ORIGINAL RESEARCH PAPER

General Medicine

ASSESSMENT OF DOTS THERAPY IN PATIENTS WITH PULMONARY TUBERCULOSIS HAVING WELL CONTROLLED TYPE 2 DIABETES MELLITUS AND POORLY CONTROLLED TYPE2 DIABETES MELLITUS

KEY WORDS: Diabetes Mellitus, Pulmonary Tuberculosis, Directly Observed Treatment Short course (DOTS)

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ABSTRACT

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 poorly controlled and well controlled type 2 DM.

Method: The patients of either sex with pulmonary tuberculosis and associated diabetes mellitus admitted in medical ward. Pulmonary tuberculosis was diagnosed by examination of sputum for AFB and by clinical and radiological assessment. Diabetes mellitus was diagnosed fromhistory, previous records and blood examination as per ADA criteria.

Results: The cure rate was 80.30% in PTB with poorly controlled diabetic group and 85.29% in PTB with well controlled -diabetic group with failure rate of 19.70% and 14.71% in PTB with poorly controlled and with well controlled diabetic group respectively.

Conclusion: Poorly controlled diabetic have an increased risk of developing tuberculosis as compared to well controlled diabetic and also they have relatively higher failure rate with DOTS. Both the disease affect each other and effective control of each affects the control of the other condition.

Introduction

The global burden of Diabetes Mellitus (DM) will be 300 million by 2025 and majority will be in the developing countries like India, China, etc. In India, it is estimated that the number of diabetes will increase upto 57 million in 2025.[1]

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 amputation and adult blindness. It is characterized by absolute /relative insulin deficiency. It presents with fatigue, weight loss, polyuria, polydipsia and polyphagia. Confirmation of diagnosis to by elevated blood glucose levels.[2]

Tuberculosis (TB) has been declared as a global emergency by WHO in 1993.[3]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 with mucoid expectoration, low grade fever, hemoptysis, dyspnoea and weight loss. Confirmation is done by sputum smear examination and chest x-ray.[4] The coexistence of both diseases is not simply acoincidence. Diabetic persons are more susceptible todevelop tuberculosis than non diabetics. What makes thediagnosis of combination difficult, is the fact thatsymptoms of complicating disease being masked bycoexisting disease. Poor glycemic control helps inproliferation of tuberculosis and tuberculosis itself leadsto poor glucose control. Thus both deteriorate eachother.[5]

DOTS is a strategy under RNTCP, approved by WHO, for the treatment of tuberculosis. It has been an effective tool on a mass basis and is being used successfully in over 180 countries worldwide. Meticulous and accurate recording of patient progress and outcomes, with prompt, reliable, and public reporting of results, have been key to DOTS progress globally.[3]The treatment of pulmonary tuberculosis with DM is a challenge in the present day scenario due to its increasing coexistence. Also uncontrolled DM is responsible for poor clinical response to anti-tuberculosis treatment.[6]

Material and Methods

The study was undertaken in Department of Medicine,S.S. Medical College &S.G.M.H., Rewa (M.P.). Thepatients of either sex with pulmonary tuberculosis andassociated diabetes mellitus admitted in medical wards and TB wards from july 2016 to june 2017. Pulmonarytuberculosis was diagnosed by examination of sputumfor AFB and by clinical and radiological assessment. Diabetes mellitus was diagnosed from history, previousrecords and blood examination as per ADA criteria[7].Patient age more than 15yrswith clinical features and/or radiology consistent with pulmonary tuberculosis and/orpositive sputum for AFB were included in study anddiabetics on treatment either Insulin or OHA and non-diabetics werecompared. Defaulter, relapse, failure cases of TBwere excluded. The treatment efficacy was gauged byclinical improvement, weight gain, radiological improvement andsputum conversion and improvement in glycemic status.

