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Original Article

Effect of Poor Glycemic Control in Newly Diagnosed Patients with Smear-Positive Pulmonary Tuberculosis and Type-2 Diabetes Mellitus

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What's Known

- Diabetes mellitus significantly increases the risk of tuberculosis (TB).
- Diabetes also affects the clinical course of tuberculosis.
- However, it is unclear what the impact of diabetes control on the outcome of TB treatment in diabetics is.

What's New

- Poor glycemic control was associated with a significantly increased risk of developing TB compared to subjects with optimal control.
- Our data suggested that poor glycemic control was associated with an increased risk of advanced and more severe TB.
- There was a profound negative effect on treatment completion, cure, and relapse rates in our patients with poor glycemic control.

Abstract

Background: There is growing evidence that diabetes mellitus (DM) is an important risk factor for tuberculosis (TB). A significant number of DM patients have poor glycemic control. This study was carried out to find the impact of poor glycemic control on newly diagnosed smear-positive pulmonary tuberculosis patients with type-2 diabetes mellitus in a tertiary care hospital.

Methods: In a hospital-based prospective study, newly diagnosed smear-positive pulmonary TB with DM patients were classified as poorly controlled diabetes (HBA_{1C}≥7%) and optimal control diabetics (HbA1c<7%). Patients were started on anti-TB treatment and followed for 2 years for severity and treatment outcome. ANOVA was used for numerical variables in the univariable analysis. Logistic regression analysis was used for multivariable analysis of treatment outcome. The significance level was kept at a P≤0.05.

Results: A total of 630 individuals who met the inclusion criteria were analyzed; of which 423 patients had poor glycemic control (PGC) and 207 patients had optimal glycemic control (OGC). The average HbA1c was 10±2.6 and 5±1.50 in the PGC and OGC groups, respectively. The mean symptom score was significantly higher in the PGC group compared with patients in the OGC group (4.55±0.80 vs. 2.70±0.82, P<0.001). PGC was associated with more extensive lung disease, lung cavitation, and positive sputum smear at the baseline. In PGC, sputum smears were significantly more likely to remain positive after 2 months of treatment. PGC patients had significantly higher rates of treatment failure (adj. OR 0.72, 95% CI 0.58-0.74, P<0.001) and relapse (adj. OR 2.83, 95% CI 2.60-2.92, P<0.001).

Conclusion: Poor glycemic control is associated with an increased risk of advanced and more severe TB disease in the form of lung cavitations, positive sputum smear, and slower smear conversion. It has a profound negative effect on treatment completion, cure, and relapse rates in patients with pulmonary tuberculosis.

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Introduction

According to the World Health Organization's Global Tuberculosis Report 2014, TB continues to be the most important infectious disease in terms of incidence and mortality. Current estimates suggest that 9 million new cases and 1.5 million deaths have occurred in 2013.[1] India, with approximately 2-3 million new cases of TB, is the world's largest TB epidemic country.[1,2] The incidence rate of TB in India is in the range of 160 to 180 per 100,000 population, which is a disproportionately high burden compared to other developing countries[1] Several risk factors have played, and will continue to play, a role in escalating this public health problem in India. One of the most important of these risk factors, the effect of which on TB was underestimated for several years in our country, is diabetes mellitus (DM) especially poorly controlled DM.

There is an accelerating pandemic of type-2 DM worldwide. Currently, 230 million people live with DM worldwide and it is anticipated that about 366 million could be affected by 2030. By that time, 80% of those will be living in low- and middle-income countries where active TB is widespread.[2-4] Eight of the ten countries with the highest incidence of diabetes are also classified as high burden countries for TB by the World Health Organization (WHO).[5] The consequences of these converging epidemics led WHO to declare both DM and TB as global epidemics. The synergistic relationship between TB and DM has been creating a growing concern around the world. Recently, WHO and the International Union Against TB and Lung Disease (The Union) have acknowledged the need for international guidelines on the joint management and control of TB and DM. They have published a provisional collaborative framework for the care and control of both diseases.[6] The recent estimates suggest that there were 20-30 million people in India with DM in 2000 and projected to reach as high as 80 million by 2030. India is advancing towards becoming the diabetic capital of the world, as every fifth diabetic in the world is an Indian. This surge in DM prevalence in India is severely affecting TB control program and the impact is similar to TB-HIV co-infection.[7,8]

