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Original Research Article

Comparative Evaluation of Short Course Chemotherapy of Patients of Pulmonary Tuberculosis with and without Diabetes Mellitus

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ABSTRACT

Tuberculosis (TB) remains a major cause of mortality in developing countries and in these countries, diabetes prevalence is increasing rapidly. The rising prevalence of diabetes mellitus in TB-endemic areas may adversely affect TB control. Patients co-affected with both diabetes mellitus (DM) and tuberculosis even have higher rates of treatment failure and death. Given the public health implications of a causal link between diabetes mellitus and tuberculosis, there is a clear need for a systematic assessment of association in the medical literature. The present case-control study was designed to evaluate the clinicoradiological profile and the response of short course chemotherapy in a total of 100 patients of pulmonary tuberculosis (PTB) with and without diabetes mellitus attending the OPD and wards of Department of Respiratory Medicine, MMIMSR, Mullana, Ambala. The results of the study indicated that the patients with TB and diabetes mellitus are older, more likely to have hemoptysis and pulmonary cavitations, be smear positive at diagnosis and remain positive at the end of 1st and 2nd month of treatment. On chest X-ray, pulmonary tuberculosis patients with diabetes mellitus (PTB-DM) had a higher prevalence of cavitary lesion(s) but no statistical significant difference was found between two groups. However, PTB-DM cases may be considered more contagious due to higher prevalence of cavitary lesions compared to those without diabetes mellitus. In conclusion, it has become imperative to use the knowledge available for active case finding, treatment of latent TB and for diagnosis, detection and treatment of diabetes mellitus, thus controlling the global merging epidemics of TB and DM.

Keywords: Pulmonary tuberculosis, Diabetes mellitus, Clinicoradiological profile, short course chemotherapy.

INTRODUCTION

Association of pulmonary tuberculosis (PTB) with diabetes mellitus (DM) has been documented by Susruta in Ayurveda in 600 AD. [1] The term 'diabetic tuberculosis' was coined by Steidl and Sosman (1927) after observing peculiar radiological features prevalent in patients of PTB associated with DM. [2] This association between DM and TB and their synergistic role in causing human disease has been recognized. Diabetes mellitus is a metabolic disorder that weakens the immune system. The frequency and enhanced severity of infections in uncontrolled diabetes were well known

before and after the discovery of insulin. [3] As per recent IDF data, 61.3 million Indians had diabetes in 2011 and this number is projected to rise upto 101.2 million in 2030. [4] Literature suggests that Indians are more insulin resistant than other population groups particularly Caucasians, and develop DM at a much younger age. [5] Westernization of diets, adoption of more sedentary life styles and urbanization are all suggested risk factors in the diabetic epidemic in India. [6]

Tuberculosis (TB) is an infectious disease caused by various strains of mycobacteria, especially *Mycobacterium tuberculosis* and usually attacks the lung. [7] Among infectious diseases, mortality from TB continues to be high. In 2010, TB was the second leading cause of death from an infectious disease worldwide (after HIV which caused an estimated 1.8 million deaths in 2008). [8] Tuberculosis patients are increasingly being diagnosed with diabetes and so are diabetes patients with TB. Diabetes poses substantial risk as evidence suggests that the emerging epidemic of diabetes is fanning the spread of TB. DM accounts for 15% of all cases of tuberculosis and 21% of smear positive TB. [9] Probability of a diabetic to get PTB depends upon the duration of diabetes, severity and control of diabetes and prevalence of PTB among general population. [10] Overall cell-mediated immunity, which is of paramount importance in protection against *Mycobacterium tuberculosis* is grossly impaired in patients with diabetes. [11]

Diabetes Mellitus is known to modify the clinical and radiological manifestations of pulmonary tuberculosis. Steidl and Sosman in 1927 described "Diabetic Tuberculosis" which explained the radiological picture of pulmonary tuberculosis as a wedge- shaped opacity with cavity formation starting in the hilum spreading to periphery to both upper and lower zones. [2] In a number of published comparative studies, chest X-ray images from patients having pulmonary tuberculosis with diabetes mellitus (PTB - DM) have been described as 'atypical' mainly because they frequently involve the lower lung fields, often with cavities. A higher frequency of multi-lobar involvement has also been described among PTB-DM patients. [12] Further, patients with diabetes mellitus, cavitary disease and radiologically extensive disease had longer sputum smear and culture conversion time than the other group. [13] Overall time to sputum culture negativity is prolonged in patients with diabetes as compared to non-diabetics. [14-16] Perusal of literature indicates that there is paucity of information regarding the use of short course chemotherapy regimen among diabetic tuberculosis cases. Keeping in view the magnitude of the problem, the present study was undertaken with the following aims and objectives:

