www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i9.17

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Effect of Glycemic Control on Radiographic Presntation of Pulmonary Tuberculosis in Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: *Tuberculosis (TB) remains to be a major cause of morbidity and mortality throughout the world. The link of Diabetes (DM) and TB is more prominent in developing countries and the higher susceptibility of tuberculosis in diabetics may be related to a longer duration of disease or due to poor glycemic control.*

Aims: *To study the effect of glycemic control on radiographic presentation of pulmonary Tuberculosis in Diabetics.*

Methodology: *It"s a prospective cross sectional study. Patients above 18 years, having Pulmonary Tuberculosis with Diabetis Mellitus were included.*

Pulmonary Tuberculosis with other immunocompromised conditions like HIV, Chronic kidney disease, Malignancy, Long term steroids, Immunosuppressive drugs were excluded.

Glycemic control was assessed by glycated haemoglobin (HbA_1C)<7 as controlled >7 as uncontrolled. Demographic, Clinical and Radiographic parameters were studied in respect to their glycemic control.

Results: *There were 200 tuberculosis patients, 88 were diabetic, with 44%prevalence. The mean age was 52.13+10.93; 52%were males, mean HbA_1C was 9.04±1.70; 93.2%had uncontrolled glycemic status.78(59.0%) had lower lung field abnormalities;mean HbA_1C 8.87, 39(29.5%)had upper lung field; HbA_1C 9.25 and 11.3%both lung fields; HbA_1C 9.36. 108(81.8%)had nodular infiltrative lesions, 18(13.6%)had cavities; HbA_1C 9.88. 83.3%had cavities in lower lung fields.*

Conclusion: *Prevalence of Diabetes among Pulmonary Tuberculosis is in the rise with uncontrolled diabetic patients predominantly affected. Lower lung field involvement with atypical radiographic presentations are more common in patients with diabetes. Patients with poor glycaemic control demonstrated cavitary lesions more than their counterparts but has no significant effect on zonal distribution of the radiographic lesion.*

Key Words: *Pulmonary Tuberculosis, Diabetes Mellitus, Glycemic control, Glycated Haemoglobin, HbA_1C,*

Introduction and Background

Tuberculosis (TB) remains to be a major cause of morbidity and mortality throughout the world. It is estimated that one-third of the world's population is infected, and the prevalence of TB has been rising in recent years globally. Worldwide in 2015, there were an estimated 10.4 million incident TB cases. 62% of these cases were males, and 90% of cases were adults. Six countries accounted for 60% of the global total: India, Indonesia, China, Nigeria, Pakistan and South Africa[1].

Incidence of tuberculosis is greatest among those with conditions impairing immunity, such as human immunodeficiency virus (HIV) infection and diabetes. Associations between diabetes and tuberculosis are increasingly recognized; the link of DM and TB is more prominent in developing countries where TB is endemic and the prevalence of Diabetes is rising. Although infection with Human Immunodeficiency Virus (HIV) is considered as the most potent risk factor for TB, the high prevalence of DM in the world and its effect on TB burden is greater than HIV infection in many studies[2].

WHO estimates that, globally, 422 million adults are living with diabetes in 2014. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014.[3] The total number of diabetic people worldwide is predicted to rise from 285 million in 2010, accounting for 3.5 million deaths, to 439 million in 2030[2,4]. Diabetes prevalence has been rising more rapidly in middle- and low-income countries. Up to 80% of patients with DM live in low income and developing countries. Asia is the epicenter of the growing burden of DM and the largest contribution is from India and China.

Notably, Pulmonary TB is the ninth most frequent complication of DM[5]. Reviews and meta-analyses suggest that the incidence of active diagnosed tuberculosis is two- to- three times higher in those with diabetes compared to those without diabetes; that diabetes increases the risk of death from diagnosed tuberculosis and that diabetes may increase the risk of tuberculosis relapse [6,7].

The definite pathophysiological mechanism of the effect of DM as a predisposing risk factor for TB is unknown, some hypotheses are suggested: depressed cellular immunity, dysfunction of alveolar macrophages, low levels of interferon gamma, pulmonary microangiopathy, and micronutrient deficiency[8]. The higher susceptibility of tuberculosis in diabetics may be related to a longer duration of disease or due to poor control of glycemic status [2]. Additionally, the risk of TB is higher among patients who are using insulin [9], particularly, those who need higher doses of Insulin .Poor glycemic control has been significantly associated with the occurrence of TB [10]. In one study, there was a correlation between active TB and the level of glycosylated hemoglobin (HbA_1C) (Hazard ratio 1.39, 95% CI: 1.18-1.63 per unit increase) [8].

