

Original Research Article

Effect of Diabetes and Pre-Diabetes and its associated risk factors on treatment outcome of TB patients attending Government Hospitals in Haldwani of District Nainital, UttarakhandSaurabh Shukla^{1*}, CMS Rawat², R.G Nautiyal³¹Assistant Professor, Department of Community Medicine, IIMS&R, Lucknow, Uttar Pradesh, India²Principal and Dean, VCSGIMS&R Srinagar, Garhwal, Uttarakhand, India³Professor, Former Dean SSJGIMSR, ALMORA, Uttarakhand, India

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Abstract

Background: Diabetes mellitus has the potential to fuel the epidemic of tuberculosis (TB). The world seems to face a looming co-epidemic of TB-diabetes, and that this is a serious public health issue we need to address urgently. DM may have a negative impact on the outcome of TB treatment: higher failure rates, higher rates of all-cause mortality, and death specifically related to TB. **Methods:** This study is a hospital based prospective study carried out in Government Medical College & Dr. Sushila Tiwari Government Hospital and S.S.J Base hospital, Haldwani, District Nainital of Uttarakhand. **400 tuberculosis patients** who were registered to DOTS center of Government Medical College, Haldwani and S. S. J. Base Hospital, Haldwani in the third quarter (July to September) of the year 2015 were included in the study by Systematic random sampling. **Results:** The mean age of the study participants was 37.8±15.9 years. Hypertension and smoking were associated with unsuccessful treatment outcome. It was seen that Diabetic patients were significantly associated with unsuccessful treatment outcome (38.2% vs 21.3%). There was no effect of Pre-Diabetes on TB treatment outcome. **Conclusion:** This converging of two epidemics should be a wake-up call for all clinicians and researchers to gear-up to meet the challenge of patients afflicted by tuberculosis as well as diabetes. It is time that the “unhealthy partnership” of tuberculosis and diabetes receives the attention it deserves

Keywords: Diabetes, Tuberculosis, DOTS

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Introduction

Diabetes mellitus has the potential to fuel the epidemic of tuberculosis (TB). The world seems to face a looming co-epidemic of TB-diabetes, and that this is a serious public health issue we need to address urgently.

Similarly, not only diabetes, but also prediabetes (impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)), may affect the risk and course of tuberculosis infection and disease. Various mutual risk factors most likely confound the course of TB when present with DM. If we could identify these mutual risk factors we may be able to improve the outcome of the disease.

From the various studies it is evident that diabetes increases the susceptibility of several infectious agents, primarily bacterial and fungal infections by altering host-defence and environment for the infecting microorganism[1]. That an association exists between DM and Tuberculosis has also been documented throughout history. From the ancient time until the beginning of the twentieth century, diabetes was considered a co-morbidity among tuberculosis patients[2-4]. Diabetes can also affect the response of TB treatment as it may lead to impaired renal function and an increased risk of drug toxicities. Also, DM is reported as a predictor of drug induced liver injury (DILI) [5]. Hepatic toxicity due to anti tuberculosis drugs may also be increased[6,7]. With respect to the long-term prognosis for these patients, diabetes is a risk factor for death. DM may have a negative impact on the outcome of TB treatment: higher failure rates[6,8] higher rates of all-cause mortality, and death specifically related to TB.

Now that the relationship between DM and TB has been widely accepted, there has been an influx of various recent studies and publications discussing or investigating the existence and magnitude of any such associations, and the relevance of any such associations but still there is a lacking of such studies in Uttarakhand, especially in Kumaun region. So, this study was conducted to know the prevalence of looming co-epidemic of TB-diabetes.

Material and methods**1. Study design**

It is a hospital based Prospective study.

2. Study place

This study was carried out in Government Medical College & Dr. Sushila Tiwari Government Hospital and S.S.J Base hospital, Haldwani, District Nainital of Uttarakhand.

3. Ethical clearance

Ethical clearance was obtained before conducting the study from the Institutional Ethical Committee of Government Medical College, Haldwani.

4. Study population

Tuberculosis Patients who were registered to DOTS center of Government Medical College, Haldwani and S. S. J. Base Hospital, Haldwani in the third quarter (July to September) of the year 2015 were included in the study.

