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ORIGINAL ARTICLE

Diabetes mellitus and treatment outcomes of pulmonary tuberculosis: a cohort study

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Abstract

Objectives This study aimed to investigate the impact of diabetes on the treatment outcomes among pulmonary TB patients in Yerevan, Armenia.

Methods We utilized a cohort study design that included TB patients with diabetes and TB patients without diabetes. The data collection was conducted in the National Tuberculosis Control Center, eight tuberculosis outpatient centers and the 'Prisoners' Hospital' in Yerevan, Armenia. Data were collected from an existing national TB database and patients medical records. Multivariable logistic regressions were conducted to construct the final model and test the associations.

Results The final sample included 621 patients 5.8% of whom had diabetes. The odds of having treatment failure was 8.99 times higher among TB patients with diabetes (95% confidence interval 2.51–32.23) compared to TB patients without diabetes after adjusting for weight and sputum smear status.

Conclusions Diabetes comorbidity had a negative effect on TB treatment outcomes. Countries with a high burden of both TB and diabetes need to develop mechanisms for active screening for diabetes among patients with TB and address their treatment needs carefully.

Keywords Treatment failure · Cohort study · Tuberculosis · Diabetes

Introduction

The societal burden of tuberculosis (TB) remains significant. There were 10.4 million new cases of TB and 1.8 million TB-related deaths reported globally in 2015 (World Health Organization 2016). The incidence and mortality rates vary between countries and World Health Organization (WHO) regions, whereby the differences can potentially be attributed to socioeconomic factors and migration patterns (European Centre for Disease Prevention and Control/WHO Regional Office for Europe 2013). In the WHO European region, TB incidence varies widely from 2 to 119 per 100,000 population (European Centre for Disease Prevention and Control/WHO Regional Office for Europe 2013). However, the majority of the cases occur in 18 TB high-priority countries that contribute to 87% of incident cases, 87% of prevalent cases, 92% of mortality and 99% of multi-drug-resistant (MDR) TB (European Centre for Disease Prevention and Control/WHO Regional Office for Europe 2013).

Past studies have reported an association between diabetes and an increased risk of developing TB (Stevenson et al. 2007a). Systematic reviews showed that people with diabetes had 1.5–8 times higher risk of developing TB than those without (Jeon and Murray 2008; Stevenson et al. 2007a). Considerable evidence demonstrates that diabetes impairs immune responses that body needs to resist to the

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Mycobacterium tuberculosis infection, increasing the susceptibility to TB (Harries et al. 2009). Diabetes itself is a global health challenge. About 9% of the world population has diabetes, and the prevalence continues to increase (International Diabetes Federation 2015). It is also the eighth leading cause of death in most high-income countries (NCD Alliance n.d.).

Current evidence suggests that patients with TB who have comorbid diabetes have poor TB treatment outcomes (Alisjahbana et al. 2007; Han et al. 2016). The systematic review of 33 studies concluded that diabetes increases the risk of failed treatment and death among patients with tuberculosis (risk ratio (RR) = 1.69 (95% CI 1.36–2.12) (Baker et al. 2011). According to past studies, poor outcomes can be attributed to a number of potentially modifiable and non-modifiable risk factors including age, gender, human immunodeficiency virus (HIV/AIDS) and other comorbidities, drug-resistant (DR) TB, previous history of TB, having the combined form of TB (pulmonary and extra-pulmonary), socioeconomic status (e.g., unemployment, homelessness), malnutrition, lower weight, alcoholism and smoking (Quy et al. 2006; Santha et al. 2002; Sterling et al. 2006). Furthermore, after adjusting for these factors, the risk of TB treatment failure and death is still high in this population (Baker et al. 2011; Dooley et al. 2009; Mboussa et al. 2003).

Armenia is a country with 3 million population. Yerevan is the capital city of Armenia where more than 40% of the population resides (National Statistical Service of the Republic of Armenia, n.d.). Up until 2017, Armenia was among high TB-burden countries (European Centre for Disease Prevention and Control (ECDC) n.d.). In 2015, the incidence rate of TB in Armenia was reported to be 46 per 100,000 population (European Center for Disease Prevention and Control 2016). Among new and relapse TB patients in Armenia, the success rate of treatment was 79% in 2016 (European Centre for Disease Prevention and Control (ECDC) n.d.), which was below the WHO target success rate of 85% (World Health Organization 2012).

