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Research Article

AN OBSERVATIONAL STUDY ON THE OUTCOME OF ANTITUBERCULAR AND ANTIDIABETIC THERAPY IN PATIENTS OF TUBERCULOSIS WITH DIABETES MELLITUS AS COMORBIDITY

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ABSTRACT

Aim and Objectives: Overall goal: To observe and compare the effect of antitubercular and antidiabetic therapy on patients of tuberculosis with diabetes mellitus as comorbidity. To study the effect of antidiabetic therapy on treatment outcome of tuberculosis. To study the effect of antitubercular drugs on glycemic control of patients of tuberculosis with diabetes mellitus

Methods: A total of 134 patients of tuberculosis with and without diabetes mellitus were approached for enrollment in this prospective observational cohort study as per NTEP guidelines. Effects of antitubercular therapy on antidiabetes drugs and vice versa during this study were observed and noted. A comparison of outcomes between two groups of patients of tuberculosis with diabetes and tuberculosis without diabetes was done according to outcome parameters.

Results: Mortality was found in patients on ATT+ADD nearly 11.94% (n=8) as compared to patients on ATT only 2.98% (n=2). Delayed sputum conversion with higher sputum positive rate (1+) among patients on ATT+ADD (23.89%) and mean HbA1c value at the end of the continuous phase (CP) was 6.7±1.07 among patients on ATT+ADD.

Conclusion: The patients on ATT+ADD have higher sputum positivity rates and poor treatment outcomes as compared to patients on ATT alone. Poor glycemic control in patients receiving ATT+ADD unfavorably leads to poor compliance with antitubercular therapy.

Keywords: Antitubercular therapy, Antidiabetic therapy, Tuberculosis, Diabetes mellitus, Glycemic control.

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INTRODUCTION

Tuberculosis is a major health problem in developing countries. Patients of TB with DM have routinely poor outcomes to customary antitubercular therapy [1]. Furthermore, antitubercular drugs interact with antidiabetic drugs [2].

The effect of DM on TB treatment outcome shows that suboptimal control of diabetes predisposes the patient to TB and is one of the most common causes of poor response to antitubercular treatment [1].

Tuberculosis also affects diabetes by causing hyperglycemia and causing impaired glucose tolerance [3]. The drugs used to treat TB (especially rifampicin and isoniazid) interact with oral antidiabetic drugs and may lead to suboptimal glycemic control [4]. Hence, oral antidiabetic drugs may interact with antitubercular drugs and lower their efficacy [4]. Therefore, antidiabetic drugs and antitubercular drugs interact with each other at multiple levels and affect each other functioning [1,4].

This study helps to better the existing data regarding knowledge about diabetes in tuberculosis patients, its mortality, morbidity, and also the impact of diabetes on tuberculosis treatment outcome(s).

METHODS

This study was conducted as per NTEP guidelines. Patients who come to OPD and IPD of respiratory medicine at tertiary health-care centers have symptoms of tuberculosis. After confirmation of tuberculosis and/or tuberculosis with diabetes mellitus of two groups, patients were approached for informed consent and to be part of the study. All investigation, reports, and treatment details were observed and noted.

Effects of antitubercular therapy on antidiabetes drugs and vice versa were observed and noted. Comparison of outcomes between two groups in patients of tuberculosis with diabetes and tuberculosis without diabetes to be done according to outcome parameters.

Time taken for sputum conversion during antitubercular treatment was observed (sputum smear examination done according to the duration of therapy at 2 and 6 months in drug-sensitive patients, at 3, 4, 5, and 6 weeks in drug-resistant shorter MDR and 9, 12, 15, and 18 weeks, in oral longer MDR) in study participants (patients of tuberculosis with diabetes and patients of tuberculosis without diabetes).

The outcome of antitubercular treatment in patients of diabetes mellitus (existing or newly diagnosed), morbidity, and mortality was observed and compared with patients of tuberculosis without diabetes mellitus.

Ethical Approval

The Institutional Ethics Committee approved the study (Approval No. GMCS/STU/ETHICS/Approval/6598/21; Date: 20/03/2021).

RESULT

In our study, 67 patients were diagnosed with tuberculosis with diabetes mellitus and were given antitubercular treatment plus antidiabetic drugs (ATT+ADD). 67 patients were diagnosed with tuberculosis and were given antitubercular treatment (ATT).

