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Prevalence and risk factors of pulmonary tuberculosis among people living with diabetes mellitus at the National Referral Hospital, Thimphu, Bhutan

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ABSTRACT

Introduction: Diabetes mellitus (DM) is increasing the risk of pulmonary tuberculosis (PTB) with concern over the convergence of these two diseases. Although screening for PTB among people with DM has been recommended by WHO, it has not been implemented in Bhutan yet. Objective: The aim of this study was to determine the prevalence and risk factors of PTB among people living with DM at the National Referral Hospital (NRH), Thimphu, Bhutan. **Methods**: This was a cross-sectional study conducted from 1st June – 9th October 2018. All 343 consenting DM patients were screened for PTB using the WHO recommended questionnaire and those with TB positive symptoms were tested for active PTB using sputum smear microscopy and Gene-Xpert. A descriptive statistical analysis was performed using SPSS 21. **Results:** The prevalence of PTB among people living with DM was 0.87% (95% CI: 0.20-2.50).The mean age was 54.95 (± 13.2 years) and all were DM type II. The median duration of diabetes was 4 years (range of 0.1-40 years), an average level of HbA1c 7.47 (± 2.6), and median duration on DM medication was 4 years (range of 0.1-40 years) with the majority (88.9%) on oral hypoglycemic drugs. Good glycemic control (HbA1c< 7) was achieved by 39.4% of individuals. PTB risk factors included PTB positive symptoms (7.0%), prior PTB history (5.5%) and recent contact with PTB patient (5.0%). Additional known PTB risk factors were smoking (7.6%), alcohol use (4.1%) and low body mass index (1.5%). **Conclusions:** Although the prevalence PTB was low, health education, proper case management and risk based screening for PTB among DM is recommended.

Keywords: Bhutan; Diabetes mellitus, Pulmonary tuberculosis; PTB risk factors.

INTRODUCTION

Tuberculosis (TB) and Diabetes Mellitus (DM) are major public health problems globally[1]. Despite significant achievement made in TB control, it is still one of the top ten leading causes of mortality related to an infectious agent. There was an estimated 10 million incident cases of TB and 1.3 million died from the disease in 2017[1]. On the other hand, an estimated 422 million adults were living with diabetes in 2014, with 1.6 million deaths attributed to DM in 2016[2]. Globally the prevalence of TB among DM patients ranged from 0.38% to 14% with an overall median prevalence of 4.1% (IQR 1.8%-6.2%). The prevalence was relatively higher in the studied countries of Asia and the African continents with older age, tobacco smoking, sedentary lifestyle and poor glycemic control identified as risk factors for TB and DM comorbidity[3].

With an increasing burden of DM, concerns have been raised about the emerging co-epidemics of DM and TB posing additional challenges to disease control and management, especially in low and middle income countries[4]. In addition, DM increases TB risk by three fold (RR =3.11, 95% CI: 2.27 - 4.26) and affects the clinical outcome leading to reduced therapeutic efficacy and poor disease prognosis[5].

The increasing burden of DM may hinder the Sustainable Development Goal (SDG) of ending the TB epidemic by 2030. Therefore, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Diseases (IUATLD) strongly recommended bidirectional screening for active TB case among DM patients and vice versa[6]. Many countries in the Southeast Asian region have already integrated TB screening in diabetes[7,8].

Bhutan has relatively a low TB burden compared with other countries in Southeast Asia[9]. In 2016, the TB prevalence was 190 cases per 100,000 and the mortality rate from the disease was 9.5 per 100,000 population[10,11]. Furthermore, the nationwide non-communicable diseases (NCD) stepwise approach to surveillance (STEPS) survey in 2019 found that 1.9% of the Bhutanese population have raised fasting glucose[12]. In addition, at the health facility level, incidence of diabetes tripled from 53 per 10,000 in 2011 to 164 per 10,000 in 2015 with 3% of all deaths attributed to DM[13,14].

With the rising burden of these two diseases, the public health implications of the convergence of TB and DM is

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a significant public health concern. Therefore screening for TB among people with DM may be carried out as an important strategy to reduce burden and mortality associated with TB. The National TB Guidelines of the Ministry of Health of Bhutan recommends bi-directional screening for TB in DM patients and vice versa[15]. However, in practice, TB screening is not integrated into routine DM care.