Till now there were only few articles which studied the effects of glycemic control on the radiographic presentation of TB, even the studies had conflicting results. More over newly diagnosed diabetics are also increasing in patients with Pulmonary Tuberculosis. So in this study we want to see the association of glycemic control on radiographic presentation in Pulmonary Tuberculosis.

Aims and Objectives

To study the effect of glycemic control on radiographic presentation of pulmonary Tuberculosis in patients with Diabetes mellitus.

Materials and Methods

Study design and patient population: It was a prospective cross sectional study, patients presented to the department of Pulmonary medicine Dr PSIMS & RF over a period of one year were taken into the study. Pulmonary Tuberculosis was diagnosed on the basis of clinical presentation, sputum smear microscopy for acid-fast bacilli and chest radiograph. Patients who 1) had a history of DM 2) were treated with insulin or diabetes- specific hypoglycemic agent 3) Denovo by measurement of random and fasting blood glucose (RBG and FBG) were considered as having Diabetes Mellitus.

Inclusion Criteria

Patients of more than 18 years, diagnosed to have both Pulmonary Tuberculosis and Diabetes Mellitus were included in the study.

Exclusion Criteria

Patients having Pulmonary Tuberculosis with other immune compromised conditions like HIV, Chronic kidney disease, Long term steroids,

Malignancy, Immunosuppressive drugs were excluded from the study

Methodology

Institutional ethical committee approval was taken. After obtaining written consent, demographic data, symptomatology and relevant information were collected from the patients. The type of TB was recorded from the notification record as new or previously treated; default, relapse and treatment failure patients were all considered as previously treated. BMI was calculated as weight in Kg divided by height in meters2; values <18 as under nutrition, 18-25 considered as normal BMI, >25 as overweight and >30 as obese.

All patients were undergone routine investigations, sputum smear microscopy for AFB, viral markers and chest radiograph. Glycemic control was assessed by glycated haemoglobin (HbA_1C) using calorimetric method. Patients with HbA_1C of <7 were considered to have controlled and HbA_1C >7 as uncontrolled glycemic status.

Reading of the chest radiographs was focused on 1) the type of lung parenchymal lesion as nodular infiltrates, consolidation, cavitation and others ; pleural effusion and fibrosis were included in others 2) location of opacity as upper lung field, lower lung field and diffuse.

Upper lung field was defined as lesion involving the upper zone and lower lung field as the involvement of mid and lower zone. Demographic profiles and Radiographic parameters of the patients were studied in respect to their glycemic control.

Statistical analysis was done using SPSS version 12.01. Data were described as mean with S.D. and frequencies. Mann-Whitney U and Kruskal Wallis tests were used in calculating P values. P value less than 0.05 was considered as statistically significant.

Results

There were 200 tuberculosis patients who presented to DR PSIMS & RF over a period of one year, of them 88 patients were diabetic, with a prevalence of 44%. 88 patients who were having both diabetes and pulmonary tuberculosis were studied; out of which 52% were males and 48% were females. The mean age was 52.13±10.93, most patients were in the age group of 40- 60 years (68%). Demographic data are described in table:1.

Most patients in the study group 93.2% had uncontrolled glycemic status with HbA_1C of more than 7 (table:2 ,fig:1).The mean HbA_1C was 9.04±1.70, 9.5 in males and 8.5 in females. The mean HbA_1C values were shown in table:3. when compared to new cases, retreatment cases (defaulters, relapse and treatment failures) had higher mean HbA_1C of 10.01 $p<0.01$; Test applied: Mann-whitney U; highly significant. Majority of the patients 93.2% had cough as a presenting symptom with mean HbA_1C of 9.02 followed by dyspnea and fever, but patients with fever 70.4% had high mean HbA_1C of 10.12. There is no correlation of mean HbA_1C levels with symptomatology.