Overall ATT Regimen Distribution

Figure 1 depicts the antitubercular treatment (ATT) regimen distribution in the study population was found that among the study

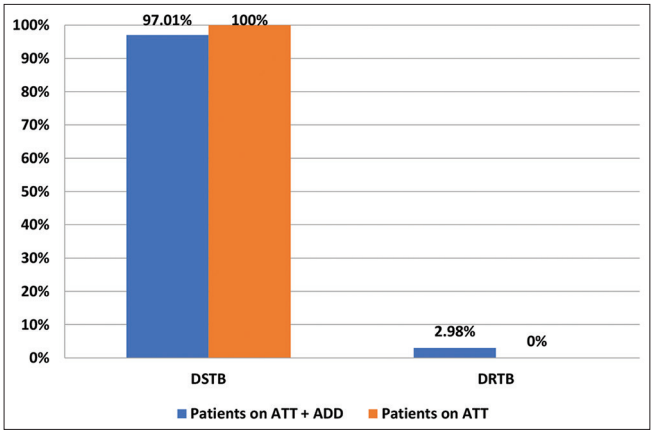

Fig. 1: Overall ATT regimen distribution (n=134)

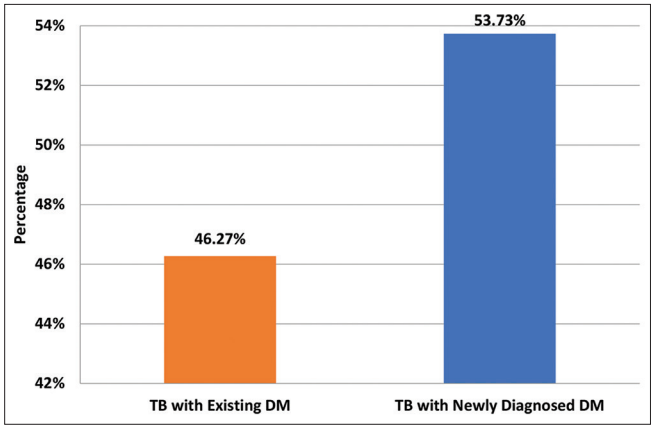

Fig. 2: Overall diabetic distribution (n=67)

population, there was a predominance of drug-sensitive tuberculosis (DSTB) in patients on ATT+ADD (n=65, 97.01%) and patients on ATT (n=2, 2.98%) as compared to drug-resistant tuberculosis (DRTB) inpatient on ATT+ADD (n=67, 100%) and patients on ATT (n=0, 0%).

Overall diabetic distribution

Figure 2 depicts the diabetic status-wise distribution of the study population was found that among the study population, there was a predominance of newly diagnosed DM with TB (n=36, 53.73%) as compared to existing DM with TB (n=31, 46.27%).

Descriptive analysis of sputum positivity in the study population:

Figure 3 depicts the study population, sputum positivity was 1+, 2+, and 3+, others (clinically diagnosed, microbiologically confirmed, and scanty) in 26 (20%), 23 (16%), 25 (19%), and 60 (45%) respectively.

Association of antidiabetic therapy and sputum positivity of study population

Table 1 depicts the study population, sputum positivity among the patients on ATT and ADD, 16 (23.89%) had positivity 1+, 14 (20.9%) had positivity 2+, 15 (22.39%) had positivity 3+, and 22 (32.84%) had positivity other (clinically confirmed, CBNAAT diagnosed, and microbiologically diagnosed). Among the patients on ATT, 10 (14.92%) had positivity 1+, 9 (13.43%) had positivity 2+, 10 (14.92%) had positivity 3+, and 38 (56.71%) had positivity other (clinically confirmed, CBNAAT diagnosed, and microbiologically diagnosed). The difference in the proportion of diabetic status between sputum positivity was not statistically significant (P value 0.05173).

Correlation of antidiabetic therapy and treatment outcomes of tuberculosis in the study population

Figure 4 depicts the correlation between antidiabetic therapy and treatment outcomes of tuberculosis in the study population. It was found that among the patients on ATT and ADD, 40 (59.7%) were categorized as cured, 17 (25.37%) as treatment completed, and 8 (11.94%) died; in 1 (1.49%) patient, treatment was changed and 1 (1.49%) was lost to follow-up. Among the patients on ATT, 43 (64.17%) were categorized as cured, 22 (32.83%) as treatment completed, and 2 (2.98%) died. The difference in the proportion of diabetic status between treatment outcomes was not statistically significant (P value 0.1153).