The prevention and treatment of both TB and DM present major public health challenges in all settings across the globe, particularly when DM is poorly controlled. Given the rising incidence trends of both diseases, it is generally important to understand the association in detail within this setting so that any relevant information can be utilized to aid local TB and DM prevention and control. Evidence from clinical practice and the literature suggests that approximately half of the most common chronic disorders like DM are undetected, that half of those detected are not treated, and that half of those treated are not controlled: the 'rule of halves' is still applicable in Indian population.[9] In our country, a significant number of DM patients remain undiagnosed and also uncontrolled or poorly controlled after diagnosis. Several studies done in the past proved that DM is associated with increased incidence of TB, but studies linking poor glycemic control and the severity of TB are scarce. Therefore, the present study was planned to understand the impact of PGC pre-treatment on the severity of TB and TB treatment outcome in newly diagnosed pulmonary TB (PTB) patients with type-2 DM.

Patients and Methods

In this prospective study, 630 newly diagnosed smear-positive pulmonary TB (PTB) patients with DM were enrolled during January 2012 to December 2014. The patients were registered for treatment in the Departments of Pulmonary Medicine, Internal Medicine, Diabetes and Endocrine Department and DOTS centre (TB unit) at a tertiary care hospital. The diagnosis of smear-positive PTB was done according to the RNTCP (revised national tuberculosis control program in India, 2013) criteria and Type-2 DM according to guidelines from WHO. The exclusion criteria were pregnancy, HIV infection, connective tissue disorders, chronic renal failure, chronic liver disease, malignancies on long-term steroid or cytotoxic drug therapy, chronic alcoholics, and previously treated for TB.

Procedure

Patients diagnosed as new smear-positive PTB were enrolled for the study after meeting the inclusion criteria as per RNTCP guidelines of India. A new smear-positive case is defined as a patient with one or more initial sputum smear examinations positive for acid-fast bacilli.[10] Informed consent was obtained from all participants regarding the required investigations and the purpose of the study. Ethical approval was obtained from the statutory board of Karnataka Lingayat Education University. A symptom score (0–6) was calculated based on the presence of cough, hemoptysis, dyspnea, fever, night sweats, and weight loss (1 point for each symptom was assigned). Patients with a symptom score 4 were classified as having highly symptomatic disease.[11]

DM screening was done as per national guidelines. In short, FBG>126 mg/dl indicates DM, FBG≥110 mg/dl to <126 mg/dl indicates

impaired fasting glucose, and FBG<110 mg/dl is normal.[12] Random blood sugar testing was done in patients with unclear DM status and if it was more than 200 mg/dl, they were further evaluated with fasting and postprandial blood sugars (FBS and PPBS). If FBS was more than 126 mg/dl or PPBS more than 200 mg/dl, the patients were confirmed as having DM. All participants were assessed by glycosylated hemoglobin (HbA1c) evaluation. Patients with HbA1c levels>7% were considered to have poor glycemic control.[13] The patients with PTB and DM were then subjected to chest radiography (posterior-anterior view). A pretreatment chest radiograph was read by two qualified pulmonologists blinded to patients' disease status. The films with discordant reading were read by a third reader. Reading of the chest radiographs focused on lung parenchymal opacity and cavitation. Radiological lesions on chest X-ray were classified into minimal, moderately advanced, and far advanced as per American Thoracic Society (ATS) criteria.