Inclusion criteria

All diagnosed TB patients (both pulmonary and extrapulmonary) who gave consent were recruited into the study

Exclusion criteria

- Those patients who refuse to participate.
- Patients who were transferred out

1. Sampling method

Systematic Random sampling

2. Sample size

The total sample size was estimated by using the formula: $n = 1.96 * 1.96 * PQ/D^2$

Level of significance = 5%

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Expected prevalence = 50%
 Permissible level of error in the estimate = 5%
 P = prevalence of morbidity (50 %)
 Q = (1-P) that is (50 %)
 D = permissible level of error in the estimate which is taken as 5%
 Sample Size (n) = $(1.96)^2 (0.5) (0.5) / (0.05)^2$
 = 384.16
 = 385 ; so we took 400 TB patients as our sample
 k =N/n
 = 836/385
 = 2.17 ≈ 2
 : k is sample interval
 : N is total TB patients in both TB unit in 3rd quarter of 2014
 : n is sample size calculated.
 So, we selected every alternate TB patient in our study to complete our sample which was 400.

Data collection

A predesigned and pretested semi structured questionnaire was administered and required information was obtained from the Tuberculosis patients registered in the DOTS center using the interview method. Questionnaire consisted of 7 parts which included socio-demographic profile, morbidity history, personal history, past history, family history, symptoms and examination including investigations.

Study Tools

1. Interview
2. Clinical examination
3. Investigation and
4. Record analysis

All patients were subjected to the following:

1. Medical history taking.
2. Clinical examination including both general and local examination..
3. Radiological examination: Plain chest X-ray PA view
4. Sputum analysis: by Ziehl Neelsen stain for acid fast bacilli.
5. Follow up: It was done at 5th month
- i. Clinically: as regards symptomatic improvement and weight gain.
- ii. Radiologically: by plain chest X-ray.
- iii. Laboratory: by repetition of blood picture, ESR, liver and kidney functions.

iv. Sputum smear analysis by ZN stain as two samples were collected for smear examination.

Interpretation of laboratory tests

Fasting blood glucose was done in all patients with a glucometer. Pre diabetes and Diabetes were diagnosed as per WHO guidelines. The sputum smear result, HIV status, and the Tuberculin test were reviewed from the Case Folders. Grading of Sputum was done according to RNTCP guidelines.

1. Data analysis and presentation

The data obtained on a predesigned, pretested semi structured questionnaire was coded & entered in Microsoft Excel. Analysis was done using SPSS version 22 and descriptive interpretation of data was done. The comparison of means was done using the student t-test while qualitative variables was compared using the Chi-square test. P value less than 0.05 were taken as significant.

Results

The mean age of the study participants was **37.8±15.9 years**. Among those male participants (**42.5±15.3 years**) were significantly older than female participants (**34.7±15.9 years**). Mean BMI of the TB patients was **20.5±4.1 kg/m²** with female participants (**22.6±5.1 kg/m²**) having significantly higher mean BMI than Male (**19.8±3.2 kg/m²**). Hinduism (73.8%) was the predominant religion among study participants.

Gender difference was significantly noted in sociodemographic characters like marital status (76% vs 56.5%) with majority of male being married, education (83.3% vs 74%) with majority of male being educated, and occupation (72% vs 39.6%) with majority of male being employed.

Gender difference was not noted in the dwelling areas, i.e., urban vs rural. Smoking habit in any form (50.8% vs 9.7%) and consumption of alcohol (43.1% vs 3.9%) was significantly higher among male. There was no significant difference in systolic blood pressure whereas diastolic blood pressure was higher in men compared to women (79.4±7.1 vs. 77.8±6.1 mmHg). The proportion of subjects with positive family history of TB was more among men (25.2% vs 14.3%).