Comparison of mean Fasting Blood sugar (FBS: mg/dl) in patients on ATT+ADD

Figure 5 depicts the comparison of mean FBS (mg/dl) in patients on ATT+ADD was found that the mean FBS value at the initiation of therapy was 121.4 ± 62.372 mg/dl, at the end of the intensive phase (IP) was 169.37 ± 41.280 mg/dl, and at end of the continuous phase (CP) was 179.47 ± 58.188 mg/dl. Considering the initiation of ATT as the baseline, the mean difference of FBS (47.97 mg/dl at the end of IP was statistically not significant, P value 0.86645).

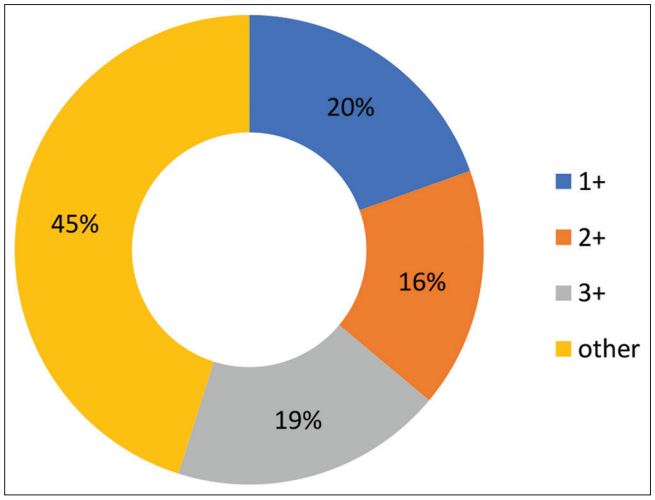

Fig. 3: Overall sputum positivity in the study population (n=134)

Table 1: Antidiabetic therapy and sputum positivity in the study population (n=134)

Sputum positivity	Patients on ATT and ADD, n (%)	Patients on ATT, n (%)
1+	16 (23.89)	10 (14.92)
2+	14 (20.9)	9 (13.43)
3+	15 (22.39)	10 (14.92)
Other	22 (32.84)	38 (56.71)
Total	67 (100)	67 (100)
Chi-square test	7.7382	
p	0.05173	

ATT: Anti-tubercular treatment, ADD: Antidiabetic drug

Comparison of mean Postprandial Blood Sugar (PPBS: mg/dl) in patients on ATT+ADD

Figure 5 depicts the comparison of mean PPBS (mg/dl) in patients on ATT+ADD was found that the mean PPBS value at the initiation of therapy was 221.92 ± 57.1774 (mg/dl), at the end of the intensive phase (IP) was 234.49 ± 65.5643 (mg/dl), and at end of the continuous phase (CP) was 253.77 ± 71.394 (mg/dl). Considering the initiation of ATT as the baseline, the mean difference of PPBS (12.57 mg/dl) at the end of IP was statistically not significant (P value 0.9373).

Comparison of mean HbA1c (%) in patients on ATT+ADD

Figure 5 depicts the comparison of mean HbA1c (%) in patients on ATT+ADD was found that the mean HbA1c value at the initiation of therapy was 10.7 ± 1.15 (%), at the end of the intensive phase (IP)

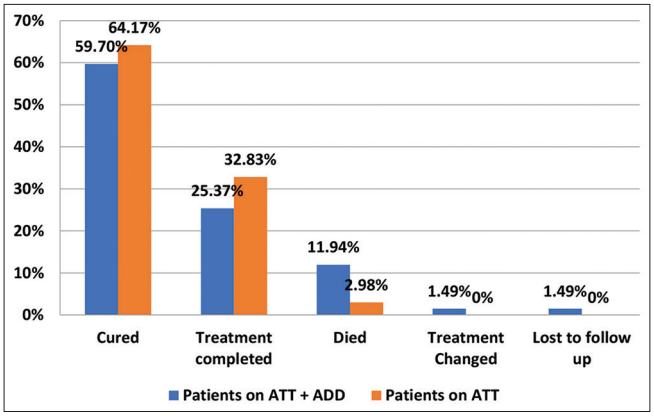

Fig. 4: Correlation of antidiabetic therapy and treatment outcomes of tuberculosis in study population (n=134)

