Spectrum and Correlation of Clinical, Radiological and Biochemical Parameters in Tuberculosis in a Hospital in South India

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ABSTRACT

BACKGROUND

Tuberculosis (TB) remains a major public health problem in India. TB worsens glycaemic control in patients with diabetes mellitus (DM), complicating the treatment for each condition leading to poor treatment outcomes and increase in morbidity / mortality. Human immunodeficiency virus - tuberculosis (HIV-TB) co-infections are on the rise. The objectives of the study were to describe various comorbidities in patients with tuberculosis, determine expected radiological presentations in these patients and to determine prognosis altering metabolic indicators in patients with TB.

METHODS

A prospective cross-sectional study using data of 40 microbiologically diagnosed TB patients admitted in wards of C.G. Hospital, JJM Medical College, Davangere, from January to March 2020 was done. Chest x-rays, clinical and haematological tests were analysed.

RESULTS

TB patients with DM, kidney disease, HIV presented with higher count of fibrosis, cavities and infiltrates on chest radiographs, and was worse with renal function. Hospitalisation was prolonged in patients with anaemia, multidrug-resistance tuberculosis (MDR-TB), urosepsis, and HIV as compared to patients with no comorbidities. MDR-TB showed more fibrosis. Patients with urosepsis had higher incidence of multiple lesions and effusion by 4 times.

CONCLUSIONS

Increased HbA1c and sugar levels lead to increase in lesions on chest x-ray in tuberculosis. Good glycaemic control in TB is a must to achieve good control of DM and reduce hospitalisation.

KEYWORDS

Tuberculosis, Diabetes Mellitus, HbA1c, Chest X-Ray

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BACKGROUND

Tuberculosis is one of the major public health problems in India, with 2.15 million cases in 2018.[1] Majority of the TB burden is among the working age group. The 89 % of TB cases come from the age group of 15 - 69 years. About 2 / 3 of the TB cases are males.[1] TB remains a major cause of death from a single infectious agent among adults in developing nations. TB is also a major disease manifesting in association with HIV.[13]

A normal chest x ray has a high negative predictive value for the presence of active TB. On the other hand, presence of characteristic radiographic findings in appropriate clinical settings may be sufficient to diagnose TB even in the absence of sputum positivity. Even then, disease activity may not be accurately assessed by radiographs and the frequency of false-negatives is higher in HIV-positive patients.[2]

15 % of TB patients may have diabetes. Diabetic patients who are on anti-tubercular therapy (ATT), have a higher chance of morbidity / mortality. Worse glycaemic control in diabetics is noticed which may be TB or ATT induced.[3]

Studies have shown that TB in diabetics have atypical radiological findings of lower lobe involvement, along with lower incidence of sputum acid-fast bacillus (AFB) / culture positive cases, which can make the diagnosis more difficult, worsen prognosis, prolong therapy with higher incidence of extra pulmonary TB was seen.[4,5] Studies have shown higher bacterial load and higher chance of transmission to close contacts of TB in diabetes. Studies have shown cavitation as the hallmark of post primary TB.[6,14]

Our objectives were to describe various comorbidities in patients with tuberculosis, to determine expected radiological presentations in these patients and to determine prognosis altering metabolic indicators in these patients.

METHODS

This was a prospective cross-sectional hospital-based study of patients admitted in the Department of General Medicine at Chigateri General Hospital, JJM Medical College, Davangere. The inclusion criteria were defined as patients microbiologically diagnosed with pulmonary and extra-pulmonary tuberculosis along with other comorbidities, age between 18 to 85 years with informed written and oral consent.

The exclusion criteria were patients with malignancies, unconfirmed TB, ICU patients and patients in the ER. The study has a sample size of 40 patients over a duration of January to March 2020. The study was conducted after the approval of the institutional ethics committee. Informed written consent was obtained from all patients prior to their enrolment in this study.