As per the radiographic presentation , out of 88 patients studied, majority had only lower lung field abnormalities 52(59.0%) with mean HbA_1C of 8.87 ; 26(29.5%) had only upper lung field involvement with mean HbA_1C of 9.25 and 11.3% had involvement of both lung fields with HbA_1C 9.36. ($p=0.589$); Test applied: Mann-Whitney U; not significant. Lower lung field involvement was common among females and older age group with a mean age of 53years.(table:4, fig:2)

The type of lesion was determined, most of them 72(81.8%) had nodular infiltrative lesions with mean HbA_1C of 8.88.12(13.6%) had cavitary lesions , their mean HbA_1C of 9.88 was higher when compared to all other lesions, among them, 83.3% had cavities in lower lung fields and females had more cavities than males. (table: 5,fig:3)

Regarding sputum status relatively high proportion of them79.54% were sputum smear positive for AFB with mean HbA_1C of 9.3, only 18 were sputum negative. $p=0.04$; Test applied: Mann-Whitney U; significant.(table:3)

Table 1: Demographic characters

Parameter	Range / Proportion	Frequency	Percentage
Age	< 40	12	13.60 %
	40 – 60	60	68.10%
	> 60	16	18.10%
Sex	Male	46	52%
	Female	42	47.70%
BMI	<18	6	6.80%
	18 – 25	74	84%
	>25	8	9%
Type of case	New case	14	77.20%
	Default	4	18.20%
	Relapse	16	5%
DM duration	Denovo	14	15.90%
	2 months – 5 years	50	37.80%
	5 – 10 years	20	15.10%
	> 10 years	4	4.50%

Table 2 Frequency of HbA_1C

Range	Frequency	Percentage
<7	6	6.80%
7 – 9	40	45.40%
> 9	42	47.70%

Table 3: Mean HbA1c in relation to demographic and clinical parameters

Parameter	Range / Proportion	Frequency	HbA_1c			Mean HbA_1c
			< 7	7 – 9	>9	
Age	20 – 40 years	13.60%	0	4	8	9.2
	41 – 60 years	68.10 %	6	28	26	9.02
	> 60 years	18.10%	0	8	8	8.97
Gender	Male	52%	2	16	28	9.5
		47.70%	4	24	14	8.5
Duration of Diabetes	Denovo	15.90%	0	6	8	9.38
	< 5 years	37.80%	4	22	24	9.16
	5 – 10 years	15.10%	2	10	8	8.49
	>10 years	4.50 %	0	2	2	9
Type of case	New case	77.20%	6	36	26	8.6
	Relapse	5.00%	0	2	2	9.5
	Defaulter	18%	0	2	14	10.76
Symptoms	Cough	93.20%	6	38	38	9.02
	SOB	77.20%	4	24	40	9.42
	Fever	70.40 %	4	20	38	10.12
Sputum status	Neg	20.40 %	2	12	4	8
	Scanty, +1	25.00 %	0	12	10	8.96
	2+ and 3 +	54.50 %	4	16	28	9.46

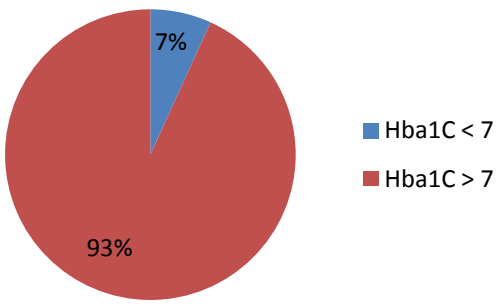
Table 4: - Mean HbA1c in relation to Radiographic Zones

X ray zone	Frequency	Percentage	Mean HbA1c	Males	Females	Mean Age
Upper lung field	26	29.54 %	9.25	16	10	49.9
Lower lung field	52	59%	8.87	28	24	52.4
Both	10	11.30%	9.36	2	8	56.2

Table 5: Mean HbA1c relation to radiographic lesions

Chest X ray lesion	Frequency	Percentage	Mean HbA1c	Upper lung field	Lower lung field	Both	Mean age	Male	Female
Infiltrates	72	81.80 %	8.88	22	46	2	51.8	38	34
Cavity	12	13.60 %	9.88	8	10	6	57	4	8
Consolidation	4	4.50 %	9.44	2	2	0	43	4	0
Others	6	6.80 %	7.76	2	4	0	53.3	6	0