Out of 400 patients, 49(12.3%) patients had Pre-Diabetes and 98(24.5%) had diabetes and prevalence of diabetes was significantly higher in men compared to women [(28.5% vs 18.2%); p = 0.02]

Table1: Socio-demographic Characteristic of Study Participants

SNo.	Characteristic	Total	Male	Female	Pvalue	
1.	Age (years)	37.8±15.9	42.5±15.3	34.7±15.9	<0.001	
2.	BMI (kg/m ²)	20.5±4.1	19.8±3.2	22.6±5.1	<0.001	
3.	Religion	Hindu	295(73.8)	184(74.8)	111(72.1)	0.08
		Muslim	92(23.0)	56(22.8)	36(23.4)	
		others	13(3.3)	6(2.4)	7(4.5)	
4.	Marital Status	Married	274(68.5)	187(76.0)	87(56.5)	<0.001
		Unmarried	102(25.5)	43(17.5)	59(38.3)	
		Widowed	24(6.0)	16(6.5)	08(5.2)	
5.	Location	Urban	149(37.3)	87(35.4)	62(40.3)	0.32
		Rural	251(62.7)	159(64.6)	92(59.7)	
6.	Education	Illiterate	81(20.3)	41(16.7)	40(26.0)	0.024
		Literate	319(79.7)	205(83.3)	114(74.0)	
7.	Occupation	Unemployed/housewife/ student	162(40.5)	69(28.0)	93(60.4)	<0.001
		Employed	238(59.5)	177(72.0)	61(39.6)	
8.	Smoking	Present	140(35.0)	125(50.8)	15(9.7)	<0.001
		Absent	260(65.0)	121(49.2)	139(90.3)	
9.	Alcohol	Present	112(28.0)	106(43.1)	6(3.9)	<0.001
		Absent	288(72.0)	140(56.9)	148(96.1)	
10.	Blood Pressure	SBP	121.8±12.2	121.9±12.9	121.6±11.1	0.73
		DBP	78.8±6.7	79.4±7.1	77.8±6.1	0.007
11.	Family H/O TB	Present	84(21.0)	62(25.2)	22(14.3)	0.009
		Absent	316(79.0)	184(74.8)	132(85.7)	
12.	Pre-Diabetic	Present	49(12.3)	33(13.4)	16(10.4)	0.37
		Absent	351(87.7)	213(86.6)	138(89.6)	

13.	Diabetes	Present	98(24.5)	70(28.5)	28(18.2)	0.02
		Absent	302(75.5)	176(71.5)	126(81.8)	

Effect of various factors on TB treatment outcome is shown in Table 2.

There was no effect of increasing age, Gender, or marital status on treatment outcome of the patients. Education level and occupation was significantly associated with TB treatment outcome. It was found that uneducated people had more unsuccessful outcome of treatment as compared to educated people [odds ratio 1.82 (1.03-3.22); p value 0.036]. It was also seen that unemployed people had more unsuccessful outcome of TB treatment [odds ratio=1.84 (1.11-3.04); p value 0.02]. It was seen that Diabetic patients were significantly associated with unsuccessful treatment outcome (38.2% vs 21.3%) [odds ratio= 2.28 (1.34-3.89); p value 0.002]. There was no effect of Pre-Diabetes on TB treatment outcome.

Table2: Effect of various factors on TB treatment outcome

	Characters	Unsuccessful		Successful		Total		Odds ratio (95% CI)	P value
		No.	%	No.	%	No.	%		
Age	<30 years	31	40.8	138	42.6	169	42.3	1.08 (0.65-1.79)	0.78
	≥30 years	45	59.2	186	57.4	231	59.2		
Sex	Male	48	63.2	198	61.1	246	61.5	1.09 (0.65-1.83)	0.74
	Female	28	36.8	126	38.9	154	38.5		
Marital status	Married	51	67.1	223	68.8	274	68.5	1.08 (0.64- 1.85)	0.77
	Unmarried/widowed	25	32.9	101	31.2	126	31.5		
Education	Uneducated	22	28.9	59	18.2	81	20.3	1.82 (1.03-3.2)	0.036
	Educated	54	71.1	265	81.8	319	79.8		
Occupation	Unemployed	40	52.6	122	37.7	162	40.5	1.84 (1.11-3.04)	0.02
	Employed	36	47.4	202	62.3	238	59.5		
Diabetes	Present	29	38.2	69	21.3	98	24.5	2.28 (1.34-3.89)	(0.002)
	Absent	47	61.8	255	78.7	302	75.5		
Pre-Diabetes	Present	12	15.8	37	11.4	49	12.3	1.39 (0.34-1.39)	(0.3)
	Absent	64	84.2	287	88.6	351	87.8		

Effect of various risk factors in TB treatment outcome is shown in table 3. It was seen that patients with Past history of TB had unsuccessful treatment outcome [odds ratio 3.21 (1.89-5.62); p value <0.001]. Hypertension was also associated with unsuccessful treatment outcome [odds ratio=3.15 (1.69-5.88); p value<0.001]. It was also seen that smokers were associated with poor TB treatment outcome [odds ratio=1.78 (1.07-2.96); p value 0.02]. There was no effect of alcohol intake, type of TB case and HIV status on TB treatment outcome.