Results

Our study on 100 diagnosed patients of pulmonarytuberculosis with Type 2DM, of which 66 were poorly controlled diabetics and 34 were well control diabetic. All were registered in DOTS and followed up monthly for sputum conversion,radiological conversion and weight gain, FBS and every 3 monthly for HbA1C.Out of 66 cases 41(62.12%) were PTB with poorly controlled diabetics, the result being statistically significant ($p<0.001$). The males predominated study (61%).Occurrence of PTB with poorly controlled type 2 DM was more 54/61(88.52%) as compared to females 12/39 (30.76%).Though majority patients were Hindus (89%), the Muslims 5/6 (83.33%) had more PTB with poorly controlled diabetics. Also the rural population outnumbered urbans in PTB with poorly controlled diabetics [38/50(76.0%) v/s 28/50(56.0%)]. The prevalence of PTB with poor control diabetic was found to be more in lower socioeconomic class 45/64(70.31%).The cough (86%) was most common presentingsymptom in both group. Symptoms like fever, cough were more common in PTB with poorly controlled diabetics. Dyspnoea, anorexia, fatigue and weight loss were more common in the PTB with well control diabetic group. The tobacco (40%) was major addiction in both thegroups. 69% patients were having diabetes since more than 5 years duration, out of which 40 (57.97%) were PTB with poorly controlled diabetics. 42% patients were taking OHA, of which 32(76.17%) were PTB with poor control diabetics. Smoking habit was found in 20 patient, of which 9(45.0%) were PTB with poor control diabetic and 11(5.0%) were

PTB with well control diabetic. Alcohol intake was present in 19 patients 10(52.63%) of which were PTB with poor control diabetic.The most (60%) patients had weight between 30-45 kg , of which 49 (81.66%) were PTB with poor control diabetic. The pallor was the mostcommon sign in both groups 47/66(71.21%) and 23/34 (67.64%) in PTB with poor control and well control diabetic respectively, while edema wasseen more in PTB with poor control diabetic group 10/66 (15.15%). The sputumpositivity was more in PTB with poor control diabetic group 46/66(67.64%) comparedto PTB with well control diabetics 22/34(32.35%).The CXR showed bilateral involvement of lungs, morein PTB with poor control diabetics 44/59(74.57%) as compared to PTB with poor control diabetics15/59(25.42%). Also the PTB with poor control diabetics showed predominant lower lobe lesion 26/32(81.25%) as compared to PTB with well control diabetics 6/32(18.75%). Cavitatory lesion was more in PTB with poor control diabetics 22/25(88.0%).

Table-1 Distribution of cases according to extent of tuberculosis and duration of diabetes

S No.	Extent of TB	Duration of diabetes				Total
		<5 yrs (n=31)	%	>5 yrs (n=69)	%	(n=100)
1.	Minimal	7	46.66	8	53.33	15
2.	Moderately advanced	11	47.82	12	52.17	23
3.	Far Advanced	13	20.96	49	70.03	62

Statistically significant p<0.05

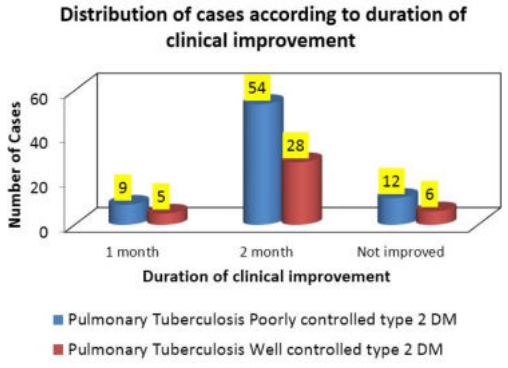
49/62 (79.03%) patients with far advanced disease had diabetes with duration more than 5 years. Thus as the duration of diabetes increases, extent of diabetes increases.