Tuberculosis patients were screened based on clinical examination and chest x-ray and TB was confirmed by sputum acid fast bacilli and cartridge based nucleic acid amplification assay (CBNAAT). Forty confirmed TB patients were subjected to blood investigations like complete blood count, liver function tests, renal function tests, fasting blood sugar, glycosylated haemoglobin, urine routine and lipid profile, electrocardiogram and chest x-ray PA view. These investigations were done for all the patients. Chest x-ray were analysed and lesions were identified as fibrosis, cavity, fibrocavitatory, effusion, infiltrates and hilar shadows. Data analysis was conducted. Descriptive statistics, Kruskal-Wallis test, analysis of variance (ANOVA) statistical analysis were applied. P-value of < 0.05 was considered statistically significant.

RESULTS

We enrolled 70 patients in the general medicine ward of CG Hospital Davangere. After excluding patients in the ICU (N = 5), post thoracotomy patients (N = 5), and patients who were TB suspects but were not microbiologically confirmed (N = 20) were excluded. Three patients who had clear CXR with acid-fast bacillus (AFB) were included. Two patients had negative AFB, but were confirmed on CBNAAT were included in the study. A total 40 subjects were included in final analysis. No mortalities were witnessed in this study population.

The mean age of our study population was 49.2 years with youngest being 18 years and oldest patient 72 years. Six patients had pleural effusion, 2 had bronchiectasis, eleven had fibrocavitatory, two hydropneumothorax, two patients with parenchymal involvement, two patients had hilar shadows and three patients had normal chest x-ray. Males were 18 in number and females were 22 in number in our study population. Half (N = 20) were anaemic, (Hb < 10 g / dL). 18 out of 40 patients had total white cell counts (> 11000 cells / dL). Four patients suffered with thrombocytopenia (< 1.5 L / dL).

Total bilirubin, indirect or direct bilirubin were not deranged in our study. 85 % patients had hypoalbuminemia (< 3.5 g / dL). 60 % had hypoproteinaemia (< 6.5 g / dL). Total number of diabetics in our study was 21, all of them being newly diagnosed (HbA1c > 6.5 %). The mean fasting blood sugar was 200 mg / dl in diabetics and 104 mg / dl in non-diabetics with HbA1c of 7.8 % and 5.7 % respectively.

Total cholesterol, triglycerides and low-density lipoprotein (LDL) were not deranged in our study. There were 10 % patients with very low-density lipoprotein (VLDL) more than 35 mg / dL. 14 patients had an increase in cholesterol / high-density lipoprotein (HDL) > 5 and 25 % patients had HDL between 42 mg / dL and 88 mg / dL.

The radiographs were analysed and classified into cavity, effusion, fibrocavitatory and with multiple lesions (> 2 lesions) including hilar lymphadenopathy, fibrosis, diffuse infiltrates, bronchiectasis. Patients with multiple lesions had a higher value of HbA1c > 7.5 % compared to normal radiograph and fibrocavitatory lesions (6.3 %, 5.6 % respectively). (Table 1) Female patients had more incidence of multiple lesions as compared to men, while men presented with cavities. Total leukocyte counts (TLC) were increased in patients with multiple lesions on CXR. Renal function was highly deranged in patients with effusion when compared with other radiological findings.

Urosepsis (urinary tract infection) was detected in 16 patients and was confirmed by urine routine and urine culture. Eight of them had UTI due to *E. coli*, four of them klebsiella and four proteus. Presence of urinary tract infection was significantly associated with lower incidence of cavity. In 16 patients with UTI, 25 % had cavities, 37.5 % had effusion and 37.5 % had fibrosis. In 22 patients with no UTI, 68 % had cavity, 0.9 % had effusion and 40.9 % had fibrosis. UTI was also associated with deranged urea and creatinine. Presence of glycosuria was associated with fibrosis and hilar lymph nodes. (Table 2). Patients with diabetes have significantly increased fibrosis and cavity. Diabetes along with chronic kidney disease (CKD) had higher incidence of pleural effusion. Three patients with HIV had diffuse infiltrates on x-rays. Cavity lesions were seen predominantly in TB infection with no comorbidities or patients with liver disease. (Table 3). The data showed that patients with deranged renal function test (RFT) had more effusion (Table 3). The various radiological presentations had no relation with the blood counts or haemoglobin of the patients. Presence of anaemia, was more in the younger population, and was positively associated with leukopenia and prolonged hospitalisation significantly by 3 days. Urosepsis, HIV, MDR-TB and type 2 diabetes in the patients prolonged hospitalisation stay. Seven patients with previous history of TB had no comorbidities, eight patients with history of previous TB had diabetes. MDR-TB was more common in patients with comorbidities.

