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Original Research

The Impact Of Diabetes On Sputum Conversion In Treatment Of Pulmonary Tuberculosis

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ABSTRACT

Background: India is the world's largest TB epidemic country, with approximately 2-3 million new cases of TB. Diabetes mellitus (DM) is an emerging chronic health condition of developed and developing countries. It increases the risk of developing active TB by a factor of 2–3 compared with normal population. Materials And Methods: Patients with sputum smear positive pulmonary tuberculosis with diabetes mellitus were enrolled for a prospective observational study at GMC Jammu in India. Diagnosis of Diabetes Mellitus was based on the following criteria: Blood Sugar Fasting > 126 mg/dl, Blood Sugar (after 2 hrs during OGTT) > 200mg/dl and HbA1C > 6.5%. Results: Persons with diabetes mellitus (DM) have a 3-fold increased risk of developing tuberculosis. The median age of the Diabetic patients was significantly higher than the non-diabetics. Magee et al reported that TB–DM patients were significantly more likely to be older. After 2 months of treatment, the sputum positivity decreased in both the groups. There were significantly more Diabetics (28%) as compared to non- diabetics for AFB ($P<0.05$). Conclusion: After anti-TB treatment, the sputum positivity decreased in both the diabetics and non-diabetics. However, decrease was less in diabetic patients at 2 months of treatment. Increasing age was an independent risk factor of increased risk of symptoms. Patients having both tuberculosis and DM should be screened for TB in early stages.

Keywords: Diabetes, Sputum Conversion, Pulmonary Tuberculosis.

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INTRODUCTION

Tuberculosis continues to be the most important infectious disease in terms of incidence and mortality. Current estimates suggest that 9 million new cases and 1.5 million deaths have occurred in 2013.[1] India is the world's largest TB epidemic country, with approximately 2-3 million new cases of TB. The incidence rate of TB in India is in the range of 160 to 180 per 100,000 population, which is a disproportionately high burden compared to other developing countries.[2] Several risk factors have played, and will continue to play a role in escalating this public health problem in India. One of the most important of these risk factors the effect of which on TB was underestimated for several years in our country is diabetes mellitus. Diabetes mellitus is a well-known risk factor for TB. It increases the risk of developing active TB by a factor of2–3 compared with normal population [3,4]. Diabetes mellitus (DM) is an emerging chronic health condition of developed and developing countries. In the United States, 23.1% of individuals over 60 years of age are diabetic, and is the seventh leadingcause of

death. In developing countries, the number of individuals with diabetes mellitus is expected to increase from 84 million people in 1995 to 228 million people by *2025*.[5] The synergistic relationship between TB and DM has been creating agrowing concern around the world Recently WHO and the InternationalUnion against TB and Lung Disease (The Union) have acknowledged the need for international guidelines on the joint management and control of TB an DM. The first report of the association between DM and TB was documented by Avicenna (980-1027 AD) over one thousand years ago**.(6)** Since that time, the relationship between diabetes mellitus (DM) and tuberculosis (TB) and the nature of their interaction with regards to co morbidity are largely suggested by numerous epidemiological studies.

Although the definite pathophysiological mechanism of the effect of DM as a predisposing risk factor for TB is unknown, some hypothesesare suggested:[7]

- depressed cellular immunity
- dysfunction of alveolar macrophages
- low levels of interferon gamma
- pulmonary microangiopathy and
- micronutrient deficiency

AIMS: To study the impact of Diabetes Mellitus on sputum conversion in treatment outcome of patients with sputum smear positive pulmonary tuberculosis.

STUDY DESIGN:

The present study entitled "The impact of Diabetes Mellitus on sputum conversion of patients with sputum smear positive pulmonary tuberculosis" at GMC Jammu was a prospective observational study conducted from November 2018 to October 2019.