Table -2 Distribution of cases according to extent of tuberculosis and glycemic control

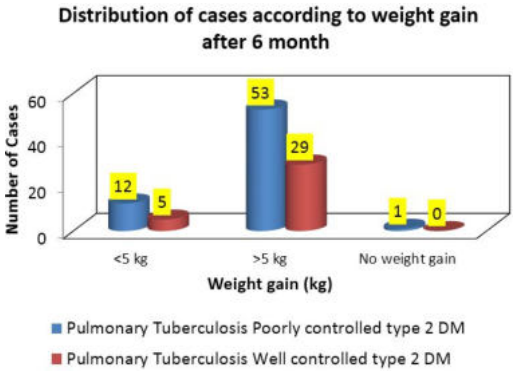
Sr No	Extent of tuberculosis	Pulmonary tuberculosis				Total (n=100)
		Poorly controlled type 2DM (n=66)		Well controlled type 2DM (n=34)		
1.	Minimal	8	53.33%	7	46.66%	15
2.	Moderately advanced	18	52.77%	17	42.22%	35
3.	Far Advanced	40	80.0%	10	20.0%	50

Statistically significant p 0.012

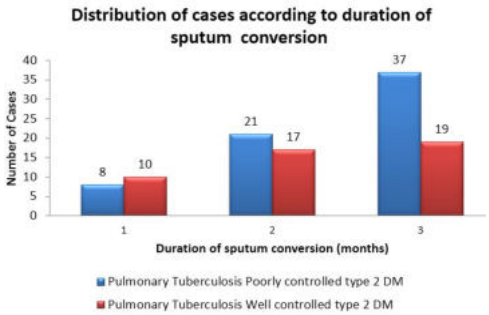
The above table shows that 7 (46.66%) out of 15 cases with minimal lesion have good glycemic control. Whereas 40 (80.0%) out of 50 with far advanced lesion have poor glycemic control. Thus as glycemic control worsens, extent of disease increases.



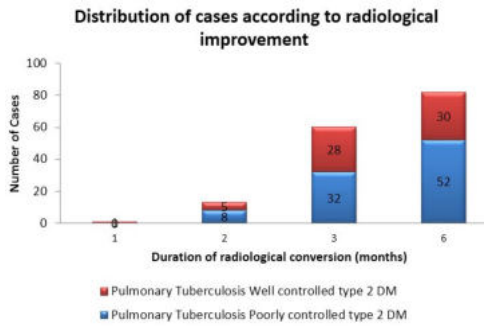
The above graph shows that at the end of 1 month after taking DOTS and anti-diabetic medication clinical improvement was similar in both group (13.63 % and 14.70 % respectively) whereas after 2 month treatment improvement was observed in 54 out of 66 (81.81%) cases having PTB with poorly controlled and 28out of 34 (82.35%) cases who were having PTB with well controlled type 2 diabetes. No clinical improvement was observed in 12 (18.18%) out of 66 in pulmonary tuberculosis with poor controlled diabetic group whereas 6 (17.64%) patients of pulmonary TB with well controlled type 2 DM does not show clinical improvement.



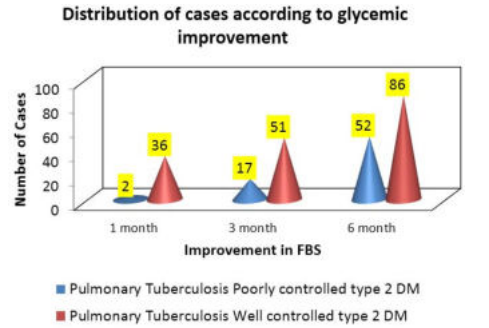
Above graph shows, after 6 month 53 out of 66 (80.30%) cases of PTB with poorly controlled type 2 diabetic shows weight gain more than 5 kg and 29 out of 34 (85.29%) cases of PTB with well controlled type 2 diabetes shows more than 5 kg weight gain. 1 (1.51%) patient of pulmonary tuberculosis with poor control type 2 DM did not show any weight gain.



The above graph shows that rate of sputum conversion in TB-DM was 26.47%, 55.88% and 82.35% at the end of 1 month, 2 months and 3 months respectively. At the end of 3 month of treatment by DOTS sputum conversion rate was 80.43% in PTB with poorly controlled diabetic and 86.36% in PTB with well controlled diabetic.



