

TO ANALYSE THE CLINICAL AND RADIOLOGICAL CHARACTERISTICS OF PATIENTS WITH DIABETES MELLITUS AND MULTI-DRUG RESISTANT TUBERCULOSIS (MDR-TB)

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Abstract

Background: Research has shown the reciprocal relationship between diabetes and tuberculosis. There is a hypothesis that suggests that diabetes has a negative impact on the progress of TB therapy. Moreover, individuals with tuberculosis have a decline in their ability to regulate blood sugar levels in the presence of diabetes. A possible possibility for the association between TB and diabetes is the compromised immune response in diabetic persons. At now, there is a scarcity of research on diabetic mellitus (DM) in tuberculosis (TB) patients, and no studies have been conducted in the specific location of interest. Furthermore, there is a scarcity of research that illustrate the clinical and radiological characteristics of diabetes mellitus in multidrug-resistant tuberculosis. **Aim:** To analyse the clinical and radiological characteristics of patients with Diabetes Mellitus and Multi-Drug Resistant Tuberculosis (MDR-TB). **Material & Methods:** The research included 120 patients who had been diagnosed with MDR-TB and having DM. All patients diagnosed with Multidrug resistant Tuberculosis (MDR-TB) were admitted to treatment programme under NTEP in the Chest & TB hospital and underwent a pre-treatment examination. Prior to enrolment, the procedure was thoroughly elucidated to the patient/care provider, and informed permission was obtained from each patient. **Results:** The most prevalent symptom was cough with expectoration, seen in 110 instances (91.67%), followed by fever, present in 80 cases (66.67%). Weight loss was seen in 69 instances, accounting for 57.5% of the total. Loss of appetite was reported in 66 patients, representing 55% of the sample. Breathlessness was evident in 65 cases, accounting for 54.17% of the total, while hemoptysis was reported in 12 cases, representing 10% of the sample. Among the 120 research participants, 116 (97.5%) patients had a prior history of ATT, whereas 4 (2.5%) patients did not have any previous experience of ATT. Ninety-five individuals, accounting for 79.17% of the total, had parenchymal infiltration. 29 research participants (24.17%) had cavitation, whereas 45 (37.5%) had fibrocavitary illness. Conversely, fibrosis was detected in 25 (20.83%) participants in the research. Three patients (2.5%) had both pulmonary and extra- It is important to assess the clinico-radiological features when medications have not effectively reached the required levels to combat all the mycobacteria population.

INTRODUCTION

Tuberculosis is the most widespread infection globally. India accounts for 25% of the worldwide TB load. In spite of extensive national and

worldwide efforts to manage and eradicate TB, around 10 million cases of active tuberculosis were recorded in 2019, resulting in an estimated 1.2 million fatalities.^[1] According to a synthesis of research conducted in various regions, India is