Diabetes is the seventh leading cause of death in Armenia contributing to 4.6% of total deaths in 2015 (Andreasyan et al. 2016). In 2016, the prevalence of diabetes diagnosed by a doctor among 15 years and older population in Armenia was 2.6% (Andreasyan et al. 2016). Existing studies suggest lack of appropriate diabetes management at primary care level and poor self-management among diabetes patients in Armenia (Kühlbrandt et al. 2014).

Armenia follows the forth WHO treatment guideline for national TB programs (the 2013 revision)—all drug-sensitive (regular) TB patients receive 2 months of intensive TB treatment at a TB inpatient care facility followed by four months of directly observed therapy (DOT) at a TB outpatient center (World Health Organization n.d.). There are exceptions for sputum-smear-negative (SS−) patients who may receive the intensive phase of the treatment in TB outpatient centers. In addition, as a part of the national TB control program, the penitentiary system organizes the TB treatment of the prisoners in the prison hospital located in Yerevan. Here, under the control of the National Tuberculosis Control Center (NTCC) they provide TB treatment and diagnosis following the same national and WHO guidelines. Patients with DR TB (including MDR and XDR) have a treatment lasting 21–24 months including both the intensive and ambulatory treatment phases (World Health Organization n.d.). Independent assessments demonstrate that the same treatment regimen and similar practice is used in the penitentiary system in Armenia (Grigoryan et al. 2008).

Patients with diabetes are among the higher-risk populations for TB. After the TB diagnosis, patients are screened for glucose levels in the blood and, if needed, are referred to a narrow specialist. Similarly, diabetic patients are being checked for early identification of TB (RA Government Decree N 21 2008).

No prior study has investigated the association between TB and diabetes in Armenia. Investigations of the association between diabetes and TB treatment outcomes could help to improve care and treatment outcomes of patients with diabetes and TB. The aim of this study was to investigate the impact of diabetes on treatment outcomes among pulmonary TB patients in Yerevan, Armenia.

Methods

Study design and study population

We utilized a cohort study design that enrolled patients with pulmonary TB. The study population included all adult patients registered and treated in Yerevan outpatient TB care facilities (including patients from the penitentiary system) whose treatment outcomes were recorded in the National Tuberculosis Control Center (NTCC) database for the period from January 1, 2013 to December 31, 2014. Patients with missing or incomplete outpatient medical records and those transferred to other cities during the TB treatment period were excluded from the study. Two groups of TB patients, those with and without diabetes, have been followed from the day of TB diagnosis to the day of their treatment outcome. TB patients were considered to have diabetes if a diagnosis of diabetes was recorded in their outpatient medical card.

Data collection sources and methods

We developed a structured data abstraction form to capture information about patients' TB status, comorbidities and other characteristics, and TB treatment outcomes. Data

collection was conducted in two stages from February to April 2015. During the first stage, the study team reviewed the NTCC electronic database to obtain the list of all eligible TB cases and extract their demographic characteristics and height, classification of their TB treatment history, type of TB, sputum smear (SS) status and treatment outcome. Following the WHO definition, each patient's TB treatment outcome was classified as 'treatment success' (cured or treatment completed), 'treatment failed,' 'died,' 'lost to follow-up' and 'not evaluated' (World Health Organization 2013).

During the second stage, the study team collected information on comorbidities (including diabetes) and weight for each eligible TB case from their medical records available from the TB outpatient centers and the Yerevan 'Prisoners' Hospital.'

The Institutional Review Board of the American University of Armenia reviewed and approved the study protocol. Considering the nature of the study (secondary data analysis), the requirement of the informed consent was waived.

Statistical analysis

We used the Statistical Package for the Social Sciences (SPSS SPSS Inc. Released 2007. SPSS for Windows, version 16.0. Chicago, SPSS Inc.) for data analysis. Categorical data were summarized as frequencies and percentages, and continuous data as means and standard deviations. Differences in baseline characteristics between diabetic and non-diabetic TB patients were compared using the *t*-test for continuous variables and Chi-square test for categorical variables. We conducted a simple and multivariable logistic regression analysis to test the associations between the main independent (diabetes status) and dependent (treatment outcome) variables and to test for confounding. All p values < 0.05 were considered to be statistically significant. Variables that were statistically significantly associated with both dependent and independent variables in either direction were considered as confounders and were included in the final logistic regression model. We used the two-sample comparison of proportions formula (Vorburger n.d.) to calculate study power under different sample size estimates and Type I error level of 0.05. The calculated power for a sample of 525 was 0.75.