SELECTION OF PARTICIPANTS:

The study group comprised of patients attending OPD or admitted in ward at GMC, Jammu after fulfilling inclusion and exclusion criteria. All patients with a diagnosis of sputum smear positive pulmonary tuberculosis were enrolled. Thorough history and physical examination was done in all the patients and information collected. Diagnosis of Diabetes Mellitus was based on the following criteria:

- Blood Sugar Fasting > 126 mg/dl
- Blood Sugar (after 2 hrs during OGTT) > 200 mg/dl
- Blood sugar random >200 mg/dl.
- HbA1C > 6.5%

Age and gender-matched controls were enrolled in the study for comparison.

INCLUSION CRITERIA:

(A) CASES:

- Age more than or equal to 18 year
- Sputum positive pulmonary tuberculosis with diabetes mellitus

(B) CONTROLS:

- Age more than or equal to 18 year.
- Sputum positive pulmonary tuberculosis without diabetesmellitus.

EXCLUSION CRITERIA:

- Old treated pulmonary tuberculosis patients
- Smear negative pulmonary tuberculosis
- MDR –TB cases
- Defaulters
- Treatment failure/relapse

RESULTS

A total of 100 patients with sputum positive pulmonary tuberculosis with and without diabetes mellitus were included in our study. After taking history and performing physical examination, information was collected regarding symptoms of tuberculosis. Demographic parameters were noted. Diagnosis was basedupon sputum smear examination in the hospital. Necessary lab investigationswere done.

Table 1: Comparison of age between diabetic and non-diabetic.

distributionin years	Diabetic		Total	P value
	No(n=50)	Yes(n=50)		
<=20	3 (6.00%)	0 (0.00%)	3 (3.00%)	0.0003
21-30	13 (26.00%)	1 (2.00%)	14 (14.00%)	
31-40	12 (24.00%)	5 (10.00%)	17 (17.00%)	
41-50	8 (16.00%)	15 (30.00%)	23 (23.00%)	
51-60	8 (16.00%)	16 (32.00%)	24 (24.00%)	
>60	6 (12.00%)	13 (26.00%)	19 (19.00%)	
Mean ± SD	40.78 ±14.89	53.02 ± 11.24	46.9 ± 14.29	<.0001
Median(IQR)	39(28 - 54)	52(45 - 61)	47.5(37 - 59)	

Among diabetics, there were 74% males and 26% females; and among non- diabetics there were 70% males and 30% females. The gender distribution among the two groups was comparable. (P>0.05)(Table 2)

Table 2: Comparison of gender distribution between diabetic and non-diabetic.

Gender distribution	Diabetic		Total	P value
	No(n=50)	Yes(n=50)		
Female	15 (30.00%)	13 (26.00%)	28 (28.00%)	0.656
Male	35 (70.00%)	37 (74.00%)	72 (72.00%)	
Total	50 (100.00%)	50 (100.00%)	100 (100.00%)	

Pre-treatment, all the patients had sputum positivity for AFB. Majority of thepatients in both the groups had 1+ sputum positivity i.e. 52% Diabetics and 50% non-diabetics. On comparison, there was no statistical significant difference in the sputum positivity between the two groups. (P>0.05) (Table III)

Table III: Comparison of sputum microbial load (3+& 2+) betweendiabetic and non-diabetic.

Sputum microbial load (3+& 2+)	Diabetic		Total	P value
	No(n=50)	Yes(n=50)		
1+	25 (50.00%)	26 (52.00%)	51 (51.00%)	0.077
2+	7 (14.00%)	10 (20.00%)	17 (17.00%)	
3+	0 (0.00%)	4 (8.00%)	4 (4.00%)	
Scanty	18 (36.00%)	10 (20.00%)	28 (28.00%)	
Total	50 (100.00%)	50 (100.00%)	100 (100.00%)	

After 2 months of treatment, the sputum positivity decreased in both the groups. There were only 14(28%) diabetics as compared to 5(10%) non- diabetics with sputum positivity for AFB. On comparison, there was a statistically significant difference in the sputum positivity between the two groups after 2 months of treatment. (P<0.05) (Table IV)

Table IV: Comparison of sputum for AFB after 2 months betweendiabetic and non-diabetic.