1. To study the clinical and radiological profile of patients of pulmonary tuberculosis with and without diabetes.
2. To study the response of short course chemotherapy in terms of sputum conversion and radiological clearance in patients of pulmonary tuberculosis with and without diabetes.

MATERIALS AND METHODS

The present hospital based case-control study was undertaken in the Department of Respiratory Medicine, Maharishi Markandeshwar Institute of Medical Sciences & Research, Mullana, Ambala. Fifty known diabetic patients diagnosed with pulmonary tuberculosis, as per WHO TB definitions, without any history of rheumatoid arthritis, hypertension, coronary artery disease, renal failure, HIV infection, patients on immunosuppressive drugs, those who had undergone gastrectomy or suspected cases of multidrug-resistant tuberculosis (i.e. Tuberculosis resistance to isoniazid and rifampicin, with or without resistance to other anti tubercular drugs), [17] in the age range of 20 –70 years irrespective of sex attending the OPD and wards of Respiratory Medicine department of M.M Institute of Medical Sciences & Research, Mullana-

Ambala constituted case group (Group I). Equal number of patients with pulmonary tuberculosis but without any associated diabetes was selected to serve as controls (Group II). For data analysis, the patients included in the study were divided into two groups as follows:

Group I: Fifty patients of pulmonary tuberculosis with diabetes mellitus (PTB-DM).

Group II: Fifty patients of pulmonary tuberculosis without diabetes mellitus (PTB).

The difference between group I and II was studied with respect to different demographic and clinical parameters. Acid Fast Bacilli microscopy for diagnosis of pulmonary tuberculosis was carried out using Ziehl - Neelsen Staining Method. [18] Patients were subjected to fasting blood sugar estimation for two consecutive days. Patient was labelled as diabetes when fasting blood sugar level was more than or equal to 126 mg% on more than one occasion. [19] Fasting blood sugar estimation was done by Glucose oxidase-peroxidase (GOD-POD) method. [20] A detailed history regarding the present or past illness was taken and the general physical examination, local examination and the systemic examination was done. Patients were put on new treatment/ re-treatment regimen as per Revised National Tuberculosis Control Programme (RNTCP) guided by WHO TB guidelines. [21] Diabetic patients were started on insulin/ oral hypoglycaemic drugs depending upon fasting blood sugar levels and willingness of patients. Target was to achieve fasting blood sugar level below 126mg%. All patients were followed up every two months in case of new treatment regimen and after two, three and five months in case re- treatment regimen for examination of sputum for acid fast bacilli (AFB) and fasting blood sugar. Sputum conversion was seen at the end of second month in new cases. If sputum examination was positive at the end of two months, sputum smear microscopy was done at end of third month and if it was still positive then microscopy was again repeated during fifth month and during the final month 72 of treatment. Sputum conversion was seen at the end of third month in re- treatment patients to study the response of diabetic tuberculosis to standard chemotherapy. If sputum examination was positive, then the microscopy was repeated at the end of fifth month and during final month of the treatment. At completion of treatment, follow up chest X-ray and sputum examination was done in patients of pulmonary tuberculosis. [22]

STATISTICAL ANALYSIS

Statistical analyses were carried out using SPSS version 20.0 software (IBM, Chicago, USA). Descriptive statistics were calculated for different characteristics of the subjects and the results were presented in terms of their Mean±SD. Independent 't' test was used to compare the means between cases and controls. Pearson's chi-square test / Fisher exact test was used to test the association/difference in proportions between the attributes. One sample 'z' test for proportions has been used to compare between two proportions for the same sample while in case of two different samples, two sample 'z' test for proportion was applied. Minimum 95% confidence interval and p value <0.05 have been considered to be statistical significant.

