Effect of type 2 Diabetes mellitus on Presentation and Treatment response of Sputum positive Pulmonary Tuberculosis

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Abstract-
Back ground: Tuberculosis (TB) is a disease of global burden almost 1/3rd of population are affected by Mycobacterium tuberculosis. approximately 9 million each year are newly affected and 2 million die from the disease. Diabetes mellitus (DM) is emerging as an epidemic which increases the risk of development of TB by 3 times. DM will increase the infective forms (sputum positive) of TB there by increasing the no. of patients infected by a source case. DM will affect both clinical presentation and treatment response of pulmonary tuberculosis. Mechanisms for increased development of TB/ increased severity of TB in diabetics are-

- Hyperglycemia favors the growth of organisms in tissues.
- Indirect effects on immune function –
- Decreased activation of macrophages due deposition of lipids in RES.
- Decreased IFN –Gamma levels.
- Altered innate and type 1 cytokine expression.
- An over synthesis of ACTH, vitamin A deficiency, over production of Glycerol.
- On treatment – Pharmacogenteic interactions b/w Rifampicin and diabetic agents and decreased absorption of Rifampicin in patients with diabetes.

Objectives: To compare clinical, microbiological and radiological characteristics of sputum positive Pulmonary Tuberculosis (PTB) in subjects with and without Diabetes mellitus at presentation and during their course of treatment.
Methods: Total of 96 sputum positive PTB subjects admitted were divided into two groups based on whether they had DM or not, consisting of 32 subjects in group with DM and 64 in group without DM. their clinical characteristics were noted at presentation and compared in two groups. Sputum and chest xray severity were compared at presentation and both groups were followed up during their treatment course which consists of daily Anti tubercular drugs (ATT), Isoniazid, Rifampicin, Ethambutol, Pyrazinamide. Response to treatment was noted in both the groups.
Results: Subjects with DM were older than subjects without DM. In both groups 75% were males. Clinical characteristics like fever, cough and breathlessness were similar in both the groups at presentation. Sputum severity was more in patients with DM at presentation. Chest xray severity was similar in both groups at presentation, lower zone involvement is more in subjects with DM 62.5% of patients with DM and 34.4% of patients without DM. At 2 months sputum smear is positive in 12.5% of patients with DM and 9.4% of subjects without DM. Chest xray was far advanced in grade in 37.5% of patients with DM and 18.8% of patients without DM. 31.2% of subjects were continued on intensive phase treatment in subjects with DM and 9.4% subjects without DM. At the end of 6 months sputum was not available in 62.5% of patients with DM and 71.9% of patients without DM. cxr grading was similar in both the groups, xray normalized in 37.5% of patients with DM and 48.4% of subjects without DM. 31.25% of patients were still continued on treatment in group with DM and 10.9% in subjects without DM.
Conclusion: No significant difference in clinical presentation in two groups at presentation. Lower zone involvement is more in patients with DM and sputum conversion is late in patients with DM requiring longer duration of treatment compared to subjects without DM.

Index Terms- Mycobacterium tuberculosis, Tuberculosis, Diabetes Mellitus, Anti tubercular drugs.

I. INTRODUCTION

Tuberculosis (TB) is one of the infectious diseases most common worldwide. Tuberculosis continues to be a major global health problem. It remains a major source of morbidity and mortality throughout the world; one-third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*. Current TB control measures what we have focuses on the detection and treatment of those with infectious forms of the disease and to prevent further transmission of the organisms.(1) Despite of the enormous success of this strategy in control of tuberculosis, the incidence of TB is declining slowly globally, at less than 2.2% annually.(2) The research community is working for an effective strategy for prevention of Tuberculosis for several decades. Current preventive strategies against TB lowered the incidence but the problem is still there. Therefore the focus of research has now shifted to the previously untargeted risk factors involved in the spread of TB. One such factor is diabetes mellitus (DM).The global burden of DM is rising; the prevalence is estimated to reach 438 million by 2030, and more than 80% of the adult cases will be in newly developed or developing countries. Diabetes mellitus (DM) is becoming a global epidemic and India.DM increased the risk of acquiring TB by 2-3 times, and is also risk factor for poor treatment outcomes of TB.A 52% increase in diabetes prevalence recorded over the

last 3 years in the 22 highest TB burden countries is thought to be responsible for a rise in diabetes-associated TB cases from 10% in 2010 to 15% in 2013. It is therefore important to address the global diabetes epidemic in order to help improve TB prevention and optimize clinical care for people with TB/diabetes co-morbidity.(3)The diagnosis of Diabetes implies death sentence with in five years before the discovery of insulin and the cause of death is usually infection, mostly Tuberculosis.(4) TB occurs in an increasing frequency among diabetics and appears to aggravate Diabetes, with patients requiring higher doses of drugs either insulin/ oral hypoglycemic for glycemic control. With the advent of effective AntiTubercular drugs and hypoglycemic agents, the prognosis of pulmonary tuberculosis complicated by diabetes is not as grave as it was in the past. DM causes dysfunction of the immune system thereby can increase the susceptibility to various infections including TB. DM also affects the pulmonary physiologic functions.(5) At the same time, TB can also increase the blood glucose levels and trigger "latent diabetes" or be a factor in its decompensation. DM is known to modify the clinical features of pulmonary tuberculosis.(6) The radiological involvement may also be different in diabetics with higher rate of lower field involvement first described by Sosman and Steidl(7) and thus leading to misdiagnosis of Tuberculosis. The Ant tubercular drugs like Rifampicin and Pyrazinamide can influence the glycemic control and conversely DM can also have negative effect on TB treatment.(8) DM has been associated with increased risk of treatment failure and relapse in TB patients as mentioned by several studies.(9) Experts have raised concern about the merging epidemics of tuberculosis and diabetes particularly in the low to medium income countries like India and China that have the highest burden of TB in the world, and are experiencing the fastest increase in the prevalence of DM. There is good evidence that DM makes a substantial contribution to TB incidence. The huge prevalence of DM in India, may be contributing to the increasing prevalence of TB. This study looks at the link between these two merging epidemics.