expected to have the highest rise in diabetes cases.^[2] The management and containment of tuberculosis are under risk due to the rise and intensification of multi-drug resistant tuberculosis (MDR-TB).^[3] The worldwide pandemic of diabetic mellitus (DM) presents a major obstacle to the TB control programme.^[4] In 2013, the International Diabetes Federation (IDF) estimated that there were 382 million persons worldwide with diabetes, with 80% of them residing in low- and middle-income nations. It is projected that the worldwide burden of diabetes will continue to rise, reaching 592 million by 2035.^[5] Individuals with diabetes had a much higher risk of developing tuberculosis, with a two- to three-fold increase compared to those without diabetes.^[6] According to data from 2013, around 15% of adult tuberculosis cases globally were caused by diabetes. This translates to almost 1 million cases of tuberculosis linked with diabetes per year.^[2] The compromised immune system in individuals with diabetes is believed to have a role in the progression of latent tuberculosis infection to active cases. In addition, individuals with tuberculosis (TB) who also have diabetes mellitus (DM) have a less favourable response to therapy compared to those without DM. Consequently, they face an elevated risk of experiencing treatment failure, mortality, and recurrence after successful recovery.^[7] The occurrence of treatment failure is an additional and major obstacle to the worldwide tuberculosis control programme, particularly in cases of drug-resistant tuberculosis.^[3,8] The worldwide spread of multi-drug resistance is a significant challenge since it is difficult to treat, costly, and places a substantial financial burden on poor nations.^[8] The majority of instances of multidrug-resistant tuberculosis (MDR-TB) result from a combination of medical mistakes, insufficient and incomplete therapy, and lack of patient adherence to treatment for susceptible tuberculosis.^[9] Studies also suggest that individuals with multidrug-resistant tuberculosis (MDR-TB) with the additional condition of diabetes mellitus (DM) have a worse response to therapy in comparison to MDR-TB patients without diabetes.^[10] Research has shown the reciprocal connection between diabetes and tuberculosis. There is a hypothesis that suggests that diabetes exacerbates the clinical progression of tuberculosis therapy. Moreover, individuals with tuberculosis see a decline in their ability to regulate blood sugar levels, which is particularly problematic for those with diabetes. A possible possibility for the association between TB and diabetes is the compromised immune response in diabetic persons. A recent comprehensive study found that individuals with diabetes mellitus (DM) had a risk of contracting tuberculosis (TB) that is roughly three times greater than those without DM.^[11] India, known as the "Diabetes Capital" of the world, is expected to have 62-80 million individuals with diabetes mellitus by 2030. The prevalence of diabetes in drug-susceptible tuberculosis (DSTB) in

India is 20%, whereas in multidrug-resistant tuberculosis (MDR TB) it is 11.7%. Presently, there is a scarcity of research on diabetic mellitus (DM) in tuberculosis (TB) patients, particularly in the specific geographical region being studied. Furthermore, there is a scarcity of research that accurately portray the clinical and radiological characteristics of diabetes mellitus in multidrug-resistant tuberculosis. Against this background, the present investigation was undertaken with the aim of establishing a link between the severity of diabetes (HbA1C) and the clinical and radiological findings (Chest X-ray).

MATERIALS AND METHODS

This observational prospective research was conducted at the Department of Chest and Tuberculosis. The research included 120 patients who had been diagnosed with Multidrug Resistant tuberculosis (MDR-TB) with DM. The research also included patients who were not resistant to multiple drugs but had resistance to Rifampicin. It should be emphasised that the occurrence of R resistance is quite uncommon in the absence of H resistance. The majority of cases where there is resistance to DST (drug susceptibility testing) for the R drug will also exhibit resistance to the H drug, indicating MDR-TB.

This research included patients who had proven signs of medication resistance by CBNAAT (Cartridge Based Nucleic Acid Amplification) and Line Probe Assay (LPA), and who were over 18 years old. The research excluded patients who had suspected multidrug resistance, were critically sick or moribund, had extra-pulmonary tuberculosis, were resistant to just isoniazid, or had extensively drug resistant tuberculosis (XDR-TB).

Methodology

All DM patients diagnosed with Multidrug resistant Tuberculosis (MDR-TB) were admitted to treatment programme under NTEP in the Chest & TB hospital and underwent a pre-treatment examination. Prior to enrollment, the procedure was thoroughly elucidated to the patient/care provider, and informed permission was obtained from each patient. The patients were interviewed to gather demographic information and obtain a comprehensive clinical history, including the duration of illness, smoking habits, substance abuse, mental health conditions, diabetic history, previous tuberculosis treatment, family history of tuberculosis treatment, and any contact with tuberculosis patients. Every patient had a chest radiograph. The acquired data was subjected to statistical analysis and organised to derive reliable results.

RESULTS

The majority of patients were men, accounting for 80 individuals (66.67%), while females made up 40 individuals (33.33%) of the patient population. Our research found that the highest proportion of patients, 45 (37.5%), were between the age range of 20-30 years. This was followed by 23 patients (19.17%) who were younger than 20 years old. The age category with the fewest number of patients was 50-60 years, namely 9 individuals, which accounted for 7.5% of the total. The average age was 35.85 ± 3.66 years. Among the 120 patients, 51 (42.5%) were from rural regions and 69 (57.5%) were from metropolitan areas. The majority of the patients in this research were labourers, accounting for 44 individuals or 36.67% of the total. Private job workers constituted the second largest group, with 20 individuals or 16.67%. There were 13 jobless patients, making up 10.83% of the sample. Farmers included 24 patients or 20% of the total, while government employees accounted for 11 individuals or 9.17%. In this research, out of a total of 120 cases, 72 patients (60%) were found to be resistant to Rifampicin alone, while 48 patients (40%) were resistant to a combination of Rifampicin and Isoniazid (RH) (Table 1).