RESULTS AND OBSERVATIONS

The present study found that the mean age (in years) of patients in group I (PTB- DM) was 48.24±11.21, while it was 41.74±14.88 in case of group II (PTB) patients with the mean difference between the two groups being statistically significant (p <0.05). Out of 100 patients included in the study, there were 59 males and 41 females. In group I, 54% cases were males while 46% females were included. In comparison, Group II (controls) comprised of 64% males and 36% females. The difference between two groups was not statistically significant (p >0.05). Furthermore, while all the patients in group

I as well as group II presented with the clinical symptoms of fever and cough with expectoration, it was found that hemoptysis was a more common symptom in patients of pulmonary tuberculosis (group II) [n=12, 24%] as compared to group I consisting of patients of pulmonary tuberculosis with diabetes mellitus where only 20% patients presented with complaint of hemoptysis. However, the difference was not statistically significant between the two groups (p>0.05).

In an attempt to study the relationship between diabetes mellitus and pulmonary tuberculosis in group I patients, it was revealed that 28 (56%) cases were known diabetic before the diagnosis of pulmonary tuberculosis was made while in rest of 22 (44%) patients, diabetes mellitus and pulmonary tuberculosis were diagnosed simultaneously. In addition, out of 28 cases where diabetes mellitus antedated pulmonary tuberculosis, only 08 (28.6%) cases were controlled diabetics while 20 (71.4%) patients had uncontrolled diabetes. One sample z test for proportions showed that the difference in the proportions between the two groups was highly statistically significant (p <0.001). Amongst 50 patients of group I (PTB-DM), 20 patients (40%) were put on oral hypoglycemic agents (OHA) while 26 (52%) were put on insulin only. Four patients (08%) were put on combination of both OHA & Insulin.

There was no patient in group I (Diabetic group) with mild pulmonary tuberculosis. Patients were having either moderate (n=30) or extended disease (n=20) while in group II (non diabetic group) mild pulmonary tuberculosis was present in 20 (40%) patients. Rest of twenty patients had moderate while 10 had extensive disease as shown in Table I.

Table I: Showing Radiological Features (Extent of Lesion) In Study Patients

EXTENT OF LESION	GROUP I	GROUP II	TOTAL
MILD	0	20	20
MODERATE	30	20	50
EXTENSIVE	20	10	30
Total	50	50	100
Chi square value = 25.3, degrees of freedom = 2, p value = <0.001			

Chi square test revealed that there was a statistically significant difference between the two groups of patients in terms of their extent of lesion (p<0.001). Only two patients in group I comprising of pulmonary tuberculosis with diabetes mellitus patients had right sided involvement of lower zone of lungs. In contrast, no patient of pulmonary tuberculosis (group II) showed lower zone involvement on right side. At the start of treatment, the demonstrable cavitations were present in 68% (n=34) diabetics with tuberculosis patients in group I while in group II of pulmonary tuberculosis patients, the cavitations were present in 60% (n=30) patients. No cavitations were observed in 16 patients of group I and 20 patients of group II. The difference amongst two groups was statistically insignificant (p>0.05).

Table II: Showing Various Anti Tubercular Treatment (ATT) Regimens Used In The Study Patients

REGIMEN USED		GROUP I	GROUP II	Total
CATEGORY I	NEW	37	39	76
CATEGORY II	DEFAULT	02	04	06
	RELAPSE	11	07	18
Total		50	50	100
chi-square value = 0.219 , degrees of freedom = 1, p value = 0.640				

As clear from table II, majority of patients newly diagnosed for TB included in both group I and group II (37 cases and 39 controls) were given Category I anti tubercular treatment (ATT) comprising of four drugs namely Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. A total of 24 patients comprising of 06 defaulters and 18 relapse cases (out of which 13 patients were in group I and 11 patients in group II) were put on Category II anti tubercular treatment (ATT) on the basis of previous history of ATT with addition of injection Streptomycin in combination with the above mentioned four drugs included in Category I.

In an attempt to study the sputum conversion rates among patients included in the study with respect to category of treatment regimen followed for PTB, it was observed that at the end of two month of intensive phase of treatment, out of 37

patients on Cat I in group I (PTB-DM), 30 patients had achieved sputum conversion compared to 36 in group II (PTB) comprising of a total of 39 patients on Cat I (Table III).