II. MATERIALS AND METHODS

The present study was conducted from October 2012 – September 2014, in the inpatients admitted in Kasturba hospital, Manipal after obtaining institutional ethical committee clearance (IEC 396/2012).

Study method: Prospective cohort study.

Sample size: 32 in patients with DM group and 64 in patients without DM group. Sample size was calculated based on following formula:

$$n=\frac{\left[z_{1-\alpha/2}\sqrt{2\bar{P}(1-\bar{P})}+z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right]^2}{(P_1-P_2)^2}$$

P_2- Proportion of disease (incidence) present in the unexposed group.

P_1-Proportion of disease (incidence) present in the exposed group.

$$P_1=(RR)P_2\quad \bar{P}=\frac{P_1+P_2}{2}$$

RR – Anticipated Relative Risk.

α- Significance level (0.05), $1-\beta$ – Power of the study (80%).

N=26 per group with RR of 2.

(Minimum sample size in each group should be 22).

We have taken in 1:2 ratio for patients with DM and without DM, 32 patients were taken in DM group and 64 patients in patients without DM group. All newly detected sputum positive pulmonary Tuberculosis patients during our study period selected and screened them for diabetes (RBS, FBS, PPBS or HbA1C), presence or absence of diabetes was by ADA 2012 criteria[110] and divided them into two groups whether they have diabetes or not.

They have been selected into the study after informed consent after fulfilling inclusion and exclusion criteria

Inclusion criteria:

1. Age: more than 18 years.
2. Newly diagnosed sputum positive pulmonary tuberculosis patients with and without DM.

Exclusion criteria:

- Other forms of tuberculosis – including sputum negative TB.
- Retroviral disease and other immunosuppressive diseases, patients on steroids.
- Cirrhosis of liver,
- Patients who cannot be followed up during their treatment period,
- Not on regular treatment – defaulters &MDR TB.

Their clinical details at presentation (symptoms, history and examination) were noted and were analyzed as typical for tuberculosis or not. 6 classical symptoms were taken as typical for tuberculosis and for each patient Symptom Score was calculated based on number of these 6 symptoms that patient presented with

Symptom Score:

1. Cough
2. Expectoration
3. Breathlessness
4. Fever
5. Weight loss
6. Hemoptysis

Other symptoms were taken as atypical symptoms like easy fatigability, chest pain not typical of pleuritic type, vomiting. At the time of admission based on patients ability to perform daily living activities Karnfosky performance score was calculated for each patient.[111]

Table 1: Karnofsky Performance scoring

• Able to carry on normal activity and to work • No special care needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease

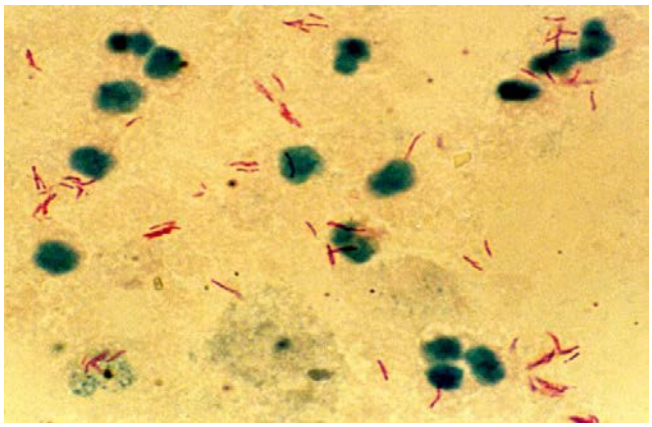
• Unable to work • Able to live at home and care for most personal needs • Varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most of own personal needs
	50	Requires considerable assistance and frequent medical care
• Unable to care for self • Requires equivalent of institutional or hospital care • Disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal processes progressing
	0	Dead

Their body weight and height were measured and BMI was calculated.

Confirmation of Tuberculosis was done by Sputum smear microscopy (AFB staining by Ziehl-Neelssen method) and microscopic smear was graded into 3 categories based on severity.[112]

1. + - 1-9 bacilli per slide
2. ++ - 10 or more bacilli per slide
3. +++ (numerous) - 10 or more bacilli in most oil immersion fields.

Figure 1: Zeihl-neelssen staining – AFB smear



Chest x-ray was analysed noted the presence or absence of cavities, number and location of cavities, infiltrates or air space opaicites, consolidation, hilar enlargement, fibrosis, pleural effusion, pneumothorax and for any other findings.

