

Original article

Effect of Glycemic control on pulmonary Tuberculosis in Diabetics

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Abstract:

Introduction: Diabetes Mellitus was a known risk factor for Tuberculosis, link of DM and TB is more prominent in developing countries where TB is endemic and the prevalence of DM is rising. The higher susceptibility of Tuberculosis in diabetics may be related to a longer duration of disease or poor glycemic control.

Aims: To study the effect of glycemic control on presentation of Pulmonary Tuberculosis.

Methods: It's a prospective cross sectional study. Patients above 18 years, having Pulmonary Tuberculosis with Diabetes Mellitus over one year 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 glycosylated haemoglobin (HbA_{1c}), <7 as controlled >7 as uncontrolled. Demographic, Clinical, Microbiological and Radiographic parameters of the patients were studied in respect to their glycemic control.

Results: There were 300 tuberculosis patients, 132 were diabetic, with 44% prevalence. The mean age 52.13±10.93, 52% males, mean HbA_{1c} 9.04, 93.2% had uncontrolled glycemic status. 93.2% had cough with mean HbA_{1c} 9.02. 79.54% were sputum AFB positive, mean HbA_{1c} 9.378 (59.0%) had lower lung field abnormalities; mean HbA_{1c} 8.87, 39 (29.5%) upper lung field; HbA_{1c} 9.25 and 11.3% both lung fields; HbA_{1c} 9.36 (81.8%) had nodular infiltrative lesions, 18 (13.6%) cavities with high HbA_{1c} 9.88.

Conclusion: Prevalence of diabetes among pulmonary tuberculosis is on the rise with uncontrolled diabetics predominantly affected. Poor glycemic control has significant effect on sputum smear positive rates, more number of cavities and on patients with retreatment regimens, with no effect on symptoms and radiographic distribution of the lesion.

Key Words: Pulmonary Tuberculosis, Diabetes Mellitus, Glycosylated Haemoglobin, HbA_{1c}, AFB.

Introduction:

Diabetes Mellitus (DM) was a known risk factor for Tuberculosis (TB) in the past, but this was mostly neglected during the second half of the 20th century, with the advent of widely available treatment for both diseases. In recent decades, with the increasing prevalence of TB, particularly Multi Drug Resistant TB (MDR-TB), and DM cases in the world, the relationship is re-emerging as a significant public health problem. 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^[1]. The prevalence of TB has been rising in recent years globally. It is estimated that in 2014 there were 9.6 million new

cases of TB. Out of them 5.4 million men, 3.2 million women and 1.0 million were children. Globally, 12% of the 9.6 million new TB cases in 2014 were HIV-positive [2] Worldwide, 70% of diabetics live in TB endemic Countries. In the 22 countries with the highest burden of TB, the prevalence of DM in the general population ranges from 2% to 9% [3], and eight of the ten countries with the highest incidence of DM are also classified as high burden countries for TB by the World Health Organization (WHO) [4]. 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 [1,5,6]. Up to 80% of patients with DM live in low income and developing countries [7]. Asia is the epicenter of the growing burden of DM [5] and the largest contribution is from India and China [8].

Notably, Pulmonary TB is the ninth most frequent complication of DM [9] and due to a rising prevalence of DM, the relative contribution of DM to the TB epidemic is increasing [1, 5]. 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 [10, 11]. The higher susceptibility of tuberculosis in diabetics may be related to a longer duration of disease or due to poor control of glycemic status [1, 12]. Additionally, the risk of TB is higher among patients who are using insulin [13], particularly, those who need higher doses of Insulin [14, 15]. Poor glycemic control has been significantly associated with the occurrence of TB [16]. 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) [10].

Till now there were only few articles which studied the effects of glycemic control on the presentation of TB, even the studies had conflicting results. The presentation of Pulmonary Tuberculosis with Diabetes is also changing, in contrast to the previous studies showing lower lung field tuberculosis more number of patients are having upper lobe lesions and atypical presentations. 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 with Pulmonary Tuberculosis so that the patients can be screened early and treated properly both for Diabetes and Tuberculosis.