A study in the recent past reported the overall proportion of pulmonary TB and extra pulmonary TB in the country as 52.6% and 47.1%, respectively. Nearly half (49%) of all the TB cases reported in Bhutan was predominantly pulmonary TB in 2016[16]. Although studies on the prevalence of TB among DM patients have been conducted elsewhere, there is no scientific study done in Bhutan. In view of the high prevalence of pulmonary TB and the growing burden of DM in Bhutan, this study was conducted to determine the prevalence of PTB and PTB risk factors among people living with DM at the National Referral Hospital, Thimphu, Bhutan, using the WHO recommended TB screening questionnaire[17].

METHODS

This study used a cross-sectional survey design. Trained research assistants (RAs) collected data from 1st June – 9th October 2018 from the DM clinic at Jigme Dorji Wangchuk National Referral Hospital (JDWNRH) in Thimphu, Bhutan. As the national referral center, JDWNRH provides health services to referred cases from other districts of Bhutan. The DM clinic has approximately 3500 DM cases registered for care as of 2018. Ethical approval for this study was obtained from the Research Ethics Board of Health, Bhutan (REBH/Approval/2018/011 dated 7th May, 2018).

As the country estimate for DM with TB is not available, the sample size for this study was estimated using Taro Yamane formula[18]. A total of 3500 DM patients visited DM clinic at JDWNRH in 2018. Considering sample error of 5%, a sample size of 359 was calculated as follows:

n= N/1+N(e)2
=3500/1+3500(0.05)2
=3500/1+8.75
=3500/9.75
=359

Participants were selected using systematic random sampling. Every tenth patients who visited the DM clinic during clinic days were enrolled for the study after obtaining written informed consent. Only 343 DM patients could participate in this study with a refusal rate of nearly 5% which was attributed to patient's inconvenience associated with repeated follow up visits for blood sugar and sputum tests.

Known DM patients registered with the DM clinic, who consented to participate, were interviewed by trained enumerators using a structured questionnaire that contained information about socio-demographic characteristics, medical history including history of PTB, PTB risk factors, DM medications used and treatment duration. Four trained RAs administered the WHO recommended TB screening questionnaire that included screening for cough longer than two weeks, coughing of blood, fever, night sweats and weight loss or loss of appetite[17]. Patients having at least three of the above symptoms were considered having positive PTB symptoms. Any positive symptoms among the DM patients led to the collection of expectorated sputum on three occasions - the first one on the day of interview and rest in the subsequent days. All sputum specimens collected underwent fluorescent microcopy for acid fast bacillus (AFB).

A patient with at least two sputum smears that were positive for AFB by direct smear microscopy or a patient with at least one sputum smear positive for AFB by microscopy and chest X-ray findings were confirmed as Smear-positive PTB[15]. For positive smears, gene-Xpert MTB/RIF assays were performed to confirm the diagnosis as well as to rule out multi drug resistant (MDR) TB.

For anthropometric assessments, all participants had their height and weight measured to calculate the BMI. Majority of the patients had their Fasting blood sugar (FBS), 2 hour postprandial blood sugar (PPBS) levels and glycated hemoglobin A (HbA1c) measured from the laboratory, one day before visiting the DM clinic. Few enrolled patients who did not have the blood reports were asked to come in fasting for the blood test the next day. The FBS and PPBS levels were measured at the laboratory by staffs using glucose reagent kit containing hexokinase colorimetric assay reagents. HbA1c was measured using a Norudia Glycated Hemoglobin kit containing enzymatic assay reagents.

Good glycemic control or controlled DM was defined as HbA 1c <7% or pre-prandial fasting blood sugar 80–130 mg/dL and 2 h postprandial blood sugar <180 mg/dL[19].

The individual patient data was double-entered into EpiData software version 3.1, validated and then analyzed using SPSS (version 21). The primary outcome of the study was the prevalence of PTB.

Secondary outcomes included the prevalence of PTB risk factors. Data was summarized using descriptive statistics.