Results

Administrative results

The total number of eligible TB patients who were treated in nine outpatient TB facilities and in the 'Prisoners' Hospital' of the Ministry of Justice of the Republic of Armenia was 839. One of the outpatient TB facilities having the medical records of 159 patients (or 19% of the original sample) refused to participate in the study. During the second data collection stage, 12 patients were excluded because they were transferred out of Yerevan or Armenia shortly after registration in the database. Another 47 patients were excluded due to missing or incomplete medical records. The final sample therefore comprised 621 patients.

Patient characteristics

In the study sample of 621 patients, the prevalence of physician-diagnosed diabetes was 5.8% ($n = 36$).

Table 1 presents the baseline characteristics of the study population by diabetes status. The average age of the study population was 46.7 years, and 82% were males. Patients with diabetes were significantly older (mean age of 52 years vs. 46 years, $p = 0.013$), heavier (mean weight of 65.6 kg vs. 61.3 kg, $p = 0.002$) and with higher prevalence of sputum-smear-positive (SS+) patients (prevalence of 50.0% vs. 30.8%, $p = 0.064$) than those without diabetes. HIV prevalence in diabetic and non-diabetic groups was 2.8% and 6.2%, respectively. In the total sample, the highest prevalence after diabetes and HIV was cardiovascular disease and mental disorders, 4.5% and 5.7%, respectively. The average total number of comorbidities was 0.31 in the total sample and not significantly different between the groups. Apart cirrhosis, no significant differences were found in individual comorbidities.

TB treatment outcomes

During the TB treatment period, 6.0% ($n = 37$) of the patients died including 8.3% ($n = 3$) from the diabetes group and 5.8% ($n = 34$) from the non-diabetes group (Table 2). In total, 9.5% ($n = 59$) of patients were lost to follow-up, including 8.3% ($n = 3$) from the diabetes and 9.6% ($n = 56$) from the non-diabetes group. A 'treatment success' outcome was reported for 82.1% ($n = 510$) of patients, whereas a 'treatment failed' outcome was reported for 2.4% ($n = 15$). 'Treatment failed' was the only treatment outcome that was significantly different between the groups: 11.1% ($n = 4$) of TB patients with diabetes and 1.9% ($n = 11$) of those without diabetes. None of the patients in the study sample had a 'not evaluated' TB treatment outcome.

Multivariable logistic regression analysis

For the final multivariable analysis, we excluded the cases of patients who died and/or were lost to follow-up because

Table 1 Baseline characteristics of the patients registered and treated in Yerevan outpatient tuberculosis care facilities whose treatment outcomes were recorded in the National Tuberculosis Control Center database for the period from 2013 to 2014 by their diabetes status

Characteristic	%, Mean, SD	Total sample $n = 621$	Patients with diabetes $n = 36$	Patients without diabetes $n = 585$	p value
Age, years	Mean (SD) *N*	46.73 (16.31) 620	52.41 (13.09) 36	46.39 (16.43) 584	0.013
Weight (in the beginning of the treatment), kg	Mean (SD) *N*	61.85 (11.29) 599	67.53 (13.11) 34	61.51 (11.09) 565	0.002
Gender					
Male	% (*n*/*N*)	81.80 (508/621)	80.56 (29/36)	81.88 (479/585)	0.842
Female		18.20 (113/621)	19.44 (7/36)	18.12 (106/585)	
History of imprisonment					
Yes	% (*n*/*N*)	6.12 (38/621)	8.33 (3/36)	5.98 (35/585)	0.568
No		93.88 (583/621)	91.67 (33/36)	94.02 (550/585)	
Type of TB					
DST[a]	% (*n*/*N*)	84.70 (526/621)	86.11 (31/36)	84.62 (495/585)	0.809
DR		15.30 (95/621)	13.89 (5/36)	15.39 (90/585)	
TB treatment history					
New	% (*n*/*N*)	73.43 (456/620)	75.00 (27/36)	73.33 (429/585)	0.922
Previous history of TB treatment		26.57 (164/620)	25.00 (9/36)	26.67 (155/585)	
SS status					
SS+	% (*n*/*N*)	31.93 (198/620)	50.00 (18/36)	30.82 (180/584)	0.064
SS−		68.06 (422/620)	50.00 (18/36)	69.18 (404/584)	
HIV status					
HIV positive	% (*n*/*N*)	6.28 (39/621)	2.78 (1/36)	6.50 (38/585)	0.601
HIV negative		86.47 (537/621)	88.89 (32/36)	86.32 (505/585)	
HIV status unknown		7.25 (45/621)	8.33 (3/36)	7.18 (42/585)	
Combined form of TB (pulmonary + extra pulmonary)	% (*n*/*N*)	2.42 (15/621)	2.78 (1/36)	2.39 (14/571)	0.886
Total number of comorbidities[b]	Mean (SD) *N*	0.31 (0.62) 613	0.57 (0.81) 35	0.30 (0.60) 578	0.183
Mental disorders	% (*n*/*N*)	4.37 (27/618)	2.78 (1/36)	4.47 (26/582)	0.608
Cardiovascular disease	% (*n*/*N*)	4.32 (26/602)	4.23 (24/567)	5.71 (2/35)	0.617
Hepatitis C	% (*n*/*N*)	4.71 (29/616)	11.11 (4/36)	4.31 (25/580)	0.105
Cirrhosis	% (*n*/*N*)	0.32 (2/618)	5.56 (2/36)	0 (0/582)	0.001

