THE PREVALENCE AND DETERMINANTS OF ACTIVE TUBERCULOSIS AMONG DIABETES PATIENTS IN TERTIARY CARE HOSPITALS OF NEPAL 2018

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ABSTRACT

Introduction: Researches implicated diabetes as independent risk factor for multi-drug resistant tuberculosis and unfavorable outcome of treatment. There is no data to address the association between diabetes mellitus (DM) and tuberculosis (TB) in Nepal. Thus we assessed the burden and demographics of active tuberculosis among diabetic patients attending tertiary care hospitals in Nepal.

Methods: A cross-sectional study was conducted in adult DM patients attending seven tertiary care hospitals representing five development region of the country. Relevant data were collected and participants were screened for active TB (symptom screening and microbiological diagnosis).

Results: Among the 520 enrolled DM patients screened, 23 had active TB. The prevalence was 4.42% (CI 2.96 - 6.54). The positive cases had older age group with the mean age of 59.73 ± 17.36 years with male predominance of 78% (18/23). Among the 23 positive cases, only two (8.69 %) had extra pulmonary TB. Diabetic control had significant (p=0.006) relationship to develop Tuberculosis. The comorbid conditions e.g., Hypertension (OR 13, 95% CI: 4.54 to 37.14); diabetic nephritis (OR 9.25, 95% CI: 2.03 to 42.20); and Diabetic neuropathy (OR 26.66, 95% CI: 5.16 to 137.71) are significant risk factors to develop tuberculosis among the diabetes patients. There were no significant differences in occupation, literacy rate, tobacco or alcohol consumption, HbA1c levels between TB and non-TB participants.

Conclusion: The prevalence of tuberculosis among diabetic patients is low in Nepal. This is the result of tertiary care hospital outdoor patients only, thus representativeness was compromised. Thus to assess the magnitude of comorbidities, mandatory screening in all level were recommended.

Key words: Diabetes, Tuberculosis, Prevalence

INTRODUCTION

The burden of diabetes and tuberculosis are enormous, particularly in developing countries. The International Diabetes Federation has reported that there were 451 (95% CI 367 – 585) million cases of diabetes worldwide in the year 2017 and about 79% of people with diabetes live in low- and middle-income countries.[1] Meanwhile, the World Health Organization has reported that an estimated 10.4 million cases of tuberculosis occurred worldwide in the year 2016 and 87% of all the cases occurred in the 30 high-burden countries, many of which are low and middle income countries.[2] The interactions between these two diseases present additional clinical as well as a public health challenge. Diabetes has long been recognized as an important risk factor for tuberculosis. The widely quoted systematic review published in 2008 had found that DM was associated with an increased risk of TB by three-fold (Relative Risk 3.11, 95% CI 2.27-4.26).[3] The more recent studies have however estimated this risk to be between 1.77 (95% CI 1.48–2.11) to 2 (95% CI 1.78 – 2.24).[4,5] A systematic review

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and meta-analysis has also reported that diabetes confers a small but statistically significant risk of latent TB infection (pooled odds ratio 1.18 (95% CI, 1.06–1.30).[6] Diabetes also affects the natural history of tuberculosis and is associated with the worse treatment outcomes. It is associated with the delayed sputum conversion (aOR 1.51, 95% CI 1.09 to 2.10) and a higher probability of treatment failure (aOR 2.93, 95% CI 1.18 to 7.23).[7] A systematic review has implicated diabetes as a risk factor for death (RR, 1.89; 95% CI, 1.52 to 2.36), and increased risk of relapse (RR, 3.89; 95% CI,2.43 to 6.23) as well.[8] In another meta-analysis, diabetes has also been identified as an independent risk factor for the multi-drug resistant tuberculosis (OR 1.71; 95% CI = 1.32, 2.22).[9] Conversely, tuberculosis in itself can worsen glycemic control among the people with diabetes. The interactions between the drugs can further complicate the picture, leading to a reduction in the effectiveness of both tuberculosis and diabetes treatments, as well as potential worsening of drug side-effects.[10, 11] Available studies have reported that the prevalence of active tuberculosis among the people with diabetes range from 0.38% to 14% with the overall median global prevalence as 4.1% (IQR 1.8%-6.2%). The median prevalence from Asia has been reported as 3.5% (IQR 0.9 – 10.5%).[12] A screening program in six diabetes clinics of tertiary healthcare centers in India identified 18 cases of active tuberculosis as a result of the screening program.[13] Another study at a single tertiary care hospital from Bangladesh identified 37 cases of active tuberculosis while screening the people with diabetes.[14] A cross-sectional study in a tertiary care center in Eastern Nepal detected eight cases of tuberculosis among the 100 patients with established diabetes.[15]