RESULTS

Table 1 shows the demographic information and DM characteristics of the patients. Among 343 DM patients screened for PTB, 198 (57.7%) were female, 199 (58.0%) had no formal education and all the cases were type II DM. About 68.2% were from the low-income category of < Nu.100, 000 per year. The mean age was 54.95 (± 13.2 years). The median duration of diabetes was 4 years (range of 0.1-40years) with an average level of HbA1c of 7.47 (± 2.6). The median duration on DM medication was 4 years (range of 0.1-40 years) with the majority (88.9%) on oral hypoglycemic drugs. Good glycemic control (HbA1c< 7) was achieved among 39.4% of them.

PTB Prevalence and risk factors

Table 2 presents PTB prevalence, risk factors and PTB symptoms. The risk factors included: positive prior PTB history (5.5%), recent

Table 1. Demographic and DM characteristics of the patients attending diabetic clinic at the National Referral Hospital, Thimphu, Bhutan from 1st June - 9th October 2018 (*n*=343)

Characteristics	*n* (%)
Age (Mean ± SD): 54.9± 13.2	
≤40 years	43 (12.5)
>40 years	300 (87.5)
Sex	
Male	145 (42.3)
Female	198 (57.7)
Education Level	
No formal education	199 (58.0)
Primary	60 (17.4)
Secondary or higher	84 (24.6)
Occupation	
Government and Non-government employee	72 (21.0)
Self-employed and retired	66 (19.2)
Home maker	115 (33.5)
Unemployed	87 (25.4)
Students	3 (0.9)
Income (in Ngultrum/year)	
50,000-100,000	234 (68.2)
100,001-200,000	53 (15.5)
200,001-300,000	42 (12.2)
≥ 300,00	14 (4.1)
DM Characteristics	
Median duration of DM (min-max)	4 (0.1 - 40) years
Median duration of medication (min-max)	4 (0.1 - 40) years
HbA1c Mean (SD)	7.5 (±2.6)
Oral Hypoglycemic	305 (88.9)
Injectable Insulin	17 (5.0)
Oral hypoglycemic with Insulin	19 (5.5)
No medications	2 (0.6)
Controlled DM (HbA1c<7)	150 (43.7)
Poorly controlled DM(HbA1c>7)	133 (38.8)
Controlled DM (FBS<130, PPBS<180mg/dl)	135 (39.4)
Poorly controlled DM (FBS>130, PBS>180mg/dl)	208 (60.6)

Note: SD: Standard deviation

contact with PTB patient (5.0%), current smoker (7.6%), and alcohol use (4.1%). While seven percent reported any of the three PTB symptoms, 12.8% reported cough >two weeks, 7.6% fever and 8.5% weight loss. Of the 343 participants, one was already a known PTB patient and was under treatment. Of the 55 patients who had symptoms suggestive of PTB and were referred for evaluation, two new PTB cases were detected which were positive on both smear microscopy and gene Xpert. There was no case of MDR TB. Both cases were initiated on PTB treatment. Overall, the prevalence of PTB among DM patient was 0.87% (95%CI:0.20-2.50).

Table 2. PTB prevalence and risk factors among DM patients attending the diabetic clinic at the National Referral Hospital, Thimphu, Bhutan from 1st June - 9th October 2018 (*n*=343)

	n (%)
Pulmonary Tuberculosis risk factors	
Past history of PTB	19(5.5)
PTB case at home	17(5.0)
Shared same room with PTB patient	16(4.7)
Current Tobacco Smoking	26(7.6)
Past Tobacco Smoking	68(19.8)
Current Alcohol user	14(4.1)
Past Alcohol user	135(39.4)
Underweight (<18.5)	5(1.5)
Normal (18.5–24.9)	71(20.7)
Overweight/Obese (>25)	244(71.1)
Pulmonary Tuberculosis Symptoms	
Cough > two weeks	44(12.8)
Cough with blood in sputum	11(3.2)
Fever with night sweats	26(7.6)
Weight loss and loss of appetite	29(8.5)
Any of the three symptoms (positive PTB symptoms)	27(7.0)
DM patient already diagnosed with PTB (known case)	1(0.3)
DM patient diagnosed with new PTB after investigation	2(0.6)
Patient identified with PTB (new and old)	3(0.87%) [95%CI:0.20-2.50)

Note: PTB: Pulmonary Tuberculosis

DISCUSSION

In our study we found that the overall prevalence of PTB among DM patients is 0.87 % (95% CI: 0.20-2.50). The result of this study corroborated with similar studies conducted at a tertiary hospital in South India[20] and a community hospital in China[7] where the prevalence was found to be 0.1% and 0.5% respectively. Likewise, in a prospective observational study carried out in six tertiary health facilities in India involving a large sample of 31,146 DM patients, only 18 new TB cases were detected, majority of whom had smear-positive PTB[21]. A study conducted in Pune in India failed to detect any new prevalent TB cases among 675 DM patients[8].