Cxr was graded into minimal, moderately advanced and far advanced categories as per national Tuberculosis association USA 1961 guidelines.[112]

Table 2: Grading of severity of pulmonary TB active disease in the CXR

1. **Minimal** -Slight to moderate density, no cavities, small part of one\both lungs, total extent not > volume of lung one side the space above 2nd chondrosternal junctions and T4\T5
2. **Moderately advanced** -Slight to moderate density lesions one\both lungs. Total extent <disseminated lesions total volume of one lung or equaling in both lungs or dense and confluent lesions 1\3 the volume of one lung, total diameter of cavities if present <4 cm.
3. **Far Advanced** -More extensive than moderate.

Comparision of clinical, microbiological and radiological parameters between patients with diabetes and without diabetes was done at presentation.

All the patients have been started on treatment with 4 first line Anti Tubercular Drugs.

1. Isoniazid
2. Rifampicin
3. Ethambutol
4. Pyrazinamide.

For diabetes patients who were known diabetic or newly detected diabetic were put on Antidiabetic medications (Oral Hypoglycemic agents or Insulin or Both) as per clinician decicsion and patient response along with 4 drug ATT mentioned as above.

Patients have been followed up during their treatment period and they were evaluated at 2months and 6 months period in clinical microbiological and radiological aspects.

Their symptoms were analysed at follow up and were graded as per symptom score mentioned above.

Sputum smear analysis was done for patients whoever can give sputum for examination and analysed as positive for AFB or not.

Chest x-ray at each follow up was done and graded as mentioned above.

Treatment which they were on were noted during follow up (whether they were on intensive phase or continuation phase or completed both and stopped treatment).

Continuation phase was with 2 drugs – Isoniazid and Rifampicin.

Patients with and without DM were compared in clinical improvement, sputum conversion and radiological improvement at each visit and treatment differences between the two groups was observed and analyzed.

Statistical analysis:

- Mean was calculated for continuous variables which were normally distributed.
- Median was calculated for continuous variables which were non-normally distributed.
- Pearson's Chi square analysis was used for categorical variables and Fischer's exact test when necessary.
- Independent sample Student t test was used for normally distributed continuous variables.

- Mann Whitney U test was used for non normally distributed continuous variables.
- Data was analyzed using SPSS 20.

III. RESULTS

A. Baseline characteristics:

Of 96 patients, who were pulmonary tuberculosis proven by sputum positivity, 32 were with diabetes mellitus and 64 were without diabetes mellitus.

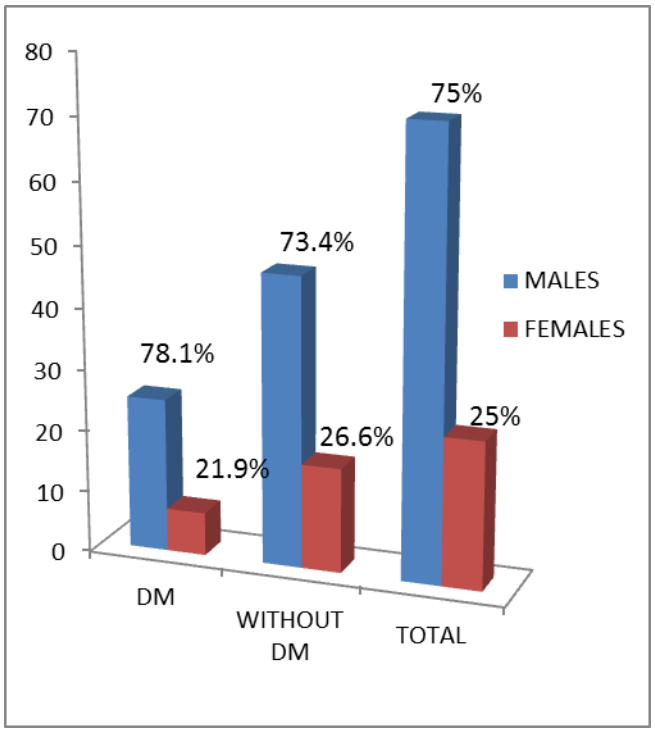
Mean age distribution is around 16 years later in diabetics than in non-diabetics.

Males are more in number than females with no gender difference in presentation among two groups of patients observed.

Table 3: Age Distribution among two groups

	N	Mean	SD	Min.	Max.
PTB+DM	32	54.63	9.8	36	85
PTB	64	37.95	15.6	17	75

Figure 2: Sex distribution



71.9% of patients in PTB group were from village compared to 53.1% in patients with DM, significant number of people were from city in patients, but not statistically significant.

Patients with Diabetes Mellitus presented after long duration of symptoms (>6 weeks duration) with significant P value (0.015).

Table 4: Duration of symptoms

IN Weeks	PTB+DM	PTB
<4 weeks	12(37.5%)	14(21.9%)
4-6 weeks	5(15.6%)	29(45.3%)
>6 weeks	15(46.9%)	21(32.8%)

Clinical characteristics at presentation were similar in both the groups. No significant difference between the two groups among presentation, but patients with DM presented with more atypical symptoms for tuberculosis like easy fatigability and chest pain (non pleuritic) which was statistically significant (P value -0.035). Weight loss was more in patients without DM than in patients with DM, this is in contradictory to what we expect.