Table III: Showing distribution of sputum conversion with respect to category

GROUP	CATEGORY	SPUTUM CONVERSION		TOTAL
		2nd MONTH	3rd MONTH	
Group I (PTB-DM)	CAT I	30	05	35
	CAT II	05	07	12
Group II (PTB)	CAT I	36	03	39
	CAT II	10	01	11
TOTAL		81	16	97
Chi-square value = 5.41, degrees of freedom = 1, p value = 0.021				

Similarly, out of 13 patients on Cat II in group I (PTB-DM), 05 achieved sputum AFB smear conversion at the end of 2nd month as compared to 10 out of 11 patients on Cat II in group II (PTB). At the end of 3rd month of treatment, 05 patients on Cat I in group I (PTB-DM) had achieved sputum conversion compared to 03 in group II (PTB). Similarly, out of 13 patients on Cat II in group I (PTB-DM), 07 achieved sputum AFB smear conversion at the end of 3rd month as compared to only one patient on Cat II in group II (PTB).

Two patients on Cat I in group I (PTB-DM) showed treatment failure with sputum smear positivity even at the end of fifth month of treatment. In addition one patient on Cat II of PTB-DM group also could not achieve sputum smear negativity even at the end treatment. Chi-square test revealed that the difference in the time for sputum conversion among two groups with respect to category of treatment regimen followed was statistically significant ($p < 0.05$). Further, the distribution of sputum conversion status according to the type of diabetic treatment given was studied which depicted that 17 patients put on OHA only, took longer time for sputum conversion out of which 07 had sputum negativity at 2nd month while 10 had sputum smear conversion at 3rd month of treatment (Table IV).

Table IV: Showing distribution of sputum conversion according to the type of diabetic treatment

DIABETIC TREATMENT	SPUTUM CONVERSION		TOTAL
	2nd MONTH	3rd MONTH	
OHA	07	10	17
INSULIN	25	01	26
OHA + INSULIN	03	01	04
TOTAL	35	12	47
Chi-square = 16.3, degrees of freedom = 1, p value = <0.001			

In comparison, patients on insulin were 26 in number. Majority of patients (n=25) on insulin got sputum negative at 2nd month while only one patient took longer time for sputum conversion (at the end of 3rd month). Three patients using both OHA and insulin had sputum conversion by the end of 2nd month, while single patient achieved sputum negativity at the end of 3rd month. Chi-square test revealed that the difference between status of sputum conversion of patients put on different treatment regimens was statistically highly significant ($p < 0.001$)

During the course of the present study, there was appearance of drug induced hepatitis in 02(4%) patients of pulmonary tuberculosis with diabetes mellitus (group I) and only one patient of pulmonary tuberculosis (group II). Drug rashes were observed in 02 patients included in group I while hypoglycemia was noticed in a single patient of the same group.

Table V: Showing treatment outcomes in two groups

REGIMEN USED	GROUP I	GROUP II	TOTAL
6 MONTHS (CAT I)	37 (02 – Treatment Failure, 01 – Default Treatment, 34 – CURED)	39 (39 CURED)	76
9 MONTHS (CAT II)	13 (1 – Treatment Failure, 12 – CURED)	11 (11 CURED)	24
Total	50	50	100
Chi-square value = 0.220 , degrees of freedom = 1, p value = 0.639			

As shown in Table V, 37 (74%) patients in group I were given six months regimen (Category I) while 13 (26%) patients were given nine months treatment (Category II). In contrast, 39(78%) patients in group II were put on six months treatment regimen (Category I) and 11 (22%) patients were given nine months regimen of treatment (Category II). Out of 37 patients on Cat I in group I, 34 patients showed improvement meaning thereby that their sputum for acid fast bacilli was negative, were completely asymptomatic and X-ray showed marked improvement while 2 patients had treatment failure with their sputum for acid fast bacilli being positive even after six months treatment because patients showed non compliance to the diabetic treatment prescribed i.e. insulin administration in spite of high blood sugar levels and one case was defaulter. Out of 13 patients on nine months treatment regimen in group I, 12 were completely cured and 01 patient had treatment failure as he was not taking proper and regular ATT. In contrast, all the patients in group II whether on Cat I or Cat II showed complete resolution of symptoms and lesions on X-ray. Chi-square test revealed statistically insignificant difference among the patients cured ($p>0.05$).