Sputum for AFB after 2months	Diabetic		Total	P value
	No(n=50)	Yes(n=50)		
Negative	45 (90.00%)	36 (72.00%)	81 (81.00%)	0.022
Positive	5 (10.00%)	14 (28.00%)	19 (19.00%)	
Total	50 (100.00%)	50 (100.00%)	100 (100.00%)	

After 3 months of treatment, the sputum positivity decreased further in both the groups. There were only 5(10%) diabetics as compared to 1(2%) non- diabetics with sputum positivity for AFB. On comparison, there was no statistically significant difference in the sputum positivity between the two groups after 3 months of treatment. (P>0.05) (Table V)

Table V: Comparison of sputum for AFB after 3 months betweendiabetic and non-diabetic.

Sputum for AFB after 3 months	Diabetic		Total	P value
	No(n=50)	Yes(n=50)		
Negative	49 (98.00%)	45 (90.00%)	94 (94.00%)	0.204
Positive	1 (2.00%)	5 (10.00%)	6 (6.00%)	
Total	50 (100.00%)	50 (100.00%)	100 (100.00%)	

After 5 months of treatment, the sputum positivity decreased further in both the groups. There was only 1(2%) diabetics as compared to 0(0%) non- diabetics with sputum positivity for AFB. On comparison, there was no statistically significant difference in the sputum positivity between the two groups after 5 months of treatment. (P>0.05) (Table VI)

Table VI: Comparison of sputum for AFB after 5 months betweendiabetic and non-diabetic.

Sputum for AFB after 5 months	Diabetic		Total	P value
	No(n=50)	Yes(n=50)		
Negative	50 (100.00%)	49 (98.00%)	99 (99.00%)	1.000
Positive	0 (0.00%)	1 (2.00%)	1 (1.00%)	
Total	50 (100.00%)	50 (100.00%)	100 (100.00%)	

DISCUSSION

Persons with diabetes mellitus (DM) have a 3-fold increased risk of developing tuberculosis. This increased risk has been ascribed to the intracellular nature of TB infection and impaired T-cell-mediated immune response in persons with DM. Increasing rates of obesity and metabolic syndrome have led to an increasing prevalence of DM in many regions ofthe world.[8] Response to anti-TB treatment has been reported to be slower and associated with worse outcomes in patients with both DM and pulmonary TB. Delayed sputum smear and culture conversion after 2 months of therapyand increased treatment failure, relapse, and death in patients with DM beingtreated for TB have been described; however, other studies found no differences in bacteriologic response and TB treatment outcomes comparing persons with and without DM [8,9]. The median age of the Diabetic patients was significantly higher than the non-diabetics (52 v/s 39, P<0.0001) Most of the diabetics were> 40 yearsand non-diabetics were< 40 years. Our findings are at par with previous studies. Dousa *et al* also found that mean age of diabetic patientswas significantly higher than the non-diabetics (47.5 v/s 33.5, P<0.001). Yuan B *et al* also found that diabetics had significantly higher mean age than non-diabetics