Table 5: Symptoms at presentation

Symptom	PTB+DM	PTB	p value
Cough	31(96.9%)	63(98.4%)	
Expectoration	29(90.6%)	60(93.8%)	
Breathlessness	6(18.8%)	8(12.5%)	
Hemoptysis	4(12.5%)	6(9.4%)	
Fever	24(75%)	54(84.4%)	
Weight loss	15(46.9%)	35(54.7%)	
Symptom score(>4)	14(43.8%)	35(54.7%)	0.3
Karnofsky scoring(<80)	9(28.1%)	15(23.4%)	0.6
Atypical symptoms	11(34%)	10(15.2%)	0.035

Baseline characteristics were comparable in both groups.

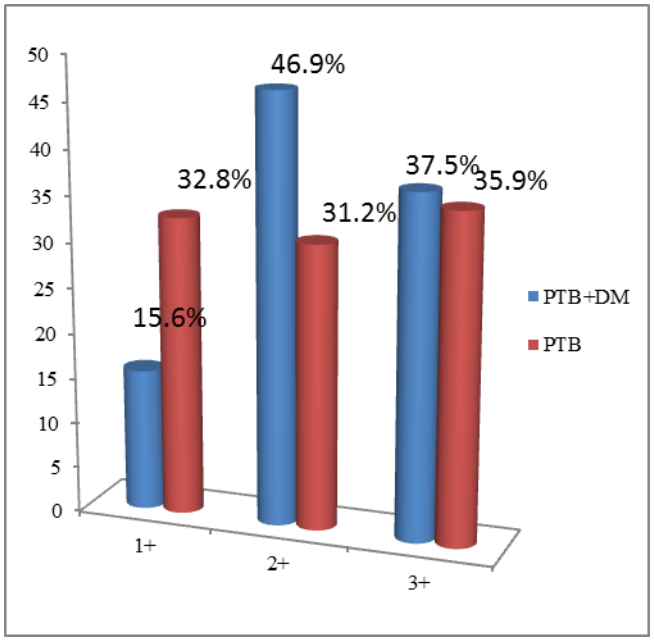
Table 6: Baseline characteristics

	PTB+DM(SD)	PTB(SD)
BMI	21.65(2.9)	18.11(2.86)
HB	12.4(1.6)	11.8(1.93)
ESR	53.39(20.37)	51.22(23.03)
TC	9764.52(3613.54)	10254.69(3360.83)
FBS	191.13(64.61)	89.63(12.33)
GLYCO HB	10.54 (2.23)	5.60(0.33)

Mean HBA1C in DM group at presentation was 10.54 and in patients without DM group was 5.6.Mean HB was more in patients with DM group than in patients without DM. Mean BMI was more for patients with DM than in other group.

Sputum severity grading based on sputum microscopy by Zeihll-Neelsen method was similar in both the groups at presentation with p value of 0.168 which was not significant statistically. No significant difference between the two groups in sputum severity at presentation, less severe (1+) in 32.8% of patients in PTB group without DM compared to 15.2% in DM group. Sputum was 3+ in 37.5% of patients in DM group and 35.9% in group of patients without DM.

Figure 3: Sputum severity at presentation



Radiological findings:

Grade of x-ray at presentation: No significant difference in severity of X-ray at presentation between the two groups. Far advanced is slightly more in patients with DM. Xray at presentation was Minimal 12.5% of patients with DM and 14.1% of patients without DM, Moderately advanced in 31.2% with DM and 35.9% of patients without DM and Far advanced in 56.2% of patients with DM and 50% of patients without DM.

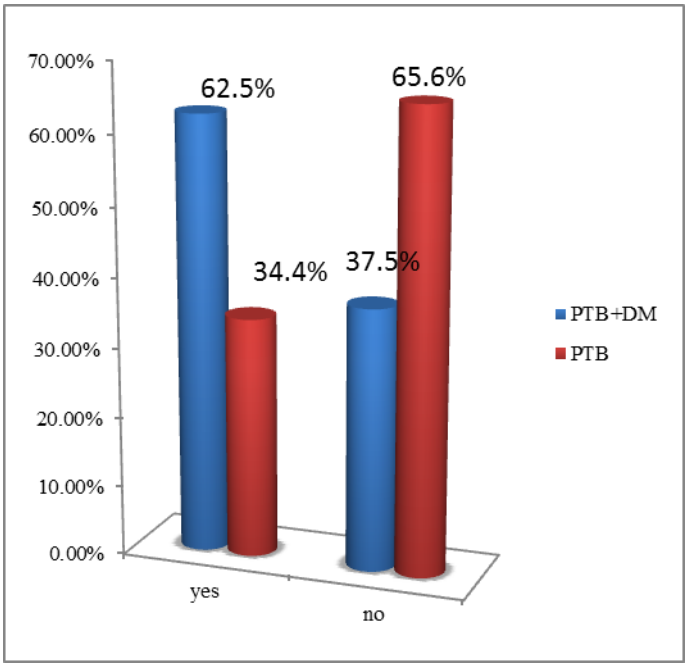
Table 7: Grade of X-ray:

Grade	PTB+DM	PTB
Minimal	4(12.5%)	9(14.1%)
Moderately Advanced	10(31.2%)	23(35.9%)
Far Advanced	18(56.2%)	32(50%)

Fisher Exact test was used. P value of 0.87.