For optimal outcomes of both the conditions, therefore, people with diabetes should be considered for evaluation of tuberculosis and vice –versa. World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease launched the Collaborative Framework for the care and control of diabetes and tuberculosis in 2011.[16] It provides a guidance to the policy makers and health-care professionals in combating the dual epidemic with an emphasis on operational and clinical research to build-up and strengthen the evidence base for action. It has been further emphasized in the Bali declaration in 2015 which declared the looming tuberculosis-diabetes co-epidemic as a public health priority and called for early and decisive action.[17]

Nevertheless, the adaptation and implementation of the collaborative framework under national programs have been slow. Several programmatic issues challenge the implementation of the TB-Diabetes bidirectional screening and its cost-effectiveness, particularly in the resource limited settings.[18] The lack of non-communicable disease program or systematic and decentralized diabetes management centers in many developing countries make it more difficult to implement an effective collaborative model of care.[19]

Thus, it is imperative that the people with diabetes are screened for tuberculosis and vice-versa using the cost-effective screening strategies available, which are also feasible under the programmatic conditions. In this study, we aimed to estimate the prevalence of active tuberculosis among the people with established diagnosis seeking care at large public healthcare centers using the existing tools as per the national tuberculosis program protocols. We also aimed to assess the risk factors for developing active tuberculosis among the diabetic population to help identify the most appropriate individuals who will likely benefit from TB screening. This study also assessed the baseline knowledge of tuberculosis among those patients with diabetes mellitus

METHODOLOGY

This study aimed to assess the prevalence of active tuberculosis among the people with established diabetes. Therefore, a cross-sectional research design had been applied. The study sites were selected purposely. The diabetes care in Nepal is mainly provided through tertiary care centers or specialized private centers by endocrinologists and internists. These centers are concentrated in more accessible cities and Kathmandu, the capital city, contributes to a significant proportion of patients who seek diabetes care. Accordingly, this study had identified one major city in each of the five development regions. The centers identified are all large public hospitals, preferably university hospitals with a high volume of patients and services for diabetes management. Due to the high volume of patients, three major university teaching

hospitals had been identified from Kathmandu valley. Thus the sites were Institute of Medicine, Tribhuvan University Teaching Hospital, National Academy of Medical Sciences, Bir Hospital and Patan Academy of Health Sciences, Patan Hospital from central region; BP Koirala Institute of Health Sciences from Eastern region; Pokhara Academy of Health Sciences, Gandaki Regional Hospital from western region; Bheri Zonal Hospital from Mid- Western region and Seti Zonal Hospital from Far-Western region.

People with established diabetes mellitus, who were attending to above hospitals during study period (August to October, 2019). The primary sampling units were each of the study site with diabetes clinics selected for the study and secondary sampling units were patients with established diabetes mellitus attending those hospitals.

The sample size had been calculated by the formula n = $Z^2P(1-P)/d^2$. P is expected the prevalence active TB among the people with diabetes taken as 3.5%[12.] An additional 20% non-response rate had been estimated. Multi stage sampling was done. First stage was done by selecting each center considered as a cluster. Within each cluster, second stage was by systematic random sampling. The first sample was selected randomly and then every 5th patient with diabetes were included in the study till the required number of participants was obtained.

Consented adults of 16 or more years of age with established diabetes mellitus according to ADA 2018 criteria for the diagnosis of Diabetes were included in the study.

In every study site, a focal person took the responsibility in close collaboration with the head of the institution to coordinate the data collection. A team from the SAARC TB and HIV/AIDS center comprising of the Principal Investigator and study team members visited each study sites and short training was done. A definite algorithm (Referenced by the national tuberculosis program) were followed to screen the study participants.

Operational definitions were clearly defined in the data collection tool. The strategy of screening for active TB and testing them for confirmation has been validated and recommended by the World Health Organization, including in the settings of TB prevalence surveys.[20, 21]

Data management and analysis

Data entry was done in Microsoft Excel 2016 and Analysis in IBM SPSS 23. Socio-demographic and other relevant characteristics of the study participants using mean, standard deviation, median and percentages as appropriate. Data was statistically analyzed with the significance level setting as two-tailed and at p value <0.05. Descriptive statistics for continuous variables were described as means ± standard deviation, while categorical data were reported as frequency and percentage. Differences between the two groups (males and females) were compared using Fisher's exact test for categorical variables, or independent t-test for continuous variables. Odds ratio were calculated to identify the risk factors associated with active tuberculosis.