Table 3: Effect of various risk factors on treatment outcome

	Characters	Unsuccessful		Successful		Total		Odds ratio (95% CI)	Pvalue
		No.	%	No.	%	No.	%		
History of TB	Present	30	39.5	54	16.7	84	21.0	3.21 (1.89-5.62)	<0.001
	Absent	46	60.5	270	83.3	316	79.0		
HTN	Present	20	26.3	33	10.2	53	13.3	3.15 (1.69-5.88)	<0.001
	Absent	56	73.7	291	89.8	347	86.8		
Alcohol	Absent	50	65.8	238	73.5	288	72.0	1.43 (0.84-2.46)	0.18
	Present	26	34.2	86	26.5	112	28.0		
Smoking	Present	35	46.1	105	32.4	140	35.0	1.78 (1.07-2.96)	0.02
	Absent	41	53.9	219	67.6	260	65.0		
Type of TB	Extra pulmonary	9	11.8	48	14.8	57	14.2	0.77 (0.36-1.65)	0.50
	Pulmonary	67	88.2	276	85.2	343	85.8		
HIV status	Positive	1	1.31	4	1.25	5	1.26	1.07 (0.12-9.68)	0.95
	Negative	75	98.69	320	98.75	395	98.74		

Multivariate analysis of various factors is shown in Table 4.

Non-significant variables: Age, Sex, marital status, alcohol intake, type of TB, HIV status. Table 4 shows that education and occupation was significantly associated with treatment outcome. Uneducated group were at a higher risk of unsuccessful treatment outcome as compared to educated group [odds ratio 1.917 (1.05-3.52)]. Unemployed patients were also at a higher risk of unsuccessful treatment as compared to employed patients [odds ratio 2.34 (1.28-4.29)]. Patients with history of TB were at a higher risk of having unsuccessful treatment as compared to patients having no history of TB; [odds ratio 2.99 (1.64-5.45)]. Hypertension was also associated with higher risk of unsuccessful treatment as compared to patients with no history of hypertension; [odds ratio 2.46 (1.25-4.82)]. Presence of DM was also associated with unsuccessful treatment outcome as compared to patients with no DM; [odds ratio 1.95 (1.10-3.46)].

Table 4: Multivariate Analysis of various characters on unsuccessful treatment outcome

Explanatory variable	Odds ratio	95% CI	Pvalue
Marital status	Married	1.00	
	Unmarried/ widowed	1.31	0.65-2.63
Education	Educated	1.00	
	Uneducated	1.917	1.05-3.52
Occupation	Employed	1.00	
	Unemployed	2.34	1.28-4.29
History of TB	Absent	1.00	
	Present	2.99	1.64-5.45
History of HTN	Absent	1.00	
	Present	2.46	1.25-4.82
Smoking	Absent	1.00	

	Present	1.05	0.49-1.72	0.91
Diabetes	Absent	1.00		
	Present	1.95	1.10-3.46	0.02
Pre-Diabetes	Present	1.00		
	Absent	0.66	0.29-1.47	0.86