No difference between upper zone involvement in two groups, but patients with DM had more number of lower zone involvement. Lower zone involvement is more in patients with DM than in patients without DM which was statistically significant (p value of 0.009). No significant difference between the two groups in cavities except slightly higher in patients with DM, present in 37.5% of patients with DM and 35.9% of patients without DM.

Figure 4: Lower zone involvement



No difference in other features of X-ray presentation in both groups.

Table 8: Other x-ray characteristics

Presentation	PTB+DM	PTB
Pleural effusion	1 (3.1%)	1(1.6%)
Pneumo thorax	0(0%)	1(1.6%)
Consolidation	11 (34.3%)	18 (28.12%)
Bronchiectasis	2 (6.1%)	1 (1.6%)
Lung abscess	1 (3.1%)	0(0%)
Miliary	1 (3.1%)	2 (3.1%)

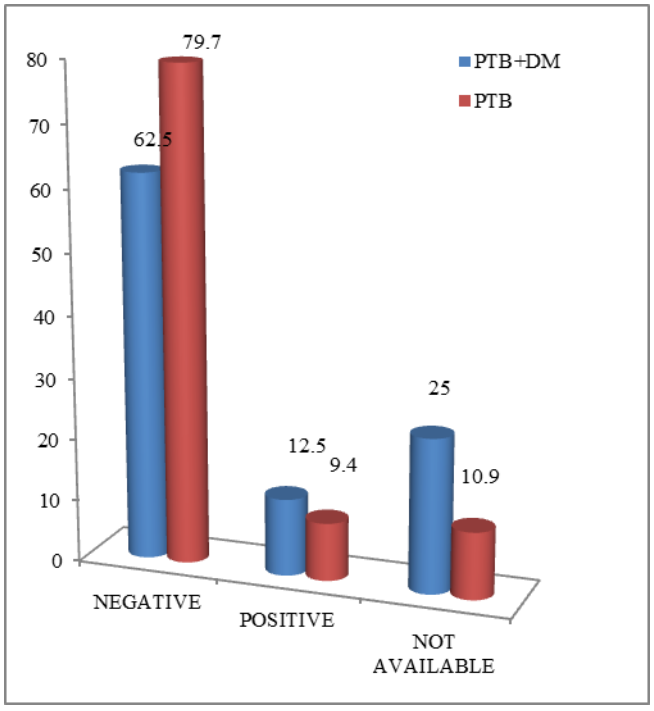
At the end of 2 months:

Significant number of people (40.6%) in diabetes group still have symptoms compared with the other group without diabetes

(20.3%) at the end of 2 months, which are cough and expectoration in most of the patients (P value – 0.045).

Sputum microscopy was still positive for AFB in 12.5% of patients with DM and 9.4% of patients without DM. Sputum conversion at the end of 2 months was more in tuberculosis patients without diabetes mellitus compared to patients with diabetes mellitus, but it is not statistically significant (P value 0.13).

Figure 5: sputum microscopy at 2 months



X-ray at 2 months:

X-ray was normal at 2 months in 9.4% of patients with DM and 12.5% of patients without DM, still far advanced in 37.5% of patients with DM and only 18.8% of patients without DM.

Improvement of X-ray at 2months was more in patients without DM.

X-ray at the end of 2months is still severe (Far advanced) in more number of patients with Diabetes Mellitus compared to the other group which is statistically significant (P value of 0.046). Cavity was persisting in 3 patients in DM group (9.4%) and 5 patients in without DM group (7.8%) at 2months.

Table 9: X-ray severity at 2 months:

X-ray at 2months	PTB+DM	PTB
Normal, Minimal, Moderately advanced	20(62.5%)	52(81.2%)
Far Advanced	12 (37.5%)	12(18.8%)

Treatment at 2 months:

At the end of 2 months significant number of people with Diabetes mellitus group are still continued to be on intensive regimen (31.2%) compared to the group without Diabetes mellitus (9.4%). (P value was 0.007).

Table 10: Treatment at 2 months

At end of 2months	PTB+DM	PTB
Completed intensive phase	22 (68.8%)	58 (90.6%)
Continued on intensive phase	10(31.2%)	6(9.4%)

Pearson chi square analysis was used. p value was 0.007 – significant.

At the end of 6 months:

Clinical picture at the end of 6 months showed improvement in both the groups; almost all the patients were asymptomatic in both groups except 2 patients. Only 2 patients in diabetes group still have persisting cough and expectoration. One patient is of COPD with recurrent respiratory tract infections, negative for AFB. Other patient turned to be MDR TB.

No significant difference between the two groups in sputum conversion P value – 0.45, positive in 1 patient with DM (3.1%) and none in patients without DM.

X-ray normalized at 6 months in 37.5% of patients with DM and 48.4% of patients without DM. Improvement of X-Ray is more in patients without DM compared to the other group but it is not statistically significant.

Patients without tuberculosis completed treatment by 6 months in most of the patients compared to the patients with diabetes mellitus significantly (P value -0.014). 6 (9.4%) patients developed ATT induced hepatitis in patients without DM and only 1 (3.1%)

IV. DISCUSSION

DEMOGRAPHIC PROFILE:

Present study was conducted from September 2012- august 2014, included 96 patients with sputum smear positive pulmonary tuberculosis, of which 32 were with type 2 Diabetes mellitus (DM) and 64 were without diabetes after fulfilling the inclusion and exclusion criteria.