Fig - 1 Frequency of HbA_1C



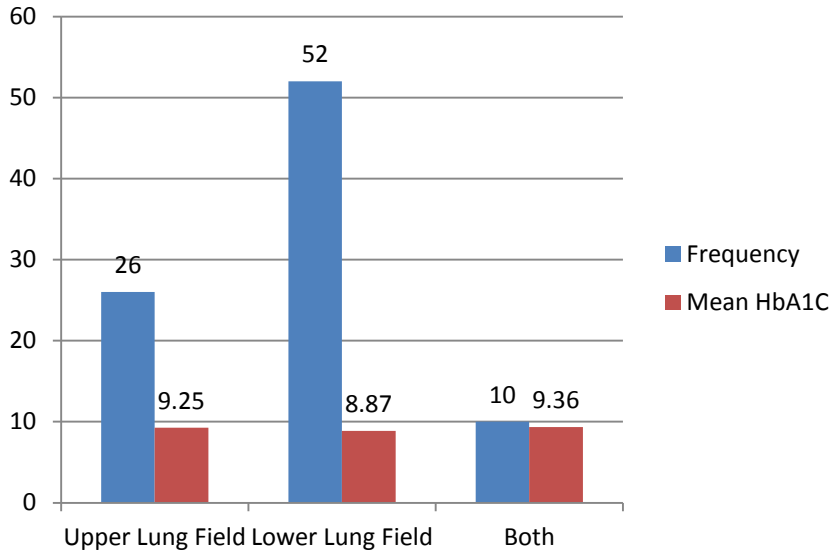


Fig 2: correlation of mean HbA1c with radiographic zone

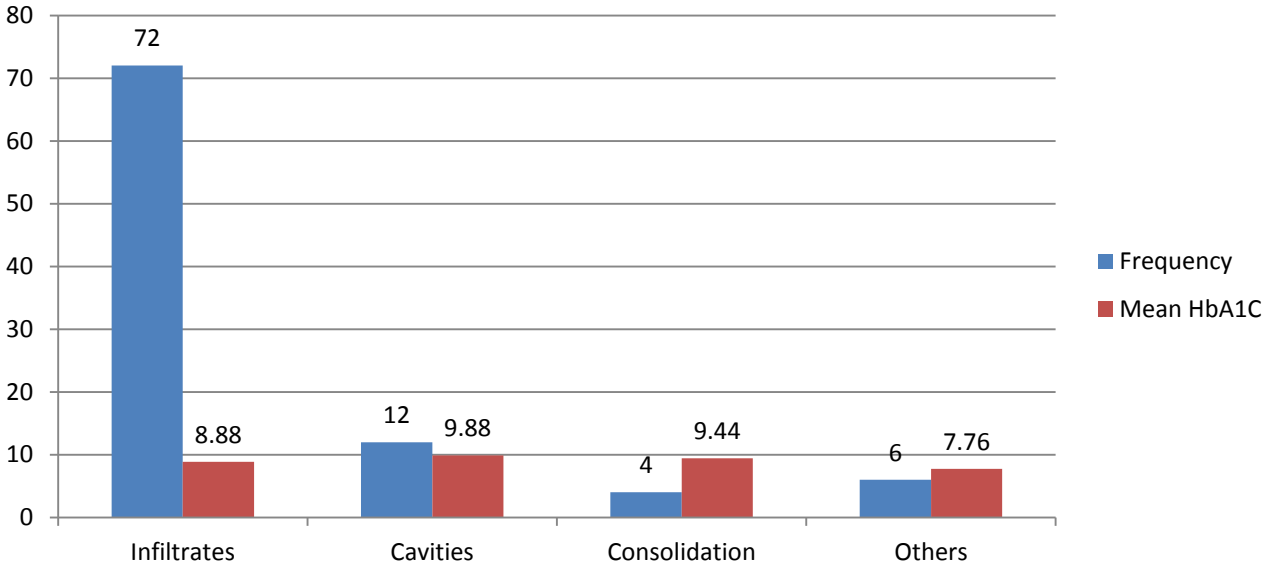


Fig 3 : Correlation of mean HbA1c with radiographic lesions

Discussion

In our study out of 200 patients with Pulmonary Tuberculosis 44% had Diabetes Mellitus. Out of which 52% of them were Males, mean age was 52.13+10.93 years, with mean HbA_1C of 9.04±1.70.

Jagadish Rawat et al, in their study showed the mean age of the patients with PTB-DM as 53.34 +_14.06 in comparison to their non- diabetic counterparts, this is corresponding to our study which showed the mean age as 52.13+10.93 years; that implies diabetic patients with Tuberculosis were relatively older; but in contrast to them our study constituted more number of males.[11]

Majority of the study population 84% had normal BMI of 18-25 ,with only 6.8% had Body mass index of <18, that means most of the diabetic patients with Tuberculosis had normal BMI which is consistent with the study done by Hiowt Amare who reported 62.7% were within the range of 18.5 to 25. [12].

Hardy Kornfeld et al studied 209 pulmonary tuberculosis patients from south India in 2016, they reported 54.1% had associated diabetes[13]. park et al in their study, showed the prevalence of

25.2% of diabetes among Pulmonary Tuberculosis patients in 2012[14]. In comparison to the previous studies, our study also showed high prevalence 44% of Diabetes among Pulmonary Tuberculosis patients .