The majority of patients included in the research had several complaints lasting for over a month. The most prevalent symptom was cough with expectoration, seen in 110 instances (91.67%), followed by fever, present in 80 cases (66.67%). Weight loss was seen in 69 instances, accounting for 57.5% of the total. Loss of appetite was reported in 66 patients, representing 55% of the sample. Breathlessness was evident in 65 cases, accounting for 54.17% of the total, while hemoptysis was reported in 12 cases, representing 10% of the sample (Table 2).

Among the 120 patients, 4 individuals (3.33% of the total) were diagnosed with HIV/AIDS. Among the co-morbidities, apart from diabetes and HIV, the most prevalent co-morbid condition was COPD, which was found in 10 cases (8.33%) and was associated to smoking. This was followed by hypothyroidism, which was present in 6 patients

(5%). The prevalence of hypertension was 3.33%, depression was 1.67%, hydro-pneumothorax was 1.67%, and ill euthyroid syndrome was 1.67%. The most prevalent addiction seen in the research was drinking, affecting 29 participants (24.17%). This was followed by smoking, which was present in 25 cases (20.83%), and heroin addiction, which was present in 2 instances (1.67%). Out of the total instances, 4 (3.33%) had different forms of drug addiction, whereas 60 (50%) of the research individuals did not have any drug addiction.

Among the 120 research participants, 116 (97.5%) patients had a prior history of ATT, whereas 4 (2.5%) patients did not have any previous experience of ATT. A history of contact was observed in 36 individuals, accounting for 30% of the total. Out of the 36 patients, 29 (24.17%) had a history of contact with a pulmonary TB case, and 7 (5.83%) had a history of contact with an MDR-TB case. Out of the total number of patients, 84 (70%) did not have any prior interaction with a tuberculosis (TB) case.

The research revealed that a majority of the patients had multiple findings on their chest x-rays. The data above indicates that unilateral disease was seen in 55 (45.33%) individuals, whereas bilateral disease was observed in 65 (54.17%) patients. Ninety-five individuals, accounting for 79.17% of the total, had parenchymal infiltration. 29 research participants (24.17%) had cavitation, whereas 45 (37.5%) had fibrocavitary illness. Conversely, fibrosis was detected in 25 (20.83%) participants in the research. Three patients (2.5%) had both pulmonary and extra-pulmonary involvement, namely the presence of pleural effusion. No instances of pneumothorax were seen in any of the research participants. Out of the patients included in our research, 12 individuals (which accounts for 10% of the total) had little illness. 38 patients, accounting for 32.76% of the total, had intermediate illness, while 70 patients, making up 60.34% of the total, had far advanced disease. The data clearly demonstrates that the past history of ATT is significantly associated with the amount of the lesion shown on the chest x-ray ($p < 0.05$) (Table 3 and 4).

Table 1: Basic profile of the participants

Profile	Number	Percentage	P value
Gender			0.12
Male	80	66.67	
Female	40	33.33	
Age			0.14
Below 20	23	19.17	
20-30	45	37.5	
30-40	15	12.5	
40-50	17	14.17	
50-60	9	7.5	
Above 60	11	9.17	
Mean Age	35.85 ± 3.66		
Area			0.23
Urban	69	57.5	
Rural	51	42.5	
Employment			0.17

Private	20	16.67	
Government	11	9.17	
Farmer	24	20	
Labourers	44	36.67	
Others	8	6.67	
Unemployed	13	10.83	