DISCUSSION

Tuberculosis (TB) remains a major global public health problem. Every year, 8.8 million people develop active TB and 1.6 million people die from this highly contagious infection that usually affects the lung; one-third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*. Diabetes mellitus (DM) is a well known risk factor for TB. Globally, there is increase in cases of type 2 DM and greatest increase in cases occurs in developing countries, where TB is highly endemic. The incidence of pulmonary tuberculosis (PTB) has been reported to be higher in diabetics than non-diabetics. Epidemiological studies have elucidated an association between DM and the development of TB disease. DM is known to modify the clinical features and radiological manifestations of PTB. Among patients afflicted with both TB and DM, diabetes is reported to be associated with poor TB treatment outcome. However, there is scarce information about the influence of diabetes on sputum conversion rates and treatment outcomes of PTB patients. The present study was aimed to study the clinico-radiological profile and the response of short course chemotherapy in terms of sputum conversion and radiological clearance in fifty patients of pulmonary tuberculosis with diabetes (PTB-DM) and fifty patients of pulmonary tuberculosis without diabetes.

In our study, majority of patients (n=17, 34%) in group I (PTB-DM) belonged to the age group of 41-50 years. Most frequent age group affected in group II (PTB) was 20-30 years which had 16 patients (32%, $p<0.05$) which clearly shows that pulmonary tuberculosis is a disease of young adults but in diabetics, it occurs most often in middle age. This has also been reported by other investigators. [23-26] The possible reason for this may be due to a compromised host's immunity that increased susceptibility to TB due to ageing. The mean ± SD age of PTB-DM group and PTB group was 48.24 ± 11.21 and 41.74 ± 14.88 years, respectively ($p<0.05$). Similar findings have been observed by Baghaei et al and Vishwanathan et al. [27, 28] This may be due to the fact that more patients are reaching the later decades where the incidence of diabetes increases. Indeed the onset of reactivation might well peak coincidentally with type 2 diabetes. The occurrence of diabetes in a patient whose TB disease is latent might well precipitate breakdown of latent infection and emergence of clinical disease.

Male predominance was observed in both group I as well as group II included in the study. A number of authors have shown increased incidence of disease in males as compared to females [23,29,30] which may be due to the fact that in most countries young

men usually have more social and labour activities than women thus favouring the transmission of the disease and/or to higher frequency of under-diagnosis in women primarily resulting from fewer opportunities among women of obtaining medical services. It might also be an accumulative effect of other risk factors such as smoking, tobacco use and alcohol consumption, which impact both TB and DM. Another reason could be the younger age of women than man since increasing age emerged as a significant risk factor for diabetes.

The most common presenting symptoms were fever and cough with expectoration in both the groups; however the prevalence of hemoptysis was higher among non-diabetic tubercular patients (Group II) [24% vs 20%]. The results were comparable with the study by Patel et al and Baghaei et al. [3, 27] Among the twenty eight cases of PTB-DM (group I) where DM was diagnosed before TB, majority of patients (n=20, 71.4%) were having uncontrolled diabetes taking inadequate treatment for the control of DM without checking their blood or urine sugar level and without any adherence to diabetic diet. 28.6% cases were on regular medications and thus have controlled blood sugar levels. The difference in proportions between the two groups of patients with controlled and uncontrolled diabetes was statistically highly significant ($p < 0.001$). So it is quite logical to conclude that tuberculosis is a complication of not only long – standing diabetes but also of inadequately treated/uncontrolled diabetes. This supports the old dictum that tuberculosis is a penalty for uncontrolled diabetes.