On the contrary, the prevalence was 1.7% in Myanmar[22] and 4.1% in Pakistan[23]. Despite the differences in prevalence among countries, with a higher prevalence reported in few countries of Asia and the African continents, a systematic review by Workneh[3] concluded that, globally the prevalence of TB among DM is low. It is estimated that 0.38% to 14% DM were affected with TB, with an overall median prevalence of 4.1% (IQR 1.8%-6.2%) and these differences could be affected by the national prevalence of TB and DM in the respective countries[3]. Nonetheless, the low prevalence of PTB among DM patients in this study as generally observed elsewhere, cannot be ignored for a developing country like Bhutan, as we are already facing double burden of non-communicable and communicable diseases[24].

Furthermore, among DM patients retained in care, glycemic control was achieved in only 39.4% of the patients, despite majority already being on medication. This finding corresponded to the country-wide review study of DM care in Bhutan, where only one-third (38%) of DM patients achieved good glycemic control[25]. The issue of high proportion of patients having poor glycemic control is a well-known problem worldwide and not exclusive to Bhutan. A meta-analysis study in Ethiopia showed that only one-third of patients [33.2% (95% CI: 21.8%-44.6%)] achieved good glycemic control[26]. Likewise, only 18% and 23.6% DM participants had adequate glycemic control in Bangladesh and India respectively[27,28]. These findings highlight the need for early implementation of optimum diabetes pharmacotherapy to maintain recommended glycemic control, to limit disease complications and improve the health of patients with diabetes.

Overall, despite the low prevalence, our finding showed that the screening of patients could result in higher case detection rate of PTB amongst DM patients. The Union and the WHO framework recommended bidirectional screening for DM and TB as one important strategy to address the burden of the two diseases[7]. While these recommendations are relevant for countries that have high burdens of TB, for low TB burden country like Bhutan, routine bidirectional screening may not be cost effective and attractive to national programs. Therefore, a study on the cost-effectiveness of such a strategy in a low yield setting like ours is warranted. Furthermore, there is a need to identify specific factors among DM patients that increases the risk of TB so that screening for PTB can be targeted and effective. Thus, we recommend risk based screening for TB focusing on high-risk groups such as those DM with PTB symptoms, presence of known PTB risk factors and patients with poor glycemic control as this approach would reduce unneeded screening of all DM patients for TB in a low prevalence setting.

Strength and limitation

Our study was the first of its kind to assess the prevalence of PTB and risk factors among DM patients in Bhutan. Despite the low prevalence, the findings from this study will guide policy makers on adopting targeted and cost-effectiveness strategies in addressing the dual burden of TB and DM.

Our study has several limitations. Firstly, with the study design being cross-sectional and the samples being restricted to DM patients receiving care at the national referral hospital, the findings cannot be generalized to the whole country. The situation may be different in district hospitals where the infrastructure and the level of services vary. Therefore, a larger quantitative prevalence study is recommended. Secondly, the current study focused on PTB and did not take into consideration extra-PTB. However, no prevalent extra PTB were found among DM during the study period. Finally, due to very low prevalence, the evaluation of association between DM, PTB prevalence and its risk factors was limited only to univariate analysis. Since the prevalence of PTB among DM was very low (<1%), the power to detect significant correlation and the strength of association between the two variables is difficult. Therefore, we suggest future studies to consider this limitation and employ random sampling with patients visiting non DM clinics.

CONCLUSIONS

Although the prevalence of PTB was low, health education, proper case management and risk based screening for PTB in DM are recommended in low prevalence settings.

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AUTHORS CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

W: Concept, design, data collection and analysis, manuscript writing and review.

PC: Design, data collection and analysis, manuscript writing and review

KD: Design, data collection and analysis, manuscript writing and review

TD: Design, data collection and analysis, manuscript writing and review

ND: Design, data collection and analysis, manuscript writing and review

Author agree to be accountable for all respects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

None

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