Diabetes Mellitus and Treatment Outcomes of Pulmonary Tuberculosis: A Cohort Study, Armenia, 2015

[a]*DST* drug sensitive, *DR* drug resistant, *HIV* human immunodeficiency virus, *SS* status status, *TB* tuberculosis

[b]Excludes HIV and diabetes

the risk factors associated with these treatment outcome categories were considered to be different. Thus the treatment outcome variable for this analysis had only two categories: 'treatment failed' or 'treatment success.' After testing for confounding, the patients' baseline weight (continuous) at TB diagnosis and SS status were identified as confounders for the relationship between diabetes status and TB treatment outcome variables; the other independent variables did not confound this relationship (analysis not shown).

After adjusting for the patients' weight and SS status, we found that the odds of treatment failure was 8.99 times higher (95% CI 2.51–32.23, $p = 0.001$) among TB patients with diabetes compared to TB patients without diabetes (Table 3).

Discussion

The presented study investigated the association of diabetes and TB treatment outcomes among adult patients with pulmonary TB registered in outpatient TB facilities and the 'Prisoners' Hospital.' The prevalence of diabetes among the TB patients (5.8%) was 2.2 times higher than

Table 2 Tuberculosis treatment outcomes of the patients registered and treated in Yerevan outpatient tuberculosis care facilities whose treatment outcomes were recorded in the National Tuberculosis Control Center database for the period from 2013 to 2014 by their diabetes status

TB treatment outcome	Total sample $n = 621$ % (n/N)	Patients with diabetes $n = 36$ % (n/N)	Patients without diabetes $n = 585$ % (n/N)	p value
Treatment success	82.13 (510/621)	72.22 (26/36)	82.74 (484/585)	0.110
Treatment failed	2.42 (15/621)	11.11 (4/36)	1.88 (11/585)	0.008
Died	5.96 (37/621)	8.33 (3/36)	5.81 (34/585)	0.535
Lost to follow-up	9.50 (59/621)	8.33 (3/36)	9.57 (56/585)	0.802

Diabetes Mellitus and Treatment Outcomes of Pulmonary Tuberculosis: A Cohort Study, Armenia, 2015

Table 3 Multivariable logistic regression for tuberculosis treatment success vs. failure among patients registered and treated in Yerevan outpatient tuberculosis care facilities whose treatment outcomes were recorded in the National Tuberculosis Control Center database for the period from 2013 to 2014

Independent variables	OR 95% CI	p value
Diabetes status	8.99 (2.51–32.23)	0.001
Weight	0.94 (0.90–0.99)	0.031
SS+	1.40 (0.87–2.27)	0.166

Diabetes Mellitus and Treatment Outcomes of Pulmonary Tuberculosis: A Cohort Study, Armenia, 2015

the prevalence of diabetes in the general (15 and over) population in Armenia (2.6%) ($p < 0.001$) (Andreasyan et al. 2016) which is in line with the existing literature suggesting that diabetes patients are more prone to developing TB (Alisjahbana et al. 2006; Jeon and Murray 2008). However, the prevalence of diabetes in TB patients reported in our study was lower than researchers reported for other countries (Alisjahbana et al. 2007; Jiménez-Corona et al. 2013; Stevenson et al. 2007b). This could be explained by lower prevalence of diabetes among general population in Armenia compared to those countries, where studies were conducted (India, Indonesia and Mexico) (Restrepo et al. 2007; Stevenson et al. 2007b) or different diagnostic approaches used in the studies (Baldé et al. 2006; Jiménez-Corona et al. 2013). In addition, to define the prevalence of diabetes in study population we used already existing, physician-established diagnosis recorded in patients' medical cards which could potentially be underreported. The current study did not also evaluate the effectiveness of implementation of the routine checkups of diabetes among TB cases as per current recommendation in the country.