Clinical, radiographic features, sputum conversion rates after 2 months and at the end of the treatment, cure rates, and relapse rates were compared between patients with poor glycemic control and that of the optimal glycemic control group. Relapse was defined as the recurrence of TB after successful completion of treatment, either proven by isolation of Mycobacterium tuberculosis or in the absence of bacteriological confirmation, recurrence diagnosed on clinical, radiological and/or histological grounds. Participants were followed for 2 years after the initiation of treatment as per RNTCP guidelines for treatment outcome. All patients received standard DM care as per national guidelines for DM care during the study period.

Statistical Analysis

Mean±SD values were calculated for normally distributed numerical outcomes. Mean±SD values for demographic characteristics among PGC and OCG were analyzed using the Mann-Whitney test. The chi-square test was used to compare non-numerical variables. ANOVA (Sigma Plot version 12.5, Systat Software Inc., San Jose, CA, USA) was used for numerical variables in the univariable analysis. Logistic regression analysis was used for multivariable analysis of treatment outcome. The significance level was kept at P≤0.05. The analysis was done after adjusting for confounding variables.

Results

From the 7,400 TB suspects screened 1,935 new PTB cases were identified. In total, 774(40%) patients had concomitant type-2 DM (old or new). About 99 patients were excluded from the study, as they did not meet the inclusion criteria. During the follow-up, 45 patients out of the 675 were lost and the remaining 630 patients were analyzed. As shown in figure 1, 423 patients had HBA1c (poor glycemic control, PGC) level≥7% and 207 patients had HBA1c (optimal glycemic control, OGC) level<7%. There were 288 (68.09%) males in the PGC group and 135 (65.22%) in the OGC group. The demographic parameters of all the patients are listed in table 1.

Symptom Score

All patients from both groups presented with fever as their main symptom. 324 (76.5%) patients from the PGC and 171(82.61%) patients from the OGC group had cough with/without expectoration. In the PGC group, night sweats and haemoptysis were present in 63 (14.9%) and 45 (10.64%) patients, respectively. Whereas in the other group, they were present in 872 (34.8%) and 9 (4.4%) patients, respectively. These differences between the groups were not statistically significant. On the other hand, dyspnoea and weight loss were significantly more often reported by patients in the PGC group: 55% vs. 17.3% and 31.2% vs. 8.9%, respectively. The mean symptom score was significantly higher in the PGC group compared with patients in the OGC group: 4.55±0.80 vs. 2.70±0.82, P<0.001.

Sputum Bacillary Load

Sputum bacillary load at presentation was significantly higher in the PGC group (with 153 (36.2%) and 234 (55.3%) patients having sputum grades of 2+ and 3+, respectively) compared to 27 (13.04%) and 9 (4.4%) patients in the other group, P<0.001.

Radiological Features

On radiographic examination, cavitary lesions were more frequently observed in patients with PGC (table 2). Among patients with PGC, 243 (57%) had multilobar involvement on CXR, 126 (29%) had isolated lower lung field involvement and 54 (12.8%) patients had upper zone involvement. This was in contrast to the involvement seen in patients with OGC, where the majority of patients had upper zone involvement (162 out of 207; 78%). Thus, patients with PGC had lower lung field and multilobar involvement more frequently as compared to patients in the other group. The difference was statistically significant, P<0.001.

Far advanced lesions and moderately advanced lesions were seen in the majority of patients