Characteristics (Mean / median)	Cavity (N = 8)	Effusion (N = 8)	Fibrocavitary (N = 11)	Multiple lesions (N = 10)	Normal CXR (N = 3)	P-Value
Age (years)- median	42.75 (44)	58 (63)	49.27 (50)	47 (50)	50 (50)	0.27
Sex						0.2
Male (N = 18)	6 (75)	4 (50)	3 (27.3)	3 (30)	2 (66.7)	
Female (N = 22)	2 (25)	4 (50)	8 (72.7)	7 (70)	1 (33.3)	
Urea (mg / dL)- median	21.575 (17.5)	101.4 (81.8)	28.79 (31.5)	30.62 (28.6)	26.03 (24.1)	< 0.01
Creatinine (mg / dL) - median	0.77 (0.75)	2.15 (1.385)	0.8 (0.79)	0.96 (1.02)	0.68 (0.7)	< 0.01
HbA1c (%)- median	8 (7.45)	7.55 (6.4)	5.67 (5.7)	8.24 (7.4)	6.13 (5.7)	0.08
Hb (g / dL) - median	10.15 (9.15)	11.14 (11.45)	10.65 (11.1)	10.3 (10.1)	8.23 (8.6)	0.08
TC (1000 / dL) - median	11.79 (10.5)	12.16 (11.5)	11.09 (9.7)	14.321 (14.2)	12.47 (10)	0.88
Albumin (g / dL) - median	3.02 (3.295)	2.23 (2.245)	2.94 (3.06)	2.54 (2.9)	2.67 (2.45)	0.17
FBS (mg / dL) - median	190.5 (160)	158.9 (129)	119.1 (104)	222.6 (172)	156.5 (116.5)	0.30
Hospital stay (days) - median	9.75 (9.5)	14.38 (12.5)	10.91 (12)	15.9 (16)	10.67 (5)	0.12
AFB (n)						0.40
Negative	0	0	0	2 (20)	0	
1 + (N = 14)	5 (63.5)	2 (25)	4 (36.4)	3 (30)	0	
2 + (N = 9)	0	2 (25)	3 (27.3)	2 (20)	2 (66.7)	
3 + (N = 13)	2 (25)	4 (50)	3 (27.3)	3 (30)	1 (33.3)	
Scanty (N = 2)	1 (12.5)	0	1	0	0	
TB (N)						
PTB	6 (75)	8 (100)	5 (45.4)	4 (40)	3 (100)	
MDR-TB	2 (25)	0	6 (54.5)	6 (60)	0	
Previous history of TB (n)	3 (37.5)	4 (37.5)	5 (45.4)	3 (30)	1 (33.3)	
Smoking (pack years) - median	10.125 (12)	7.125 (8)	3.45 (0)	3.2 (0)	9.67 (14)	0.21
Alcohol consumption (%)	7 (87.5)	4 (50)	4 (36.36)	4 (40)	3 (100)	0.12

Table 1. Characteristics of TB in Patients According to Their Radiological Presentation

Parameter	Urine Routine (Median IQR) Normal (N = 22)	Sugar 4 + (N = 2)	UTI (N = 16)	P-Value
FBS (mg / dL)	116.5 (95, 180)	518 (388.5, 389.7)	132.5 (106.5, 256.7)	0.02
HbA1c (%)	6.20 (5.70, 7.10)	13.5 (10.12, 11.37)	7.10 (5.72, 10.92)	0.02
Urea (mg / dL)	21 (14, 40)		36.3 (25, 221)	0.01
Creatinine (mg / dL)	0.7 (0.44, 0.99)		1.06 (0.8, 4.4)	0.01
Cavity (n)	15		4	
Diffuse infiltrates (n)	0		6	
Effusion (n)	2		8	
Fibrosis	9		6	

