ASSOCIATION BETWEEN DIABETES MELLITUS AND DRUG RESISTANT PULMONARY TUBERCULOSIS

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Tuberculosis, one of the major communicable diseases, threatens both developed and developing countries. Its burden is growing and is difficult to control because of emerging resistant strains. Diabetes mellitus, a condition causing immune suppression, has been growing worldwide and should be considered a high risk group for developing TB. The importance of drug resistant TB and diabetes mellitus need to be explored in the local setting. This study was designed to find out the association between diabetes mellitus and drug resistant pulmonary tuberculosis. It was a hospital based analytical study among culture positive pulmonary TB patients in Yangon General Hospital, New Yangon General Hospital and National Tuberculosis Programme from January 2018 to December 2019. A total of 100 culture positive pulmonary TB patients were recruited. Fifty percent were between 41 and 60 years' age group with male preponderance (57%). Sixty-one patients (61%) had diabetes and 39 patients (39%) had no diabetes. Overall 29% of drug resistance TB was found. It was 26.2% among diabetes and 33.3% among non-diabetes. Odd ratio of anti-TB resistance was 0.881 (95%CI= 0.259-3.001) and that of MDR TB was 0.74 (95% CI=0.11- 4.45) among diabetic patients over non-diabetic patients. When association between diabetes mellitus and anti-TB drug resistance was analyzed by using binary logistic regression with adjusted previous history of anti-TB treatment and history of TB contact, the odd ratios were 0.651 and 0.578 respectively. Both were not statistically significant (P value >0.05).

Keywords: drug resistant, pulmonary tuberculosis, culture positive, diabetes mellitus

INTRODUCTION

Tuberculosis (TB) is one of the major health problems worldwide with high morbidity and mortality. TB is one of the top 10 causes of death and the leading cause from a single infectious agent (above HIV/AIDS). Millions of people continue to fall sick with TB each year. In 2017, globally, the best estimate is that 10.0 million people (range, 9.0–11.1 million) developed TB disease. And TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV-negative people [1]. These TB burdens are driven by person to person transmission mode, and drug resistance which contributes major impact on TB control globally. Around the world, over 340,000 people are reported to have drug resistant tuberculosis in 2015 and among them, 200,000 are in South East Asia (SEA) region. Myanmar, one of the SEA countries, is at the 6th position among the 30 high Multiple Drug Resistant (MDR) TB burden countries, with an incidence of 14,000 in 2015. In Myanmar, MDR/RR-TB cases accounted for 5.1% of new cases and 27% of previously treated cases[2].

Diabetes mellitus (DM), one of the conditions causing immune suppression, is increasing in prevalence worldwide; estimated population of 422 million people with diabetes mellitus in 2016 and is expected to double in two decades as estimated by WHO on World Diabetes Day 2016. According to WHO STEP survey (2014), percentage of diabetes mellitus in Myanmar is 10.5 % in both sexes[3].

Drug resistant TB which is the major constraint of TB treatment and control is becoming an emerging issue to manage. And it is necessary to find out its association with diabetes mellitus. Globally, there are studies on DM and drug resistant TB. One of these studies stated that type 2 DM presented 4.7 fold and 3.5 fold higher risks of developing DR and MDR TB, respectively in the south east of Mexico[4]. A meta-analysis determined that diabetes mellitus was an independent risk factor for MDR TB, and there was a significant association between diabetes mellitus and MDR TB (OR=1.71)[5]. However, there are also some studies which showed no association between DM and drug resistant TB. One study from South India[6] found

that among diabetes subjects,49% were found to have resistance to any one first line anti TB drugs with 26% of all the TB infected diabetic patients in that study had MDR TB. Association between DR-TB and DM was not found in that study.

In Myanmar, there are some studies on diabetes mellitus and tuberculosis. One of them found primary drug resistance in sputum culture positive pulmonary TB among diabetes[7]. In that study prevalence of DR-TB among diabetic patients was higher than expected 5% of new TB patients and 27.1% of re-treatment cases as found in Myanmar National TB Drug Resistance Survey 2012-2013. It became the alarming figure for the burden of DR-TB among diabetic patients.

The current study was aimed to find out the association between the diabetic status and anti-TB drug resistance in patients with pulmonary tuberculosis. As the drug resistant TB is important to overcome the barriers for the effective control of tuberculosis, this study intended to explore the relationship between the two major health problems in Myanmar.