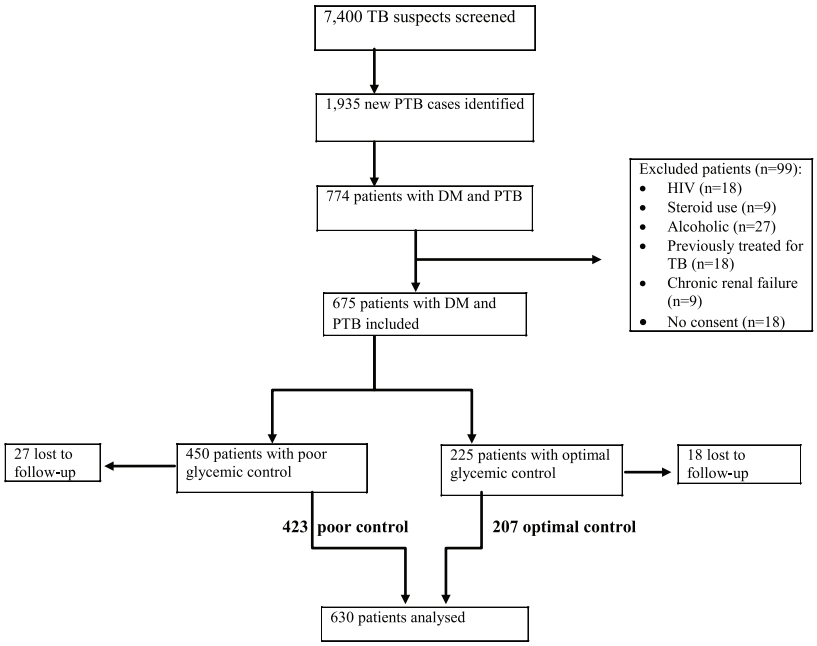

Figure 1: Inclusion criteria of patients.

Table 1: Demographic characteristics of PTB patients in both the optimal and poor control groups

Characteristic	HBA_{1C}≥7% n=423 PGC	HBA_{1C}<7% n=207 OGC	P value
Male/sex	288/423 (68%)	135/207 (65%)	0.72
Age (mean±SD)	48.26±2.35	48.91±7.97	0.65
BMI (mean±SD)	20.80±2.34	21.08±2.13	0.63
History of TB contact	27/423 (6.38%)	18/207 (8.69%)	0.72
Family history of DM	162/423	45/207	0.36
Diabetic status			
Old	315	171	0.45
New	108	36	
Rural residence	153	90	0.44
Schooling>6 years	180	99	0.68
Smokers	117 (27.6%)	63 (30.4%)	0.80

PGC: Poor glycemic control; OGC: Optimal glycemic control

Table 2: Type of lesions on CXR

Types of lesions	PGC	%	OGC	%	Total	%	P value
Cavitary	324	76.60	90	43.48	414	65.71	0.0061
Non-cavitary	99	23.40	117	56.52	216	34.29	
Total	423	100.00	207	100.00	630	100.00	

PGC: Poor glycemic control; OGC: Optimal glycemic control; Chi-square=7.5172

belonging to the PGC group compared to OGC group (40.43% vs. 4.35% and 48.9% vs. 39.1%, respectively). On the other hand, minimal lesions were seen more frequently in the optimal control group (10.6% in PCG vs. 56.5% in OCG). This difference was statistically significant, P<0.001.

Sputum Conversion at 2 Months

At the end of the intensive phase of therapy, a significant number of patients with PGC remained smear-positive compared to OGC patients (table 3).

Treatment Outcome

As far as treatment outcome (cure, failure, defaults, MDR, relapse) is concerned, patients with PGC had significantly high rates of defaults and treatment failures (table 4). Multidrug-resistant (MDR) tuberculosis, confirmed by either culture or by the Xpert MTB/RIF technique,

Table 3: Sputum conversion at 2 months

Sputum at 2 months	PGC	%	OGC	%	Total	%
Negative	270	63.83	198	95.65	468	74.29
Positive	153	36.17	9	4.35	162	25.71
Total	423	100.00	207	100.00	630	100.00

PGC: Poor glycemic control; OGC: Optimal glycemic control; Chi-square=8.1872; P=0.00422

Table 4: Treatment outcome (cure or failure)

Outcome	PGC	%	OGC	%	Total	%
Cured	324	76.60	198	95.65	522	82.86
Failure	99	23.40	9	4.35	108	17.14
Total	423	100.00	207	100.00	630	100.00

PGC: Poor glycemic control; OGC: Optimal glycemic control; Chi-square=3.9481; *P*=0.04693

was noted in 47 of 423 (11.11%) patients with PGC whereas none of the patients in the optimal control group had MDR. Univariable and multiple logistic regression analysis on treatment success and relapse in poor glycemic control patients, after adjusting for confounding variables, demonstrated a significant negative association (table 5).