This explains the increasing prevalence of DM in developing countries like India.

Most of the patients in our study 93.2% had uncontrolled glycemic status of HB A1C more than 7, this was correlating with the study done by Chen –Yuan Chiang which showed 88.8% had HbA_1C more than 7[15]. Payam Tabarsi reported 40% of their study population had normal glycemic control of less than 7 [16],this is in contrast to our study as we found only 6.8% had controlled glycaemic status and majority of the patients were in uncontrolled group. High prevalence of Diabetes; illiteracy, unawareness and low socioeconomic status of the patients may be the causes for improper control of glycemic status in our study.

Patients in the age group of 40-60 years had mean HbA_1C of 9.02, less than 40 years had HbA_1C of 9.2, above 60 years had mean HbA_1C of 8.97, which implies poor glycemic control in younger age groups; this can be due to improper distribution of the study sample in terms of age with very few members in >60 years age group and more number of patients with diabetic duration <5 yrs. we also observed higher HbA_1C values of 9.38 in denovo diabetics, when compared to HbA_1C of 8.97 in patients with DM duration of less than 10yrs, this is in contrast to previous study [17], which showed increase of HbA_1C with increase in duration of Diabetes. This may be due to 1) the patients don't know that they were diabetic 2) the infection itself maybe the cause for higher HbA_1C.

In our study when compared to new cases 77.2% with HbA_1C of 8.6, retreatment cases 22.7% were associated with higher mean HbA_1C of 10.01. This was correlating with the previous studies which showed higher failure rates higher incidence of relapses in diabetics [18]

Most of the patients 93.2% presented with cough as a common symptom with mean HbA_1C of 9.02, followed by dyspnea and fever, but there is no relation of HbA_1C on clinical symptoms. This is correlating with the study done by park who reported no differences in clinical symptoms regardless of diabetes control status[14]. In one study, they reported diabetic TB patients had more symptoms but did not have a more severe form of TB [19].

Majority of the study population 59% had involvement of only lower lung fields, 29.5% upper lung fields. In our study lower lung field involvement was common among females and older age group with a mean age of 53years. A study done by Bacakoglu F, et al showed an association between lower lung field involvement and female gender or age greater than 40 years [20]. A similar study done by Anand K Patel etal in their radiographic presentation of patients of pulmonary tuberculosis with diabetes mellitus showed higher involvement of lower lung field 84% when compared to upper lung field and cavitary lesions more frequently confined to lower lung field [21]. In contrast to our study Bashar et al and Morris JT et al reported higher involvement of upper lung field. [22,23]

The mean HbA_1C of lower lung field was 8.87, mean HbA_1C of 9.25 for upper lung fields , very high HbA_1C of 9.36 when both fields involved with no significant effect of HbA_1C on radiographic presentation. Patients commonly presented with Infiltrative lesions but the mean HbA_1C was highest 9.88 for cavitary type of lesion. Park also reported that there were no differences in radiographic findings between controlled diabetics and non-diabetics, but diabetic patients with poor glycemic control had an increased frequency of cavity [14]. In one study they reported Poor glycemic control significantly influences radiographic manifestations of pulmonary TB in patients with DM; isolated lower lung field involvement and large cavities are more common in uncontrolled diabetics than in optimal control patients[24]. The increased frequency of

pulmonary cavitary lesions in diabetic patients with poor glycemic control is probably related to reduced expression of Th1-related cytokines[25]. It is possible that proper glycemic control will not only reduce the risk of tuberculosis among diabetes patients but also attenuates the risk of cavitary lesions of pulmonary TB in diabetic patients.

People with very poor glycemic control had high sputum positivity rates with mean HbA_1C of 9.46 while HbA_1C of 8 in case of sputum negative patients. some authors reported a higher frequency of negative sputum smears among TB- DM cases [19], while others showed no association between DM and patients' bacteriology results[20]. Conflicting results might be due to the control status of DM [14].

Conclusion

Prevalence of Diabetes among Pulmonary Tuberculosis is in the rise with uncontrolled diabetic patients predominantly affected with kochs. Lower lung field involvement with atypical radiographic presentations are more common in patients with diabetes. Patients with poor glycemic control demonstrated cavitary lesions more than their counterparts but has no significant effect on zonal distribution of the radiographic lesion. Glycemic control has also significant effect on sputum smear positive rates and on patients with retreatment regimens. Therefore, atypical presentation and poor glycemic control should be kept in mind while treating patients effected with both tuberculosis and diabetes so that both the diseases can be treated properly.

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