Mean age of patients with DM was 54.63 years and patients without DM was 37.95, which was statistically significant (P <0.001). This finding is correlating with other studies (6, 10) which also showed significant age difference between the two groups. This can be explained by high prevalence of type 2 DM in older age group.

Present study showed more number of males in both groups with no difference in sex distribution in both groups. Study by Alisjahbana et al (10) also did not show difference between two groups, and Study by Shingla et al (2) also showed more number of males than females. It can be attributed to socio-cultural factors that lead to a higher risk of exposure to

*M.tuberculosis*in men and /or to a under diagnosis in women, primarily due to fewer opportunities among women to obtain medical services (11).

In our study in DM group 53.1% patients belong to rural place and 71.9% in group without DM. This finding is correlating with study by Corona et al (12) which also showed high rural incidence in patients without DM.

AT PRESENTATION:

Duration of symptoms at presentation: In our study more number of patients presented after 6 weeks of onset of symptoms belong to diabetes group 46.9% compared to 32.8% in patients without DM, this can be explained by more number of atypical symptoms in patients with DM which they might attribute to diabetes and thus delay their approach to healthcare center. **Duration of diabetes at presentation:** In our study out of 32 patients, 10 (31.25%) were newly detected diabetes, 10 (31.25%) patients were with >5 years of diabetes, 12 (37.5%) of patients were with <5 years of detection of diabetes. **Clinical profile:** Low grade fever and cough are the most common presenting symptoms which were almost similar in both the groups, correlating with Alisjahbana(10) et al and study done by shingla et al(6). There was no significant difference in two groups in other symptoms at presentation. Restrepo BI et al(13) conducted a study on Type 2 DM and Tuberculosis in United states (Mexico and Texas) which was the first reported large study of the role of Type 2 DM in a population comprising of all patients with TB identified in the control programs both in Texas and Mexico. This study also showed cough and fever were the most common presenting symptoms.

We calculated symptom score based on 6 symptoms typical of tuberculosis, as explained in methodology. In our study symptom score (SS) of >4 was observed in 43.8% of patients with DM and 54.7% of PTB patients without DM. Alisjahbana et al (10) study showed SS>4 in 63.8% of patients with DM and 48.5% of PTB patients without DM. Our study results are conflicting with study by Alisjahbana et al (10), which showed more number of symptoms in patients with DM than in without DM, but our study showed more number of symptoms in PTB patients without DM than in diabetic patients. This could be due to more number of patients in our study with atypical symptoms of tuberculosis. Karnofsky performance score was calculated for each patient based on their ability to carry out self-activities as mentioned in methodology. In our study patients with Karnofsky score (KS) of <80 were 28.1% of patients in DM group and 23.4% in patients without DM group. In study by Alisjahbana et al (10) KS was <80 in 45.7% of patients with DM and 29.4% in patients without DM group. Our study results are correlating with this study.

Sputum microscopy: Sputum microscopy results of our patients at diagnosis in our study showed

1. + in 15.6% of patients with DM and 32.8% of patients without DM,
2. ++ in 46.9% and 31.2% of patients with DM and without DM groups respectively,
3. +++ (numerous AFB) in 37.5% of patients with DM and 35.9% of patients without DM.

This did not show any significant difference between the two groups.

vStudy done by Shingla et al (6) showed numerous AFB in 65.2% of patients with DM and 54.1% of patients without DM, which was statistically significant with p value of 0.008.

Study done by Lalitha et al which showed +++ in 16.7% of patients with DM and 12% of patients without DM (p value of 0.147) which was not significant statistically.

The findings of the above studies are matching with our study.

Sputum severity when compared with control of hyperglycemia, based on GlycoHB, it showed that 90% of patients with severe sputum grade (3+) in patients with DM are poorly controlled DM (GlycoHB>8.0%).

Regarding other baseline characteristics:

- In our study Mean HBA1C in patients with DM was 10.54 and 5.6 in patients without DM. In our study most of the patients 28 of 32 (87.5%) patients with Tuberculosis had HBA1C of >8(uncontrolled diabetes) at presentation and only 4 of 32 (12.5%) had <8 in patients with DM, this finding suggests that Tuberculosis is more prevalent in patients in diabetic with poorly controlled glycaemia.
- Study done by Muhammed and Hassan (14) in 2010, to know the effect of hyperglycemia on tuberculosis included 326 diabetic patients of which 25 proven to have tuberculosis. Their study showed 80% of tuberculosis patients had GlycoHB of >7.0%.This finding of our study matches with the above study; this shows patients with poorly controlled glycaemia have high chances of developing tuberculosis infection.
- Baseline HB was more in patients with DM (Mean of 12.4) than in patients without DM (mean of 11.9), more number of patients without DM have anemia than patients with DM, this finding is correlating with study by Alisjahbana et al(10) which showed HB of 13.8 and 11.1 in patients with DM and without DM respectively. Associated obesity (good nutritional status) in type 2 DM can explain this finding.
- BMI was 21.65 in patients with DM and 18.11 in patients without DM, this is correlating with study by Alisjahbana et al(10) which also showed same finding of low BMI in patients without DM, this also can be explained by associated obesity and Insulin resistance in patients with DM which is contributing to high BMI.
- No difference in number of patients with the habit of smoking were almost equal in both the groups, so effect of smoking on pulmonary tuberculosis was equal in both the groups.
- With regard to drug resistance in our study only 4 of our patients were resistant to one of the first line drugs at presentation, 3 (1 H, 1 R, 1 Z) belong to DM group and 1(to Streptomycin) patient without DM. as the numbers are very small not analyzed. In Alisjahbana et al(10) study showed drug resistance more in patients without DM, Isoniazid resistance in 8.9% of patients with DM and 15.6% of patients without DM. Resistance to Rifampicin in 1.8% of patients with DM and 6.6% in patients without DM.