Ethical approval

Ethical approval were taken from Nepal Health Research Council and appropriate local ethical board of Pokhara Academy of Health Sciences, Gandaki Regional Hospital, Patan Academy of Health Sciences, Patan Hospital

RESULTS

A total of 520 eligible participants were enrolled in the study and went through the data collection and laboratory diagnosis. Among them, 23 were diagnosed as having Tuberculosis. The prevalence counted as 4.42%. The mean age of the study subjects was 54.34 ± 12.67 years. 18 (3.5%) subjects were aged less than 30 years, 23 (4.4%) aged between 31–35 years, 34 (6.5%) of them were aged between 36–40 years, 62 (12%) subjects were aged between 41–45 years, 72 (13.8%) between 46–50 years, and 311 (59.8%) of them were aged >50 years. The mean age of the positive TB cases were 59.73 ± 17.36 years with a minimum 28years, maximum 83 years and median age of 62 years. The gender-wise demographic information of all participants is detailed in Table 1. Females were comparatively younger than male (53.57±12.12 vs. 55.40±13.17 years; p = 0.001). Gender difference were seen in educational status, occupation and personal habits. Majority of men

Table 1: Demographic details of the Study				
Characteristics	Total (n=520)	Male (n=228)	Female (291)	P value (Male vs. Female)
Age (years) Values are mean ± SD	54.34±12.67	55.40±13.17	53.57±12.12	0.001
Educational Status				
Literate	293 (56.34 %)	172 (75.43 %)	121 (41.58%)	Not significant
Illiterate	219 (42.1%)	53 (23.24%)	166 (57%)	
Personal habit				
Smoking	77 (14.8%)	56 (24.56%)	21 (7.21%)	Not significant
Alcohol	59 (9.8%)	51 (22.36%)	8 (2.75%)	Not significant
Tobacco	45 (8.65%)	35 (15.35%)	10 (3.43%)	Not significant

** χ^2 test and Fisher's exact test were done

were employed compared to women. Above 22% of men gave history of smoking or consuming tobacco in other form and about 15% consumed alcohol. Among the positive TB cases, 78% (18/23) were male and 21% (5/23) were female.
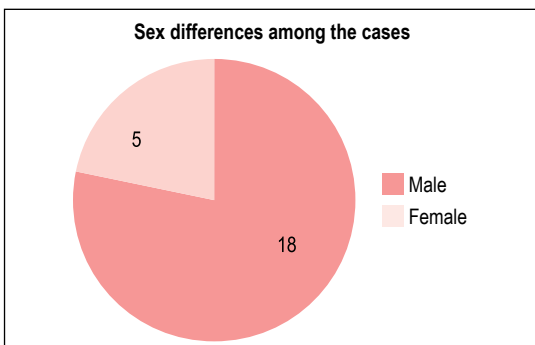

Figure 1: Shows the sex differences of the positive cases who were positive to have TB.

Among the 23 positive cases, only two (8.69 %) had extra pulmonary TB. Rest 23 (91.3%) were diagnosed to have pulmonary TB.
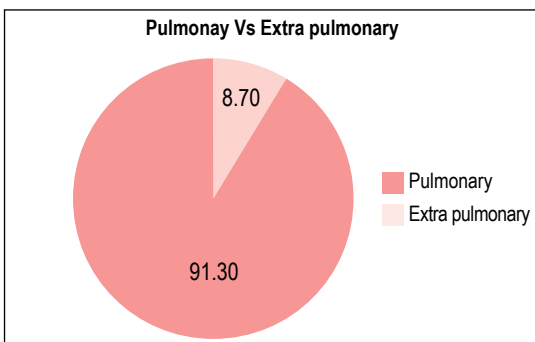

Figure 2: Common type of Tuberculosis among the diabetic patients, Nepal, 2018

While going through the demographic detail, none of the educational status, marital status shows any significant relation with the positive TB cases
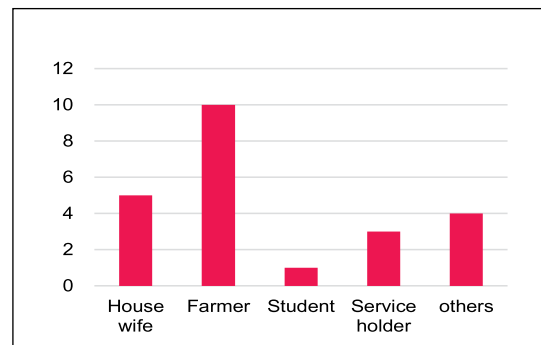

Figure 3 : The occupation of the Cases were classified

Personal habit like tobacco and alcohol consumption or chewing of betel nuts or any other addictive substance didn't show any significant relationship to develop TB among the diabetic patients. However the other co morbidities associated with diabetes showed as a risk factor to develop Tuberculosis among the participants.