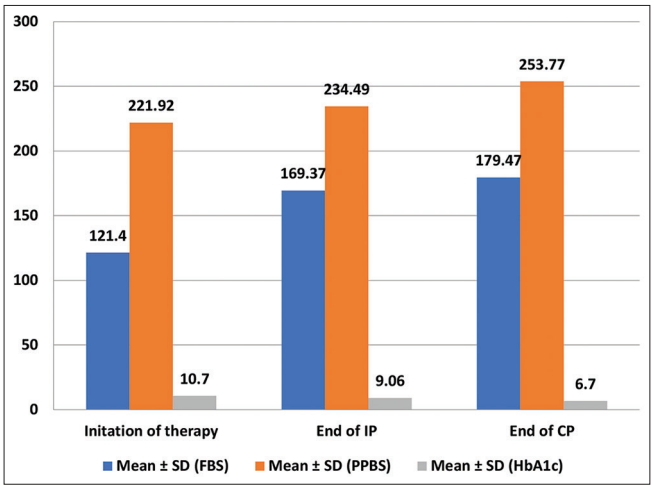

Fig. 5: Comparison of Mean FBS, PPBS, and HbA1c value in patients on ATT+ADD (n=67)

was 9.06 ± 1.40 (%), and at end of the continuous phase (CP) was 6.7 ± 1.07 (%). Considering the initiation of ATT as a baseline, the mean difference of HbA1c (1.64 %) at the end of IP (after 3 months) was statistically not significant (P value 0.9199).

Descriptive analysis of sputum status at the end of the intensive phase (2 months) after initiation of treatment in the study population

Table 2 depicts the descriptive analysis of sputum status at the end of the intensive phase in the study population was found that after 2 months of initiation of ATT, 63 (47.01%) were sputum positive and 71 (52.99%) were sputum negative.

Association of antidiabetic therapy with sputum status at 2 months after initiation of treatment in the study population

Table 3 depicts the association of antidiabetic therapy with sputum status at the end of the intensive phase after initiation of treatment in the study population was found that among the patients on ATT+ADD, 41 (61.19%) were sputum positive, and 26 (38.80%) were sputum negative. Among the patients on ATT, 22 (32.83%) were sputum positive, and 45 (67.16%) were sputum negative. Sputum positivity was higher among patients on ATT+ADD as compared to those on ATT alone. This was statistically significant (p value 0.001).

Descriptive analysis of drugs for diabetic mellitus in patients on ATT+ADD

Table 4 depicts the descriptive analysis of drugs for diabetic mellitus in the study population. It was found that among the patients in the ATT+ADD population, 56 (83.58%) were receiving

Table 2: Sputum status at end of the intensive phase (2 months) after initiation of treatment in study population (n=134)

Sputum status at end of IP	n (%)
Positive	63 (47.01)
Negative	71 (52.99)
Total	134 (100)

IP: Intensive phase

Table 3: Antidiabetic therapy with sputum status at the end of the intensive phase (2 months) after initiation of treatment in the study population (*n*=134)

Sputum status at the end of IP	Positive	Negative	Total	Chi-square test	p
Patients on ATT+ADD	41	26	67	10.814	0.001*
Patients on ATT	22	45	67		
Total	63	71	134		

ATT: Anti-tubercular treatment, ADD: Antidiabetic drug, IP: Intensive phase

Table 4: Descriptive analysis of drugs for diabetic mellitus in patients on ATT+ADD (*n*=67)

Drugs for diabetic mellitus	n (%)
Biguanides (metformin)	56 (83.58)
Insulin	23 (34.33)
Sulfonylureas (glipizide)	42 (62.68)
Biguanides and sulfonylureas (metformin+glipizide)	10 (14.92)
Alpha-glucosidase inhibitors (voglibose)	31 (46.27)

ATT: Antitubercular treatment, ADD: Antidiabetic drug

biguanides, 23 (34.33%) were receiving insulin, 42 (62.68%) were receiving sulfonylureas, 10 (14.92%) were receiving biguanides and sulfonylureas, and 31 (46.27%) were receiving alpha-glucosidase inhibitors. The patients in study groups were on polytherapy of ADD.

DISCUSSION

An 18-month prospective observational study was conducted in patients taking ATT+ADD and patients taking ATT alone and being registered under NTEP in the tertiary care teaching hospital from March 2021 to September 2022.

Antidiabetic drugs and treatment outcome

The impact of DM on outcomes of TB treatment determines that DM increases the risk of the combined outcome of treatment failure, relapse, or death [5].

Meregildo-Rodriguez ED *et al.* (2022) and Yu X *et al.* (2019) reported some OHAs could reduce the risk of latent TB infection (LTBI), active TB, poor treatment outcomes (e.g., mortality), or even poor health-related quality-of-life outcomes in tuberculosis patients with DM [6,7].