Aims and objectives:

To study the effect of glycemic control on clinical, radiographic and microbiological 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 from 2015 to 2016 were studied. Diagnosis of Pulmonary Tuberculosis was made on the basis of clinical presentation, chest radiograph findings and microscopic detection of acid-fast bacilli. Patients with DM were defined as those 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).

Inclusion Criteria: Patients of 18 years and above, diagnosed as having Pulmonary Tuberculosis along with 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: This study was approved by the institutional ethical committee. After explaining aims and objectives in detail, written consent was obtained. Personal interview was held to collect data including age, gender, symptomatology and relevant information. The type of TB was recorded from the notification record as new or previously treated. A new TB patient was defined as a patient who has never been previously treated with anti-TB drugs for as long as one month. A previously treated TB patient was defined as a patient who has been previously treated with anti-TB drugs for one month or more. 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, viral markers, chest radiograph and sputum microscopy for AFB. Glycemic control was assessed by glycated haemoglobinA1C (HbA_{1c}) using calorimetric method. HbA_{1c} <7 was taken as 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 and cavitation 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.

The grade of sputum smear at base line was defined as: negative -no bacilli in 100 high power fields; scanty as less than 10 bacilli in 100 high power fields; 10- 99 bacilli in 100 high power fields = 1+; 1- 10 bacilli in one high power field = 2+; more than 10 bacilli in one high power field = 3+.

Demographic profiles, Clinical characteristics, Microbiological and Radiographic parameters of

the patients were studied in respect to their glycemic control.

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 statically significant.

Results:

There were 300 tuberculosis patients who presented to DR PSIMS & RF over a period of one year from 2015 to 2016, of them 132 patients were diabetic, diagnosed based on FBS, PPBS and HBA1C values with a prevalence of 44%. Out of 132 patients 52% were males and 48% were females. The mean age was 52.13±10.93; most of them 68% were in the age group of 40- 60 years. The mean HbA_{1c} of study population was 9.04±1.70, with males 9.5 and females 8.5. Age, sex, BMI, DM duration and mean HbA_{1c} values are described in table: 1

Majority 93.2% had uncontrolled glycemic status with HbA_{1c} of more than 7 as shown in fig: 1, table: 2 We observed denovo diabetics had high mean HbA_{1c} of 9.38 ; when compared to new cases, retreatment cases (defaulters, relapse and treatment failures) had higher mean HbA_{1c} of 10.01 (table: 1). p<0.01; Test applied: Mann-whitneyU; highly significant. The most common clinical presentation was cough 93.2% 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.

Regarding sputum status relatively high proportion of them 79.54% were sputum smear positive for AFB with mean HbA_{1c} of 9.3, only 27 were sputum negative.(p=0.04; Test applied: Mann-Whitney U; significant) fig: 2 . As per the radiographic presentation , out of 132 patients studied, majority had only lower lung field abnormalities 78(59.0%) with mean HbA_{1c} of 8.87

; 39(29.5%) had only upper lung field involvement with mean HbA_{1c} of 9.25 and 11.3% had involvement of both lung fields hba1c 9.36. (p=0.589; Test applied: Mann-WhitneyU; not significant)fig:3The type of lesion was determined, most of them 108(81.8%) had nodular infiltrative

lesions with mean HbA_{1c} of 8.88. 18(13.6%) had cavitary lesions , their mean HbA_{1c} of 9.88was higher when compared to all other lesions, among them,83.3%had cavities in lower lung fields. Clinical features, radiographic manifestations and sputum status are shown in table3:

Table 1: Demographic Characters

Demographic charter	Distribution	Frequency	HbA _{1c}
AGE	< 40 years	13.6 %	9.2
	40 – 60 years	68.1 %	9.02
	> 60 years	18.1 %	8.97
SEX	Male	52.3%	9.5
	Female	47.7%	8.5
BMI	< 18	6.80 %	11.7
	18 – 25	84 %	8.79
	> 25	9 %	9.25
	Denovo	15.90 %	9.38
DM Duration	2 months – 5 years	37.80 %	9.16
	5 – 10 years	15.10 %	8.49
	> 10 years	4.50 %	9.0
	New Case	77.20 %	8.5
CASES	Defaulter	18.20 %	10.6
	Relapse	5 %	9.5

Table 2: Frequency of HbA_{1c}

HbA _{1c}	Frequency
< 7	6.80%
7 – 9	45.40%
> 9	47.70%

Figure 1: Frequency of HbA_{1c}

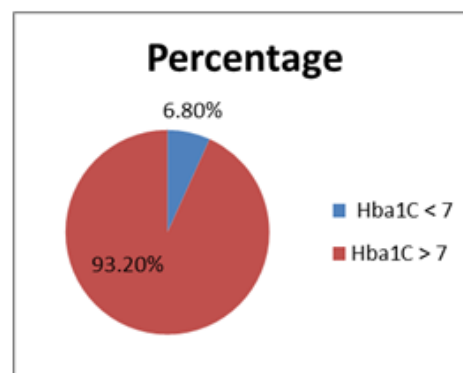


Table 3: Clinical, Radiological and Microbiological Correlation of HbA₁C with Tuberculosis

		Frequency	HbA ₁ C
Clinical features	Cough	93.2%	9.02
	Dyspnea	77.2%	9.42
	Fever	70.4%	10.12
Radiographic features	only Lower lung field	59%	8.87
	only Upper lung field	29.5%	9.25
	Both	11.3%	9.36
	Infiltration	81.8%	8.88
	Cavity	13.6%	9.88
	Consolidation	4.5%	9.44
	Others	6.8%	7.76
Sputum status	Negative	20.4%	8
	Scanty/ 1+	25%	8.96
	2+/3+	54.5%	9.46

Fig 2: Correlation of HbA₁C with Sputum microscopy presentation

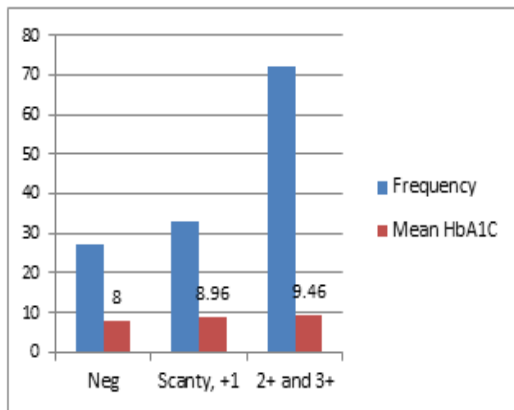
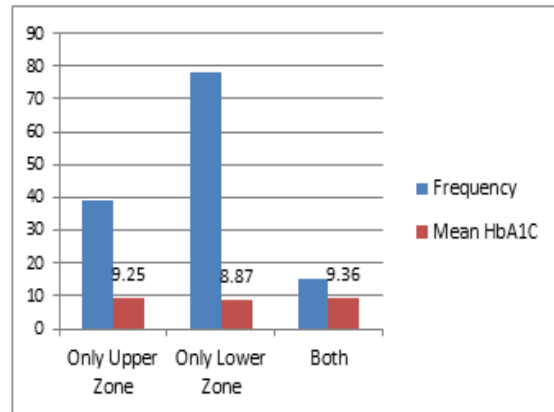


Fig 3: Correlation of HbA₁C with Radiographic presentation



Discussion:

In our study out of 300 patients with Pulmonary Tuberculosis 44% had Diabetes Mellitus. Mean age of them was 52.13±10.93 years with mean HbA₁C of 9.04±1.70, 52% of them were males.