The above graph shows that after 6 month DOTS treatment radiological conversion is seen in 52 out of 66 (78.78%) cases of PTB with poorly controlled type 2 diabetic and in 30 out of 34 (88.23 %) cases in PTB with well controlled type 2 diabetic.



Above graph shows that after 6 month of taking treatment 86% cases were of well control diabetic group. After 1,3 and 6 months of taking treatment out of 66 poorly controlled type 2 diabetic 2 (3.03%), 17 (25.75%) and 52 (78.78%) patients shows good glycemic control respectively.

Table 3 Distribution of cases according to improvement in HbA1C

SN	HbA1C	Pulmonary tuberculosis		
		Poorly controlled type 2DM (n=66)		Well controlled type 2DM (n=34)
1.	3 months	15	22.72%	49
2.	6 months	50	75.75%	84

Above table shows that after 6 month of taking treatment 84% cases shows improvement in HbA1C. After 3 and 6 months of taking treatment out of 66 PTB with poorly controlled diabetic patients 15 (22.72%) and 50 (75.75%) patients respectively showed well glycemic control.

Table -4 Distribution of cases according to outcome

S. No.	Category	Pulmonary Tuberculosis				Total
		Poorly controlled type 2DM		Well controlled type 2DM		
		(n=66)	%	(n=34)	%	
1.	Cured	53	80.30	29	85.29	82
2.	Failure	13	19.69	5	14.70	18
3.	Defaulter	0	0	0	0	0
4.	Death	0	0	0	0	0
Total	66		34		100	

Statistically insignificant p 0.538

Above table shows that

- Cure rate was 80.30 % PTB with in poorly controlled type 2 DM and 85.29 % was in PTB with well controlled type 2DM .
- Failure rate was 19.69 % in PTB with poorly control type 2 DM and 14.7 % in PTB with well controlled type 2 DM.

Discussion

The prevalence of PTB with poor control diabetic increased with age with male predominance which could be because male patients in the study similar tothe study by Kishore B et al[8], Lin S et al[9] and by Fernandes et al[10]. The abovefindings therefore highlight the importance of good glycemic control in male tubercular patients, specially the elderly.The study revealed higher prevalence of PTB with poor control DM in Muslim patients, which was supported by Jawed et al[11] study in Pakistan on 106 patient found 49% prevalence of PTB with diabetes mellitus. The higher prevalenceof impaired glucose tolerance in Muslim Tuberculosis patients may be due to their peculiar dietary habits, rich in animal fats and cholesterol, poverty and illiteracy.In our study prevalence of PTB with poor control DM in rural areas was more than urban areas similar to the study by Deshmukh et al[12] which showed 42% prevalence in rural areas. This may be attributed to increased contribution of ruralpopulation to total cases, where awareness of disease and level of literacy is low. Our study revealed not only the greaterprevalence of tuberculosis in the lower socioeconomic class but also of PTB with poor control DM as well. This may well be explainedby 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 lead to the poor glycemic control in diabetic patients. It may also lead to the early detection of pulmonary tuberculosis in patients presenting withcough secondary to these addictions. The greater percentage of patients having their weight between 30-45 kg having PTB with poor control diabetes, may be due to malnutrition related diabetes in a developing country like India and delay in starting insulin. This is similar to Fernandez et al[10]study. The radiological lesions severity increased with the duration of diabetes. The majority of our patients with far advancedlesion had diabetes for more than 5 yrs. The study of Ross JD[13] and Tripathy SR et al[14] had found most patients intheir study had diabetes prior to pulmonary tuberculosis by a period ranging from 1-5 years. The most patientswith far advanced lesion, had poor glycemic control, This suggests that as the extent of lesion increases, glycemic control worsens which could be due to fever, protracted inactivity and malnutrition stimulate the stresshormones epinephrine, glucagon, cortisol and growth hormone, which acting synergistically raise the blood sugar level inexcess of 200 mg% Guptan et al[15].Most patients in our study had Bilateral lung involvement, which was further more common in the PTB with poor control diabetic patients supported by Ziskind MM et alstudy[16].The different patterns of lesions in chest x-ray were infiltration, cavity, consolidation, fibrosis and miliary in decreasing order. Lin, Sen, Sun also found that infiltration and cavitation was the most common lung lesion in diabetics[9]. Khanna BK[17] in their study found radiologically more extensive lesion in tubercular diabetics. Fernandez et al[10] in a recent study found mainly cavitatory lesions.