METHODS

Hospital based analytical study of culture positive pulmonary tuberculosis patients in medical wards of Yangon General Hospital and New Yangon General Hospital within 2 years from January 2018 to December 2019. Patient selection was carried out according to inclusion and exclusion criteria. Selected patients were explained about the procedure and written informed consent was requested thereafter. Relevant history taking, physical examination, blood sugar monitoring in patients not previously known to have diabetes mellitus, chest X-ray, sputum smear and culture were done and recorded in proforma. To get the uniform results, capillary blood glucose monitoring was done with the specific glucometer and HbA1C was done in YGH laboratory. Culture negative cases were excluded. Culture positive pulmonary TB cases were differentiated into diabetes mellitus and non-diabetes mellitus TB cases and then proceeded the drug sensitivity testing. Individual and pattern of anti TB drug resistance was determined among TB patients with or without DM and finally found out the association between DM and drug resistant pulmonary tuberculosis.

RESULTS

There were altogether 350 patients screened for the study. Among them, 216 patients were sputum AFB or Xpert MTB/ RIF assay positive for mycobacterium tuberculosis and proceeded for sputum AFB culture. Among them, 100 culture positive pulmonary TB patients with or without diabetes mellitus were included in this study. Other 116 patients were excluded because of culture negative or low colony count in culture which were insufficient to proceed drug sensitivity testing and 2 samples being non-tuberculous mycobacterium culture results.

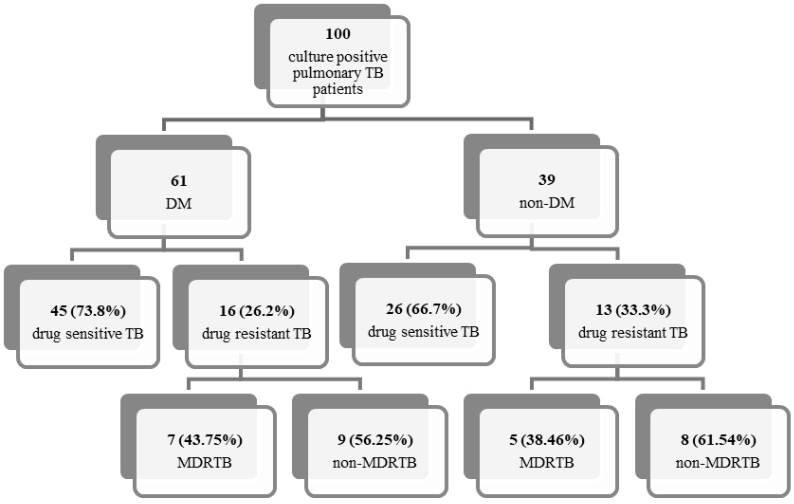

Figure (1) Summary flow diagram of distribution of anti-TB drug sensitivity among the study population