Discussion

To the best of our knowledge, this is the first kind of study in India to directly compare manifestations of PTB in optimally controlled DM and poorly controlled DM and demonstrated that clinical manifestations of PTB in diabetic patients are related to pre-treatment HbA1C. The percentage of diabetic patients with symptoms and positive-smear was higher in patients with HbA1C>7%. Our study also demonstrated that the influence of DM on the outcome of TB treatment was proportionately related to pretreatment of HbA1C. These observations complement and extend the recently published study by Chiang et al.[14] They established that the proportions of patients with any symptom, cough, hemoptysis, tiredness, and weight loss were entirely the highest in diabetic patients with PGC and these patients were significantly more likely to be smear-positive and remain smear-positive after 2 months of treatment. Our interpretations were in line with another study by Leung et al.[15] They demonstrated that among patients with the results of sputum culture at 2 months of treatment, diabetic patients were significantly more likely to be culture-positive as compared with non-diabetic patients (adj. OR 1.63, 95% CI 1.14-2.34) and the association was significantly influenced by the level of HbA1c.

Current observations of more extensive lung disease, lung cavitations, and high positive sputum smears among PGC patients were in agreement with many of those reported in previous studies.[15,16] Noteworthy evidence from the current study was that the poor PGC was negatively associated with cure or treatment completion, even after controlling the baseline socio-demographic variables, comorbidities, extent of lung disease, lung cavitations, and bacteriology. Park et al.[17] also established that uncontrolled diabetics have more cavities, high positive smear rates, and poor culture conversion after two months of therapy. Another interesting analysis by Webb and colleagues is worth mentioning, which showed a higher mean HbA1c among TB-DM in comparison to DM without TB. They also hypothesized that in patients with PGC (hazard ratio 1.39, 95% CI 1.18-1.63), per unit increase in HbA1c and contact with a TB source case (P=0.0011) was associated with prevalent TB disease.[18]

The present study confirms and complements the findings of Chiang et al.,[19] stating that the proportions of patients with DM with any cavity, cavitatory lesions over upper lung field, cavitatory lesions over lower lung field, large cavity (>3 cm), and multiple cavities were all highest among patients with PGC. The atypical radiological findings of lower lung field lesions and multilobar involvement with far advanced tuberculosis, as noted in our PGC patients, have been significantly affected by HbA1c levels similar to findings in a study by Park et al.[17] These atypical radiological manifestations will lead to a significant delay in TB diagnosis, which is a matter of serious concern. Clinicians should have a high degree of suspicion and should screen all such patients for DM and HbA1C.

The observations in our study, in spite of using standard four-drug short course regimens for drug-susceptible TB, were under a fully functioning treatment program setting that also allowed individualized regimen modification and treatment prolongation. Relapse rates were also as high as 16.5% in PGC when compared to 2.3% in OGC patients.

India TB-Diabetes Study Group (the corresponding author of the present article is also a member of the group) screened TB patients for DM. They found that the prevalence of DM in patients with TB in tertiary care hospitals was around 16% and as high as 20% in South

Table 5: Univariable and multiple logistic regression analysis on treatment success and relapse in poor glycemic control patients after adjusting for confounding variables (e.g. age, duration of DM, nutritional status (BMI), socioeconomic status, smoking, comorbidities, extent of lung disease, lung cavitations, and bacteriology)

DM status	Patients (n)	Treatment success (%)	OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Relapse (%)	Adjusted OR (95% CI)	P value
Optimal control	207	95.65	Reference		Reference		2.33	Reference	
Poor control	423	76.60	0.68 (0.58-0.74)	0.0013	0.72 (0.64-0.81)	0.0013	15.62	2.83 (2.60-2.92)	0.0014

India. They strongly recommended screening all TB patients for DM at all levels of health care facilities.[19,20] In our study, the proportion of patients with newly diagnosed DM was as high as 22.85%.