Study	All cases	Cavity	Infiltration
Ross [13]	53%	68%	44%
Tripathy Kar et al [14]	31.03%	75%	60%
Sen T et al [18]	78.60%	54%	45%
Present study 2017	**68%**	**25%**	**47%**

The sputum positivity was more in PTB with poor control DM. The patients with poor control diabetes had delayed sputum conversion. This could be due to malnutrition, lowered general bodyimmunity, impaired cellular response and comparative reduction in serum bactericidal activity of diabetics similar to conclusion from Hadden DR[19], Khanna BK[17] and Rangnath et al[20] in their respective study. Likewise sputum conversion was faster in patients with PTB with well control DM and those with lesser radiological lesions. Though poor control diabetics lagged behind in duration, they ultimately attained sputum conversion in stipulated time 80.43% in PTB with poor control diabetics and 86.36% in PTB with well control diabetics supported by studies of Banu RekhaV.V, et al[21], Kotokey RK et al[6] and Singla R et al[22].Also the radiological conversion was delayed in PTB with poor control DM group. Likewise radiological conversion lagged in thosetaking OHA and those with higher radiological grade. The results were comparable to studies by Kotokey R Ket al[6]and Nissapatorn et al[23].Nausea and vomiting were the most common side effects seen. Withdrawal of therapy was not required in any patient. Thus DOTS was well tolerated in bothgroups.The cure rate was slightly less in PTB with poor control DM with treatment failure rate of 19.69%. comparable to study of Kant L[24]and V Nissapatorn et al[23], supported later by Cox HS et al[25] in their study.

Previous study

Rangnath TS et al[20]	Sputum conversion rate	75.75%
	Cure rate	81%
	Failure rate	19%
V Nissapatorn et al[23] 2004	Sputum conversion after 2 mths	90 %
	Radiological conversion after 2 mths	65%
	Treatment failure	6%

Present Study 2017

Pulmonary tuberculosis		
	Poorly controlled type 2DM (n=66)	Well controlled type 2DM (n=34)
Clinical improvement after 2 month	81.81%	82.35%
Weight gain >5kg	80.30%	85.29%
Improvement of FBS	78.78%	-
Improvement in HbA1C	75.75%	-
Sputum Conversion (at 6 months)	80.30%	86.36%
Radiological conversion (at 6 months)	78.78%	88.23%
Cure rate	80.30%	85.29%
Failure rate	19.69%	14.70%

Conclusion

Treatmentof pulmonary tuberculosis under DOTS is effective and well tolerated in both groups. Poorly controlled diabetic patients have an increased risk of developing Tuberculosis as compared to

well controlled diabetic and also they have relatively higher failure rate with DOTS. Both the diseases affect each other. DM predisposes a person to infection chances to get infection becomes more with poorly control diabetes and infection in turn overwhelms the glycemic control. Effective control of each affects the control of the other Condition.