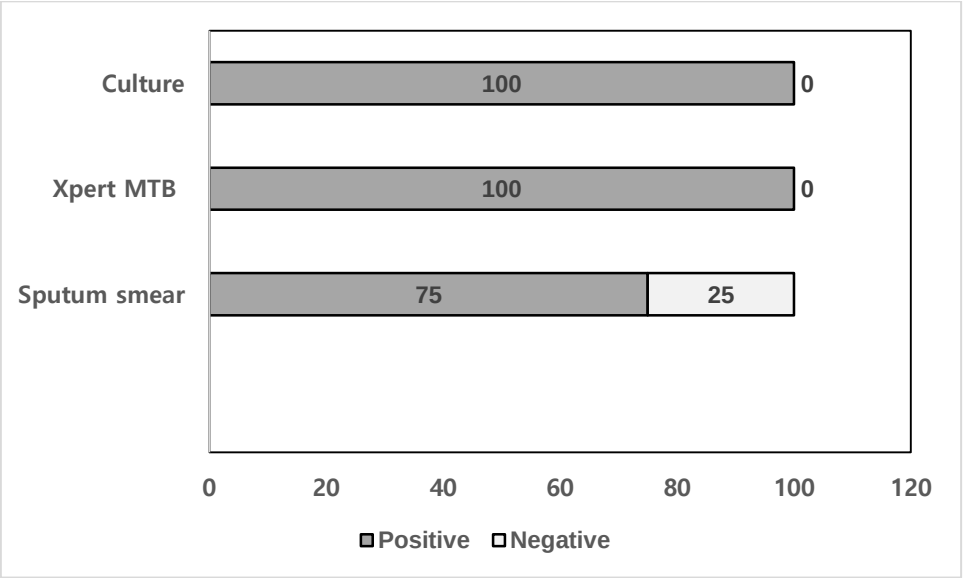

Figure (2) Sputum smear and culture results among study population

Although all the patients (100%) were culture positive pulmonary TB cases and Xpert MTB positive, only 75 patients (75%) were positive AFB for sputum smear microscopy and the left 25 cases (25%) were negative for sputum smear. Among sputum AFB microscopy positive cases, 38/ 61 patients (62%) were from TB-DM group and 37/ 39 patients (95%) from TB-non DM group.

Table (1) Anti-TB drug resistant pattern in relation to DM status

	MDR TB		Non-MDR TB		OR	95%CI	p value
	n	%	n	%			
DM	10	63%	6	37%	0.74	0.11- 4.45	0.705
Non-DM	9	69%	4	31%			
Total	19	66%	10	34%			

Among 29 anti-TB resistant cases, 66% (19 in 29 patients) were MDR cases and 34% (10 in 29 patients) were non-MDR cases (ie. mono-drug resistance or poly-drug resistance). MDRTB patients comprised 63% (10/16) of diabetics and 69% (9/13) of non-DM. Odd ratio of MDR TB among diabetic patients over non-diabetic patients was 0.74 (95% CI=0.11- 4.45). Among non-MDRTB, mono INH resistance was found in 5 patients, mono streptomycin resistance in 1 patient and poly-resistance in 4 patients.

Table (2) Association between drug resistant pulmonary TB and DM

	Anti-TB drug resistance	Anti-TB drug sensitive	OR	95% CI	p value
	n (%)	n (%)			
DM	16(26.2%)	45(73.8%)	0.881	0.259-3.001	0.840
Non-DM	13(33.3%)	26(66.7%)			
Total	29	71			

There were 29 anti-TB drug resistant patients and 71 drug sensitive patients in the study population. 26.2% (16 patients) of diabetes mellitus patients were anti-TB resistant and 73.8% (45 patients) were anti-TB sensitive. Furthermore, 33.3% (13 patients) of non-DM patients were anti-TB resistant and 66.7% (26 patients) were anti-TB sensitive. The odd ratio of anti-TB resistance among diabetic patients over non diabetic patients was 0.881 (95%CI= 0.259-3.001). When association between diabetes mellitus and anti-TB drug resistance was analyzed by using binary logistic regression with adjusted previous history of anti-TB treatment and history of TB contact, the odd ratios were 0.651 and 0.578 respectively. But both of the value were not statistically significant with P value >0.05.

Table (3) Association between drug resistant pulmonary TB and diabetic control status

Hb A1C (%)	Anti-TB resistance	Anti-TB sensitive	Total	P value
	n (%)	n (%)		
< 7.5	5 (31%)	11 (69%)	16	0.291
7.5- 9	5 (17%)	24 (83%)	29	
>9	6 (38%)	10 (62%)	10	
Total	16	45	61	

Among 16/ 61 anti-TB drug resistance cases in TB- DM group, 5/16 patients (31%) had Hb A1C <7.5%, 5/29 patients (17%) had HbA1C 7.5- 9% and 6/10 patients (38%) had HbA1C > 9%. TB-DM patients with poor glycemic control (HbA1C >9%) got higher anti- TB drug resistance (38%) than other patients. But there was no statistically significant association between anti-TB drug resistance and glycemic control (p= 0.291).

DISCUSSION

Total 100 culture positive pulmonary TB patients were involved in the study. They were differentiated into diabetes mellitus and non-diabetes mellitus TB cases and then proceeded the individual and pattern of anti-TB drug resistance. History of previous anti-TB treatments and history of TB contacts were also recorded to find out their relation with individual and pattern of anti-TB drug resistance in diabetic and non-diabetic patients. The study was done at all medical wards in Yangon General Hospital and New Yangon General Hospital, which are the main draining areas for tuberculosis patients all around Yangon region from January 2018 to December 2019. Therefore, the study population were representative of most of the pulmonary TB patients in Yangon region.