In an attempt to study the radiological features of patients included in the study, the radiological data was categorized as mild, moderate or extensive involvement. Mild involvement was defined as slight involvement of one or both lungs but in no more than one zone. If several zones in one or both lungs were involved but intact areas were present between the involved areas, the involvement was considered moderate. Otherwise, the involvement was considered as extensive. Upper lobe involvement with or without cavitary lesion(s) on chest X-ray was defined as typical pulmonary involvement. Every other radiological presentation was classified as atypical pulmonary involvement. With respect to extent of disease, none of the patients in PTB-DM group (group I) was found to have minimal disease on chest X-ray in contrast to PTB group (group II) where 20 patients (40%) presented with minimal disease. There was statistically significant difference among patients included in both groups in terms of the radiological extent of lesion ($p < 0.05$). Moderate and extensive involvements were observed in 30 (60%) and 20 (40%) patients in the case group and in 20 (40%) and 10 (20%) patients in the control group (respectively). A study conducted by Baghaei et al has observed mild, moderate and extensive involvement in 21 (46.7%), 14 (31.1%) and 10 (22.2%) patients in TB-DM group and in 32 (35.2%), 35 (38.5%) and 24 (26.4%) patients in TB group, respectively which is comparable to our findings. [27] This may be attributable to the fact that the patients were either poorly controlled diabetics or they were unaware of underline diabetes with which they were suffering from. So when tuberculosis sets in, its diagnosis gets delayed because of masking effect of diabetes mellitus or the symptoms are ascribed to poorly controlled diabetes or recurrent upper respiratory catarrh which the diabetics usually suffer from.

There was higher frequency of cavitary lesion(s) on chest X-ray in PTB-DM group (Group I) as compared to PTB group (Group II). 68% of the cases in group I had cavitary lesions while 60% was reported in non-diabetic controls. The difference between the two groups was statistically insignificant which is consistent with studies done by number of other investigators. [23,31,32] Considering the crucial immunological response to the occurrence of cavitary lesion(s) in the lungs,

several studies document phagocyte and cell mediated immunity dysfunction in diabetes mellitus which could explain our findings. [33, 34]

All the patients included in the two groups (PTB-DM and PTB) were given modern first line anti tubercular drugs in various combinations. The disease classification, treatment protocol and evaluation of treatment outcome were defined as per standard guidelines. [35] Majority of new patients included in both group I and II (37 cases and 39 controls) were treated with category I ATT regimen consisting of a two month intensive phase of four drugs (HRZE), followed by a four month continuation phase with HR. A total of 24 retreatment cases comprising of 06 defaulters and 18 relapse cases (out of which 13 patients were in group I and 11 patients in group II) who had previous history of ATT, were put on an intensive phase with five drugs (HRZES) for three months (with S for first two months only), followed by a five month continuation phase of HRE i.e. category II ATT regimen.

The relative risk of developing sputum positive PTB is up to five times higher in diabetics. [14] Sputum smear and culture conversion are important indicators for the infectivity of the patient and effectiveness of the treatment. So in the present study, sputum conversion rates were analyzed both among new and re-treatment cases included in both group I and group II. It was found that at the end of two months intensive phase of treatment, 60% patients in PTB-DM group (on Cat I regimen) had achieved sputum conversion as compared to 72% in PTB group. Among patients on Cat II regimen in both groups, 10% patients in group I (PTB-DM) became sputum negative in comparison to 20% in group II (PTB). By the end of three months of treatment, a total of 70 % patients (n=35) in PTB-DM group on Cat I regimen attained sputum AFB smear conversion compared to 78% (n=39) in PTB group. Among Cat II regimen following patients, a total of 24% patients (n=12) in group I while 22% (n=11) in group II achieved sputum conversion by the end of three months of treatment. It was observed that at the end of second month of treatment, sputum conversion rates were significantly lower in diabetics compared to non-diabetics ($p<0.05$). At the end of three months of treatment, the sputum conversion rates among PTB-DM patients were more than that among PTB patients. These results were similar to the findings of studies done by other authors. [36,37] Mean time for sputum conversion in group I (PTB-DM) was 6.4 weeks as compared to 5.6 weeks in group II (PTB). Overall time to sputum culture negativity is prolonged in persons with diabetes mellitus as compared to non-diabetics. [38] Latter is postulated to be due to higher mycobacterial burden in diabetics as compared to controls. [39]