Our findings showed that TB patients with diabetes had 8.99 higher odds to fail their TB treatment than TB patients without diabetes. Similar to our findings, two cohort studies conducted in Southern Mexico and Indonesia revealed significantly higher odds (2.93 and 7.65) of treatment failure among diabetic patients than non-diabetic patients (Alisjahbana et al. 2007; Jiménez-Corona et al. 2013).

Several studies showed that due to impaired immune system, patients with diabetes are more susceptible to infections such as influenza (Lau et al. Lau et al. 2014), herpes zoster (Muñoz-Quiles et al. 2017) and community-acquired pneumonia (Martins et al. 2016). Furthermore, diabetes also increases the likelihood of negative outcomes in these diseases when compared with patients without diabetes (Kornum et al. 2007; Lau et al. 2014; Martins et al. 2016). The mechanism of how diabetes could negatively influence TB treatment outcomes is controversial. Recent studies have suggested that patients with diabetes have a greater risk of poor drug absorption, including TB drugs. In particular, it was reported that the concentration of rifampicin in the blood of TB patients with diabetes was lower than in TB patients without diabetes (Nijland et al. 2006). In contrast, another study reported no difference between pharmacokinetics of TB drugs among patients with and without diabetes and stated that the lower levels of rifampicin in the blood of the TB patients with diabetes might be related to higher body weight (Niazi and Kalra 2012).

The effect of weight on the relationship between diabetes status and TB treatment outcome was expected, as being underweight is one of the risk factors for poor treatment outcome among TB patients (Santha et al. 2002). Moreover, research has shown that underweight patients who gain weight during TB treatment are more likely to have successful treatment outcome, whereas those who lose weight during TB treatment have poor treatment outcomes, including death or failure (Gler et al. 2013). Our results suggest that the increase in OR toward treatment failure after controlling for weight might be explained by the fact that diabetic patients were heavier at the beginning of TB treatment (mean difference of 6 kg) and were therefore less likely to be underweight.

The study has inherent limitations due to the use of medical records as the source of information. We were not able to control the way the data were recorded in the

patients' medical cards in TB outpatient facilities. Some important factors, including ones related to diabetes treatment, were recorded poorly and inconsistently, and we could not use them in our analysis. Moreover, differences in the type and amount of information recorded in medical cards of TB outpatient facilities resulted in missing values for some comorbidities. For transparency, we reported the sample size for each variable covered in our study. However, we did not control for smoking status, alcohol, body mass index and socioeconomic status, which could have potentially confounded the relationship between TB treatment outcomes and diabetes status. These variables were either not available in the medical cards or accounted for more than 20% of missing values after data collection. Another limitation of the study was the refusal from one of the outpatient TB clinics, which decreased our sample size by 19%. We, however, tested the demographic characteristics of this group of patients versus our total sample such as age and gender which were available from the electronic database. We found no significant differences in these characteristics (mean age = 43.9 vs. 46.7 years and percent males 81.0% vs. 81.8% in the missing sample versus total sample, respectively). A strength of the study was the use of physician-established diagnoses to define cases with HIV and other comorbidities rather than self-reported diagnoses. Our study is also the first in the region to evaluate the relationship between diabetes and TB treatment outcomes.

In conclusion, we found that the prevalence of diabetes was much higher among TB patients in Armenia than in the general Armenian population and that having diabetes negatively influenced TB treatment outcomes. TB patients with diabetes were more likely to have failure treatment than TB patients without diabetes. The study findings help to better understand the reasons for unsuccessful TB treatment outcome among pulmonary TB patients in Armenia and could be used to develop more tailored approaches to strengthen providers' education on TB treatment with comorbid conditions such as DM. In addition, countries which carry high burden of both diabetes and TB should pay more attention to this comorbid condition. As diabetes is estimated to be increasing rapidly and spreading in low- and middle-income countries, it is very likely that diabetes will soon surpass HIV as the most important risk factor for TB (Curbing Diabetes Vital to Controlling TB 2015). Hence, those countries need to develop mechanisms for screening diabetic patients for TB and TB patients for diabetes, and carefully address the treatment of TB patients who have diabetes comorbidity in the TB treatment guidelines. Future nationwide studies should evaluate the hypothesis generated by our study, ensuring also consistent and high-quality collected data on potential confounders that we were not able to measure such as the length of DM and treatment methods, control of glucose levels, alcohol and drug use, as well as socioeconomic and smoking status.

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Author's contributions SS, VP and LA designed the study; SS collected and analyzed the data and drafted the manuscript; VP and LA contributed to the development of the manuscript. All authors contributed toward finalizing the manuscript and approved the final version for submission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Considering the nature of the study (secondary data analysis), the requirement of the informed consent was waived.

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