictions.

Most patients studied had normal BMI. The greater percentage of BMI lowers than 18.5 in the diabetics (lean diabetics), may be due to malnutrition related diabetes in a developing country like India and delay in starting insulin. Also the overweight status (BMI >24.9) were more in the diabetics similar to Fernandez et al study (2004) [7].

The radiological lesions severity increased with the duration of diabetes. The majority of our patients with far advanced lesion had diabetes for more than 10 yrs. The study of Ross (1995) and Tripathy et al (1984) had found most patients in their study had diabetes prior to pulmonary tuberculosis by a period ranging from 1-5 years [10, 11]. The most patients with far advanced lesion, had fasting blood sugar >150mg/dL. This suggests that as the extent of lesion increases, glycemic control worsens which could be due to fever, protracted inactivity and malnutrition stimulate the stress hormones epinephrine, glucagon, cortisol and growth hormone, which acting synergistically raise the blood sugar level in excess of 200 mg% Guptan et al, (2000)[3].

Most patients in our study had unilateral lung involvement with predominant right side involvement in non diabetes and left side in diabetics. Bilateral involvement was more common in the diabetic patients supported by Ziskind MM et al study [12]. The upper zone involvement was common in non diabetic group and lower zone was common in diabetics. The different patterns of lesions in chest x-ray were infiltration, effusion, fibrosis and cavity, consolidation and pneumothorax in decreasing order. Patients with diabetes had infiltration more in lower zone and fibrosis and cavitory lesions were more in diabetics as compared to non-diabetics. The patients with diabetes had more than one cavity. Lin, Sen, Sun (1998) also found that infiltration and cavitation was the most common lung lesion in diabetics [6]. Khanna in their study found radiologically more extensive lesion in tubercular diabetics [13]. Fernandez et al (2004) in a recent study found mainly cavitary lesions [7].

Table 7: Prevalence of lesion in different study

	All cases	**Cavity**	**Infiltration**	**Pleural**
Ross 1995 [10]	53%	68%	44%	19%
Tripathy Kar et al 1984 [11]	31.03%	75%	60%	30%
Gupta, Nigam 2009 [14]	78.60%	54%	45%	10%
Present study 2010	**62%**	**76%**	**52%**	**5%**

The sputum positivity was more in non diabetic group, more so in cavitatory lesions. The patients with diabetes had delayed sputum conversion with average duration of 2 months. This could be due to malnutrition, lowered general body immunity, impaired cellular response and comparative reduction in serum bactercidal activity of diabetics similar to conclusion from Hadden in 2002, Khanna in 2004 and Kekkaku in 1970 in their respective study [`13,15,16]. Likewise sputum conversion was faster in patients taking insulin and those with lesser radiological lesions. Though diabetics lagged behind in duration, they ultimately attained sputum conversion in stipulated time 94% in diabetics and 96% in non diabetics supported by studies of BanuRekhaV.V, et al (2000), R.K. Kotokey et al (2007), Singla R et al (2008) [17,18,19].

Table 8: Radiological conversion in different study

Study	DMTB		TB	
Banu RekhaVV, 2007 [17]	55		44	
Kotokey et al 2007 [18]	2mth	3mth	2mth	3mth
	50 %	100%	90.48%	100%
Singla R et al 2008 [19]	88%		94%	
Present study 2010	**94%**		**96%**	

Also the radiological conversion was delayed in diabetics group with average duration of 2.7 months. The radiological conversion was earlier in type II diabetes (1.4months v/s 2.9month). Likewise radiological conversion lagged in those taking OHA and those with higher radiological grade. The results were comparable to studies by R.K. Kotokey et al in 2007 and Nissapatorn et al in 2004 [18, 20].

Average weight gain in non diabetics was more than diabetic. The average weight gain was more in type 2 diabetics and that too in those who were on insulin. As the grade of radiological lesion increases average weight gain decreased more so

in diabetics. Nausea and vomiting were the most common side effects seen. Hepatitis and peripheral neuropathy occurred more in diabetic group. Withdrawal of therapy was not required in any patient. Thus DOTS was well tolerated in both groups.

The cure rate was slightly less in diabetics with treatment failure rate of 5%. and higher mortality comparable to study of Kant L.and V Nissapatorn et al, supported later by Helen et al in their study [20,21,22].

Table 9: Treatment failure in different studies [11,20,21,22]

Non Diabetics		
Study		DOTS
Kant L. 2003	Treatment failure	1.7%
Helen S Cox et al 2008	Relapse	22%
Present study 2010	Treatment failure	4%
Diabetics		
Tripathy S.R et al 1984	Relapse rate	10%
	Cure rate	92%
	Mortality	5%
V Nissapatorn et al 2004	Sputum conversion after 2 mths	90 %
	Radiological conversion after 2 mths	65%
	Treatment failure	6%
Present study (2010)	Avg. duration for sputum conversion	1.8 mths
	Avg. duration for radiological conversion	2.7 mths
	Avg. weight gain	4.9kg
	Cure rate	82%

Diabetics predominantly had lower lobe involvement. Thus elderly patients with pulmonary tuberculosis and patients with lower lobe involvement should be investigated for diabetes mellitus.

Conclusion

The cure rate was almost equal in both groups with the higher mortality in the diabetics could be explained by the overall general debility in old patients and comorbid conditions.

DOTS therapy was well tolerated in all patients. Patients with pulmonary tuberculosis having age more than 40 yrs and lower lobe lesions should be subjected to O.G.T. to rule out occult diabetes.

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