Regarding the radiological findings:

We have analyzed different radiological presentations in both groups and compared with each other and X-ray was graded

into mild, moderately advanced and far advanced categories as explained in methodology, and compared between two groups.

Our study showed minimal X-ray finding at presentation in 13 patients totally of which 9 (14.1%) patients were in DM group and 4 (12.5%) patients were without DM. Far advanced in 18 (56.2%) of patients with DM and 32 (50%) of patients without DM. There is no difference in Far advanced x-ray in two groups at presentation except slightly more in patients with DM.

Alisjahbana et al (10) study showed far advanced x-ray at presentation in 52.6% of patients with DM and 50.9% of patients without DM, which was not statistically significant. This finding matches with our study.

Our study showed Cavities in 37.5% (15) of patients with DM and 35.9% (16) of patients without DM, out of these 5 patients had multiple cavities, 4 of which belong to patients without DM and only 1 patient with DM had multiple cavities. Study by Qazi et al(17) showed 20% of patients with DM had cavities. Study by Shaik MA et al(18) showed that PTB DM group of patients had significantly higher frequency of cavitary lung lesions compared to PTB without DM group (50.8% versus 39.0%, p=0.005). Study by Wang et al (19) showed 19.2% of patients with DM had cavities and 10% of patients without DM had cavities, which was statistically significant with a P value of 0.015. Study by Alisjahbana et al (10) showed more number of cavities in patients without DM than in patients with DM (40% patients with DM and 52.4% in patients without DM). Study by Carriera et al (20) in Portugal in 2012 also showed more number of cavities in patients without DM than with DM (82.1% in non-diabetic group and 63.4% in diabetic group, which was statistically significant P-0.01). Different studies have contradictory results in this regard, as far as our study is concerned, it showed more numb of cavities in diabetic patients but was not statistically significant.

Significant difference was there between two groups in our study in zone of involvement. Lower zone involvement (which is not typical of Tuberculosis) is present in 20 (62.5%) patients with DM and 22 (34.4%) patients without DM which was statistically significant , mid and lower zone involvement in 22 (68.75%) of patients with DM and 41 (64.06%) of patients without DM. there is more atypical involvement in patients with DM.

Study done by Shaikh MA et al(18), showed PTB DM group of patients had increased frequency of lung lesions confined to lower lung field compared to PTB group (23.5% versus 2.4%, p<10(- 4)), this finding is correlating with our study. Study by Qazi et al (17) showed 54% of lower zone involvement in patients with DM.

Study by Wang et al(19) results are contradictory to the above results, this study showed more number of patients without DM had lower zone involvement (15.2% in patients with DM and 22% in patients without DM), but it was not significant statistically.

Study by Carriera et al (20) also showed significant number of patients with DM had lower zone involvement than patients without DM.

In our study upper zone involvement is present in 50% of patients with DM and 56.2% of patients without DM. Our study showed involvement of right lung more commonly than left lung and bilateral involvement in patients with DM. 50% of the patients had right lung and 25% had left lung involvement. 25% of people showed bilateral involvement. Study by Qazi et al(17) showed right side involvement in 56% of patients, left side in 26% and bilateral in 16% of patients, This findings match with our study results.

AT THE END OF 2 MONTHS:

Clinical improvement: According to symptom score (based on scoring) was 0 in 59.4% (19) of patients with DM and 75% (48) of patients without DM. Score was 2 in 40.6% of patients with DM and 20.3% of patients without DM. This was statistically significant with P value of 0.045. From the above findings of our study, which showed improvement in clinical symptoms in both the groups after starting ATT, but the improvement is more in patients without DM than patients with DM.

Sputum microscopy: At the end of 2 months in our study tested for patients who could provide sputum for testing, some patients were not getting sputum for testing.

Sputum microscopy results at the end of 2 months in our study showed

1. Negative in 62.5% (20) of patients with DM and 79.7% (51) of patients without DM.
2. Positive in 12.5% (4) of patients with DM and 9.4% (6) of patients without DM.
3. Not available for testing in 25% (8) of patients with DM and 10.9% (7) of patients without DM.

Sputum conversion was more in patients without DM, but it was not statistically significant.

Study by Alisjahbana et al (10) showed sputum conversion rates of 71.3% in patients with DM and 84.3% in patients without DM. Sputum microscopy after 2 months of intensive phase was positive in 18.1% of patients without DM and 10% of patients with DM. This was not significant statistically after adjusting for confounding factors (like sputum severity at presentation, x-ray grade at presentation) in their study.

Study by Park et al(21) in Korea on 2011 studied 492 patients out of which 124 were with DM, when compared sputum culture results at 2months 14 patients showed positive at the end of 2 months out of which 8 were with DM and 6 were without DM.