Discussion

The present work was conducted to know the effect of Pre-Diabetes and Diabetes and its associated risk factors on treatment outcome of Tuberculosis patients in Haldwani block of Nainital District. With diabetes on the rise in TB-endemic areas, our findings highlight the impact of diabetes, now type 2, on TB control in regions where both diseases are prevalent. Despite a good national TB programme in India, the diabetes epidemic is hampering TB control efforts which can also be seen by the results of our study. The present study showed that prevalence rates of DM and pre-diabetes were 24.5% and 12.3% respectively among TB patients registered under RNTCP. Diabetes was more prevalent among men than women (28.5% vs. 18.2%) while there was no gender difference in the prevalence of pre-diabetes. Male predominance can be explained in a way that males are more exposed to risk factors like smoking, tobacco use and alcohol consumption which impact both TB and DM. Studies conducted in regions with dual burden had reported that the prevalence of DM ranged from 14–40% [9]. A case control study conducted in Bangalore, South India, during 2001–2003 reported that chronic disease particularly diabetes was a significant risk factor for developing TB. The prevalence rates of diabetes in TB and non-TB subjects were 22.2% and 15.9% respectively [10]. Outcome of TB treatment was seen in terms of successful (Cured, Treatment completed) vs Unsuccessful (treatment failure, Loss to follow-up, death). Diabetic patients were significantly more likely to have a treatment failure [odds ratio= 2.28 (1.34-3.89); p value 0.002] while no significant association was seen with treatment outcome among TB patients with Pre-Diabetes. Nandakumar et al [11] also found unfavourable outcome in TB patients with DM [Odds ratio 1.25 (1.02-1.53)]. Chiang et al [12] also found unfavourable TB treatment outcome in TB patients with DM [odds ratio 1.65 (1.22-2.24)]. It may be because presence of hyperglycaemia results in decreased immunity and also in impaired repair capacity. Furthermore it causes an elevated resting cytokine production in non-stimulated peripheral blood mononuclear cell (PBMCs), whereas reduced concentrations of cytokines have been seen in diabetes patients after antigen stimulation of PBMCs. This may lead to prolongation or even failure of treatment. Education level and occupation was significantly associated with TB treatment outcome. It was found that uneducated people had poor outcome of treatment as compared to educated people [odds ratio 1.82 (1.03-3.22); p value 0.036]. It was also seen that unemployed people had poor outcome of TB treatment [odds ratio=1.84 (1.11-3.04); p value 0.02]. It could be explained by the fact that better educated people have better understanding of the disease and its risk factors and adhere well to the required TB treatment. Age, sex and marital status were not found to be associated. On multivariate analysis also uneducated patients [odds ratio 1.92 (1.05-3.52)] were found to be at higher risk of unsuccessful treatment. Occupation-wise also unemployed patients were at a higher risk of unsuccessful treatment. [Odds ratio 2.34 (1.28-4.29)] History of TB, History of Hypertension, and Smoking were significantly associated with treatment outcome. It was found that patients with past history of TB had more risk of unsuccessful treatment outcome [odds ratio=3.21 (1.89-5.62); p value <0.001]. Hypertension was associated with poor treatment outcome [odds ratio=3.15 (1.69-5.88); p value <0.001] and smokers were also associated with unsuccessful TB treatment outcome [odds ratio=1.78 (1.07-2.96); p value 0.02]. It may be because cigarette smoke exposure severely impairs Type 1 immunity in the lung which may locally cause effect on innate immune cells in the lung. Study by Nandakumar et al [11] found similar results, age >45 years [odds ratio 2.06 (1.71-2.50)], pulmonary TB [Odds ratio 1.72 (1.38-2.14)], Retreatment cases [Odds ratio 1.64 (1.34-2.01)] and sputum positive

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status [Odds ratio 1.41 (1.19-1.68)] to be associated with unfavourable treatment outcome. Chiang et al [12] in their study found that male sex [Odds ratio 1.65(1.22-2.24)], age >45 years [odds ratio 2.61 (1.43-4.74)], smear positive [Odds ratio 1.53 (1.08-2.18)], smoking [odds ratio 1.48 (1.09-2.01)] and retreatment cases [odds ratio 1.86 (1.27-2.73)] and DM comorbidities [odds ratio 4.66 (3.13-6.93)] were associated with unfavourable treatment outcome.

Considering the growing trend in prevalence of diabetes and huge burden of latent TB infection amongst Indian population, there is a need for greater collaboration between RNTCP now (NTEP) and National Program for Prevention and Control for Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) in India to ensure that protocols and guidelines are in place to address the dual burden.

This converging of two epidemics should be a wake-up call for all clinicians & researchers to gear-up to meet the challenge of patients afflicted by tuberculosis as well as diabetes.

It is time that the “unhealthy partnership” of tuberculosis and diabetes receives the attention it deserves.

Being forewarned and prepared gives a better chance of reducing the dual burden of disease of DM and TB.

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