Table 2. Analysis of Urosepsis

Characteristics (Mean with Median)	ALD (N = 2)	CKD + DM (N = 4)	HIV + DM (N = 2)	HIV (N = 2)	Hydatid cyst (N = 2)	Normal (N = 16)	DM (N = 12)	P-Value
Age (years) - median	47 (47)	55 (65)	50 (50)	45 (45)	47.5 (47.5)	52.94 (52.5)	43.5 (44.5)	0.69
Sex								
Male (N = 18)	1 (50)	0	1 (50)	0	0	7	9	
Female (N = 22)	1	4	1	2	2	9	3	
Creatinine (mg / dL)	0.70	3.30	1.1	1.06	0.90	0.81	0.83	< 0.01
HbA1c (%) - median	5.10	9.20	7.40	5.50	6.40	5.65	9.30	< 0.01
UTI (n)	0	4	2	2	2	4	2	< 0.01
Albumin (g / dL) - median	1.80	2.25	2.20	1.01	2.90	2.77	3.22	< 0.01
FBS (mg / dL) - median	95 (95)	216 (200)	118.0 (120)	105 (105)	172 (174)	99.18 (110)	280.83 (282)	< 0.01
VLDL (mg / dL) - median	20	40.40	26.20	18.60	9.80	22.64	26.30	< 0.01
Hospitalization (days) - median	11.1875 (12)	14 (114)	12 (12)	14 (14)	19 (19)	6.5 (6.5)	13.83 (15)	< 0.01
AFB (n)								0.62
Negative	0	0	0	0	0	0	2 (16.67)	
1 +	0	1 (25)	1 (50)	1 (50)	1 (50)	4 (25)	6 (50)	
2 +	0	1 (25)	0	1 (50)	0	6 (37.5)	1 (8.3)	
3 +	2 (100)	2 (50)	1 (50)	0	1 (50)	5 (31.2)	2 (16.67)	
Scanty	0	0	0	0	0	1 (6.2)	1 (8.3)	
TB (n)								0.09
PTB	2 (100)	4	0	0	2 (100)	10 (62.5)	6 (50)	
MDR-TB	0	0	2 (100)	2 (100)	0	6 (37.5)	4 (33)	
Previous history of TB (n)	0	0	0	0	0	7	8	
Smoking (pack years) - median	10 (10)	1.5 (0)	7.5 (7.5)	3 (3)	0	5.1875 (0)	8.92 (10.5)	0.488
Alcohol consumption (%)	2	2	2	0	0	9	8	0.13
Effusion (n)	0	4	0	0	0	6	0	
Cavity (n)	2	0	0	0	0	12	5	
Lymph nodes (n)	0	1	0	0	0	3	5	
Fibrosis (n)	0	0	0	0	0	10 (62.5)	3 (25)	

Table 3. Characteristics of TB in Patients According to Their Comorbidities

DISCUSSION

Our study done on a total of 40 subjects, including 22 females and 18 males, was to present the correlation between parameters like fasting blood sugar (FBS), HbA1c, blood counts, radiological findings, liver function and renal functions in tuberculosis and to demonstrate the relation of TB with other comorbidities like diabetes, HIV, renal disease, and liver disease. It is shown that diabetes exhibits a risk for pulmonary tuberculosis (PTB) as shown in the study by Christie Y Jeon,[19] and in Korea,[20] may impact the radiological parameters as seen on chest x-rays.

Various biochemical parameters that were included showed presence of anaemia in 20 patients and hyperglycaemia in 26 patients, hypoalbuminemia in 34 patients, hypoproteinaemia in 20 patients, uncontrolled glycosylated haemoglobin in 18 and urosepsis in 16 patients.