In a meta-analysis by Baker et al (16) published in BMC 2011, showed that 9 studies observed sputum culture conversion at the end of 2 months , out of which 3 studies showed relative risk of <1 for conversion with DM at 2or3 months, while another 6 showed RR>1, with RR ranging from 0.79 -3.25 in different studies. Another study in their analysis found a trend towards increased time to sputum conversion with diabetes (P value-0.09).

Radiological findings: In our study when radiological findings at 2months were compared, improvement was more in patients without DM and patients with DM were still in far advanced x-ray in a comparable number which was statistically significant (P value – 0.046).

Chest x-ray Grading at 2months:

1. Normal in 3 (9.4%) of patients with DM and 8 (12.5%) patients without DM

2. Minimal in 9 (21.8%) of patients with DM and 15 (23.4%) of patients without DM.

3. Moderately advanced in 8 (25%) of patients with DM and 29 (45.3%) of patients without DM.

4. Far advanced in 12 (37.5%) of patients with DM and 12 (18.8%) of patients without DM.

Radiological improvement at 2 months is more in patients without DM, as more patients in DM group were still in far advanced stage radiological who were initially comparable to each other.

Treatment at 2 months: At the end of 2 months some of the patients in both groups completed intensive phase and has been started on continuation phase. Some patients in both groups were continued on continuation phase based on sputum microscopy results if positive or if sputum is not available for testing their treatment continuation in intensive phase has been decided based on x-ray improvement and clinical improvement.

In our study 68.8% of patients with DM were changed to continuation phase and remaining 31.2% of patients were continued on intensive phase. In patients without DM group 90.6% were completed intensive phase of treatment and 9.4% were continued on intensive phase. This was statistically significant with P value of 0.007. More number of patients in our study still required intensive phase treatment at the end of 2 months when compared with patients without DM.

AT THE END OF 6 MONTHS:

Clinical improvement: Clinical picture at the end of 6 months showed improvement in both the groups; almost all the patients were asymptomatic in both groups except 2 patients. Only 2 patients in diabetes group still have persisting cough and expectoration. One patient is of COPD with recurrent respiratory tract infections, negative for AFB. Other patient turned out to be MDR TB.

Sputum microscopy: In our study sputum smear examination was not available for most of the patients, due to patient were not able to give sputum for examination which was the most frequent limitation for sputum sample collection on outpatient basis. In the available samples, sputum microscopy results of the patients there is no difference in both groups.

1. Negative in 11 (34.4%) of patients with DM and 25 (39.1%) of patients without DM.

2. Positive in only one patient in DM group and none in patients without DM.

3. Not available for testing in 22 (62.5%0 of patients with DM and 39 (71.9%) of patients without DM.

It was not compared statistically as it was positive in only one patient.

Alisjahbana et al (10) study showed significant number of positive sputum culture results at the end of 6 months in DM group (22.2%), compared in patients without DM (9.6%) with P value of <0.05, diabetes remained as significant risk factor for sputum conversion even after adjusting for confounding factors with an adjusted OR of 2.69.

Radiological findings:

Chest x-ray at 6 months improved in both the groups.

1. Normal in 37.5% of patients with DM and 48.4% in patients without DM.

2. Minimal in 43.8% of patients with DM and 34.4% of patients without DM.

3. Moderately advanced in 15.6% of patients with DM and 17.2% of patients without DM.

4. Far advanced in 3.1% that is in one patient with DM and none in patients without DM.

Radiological improvement at the end of 6months was more for the group without diabetes mellitus.

Treatment T 6 months: In our study at the end of 6 months, treatment was completed in 68.8% of the patients with DM and 31.2% were still continued on continuation phase and in patients without DM group 89.1% completed treatment and 10.9% were continued on treatment.

Most patients with DM were continued on treatment at the end of 6 months, this was statistically significant with p value of 0.014 and one patient in DM group has been started on 2nd line ATT as he was turned out to be MDR TB during the course of treatment.

Continuation of ATT in patients without DM group can be explained by their ATT induced hepatitis and other risk factors and in patients with DM continuation of drugs might be due to effect of diabetes on ATT drug's efficacy. As DM decreases the absorption and causes lower concentrations of Anti TB drugs particularly Rifampicin(22)

Other conditions during treatment: ATT induce hepatitis in our study was diagnosed in 7 patients, out of which only one patient was with DM and other 6 patients were without DM. according to our study Hepatitis due to ATT was more common in patients without DM. this could be due to associated malnutrition in patients without DM (low BMI In patients without DM), a predisposing factor for ATT induced hepatitis.

V. CONCLUSION

- Patients with DM present at a later age compared to those without DM.
- No significant difference in symptom presentation in both groups at presentation even though atypical symptoms like easy fatigability are more common in DM group which lead to delayed presentation.
- Uncontrolled hyperglycemia is associated with high prevalence of Tuberculosis.
- Significant Lower zone involvement is observed in patients with DM.
- Slightly delayed sputum smear conversion rates at 2months (at the end of intensive phase) in DM group though not significant statistically.
- Most of the Patients with DM required longer duration of intensive and continuation phase.

VI. LIMITATIONS OF OUR STUDY

- Sputum culture for Tuberculosis and sensitivity testing (for MDR) was not included because of financial constraints.
- Sputum smear examination for all the patients was not available at the end of 6 months.

- Not compared between controlled and uncontrolled hyperglycemia, in view of small number of patients in controlled diabetic status.

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