The effects of DM and PGC on clinical parameters (lung cavitations, positive sputum smear) and slower smear conversion after initiation of treatment emphasize a serious need for prevention of community-level transmission. In the current study, even for patients with initial drug-sensitive TB, the treatment completion rates fell substantially below the WHO target of 85% among poorly controlled DM patients. The high proportion of these patients also raises concern over the emergence of drug resistance and secondary spread within the community. In our study, we noted that 47 of 423 patients (11.11%) with poor control had MBR-TB confirmed either by culture or by the Xpert MTB/RIF technique.[21] The emerging results from our study, as well as many studies discussed above, have demonstrated that a large number of DM patients with TB, despite successful treatment, still ran a substantially higher risk of developing active TB again compared with the overall TB risk in the general population. The unfavorable outcome in these TB patients with prolonged poorly controlled DM poses the risk of extended period of contagiousness and may transmit mycobacteria to their contacts for a longer period, both before the diagnosis and after the initiation of treatment.

DM is expected to delay the Millennium Development Goals of WHO. The Global Plan to Stop TB 2006-2015, established by the Stop TB Partnership, set the target for the elimination of TB by 2050 with a 50% reduction in prevalence by 2015. WHO global TB report 2013 highlighted that while significant progress is being made in many aspects of tuberculosis control, it is too slow and altogether off-target with only a 2% decrease in prevalence per year.[22,23] Such discouraging report highlights the urgent need for addressing important risk factors like DM, especially poorly controlled DM at all levels of health care services.[24] It is essential to note that interventions to decrease the prevalence of DM and optimal control of DM in patients with TB (or in the general population) may have an important impact on the incidence of TB and treatment outcome as well. In the absence of global guidelines on the collective management and control of TB and DM, national programs of all countries need to establish a coordinated response to these two diseases at both the organisational and clinical levels. It is also necessary to add DM prevention and control strategies to TB control programs and vice versa and to evaluate their effectiveness.

A major strength of our study is the prospective design, which avoided the problems of control selection in case-control studies and obscured temporality in cross-sectional studies. Availability of thorough DM and HbA1C details of all patients made it possible to demonstrate a clear relationship between PGC and PTB treatment outcome. The study is limited by the fact that it is a single-centre study, the results of which cannot be generalized. However, this provides a window of opportunity for clinicians and researchers to carry out further studies with the involvement of different geographical areas across India. In addition, studies can be performed to assess the impact of early screening for DM and HbA1C on TB treatment outcome in such high-risk patients. Our study was not powered to assess the relationship between poorly controlled DM and MDR-TB. It is essential to clarify, in a program setting by randomized controlled trials, many unanswered issues in this field (e.g. to what extent the unsatisfactory outcome of TB in DM patients can be prevented by optimal glycemic control?). Furthermore, glycemic status of patients after diagnosis and during the treatment was an important factor as this may affect the outcome of the study since post treatment HbA1c levels were not assessed. Our study was not powered to establish the association between PGC and MDR-TB. Further studies are needed to clarify the association between PGC and an increased risk of drug-resistant TB. In addition, extra-pulmonary and smear-negative pulmonary TB cases were not included in the study. Perhaps this has added to selection bias prevention.

Conclusion

Pre-treatment poor glycemic control is associated with a significant increased risk of advanced and more severe TB disease in the form of lung cavitations, positive sputum smear, and slower smear conversion after initiation of treatment. Poor glycemic control has a profound negative effect on treatment completion, cure, and relapse rates in patients with pulmonary tuberculosis with diabetes.

Conflict of Interest: None declared.

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