In our study, half of the patients were anaemic, and half patients had HbA1c > 6.5 % whereas, eight patients were pre-diabetic (HbA1c 6 - 6.5 %). A study done in Peru, has shown strong association of low Hb with TB.[10] The lower levels of HbA1c, attributing to low Hb levels is due to decrease in life span of red blood cells. Another alternate hypothesis suggested is alteration of the quaternary structure of Hb and glycation of beta globin chain occurs easily in the absence of iron.[31] A Mexican study, showed similar radiological relations as our study but showed lower total leukocyte counts of around 8800 cells / dL as compared to 12350 cells / dL in ours.[9]

Our study has shown that TB patients with FBS more than 110 mg / dl, and HbA1c > 6 % have atypical findings of bronchiectasis, hydropneumothorax, hilar involvement, and interstitial involvement. Study done in Taiwan has shown similar results.[7] Another Study done in India has shown similar results as well.[8] (Table 2). An Italian.[23] and Chinese.[28] have shown higher TB prevalence among diabetics and studies in Qatar.[30] and Texas.[29] have shown diabetes to be associated with increased risk of active TB. An Indonesian study.[26] has shown the negative effect of DM on TB treatment and screening for DM followed by adequate glycaemic control may improve the outcome of TB.

In our study, 14 patients have an increase in cholesterol / HDL ratio of > 5, compared to hypocholesterolaemia in other studies.[11] Our study also has no relation of lipid profile with TB, which coincided with a study in Ethiopia which has shown no relation of total cholesterol with TB.[12]

Our study also explored the correlation between glycaemic status and radiological manifestations of PTB in diabetic patients showing that patients with a higher level of HbA1c showed multiple lesions, fibrosis and cavitary lesions on chest x-rays, having more advanced disease. (Table 3). Chest x-ray showing cavity and multiple lesions had median HbA1c > 8 % which was consistent with the findings of the study done in Taiwan.[7] however it did not show any significance (Table 1). Our study shows the association of cavitatory lesions in patients of TB with poor glycaemic control (Table 3) as shown in the study in Taiwan,[15] and Saudi Arabia showed similar results which were more frequently confined to lower lung fields.[24]

Accompanying the unusual chest x-ray findings, our study showed that patients with diabetes had significant increase of fibrosis and cavity. (Table 3) Patients with CKD had higher risk of pleural effusions. Patients with poor blood sugar had increased risk of developing advanced disease with delayed sputum conversion and treatment failure. The substantial connection of PTB and other comorbidities showed increasing frequency of atypical radiological findings on chest x-ray making it difficult to interpret and delaying the diagnosis, resulting in considerable lung involvement and treatment failures. A meta-analysis by Meghan A Baker, et al.[18] confirmed that patients with comorbidities like diabetes and CKD have worse outcome. Subjects with UTI had a strong relation with hyperglycaemia and high HbA1c further showing the relation of TB with UTI and poor glycaemic control. Our study showed the presence of UTI was significantly associated with higher incidence of multiple lesions, effusion and diffuse infiltrates. 40 % of subjects with UTI had strong relation with hyperglycaemia and high HbA1c. Our study has shown strong relation of TB and UTI with bad glycaemic control. (Table 2)

Our study also showed the increasing risk of MDR-TB in HIV and DM (Table 3). Studies have shown HIV to be a risk factor for the development of MDR-TB.[16,22] and has shown to be associated with increasing resistance to ATT.[17] Study in John Hopkins's.[21] has shown that there is a need for assessment of drug-drug and drug-disease interactions for TB-HIV co-infection. Eight of the patients with diabetes have a previous history of TB showing reinfection. Association of alcohol and tobacco were seen with reduced incidence of fibrosis. A Kenyan study showed smoking to be a significant risk factor for developing DM in TB patients.[27] Study in Saudi.[25] showed association with diabetes did not alter the final treatment outcome among TB patients.

CONCLUSIONS

The major finding of this study has been with regard to glycaemic index, haemoglobin, protein, RFT and radiological findings. Regular blood glucose, HbA1c, sputum monitoring, prevention of anaemia can be beneficial to patients suffering from TB, to reduce hospital stay. Early detection and treatment of HIV and diabetes would be beneficial in reducing lung lesions. Compliance to treatment with above measures would reduce MDR-TB.

Limitations

The other limitations of this study was the small sample size due to poor financial condition of patients and stigma associated with tuberculosis may have reduced the correlation with other factors like lipid profile, bilirubin, smoking, hospital stay and other radiological findings.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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