Table 2: Frequency of Presenting Symptoms

Symptoms	Number	Percentage
Loss of Appetite	66	55
Weight loss	69	57.5
Cough with Expectoration	110	91.67
Breathlessness	65	54.17
Hemoptysis	12	10
Fever	80	66.67

Table 3: Radiological Features –Wise Distribution of Cases

Radiological Findings	Number	Percentage
Parenchymal Infiltration	95	79.17
Cavitation	29	24.17
Fibro-cavitary	45	37.5
Fibrosis	25	20.83
Pleural Effusion	3	2.5
Unilateral Disease	55	45.83
Bilateral Disease	65	54.17

Table 4: Association of Previous History of Att with Extent of Lesions

Previous H/O ATT	Extent of lesion			P value
	Minimal	Moderate	Advanced	
New	4	0	0	0.05
Previously treated	8 (6.90%)	38 (32.76%)	70 (60.34%)	

DISCUSSION

The existence of drug-resistant tuberculosis has been recognised from the first introduction of anti-tuberculosis medications for TB therapy. Standalone technologies for the identification and treatment of drug resistance are insufficient to fully address the issue of DR-TB. An effective approach is needed to diagnose, treat, and maintain long-term disease-free status in TB patients in order to avoid the development of resistance. In clinical settings, a treatment regimen that is insufficient or improperly delivered enables drug-resistant mutations to become the prevailing strain in a patient afflicted with tuberculosis. Hence, it is crucial to acknowledge the clinico-radiological features when medications are not effectively reaching the required levels to combat the whole population of mycobacteria.^[12,13] Our data indicates that the majority of patients, 45 (37.5%), were between the ages of 20 and 30. The second highest number of patients, 23 (19.17%), were under the age of 20. The age category with the fewest number of patients was 50-60 years, namely 9 individuals, which accounted for 7.5% of the total. The average age was 35.85±3.66 years.^[13] Udwardia and Moharil et al. likewise observed a higher prevalence of MDR-TB among younger individuals, with the average age of their research groups being 29.7 years and 33.25 years, respectively.^[14] The elevated prevalence of

treatment resistance among younger patients might be attributed to increased exposure to instances with drug-resistant strains. In our patriarchal culture Males have more access to healthcare facilities in comparison to females. The primary determinant of resistance to a certain medication is the confirmation of its previous administration as the only treatment for a duration beyond one month. In order to gather evidence of unintentional or deliberate use of a single drug for tuberculosis treatment, it is crucial to be thorough when collecting the treatment history of all suspected cases of MDR-TB. Out of the 120 cases examined in our research, 72 patients (60%) exhibited resistance to Rifampicin alone, whereas 48 patients (40%) showed resistance to both Rifampicin and Isoniazid. In a research conducted by Nirmalya Manna et al, it was shown that 53.7% of the patients exhibited resistance alone to Rifampicin, whereas 46.3% showed resistance to both Rifampicin and Isoniazid.^[15]

The majority of patients included in the research had several complaints lasting for over a month. The most prevalent symptom reported was cough with expectoration, seen in 110 cases (91.67%), followed by fever, present in 80 cases (66.67%). Weight loss was seen in 69 cases, accounting for 57.5% of the total. Loss of appetite was reported in 66 patients, representing 55% of the sample. Breathlessness was evident in 65 cases, accounting for 54.17% of the total. Hemoptysis was observed in 12 cases, representing 10% of the sample. Out of our sample