Funding: Nil
Conflict of interest: Nil

References

1. King H, Aubert RE, Herman WH. Global burden of diabetes1995-2025; prevalence, numerical estimates and projections. Diabetes care. 1998;21:1414.
2. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al: Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care.2003;26(11): 3160–3167.
3. World Health Organization. WHO tuberculosis programme: framework for effective tuberculosis control. World Health Organization.WHO/TB/94.179.1994.
4. Nigam P,Baghel PK, Jain MK, Kandamble S. Efficacy of DOTS tharepy in pulmonary tuberculosis with diabetes mellitus. Int J Med Res Rev. 2014;2(6):585-91.
5. Guptan A, Shah A. Tuberculosis and Diabetes: An Appraisal. Ind J Tub. 2000;47(1): 3-8.
6. Kotokey RK, Bhattacharya DN, Das P, Azad AK. Study of efficacy of DOTS in pulmonary tuberculosis Patients with associated diabetes. Lung india. 2007; 24(2) : 58-60.
7. American Diabetes Association. Glycemic Targets. Diabetes Care.2017 ; 40 (Suppl1): S48-S56. Available from:https://doi.org/10.2337/dc17-S009.
8. Kishore B, Nagrath SP, Mathur KS, Hazra DK, AgrawalBD.Manifest, Chemical and Latent Diabetes in Pulmonary Tuberculosis.JAPI. 1973; 21: 875-81.
9. Lin S, Shen M, Sun Y: Epidemiological characteristics of tuberculosis patients complicated with diabetes in Shanghai. ZonghuaJie He He Hu Xi ZaZhi.1998; 21 (8): 504-6.
10. Fernandez L, Hosker SN, Mesquita AM. Diabetes mellitus in Pulmonary tuberculosis. JAPI. 2004; 45(10): 774-776.
11. Jawad F, Shera AS, Memon R, Ansari G.Glucose intolerance in pulmonary tuberculosis.J Pak Med Assoc. 1995 ;45(9):237-8.
12. Desmukh MD, Master TB, David JC, Tripathi S. Diabetes complicated by Pulmonary tuberculosis. Diabetic Asso Of India.1966;2:97-102.
13. Ross JD. Progress of tuberculous diabetics coming under supervision during years 1963-65 upto 1972. Tubercle.1973; 54(2), 130-40.
14. Tripathy SR, Kar KP, Chakraborty DC, Majumdar AK. Diabetes mellitus and pulmonary tuberculosis–a prospective study. Ind J Tub. 1984;12(3):122–125.
15. Guptan A, Shah A. Tuberculosis and Diabetes:An Appraisal. Ind J Tub. 2000;47(1): 3-8.
16. Ziskind MM, Weill H, Buechner HA, Brown M.Recognition of distinctive radiologic patterns in diffuse pulmonary disease. Arch Intern Med.;114(1):108-112.
17. Khanna BK. Pulmonary tuberculosis diabetes mellitus. JIMA.1968;50(9): 407-14.
18. Sen T, Joshi SR, Udwadia ZF. Tuberculosis and diabetes mellitus: merging epidemics. J Assoc Physicians India. 2009 ;57(1):399-404.
19. Hadden DR. Glucose, Free fatty acids and insulin interrelations in Kwashiorkar and Marasmus. Lancet.1967;(2): 589-593.
20. Rangnath TS, Shivaraj BM.A study on tuberculosis treatment outcome in known diabetic patients treated under Revised National Tuberculosis Control Program in Bengaluru.International Journal of Medicine and Public Health.2015 ; 5 : 32-34.
21. BanuRekhaVV, Balasubramanian R, Swaminathan S, RamachandranR, FathimaR,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(5): 452-458.
22. Singla R, Khan N, Al-Sharif N, Ai-Sayegh MO, Shaikh MA, Osman MM. Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients.Int J Tuberc Lung Dis. 2008 Jan;10(1):74-9.
23. Nissapatorn V, Kuppusamy I, Jamaiah I. Tuberculosis in diabetic patients: a clinical perspective.Southeast Asian J Trop Med Public Health. 2004; 36 (4): 213-220.
24. Kant L. Diabetes mellitus-Tuberculosis: the brewing double trouble. Indian J Tuberc 2003;50(4): 183-4.
25. Cox HS, Morrow M, Deutschmann PW. Long term efficacy of DOTS regimens for tuberculosis: systematic review. BMJ.2008; 336 : 484-487.