Anti-TB drug resistant pattern in relation to DM status

In the current study, odd ratio of MDR TB among diabetic patients over non-diabetic patients was 0.74 (95% CI=0.11-4.45). From Global TB report (2018)[1], within 53 million population of Myanmar in 2017, estimated percentage of TB cases with MDR/RR TB was 5.1% in new cases and 27% in previously treated cases. One prospective study from India demonstrated that no one in TB-DM group shifted to MDR while 4 patients (2.7%) shifted to MDR even though other variables were strongly suggested that presence of diabetes mellitus had significant impact on tuberculosis (higher sputum positivity at the end of 2 months' treatment and poor outcome at the completion of treatment[8]. The meta-analysis of 24 observational studies from 15 different countries revealed that diabetes mellitus had a significant association with MDRTB (p= 0.031, OR= 1.97). Current study did not match with these data because rate of MDRTB was also high in non-DM population although rate was high in DM population. These could be explained by the higher rate of primary infection with a resistant strain in the majority of global MDRTB cases[9]. But one study from Taiwan coincided with the current study. It revealed that DM was significantly associated with INH resistant, but not

MDRTB in both new and previously treated TB cases[10]. In the transition of *M. tuberculosis* from drug-susceptible to drug-resistant strains, development of resistance to INH usually precedes RIF resistance, indicating the significant role of INH-related resistance in the development of MDR-TB[11].

Association between drug resistant pulmonary TB and DM

In the current study, odd ratio of anti-TB resistance among diabetic patients over non diabetic patients was 0.881 (95%CI= 0.259-3.001). The adjusted odd ratio (after adjustment of previous history of anti-TB treatment and history of TB contact) became 0.651 and 0.578 respectively. But both of the value were not statistically significant with P value >0.05. This result was in accord with a study from Saudi Arabia, revealing that pulmonary TB-DM patients had a lower prevalence of resistance to any anti-TB drugs (p= 0.007) and higher sputum conversion rates at the end of 3 months of treatment (p= 0.013). So, the association of diabetes mellitus did not alter the final treatment outcome among pulmonary TB patients[12]. Diabetes mellitus was identified as a risk factor of any drug resistant tuberculosis and was associated with sputum conversion rate, and other treatment outcomes[8,13,14]. In the current study, the rate of drug resistant pulmonary tuberculosis in diabetes mellitus patients was not statistical significantly higher than the rate of DRTB in non-DM patients. Although there was no significant association, it was speculated that the sample size was probably insufficient to detect such an association. Further studies on the association between diabetes mellitus and drug resistant pulmonary tuberculosis are needed.

In the current study, TB-DM patients with poor glycemic control (HbA1C >9%) had higher anti-TB drug resistance (38%) than other patients. But there was statistically insignificant association (p= 0.291). There were several studies which show poor impact of glycemic control on tuberculosis. The risk of TB was increased in diabetic patients with baseline HbA1C >7% [15]. And also adverse outcomes were more common in uncontrolled DM patients and unlikely in controlled DM patients[16] and Hb A1C ≥7% was independent risk factor for positive culture at 2 months of treatment[17]. All of those factors can lead to poor treatment outcomes in tuberculosis, including drug resistance. In the current study, there was cross-sectional analysis of anti-TB drug resistance in DM patients comparing with non- DM patients. If larger sample size with prospective study can be done, there can be demonstrated about the association between these two important factors; glycemic control and anti-TB drug resistance.

CONCLUSION

This study intends to explore the relationship between the two major health problems in Myanmar. It is designed to find out the individual and pattern of drug resistant pulmonary TB in patients with diabetes mellitus compared with non-diabetic patients. Concordance rate of sputum AFB microscopy results and culture results were 75% and Xpert MTB/ RIF assay and culture was 100%. Odd ratio of anti-TB resistance among diabetic patients over non diabetic patients was 0.881 (95%CI= 0.259-3.001). Adjusted odd ratio (after adjustment of previous history of anti-TB treatment and history of TB contact) became 0.651 and 0.578 respectively. But both of the value were not statistically significant with P value >0.05. Odd ratio of MDR TB among diabetic patients over non-diabetic patients was 0.74 (95% CI=0.11-4.45). Further studies on the association between diabetes mellitus and drug resistant pulmonary tuberculosis are needed. Even though overall data could not give evidence of association between diabetes mellitus and drug resistant pulmonary tuberculosis, there were a lot of learning points in related to diagnosis and treatment of pulmonary TB cases in both DM and non-DM population. These informations and data will become a helpful tool in effective management of patients with TB-DM comorbidity.

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