Meregildo-Rodriguez ED *et al.* (2022), Yu X *et al.* (2019), Marupuru *et al.* (2017), and Pan S *et al.* (2021) reported, from 12 observational studies among patients receiving ATT+ADD, that metformin prescription is significantly associated with a decreased risk of TB disease, a smaller TB mortality. Metformin prescription could not reduce the risk of LTBI and the relapse rate of TB disease [6-9].

This present study revealed that 59.70% of patients were categorized as cured and 25.37% as completed treatment. In the summarized result, we can observe that patients receiving ATT+ADD were having significant risk reduction of tuberculosis outcome as similar to Yu X *et al.* (2019) [7] and Baker MA *et al.* (2011) [5] studies. This study revealed that 11.94 % of patients died during the treatment due to poor diabetic control, which probably led to sputum-positive status at the end of the intensive phase

as compared to a control group (2.98%). Furthermore, uncontrolled DM is responsible for poor clinical response to anti-TB therapy [10].

Danger NR *et al*. (2017) suggest that DM was associated with increased sputum-culture positivity after 2 months, but not after 6 months, of TB treatment [11]. Their study also suggests that DM may reduce the efficacy of the initial phase of TB treatment, leaving patients with DM potentially infectious for a longer period of time. Although 2-month sputum-culture conversion is often used as a microbiological endpoint for assessing the efficacy of novel TB treatment regimens [12], it may in fact be a poor surrogate for relapse-free cure [13].

Yu X *et al*. (2019) study observed that metformin failed to reveal a significant anti-TB effect in TB patients with DM [7].

This present study revealed that 61.90% of patients on ATT+ADD were sputum culture positive after 2 months (end of IP) as compared to 38.80% of patients on ATT only, which is similar to Danger NR *et al*. (2017) [11] study. Our study revealed a higher rate of sputum positivity in patients on ATT+ADD as compared to patients on ATT only. Alisjahbana *et al*. (2006) reported a higher frequency of sputum-negative smears in diabetic patients [14].

ANTITUBERCULAR TREATMENT AND GLYCEMIC CONTROL

John NN *et al*. (2017), in their study, reported a higher percentage of sputum positivity and a higher rate of pulmonary TB than extrapulmonary tuberculosis in diabetic patients. It is because glucose stimulates mycobacterial growth and uncontrolled DM is responsible for poor clinical response to anti-TB therapy, which also increases the susceptibility to mycobacterial growth. Our study findings revealed a higher percentage of sputum positivity at the end of the intensive phase and a higher rate of pulmonary TB as compared to extrapulmonary TB with poor glycemic control to the antitubercular therapy [10].

Niazi AK *et al*. (2012), in their study, reported that rifampicin is a potent hepatic enzyme inducer. It accelerates the metabolism of various oral hypoglycemic agents, especially sulfonylureas and biguanides, and lowers their plasma concentration levels [4]. Therefore, it may cause hyperglycemia in diabetic patients using these drugs. Isoniazid, in contrast to rifampicin, inhibits the metabolism of oral hypoglycemic agents and may lead to an increase in the plasma levels of these drugs [4]. It interacts with sulfonylureas can antagonize and worsen the glycemic control of diabetics on this medication. It also impairs the release and action of insulin, leading to hyperglycemia even in nondiabetics [4]. Our study suggests poor glycemic control in patients receiving ATT+ADD as compared to patients receiving ATT only. Because of the interaction of ATT with ADD which may lead to poor compliance of ADD as well as ATT in patients of tuberculosis with diabetes mellitus [4].

CONCLUSION

The patients on concomitant antitubercular treatment and antidiabetic treatment have higher sputum positivity rates and poor treatment outcomes as compared to patients receiving antitubercular treatment alone, demanding glycemic control as early as possible for patients receiving polytherapy of antidiabetic drugs as metformin can reduce the sputum positivity rates and treatment outcome in patients on ATT+ADD.

The present study reported that the patients of ATT with poor glycemic control had a higher percentage of sputum positivity. This study recommends the management of glycemic levels in patients receiving ATT+ADD for better outcomes.

ABBREVIATIONS

NTEP: National Tuberculosis Elimination Program; OPD: Outdoor patients; IPD: Indoor patients; ATT: Anti-tubercular drugs; ADD: Antidiabetic drugs; TB: Tuberculosis; DM: Diabetes Mellitus; MDR: Multidrug resistance; FBS: Fasting blood sugar; PPBS: Postprandial blood sugar; IP: Intensive Phase; CP: Continuous phase.

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CONFLICTS OF INTEREST

None Declared.

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