On studying the distribution of sputum conversion status according to the type of diabetic treatment given, it was observed that only the patients who were put on OHA (n=17, 34%) took longer time for sputum conversion out of which 07 attained sputum negativity at second month of ATT treatment while 10 had sputum conversion at three month of ATT. 50% of patients who were put on insulin got sputum negative at second month while 01 patient attained sputum conversion at three month of treatment. Three patients were put on combination of insulin and OHA, who achieved sputum conversion at the end of two months while single patient became sputum negative at the end of third month of ATT. The difference between the sputum conversion status among patients of PTB-DM group put on different diabetic treatment was statistically highly significant ($p<0.001$). Almost all OHA are metabolized by cytochrome P450 systems in the liver. Rifampicin, which is the main anchor drug in the management of tuberculosis, is a powerful inducer of all the P450 systems, including CYP3A4 (where most drugs are metabolized). Due to this inducer effect, there is substantial reduction in the concentrations of sulfonylureas, thiazolidinediones and the newer

hypoglycemic drugs, thus worsening the glycemic control, which in turn impairs the ability to meet challenge of the pathogen i.e. *Mycobacterium tuberculosis.* [40] Thus close monitoring of glycemic control is required during TB treatment among diabetics. Overall experts advocate use of insulin due to its anabolic action apart from lowering the pill burden, improving appetite and promoting weight gain during the first intensive phase of TB management with co-existing DM followed by OHA in the maintenance phase of TB treatment.

As far complications of anti-tubercular drugs are concerned, only two cases (04%) developed hepatitis in group I (PTB-DM) and one case (02%) in group II (PTB). The incidence of isoniazid induced hepatitis was 02% whereas it was 01% in case of rifampicin and pyrazinamide. The risk of hepatitis is increased when combination of these drugs are used as postulated by Seaton et al. [41] The incidence of hepatotoxicity further increases as the age advances. [42] Since majority of patients in group I are older that may be responsible for slightly greater incidence of hepatotoxicity in group I than that in group II. Drug rashes were observed in only two cases in group I while one patient in PTB-DM group presented with hypoglycemia on one occasion. There is paucity of data regarding the outcome of short course chemotherapy treatment among pulmonary tuberculosis patients with associated diabetes. Some reports suggest adverse effects of diabetes on the treatment outcome of PTB patients with an increased rate of failures, defaults, deaths and relapses. [39,43] A study done by Balasubramanian et al reported that TB treatment outcome amongst TB-DM patients was good compared with TB subjects on treatment. [44] Some studies, on the contrary, showed that the association of the diabetes did not alter the response of pulmonary tuberculosis to treatment. [36,37] Hence, TB treatment outcome among TB-DM patients is still not clear.

An attempt to study the response of short course chemotherapy amongst patients of PTB-DM and PTB was made keeping in view the above facts. It was observed that in PTB-DM group, 37 patients (74%) were put on Cat I regimen while 13 patients (26%) were on Cat II regimen for 09 months. Out of 37 patients on Cat I, 34 patients (91.8%) were declared cured on the basis of sputum AFB grading, symptomatology and X-ray improvement. Two (5.4%) patients had treatment failure because patients showed non compliance to the diabetic treatment prescribed i.e. insulin administration in spite of high blood sugar levels and one patient (2.8%) defaulted the treatment. Out of 13 patients on 09 month treatment regimen in PTB-DM group, 12 (92.3%) were cured while one patient (7.7%) had treatment failure as he was not taking proper and regular ATT. Overall, the cure rate amongst PTB-DM patients was 92% with 06% of failure and 02% of default rate. Similar results were reported by Alisjahbana et al and Jindani et al. [45,46] In control group (PTB group), all the patients whether on Cat I or Cat II treatment regimen showed favorable treatment outcome. These findings can be explained by non–compliance of PTB-DM patients to treatment, poor glycemic control and lack of non-specific antibody production due to deficiency in innate and adaptive immune mechanism amongst subjects with diabetes. These may be facilitating factors for resurgence of past infections and incidence of new tuberculosis cases among DM subjects. Drug resistance leading to lower bacteriological response is another strong determinant of treatment failure in diabetic patients with TB. Prospective studies are needed to explore the underlying mechanisms for the different response to treatment in PTB-DM patients.

CONCLUSION

All the newly diagnosed pulmonary tuberculosis patients should be screened for diabetes by checking fasting and postprandial blood sugar levels on a routine basis. A diagnosis of TB should be considered in diabetes with an abnormal

chest radiograph, in the presence or absence of specific clinical symptoms. Even diabetic patients with respiratory symptoms should be screened for TB. Tight glycemic control should be implemented for diabetic TB patients to initiate early sputum conversion and reduce the infective burden to the community.

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