(50.59 v/s 41.82 P<0.01).[10] Magee *et al* also reported that TB–DM patients were significantly more likely than those without diabetes to be older.[11] These findings may be related to the fact that Type 2 DM is seen more frequently in the older age group. Among diabetics, there were 74% males and 26% females; and amongnon-diabetics there were 70% males and 30% females. The gender distribution among the two groups was comparable (P>0.05). Similar findings were reported by Dousa *et al* who also noted that number of males were comparable in diabetic versus non-diabetics(85% v/s 80%, P=0.33).[8] Yuan B *et al* also found gender to be similaramong diabetic and non-diabetics (61 men and 13 women, v/s 199 men and 86 women, P>0.50).[10] Consistent findings were reported by Magee *et al* and Sharif NM.[11,12] Monitoring sputum smears and cultures during anti-TB treatment is important to assess the patient's response to therapy. The time until conversion of cultures to negative during anti-TB treatment is used as a predictor of treatment success. DM has been associated with delayed sputumconversion and TB treatment failure.[8] Pre-treatment, all the patients had sputum positivity for AFB. Majority of the patients in both the groups had 1+ sputum positivity i.e. 52% Diabetics and 50% non-diabetics, which means there was no statistical significant difference in the sputum positivity between the two groups (P>0.05). We observed a gradual decrease in sputum positivity after treatment. After 2 months of treatment, the sputum positivity decreased in both the groups. There were significantly more Diabetics (28%) as compared to non- diabetics (10%) with sputum positivity for AFB (P<0.05) after 2 months of treatment. However, after 3 and 5 months of treatment, the sputum positivity was comparable between diabetics and non-diabetics (P>0.05) Similar to our study, Dousa *et al* also observed that the pre- treatment sputum AFB smear grade, a measure of sputum bacillary load, washigher among patients with DM compared with non-diabetic patients (*P* =.02).[8] After 2 months of anti-TB treatment, out of 134 TB patients with DM, 63 (47%) converted their sputum culture to negative compared with 98 (73%) patients without DM (*P*< .0001). Similarly, Yuan B *et al* also found that positive pre-treatment sputum smear was present in significantly more diabetics than non-diabetics.[10] At 2 and 6 months, there were no significant differences in the sputum negative conversion rates between diabetics and non-diabetics (P>0.05); however, at 12 months, significantly less number of diabetics were negative as compared to non-diabetics (P<0.05).Magee *et al* found that more TB–DM patients than TB patients without diabetes had positive cultures at baseline (p < 0.05).[11] After treatment, there was no statistically significant difference in the sputum negative conversion rate between patients with and without T2DM. There also exist studies that reported no correlation between T2DM and the treatment outcomes of TB; Prasad *et al* reported no statistically significant difference in the treatment success rate between the TB patients with/without T2DM (91% vs. 84%, P=0.06).[13] Patients with T2DM often have metabolism disorders, low immunity, and a higher bacterial load, which easily leads to bacterial clearance delays. Meanwhile, elderly patients also tend to have low immunity, decreased drug metabolism, and an increased incidence of adverse reactions, and these areall likely to affect the therapeutic effects. This suggests that joint expert treatments, which integrate multiple disciplines (including experts in endocrinology, psychiatrics, psychology, and surgery) and perform simultaneous treatment, monitoring, and standardized management against the two diseases, can achieve results better than expected. Therefore, treatments with full-process supervision and standardized management against TB combined with T2DM are particularly important.[10]

CONCLUSION

TB and DM are relatively common individually. Their relationshipand consequences are well-established. The study offers new evidence of this association from the world's second

most populous country. The results of this study underline the significance of screening in TB for DM, which has not been achieved so far. The increasing trend in the prevalence of diabetes in countries such as India, which will also affect the TB burden, so it needs to be considered. Given the growing trend in diabetes prevalenceand the enormous burden of latent TB infection among the Indian population, concentrating on the diagnosis of latent TB infection and DM screening and ensuring good metabolic control among those diagnosed with DM is essential. We found that after anti-TB treatment, the sputum positivitydecreased in both the diabetics and non-diabetics. However, decrease was less in diabetic patients at 2 months of treatment but comparable at 3 and 5 months of treatment. Increasing age was an independent risk factor of increased risk of symptoms and positive sputum for AFB after 2 and 3 months of treatment. None of the factors was significant risk factor ofsputum microbial load (3+& 2+) and sputum positivity after 5 months of treatment. Thus, patients having both tuberculosis and DM should be screenedfor TB in the early stages and undergo full supervision as well as standard management therapies so that to improve their cure rate.

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