Table 2: Relationship of the comorbidities			
Co morbidities	Odds ratio	95% CI	Significant level
Hypertension	13	4.54 to 37.14	P < 0.0001
Diabetic nephritis	9.25	2.03 to 42.20	P = 0.0040
Diabetic Neuropathy	26.66	5.16 to 137.71	P = 0.0001
Dyslipidemia	2.77	0.84 to 9.08	P = 0.0911

Table 2 shows the relationship of the comorbidities which acted as a risk factor. Among the positive

twenty three cases, the duration of diabetes calculates as 11.48 ± 7.72 years (mean ± SD). They are taking treatment of diabetes for average 9.83 years. Diabetic control had significant (p=0.006) relationship to develop Tuberculosis. We asked five questions to assess the baseline knowledge of tuberculosis among the patient with diabetes. The variables were fact tuberculosis and its cause, symptoms, transmission and risk factors and Tuberculosis. The response of these are tabulated in Table 3.

S.N.	Questions	Positive answers (%)
	Table 3: Baseline knowledge of tuberculosis among the patient with diabetes	
1.	Do you know, Tuberculosis is a curable disease or not?	60
2.	Tuberculosis is caused by?	52.17
3.	How Tuberculosis is transmitted?	60.86
4.	Do you know the risk factor for tuberculosis?	73.91
5.	Can you mention the symptoms for tuberculosis?	73.91

DISCUSSION

In this study the overall prevalence of Tuberculosis among the diagnosed diabetes patient was seen as 4.42%, which is comparable with other studies which it shows that among the 78 studies, 48 (61.5%) studies were conducted in countries of Asia and showed prevalence rates ranging from 5.1% in Saluru-South India to 44% in Kerala-India[12]. This meta-analysis also showed, overall median prevalence of DM among TB patients in Asia was calculated to be 17% (IQR 11.4%-25.8%).

Among the positive cases we see male predominance (78%). In many of the studies, diabetes was associated with a progressive shift of male predominance with tuberculosis[22]. It might be because, male are more active in outside social activities then women and in Asian countries in middle and lower socio economic group. Though the other socio cultural variables were not evaluated in this study, different factors might play important role to explain this gender gap including biological differences in disease and disease presentation and different access to health care specifically in developing countries[23]. Also the mean age of the positive TB cases were 59.73 ± 17.36 years with a minimum 28years, maximum 83 years and median age of 62 years, which shows prevalence is more in older age group. Similar phenomena was seen in some other studies where they found diabetic group of TB was older in age with longer duration of cough [24].

Pulmonary tuberculosis were more (91.3%) among the study participants. This might be because of the diagnostic hurdle and unavailability of the diagnostic facilities among the study sites. On the other hand, pulmonary tuberculosis is predominant in these settings of Nepal. Most of the positive cases were farmer (43%). Other occupation poses minimal threat to develop Tuberculosis. The exact cause of this occupational relationship were not revealed in depth.

In many studies, Diabetes mellitus itself was identified as a risk factor for developing tuberculosis infection. In this study smoking, consumption of alcohol, educational level didn't pose any threat to develop tuberculosis among the diabetes patients. But tuberculosis developed most frequently in patients with poor diabetic control and associated co morbidities were significant risk factors to develop tuberculosis.

Similarly, poor glycemic control in Asian populations represents a potentially important risk factor for TB[25]. This might be because, hyperglycemia could play a role to alter the immune responses to the causative organism of tuberculosis in diabetic patients. Some studies shown that poor Diabetes control (indicated by HbA1c level) was associated with differences in the innate and cellular cytokine responses to stimulation with purified protein derivative from M. tuberculosis, thus facilitating progression to active TB[26]. Another recent study, that recruited 4,690 elderly diabetic patients in Hong Kong, showed that the patients with greater HbA1c value (>7%) had a hazard risk of active TB that was 3 times increased compared with those who had HbA1c < 7% (HR 3.11; 95% CI 1.63–5.92, $p < 0.01$)[27].

In this study, other co morbidities related to diabetes e.g., Hypertension, Nephritis, Neuropathy and Dyslipidemia came up as significant risk factors to develop tuberculosis. The reason might be same as hyperglycemia; compromised and poor immune response;and interaction of the microorganism etc.

The study participants had overall good conception regarding tuberculosis. Several questions were asked to reveal the baseline knowledge of tuberculosis. More than half of the participants came up to have good knowledge.

However there were some limitations of the study. As much as an effort has been made to take samples representative of the whole country, many of the health centers could not be included. The private diabetes centers, which also hold a significant number of patients with diabetes, have not been included in the study. Also all the patients have not been screened for microbiological analysis. Thus the study result could not be generalize to be representative of Nepal.

Thus more comprehensive study is recommended including the private sector, indoor patients. Also it is recommended to have mandatory tuberculosis screening to all indoor and outdoor patients who will be coming to take health care.

CONFLICT OF INTEREST

None

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