The mean age of diabetics with tuberculosis in our study was corresponding to the previous study done by JagadishRawatetal which showed the mean age of the patients PTB-DM as 53.34 ±14.06 in comparison to their non-diabetic counterparts, that implies diabetic patients with Tuberculosis were relatively older; but in contrast to them our study constituted more number of males.^[17] A study done by Hardy Kornfeld et al reported 54.1% had associated diabetes out of 209 pulmonary tuberculosis patients from south India in 2016^[18]. Another study by park et.al, showed the prevalence of 25.2% of diabetes among Pulmonary Tuberculosis patients in 2012.^[19] Compared to 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.

In our study 6.8% had Body mass index of <18, majority of the study population 84% had normal BMI of 18-25, 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.^[20] Majority 93.2% of the study population constituted uncontrolled glycaemic status of HbA₁C more than 7, this was correlating with the study done by Chen –Yuan Chiang which showed 88.8% had HbA₁C more than 7^[21]. Another study done by PayamTabarsi reported 40% of their study population had normal glycaemic control of less than 7^[22], 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 glycaemic status in our study.

Patients with age above 60 years had mean HbA₁C of 8.97, 40-60 years had 9.02, less than 40 years patients had HbA₁C of 9.2, which implies poor glycaemic 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 HbA₁C values of 9.38 in denovo diabetics, when compared to hba1c of 8.97 in patients with DM duration of less than 10yrs, this is in contrast to previous study^[23], which showed increase of HbA₁C 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 HbA₁C.

In our study retreatment cases 22.7% were associated with higher mean HbA₁C of 10.01 when compared to new cases 77.2% with HbA₁C of 8.6. This was correlating with the previous studies which showed higher failure rates^[24,25,26,27] higher incidence of relapse in diabetics^[26,27] while others reported no difference^[28]. Most of the patients 93.2% presented with cough as a common symptom with mean HbA₁C of 9.02, followed by dyspnea and fever, but there is no relation of HbA₁C on clinical symptoms. This is correlating with the study done by park who reported no differences in clinical symptoms regardless of diabetes control status.^[19] A few other studies have shown that the clinical characteristics of TB do not differ among diabetic and non-diabetic patients^[1, 29, 30, 28, 31-33]. In one study, diabetic TB patients had more symptoms but did not have a more severe form of TB^[34].

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. With regard to the rate of positive smears at the time of diagnosis, results are conflicting. Although some authors reported a higher frequency of negative sputum smears among TB- DM cases^[34], others found DM as an independent risk factor for numerous acid fast bacilli on the sputum smear examination^[28,29] and some showed no association between DM and patients' bacteriology results^[35]. Conflicting results might be due to the control status of DM^[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 53 years. 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^[25]. A similar study done by Anand K Patel et al 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 cavitory lesions more frequently confined to lower lung field. In contrast to our study Bashar et al and Morris JT et al reported higher involvement of upper lung field^[36, 37].

The mean HbA_{1c} of lower lung field was 8.87, mean HbA_{1c} 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 HbA_{1c} was highest 9.88 for cavitory 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^[19]. The increased frequency of pulmonary cavitory lesions in diabetic patients with poor glycemic control is probably related to reduced expression of Th1-related cytokines.^[24, 38-40] It is possible that proper glycemic control will not only reduce the risk of tuberculosis among diabetes patients but also attenuates the risk of cavitory lesions of pulmonary TB in diabetic patients.

Conclusion:

Prevalence of Diabetes among Pulmonary Tuberculosis is in the rise with uncontrolled diabetics predominantly affected. Poor glycemic control has significant effect on sputum smear positive rates, more number of cavities and on patients with retreatment regimens, with no effect on clinical symptoms and radiographic distribution of the lesion. Therefore diabetic patients especially those with poor glycemic status should be screened regularly for tuberculosis. As *de novo* diabetics are increasing in tuberculosis patients, we recommend Koch's patients should also be investigated routinely for diabetes, so that both the diseases can be detected early and treated promptly.

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