of twenty-seven individuals, thirty cases (25%) had diabetes. Among the total of 120 patients, 4 individuals (3.33%) were identified as having HIV/AIDS. Among the co-morbidities, excluding diabetes and HIV, the most prevalent co-morbid illness was COPD, which was found in 10 cases (8.33%) and was associated with smoking. Hypothyroidism was the second most frequent co-morbid disease, present in 6 cases (5%). A study conducted by More et al. found that among 96 patients with MDR-TB, 27 (28.13%) reported having a comorbidity. This included 6 patients (29.62%) with diabetes mellitus, 2 patients (7.40%) with both diabetes mellitus and hypertension, 3 patients (14.81%) who were HIV positive, and 1 patient (3.70%) with HIV and anaemia.^[16] Datta et al. documented a 1.9% prevalence of HIV infection among patients of multidrug-resistant tuberculosis (MDR-TB).^[17] Among the 120 research participants, 116 (97.5%) patients had a prior history of ATT, whereas 4 (2.5%) patients did not have any previous experience of ATT. Our investigation found a strong correlation ($p < 0.05$) between the prior use of ATT and the severity of the lesion shown on the chest x-ray. A study revealed that a significant proportion of individuals with MDR-TB had developed acquired drug resistance. A prior medical record of ATT is a significant contributing factor to the development of drug resistance. This may be due to non-compliance or non-adherence to the prescribed treatment, frequent hospitalisations that result in exposure to drug-resistant strains, the use of single anti-TB drugs as the sole therapy, the addition of a single anti-TB drug to an ineffective treatment regimen, intolerance to drugs or adverse effects leading to discontinuation of treatment, which can ultimately lead to the emergence of drug resistance. A history of contact was observed in 36 individuals, accounting for 30% of the total. Out of the 36 patients, 29 (24.17%) had a history of contact with a pulmonary tuberculosis case, whereas 7 (5.83%) had a history of contact with a multidrug-resistant tuberculosis case. Out of the total number of patients, 84 (70%) did not have any documented contact with a tuberculosis (TB) case.

A study conducted by Mulu et al. found that among 153 instances of multidrug-resistant tuberculosis (MDR-TB), 44 individuals (28.8%) had a documented history of coming into contact with MDR-TB patients.^[19] The majority of individuals included in the research had multiple findings on their chest x-rays. The data above indicates that unilateral disease was seen in 55 (45.33%) individuals, whereas bilateral disease was observed in 65 (54.17%) patients. Ninety-five individuals, accounting for 79.17% of the total, had parenchymal infiltration. 29 research participants (24.17%) had cavitation, whereas 45 (37.5%) had fibrocavitary illness. Conversely, fibrosis was seen in 25 (20.83%) participants in the research. Out of the total number of patients, 3 individuals (2.5%) had both pulmonary and extra-pulmonary involvement,

namely the presence of pleural effusion. No instances of pneumothorax were seen in any of the research participants. Out of the patients included in our research, 12 individuals (representing 10% of the total) had little illness. 38 patients, accounting for 32.76% of the total, had intermediate illness, while 70 patients, making up 60.34% of the total, had far advanced disease.

In their study, Mishra et al. found that out of 244 patients, 224 (91.8%) had lung involvement in both lungs, while 20 (8.2%) had lung involvement in just one lung. Additionally, 209 (85.7%) patients had cavitary lung disease, while 35 (14.3%) had non-cavitary lung disease. Out of the total number of patients, 130 (58.04%) had far advanced illness in both lungs, 89 (39.7%) had moderately advanced disease in both lungs, and 5 (2.2%) had minimum lung disease in both lungs.^[20]

The research conducted by Icksan et al. examines the chest X-ray results of two distinct groups of patients: 183 individuals with DS-TB and 183 individuals with MDR-TB. The MDR-TB group consists of 177 patients (96%) with big lesions, 6 patients (4%) with medium lesions, and no patients with tiny lesions. The DS-TB group consists of 55 patients (30%) with tiny lesions, 78 patients (43%) with medium lesions, and 50 patients (27%) with extensive lesions.^[21]

The restricted infiltration of drugs into the cavity containing a high concentration of mycobacteria and a significant number of Acid fast bacilli (AFB) in moderately or severely progressed illness is thought to be a factor in the development of drug resistance. Alterations in the dimensions of cavities, together with enlargement of preexisting lesions and the emergence of new lesions, indicate the advancement and intensification of the illness. While radiological deterioration may not be a very dependable predictor of treatment resistance, it does provide further support to the clinical and bacteriological evidence of the illness.

CONCLUSION

It is important to assess the clinico-radiological features when medications have not effectively reached the required levels to combat all the mycobacteria population. This assessment helps in making timely adjustments and enhancements to national programmes, as well as evaluating trends in drug resistance patterns.

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