Original research

PREVALENCE, CHARACTERISTICS AND TREATMENT OUTCOMES OF ALL PATIENTS WITH NEW TUBERCULOSIS AND DIABETES MELLITUS IN 2011–2013, BUKHARA, UZBEKISTAN

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ABSTRACT

Diabetes mellitus increases the risk of tuberculosis (TB) by three times and adversely affects treatment outcomes for TB. To date, there are no publications about the interaction between TB and diabetes in Uzbekistan. This study therefore aimed to assess, in newly registered TB patients, the trends in annual prevalence of diabetes; the sociodemographic and clinical characteristics of those with and without diabetes; the proportion of those with and without diabetes achieving sputum smear conversion at 2, 3 and 4 months; and the final treatment outcomes for those with and without diabetes. This was a retrospective cohort study of all new TB patients with and without diabetes registered in the Bukhara region, Uzbekistan, from January 2011 to December 2013. There were 1819 patients with TB, of whom 9–10% each year were diagnosed with diabetes. Among those with diabetes and compared with those with no diabetes, there were significantly more women (57% versus 46%, $P < 0.001$), more in the older age groups of 41 years and above (95% versus 54%, $P < 0.001$), more who were married (99% versus 71%, $P < 0.001$), more with pulmonary disease (94% versus 66%, $P < 0.001$), more with smear-positive sputum (57% versus 28%, $P < 0.001$) and more with radiographic cavities (28% versus 16%, $P < 0.001$). Significantly fewer patients with diabetes smear converted at 2 months (75% versus 84%, $P = 0.03$) and more patients with diabetes had unfavourable treatment outcomes (29% versus 20%, $P < 0.01$), largely due to death (10% versus 3%, $P < 0.001$) and treatment failure (8% versus 2%, $P < 0.001$). Characteristics, smear conversion and treatment outcomes were significantly different between TB patients with and without diabetes. The TB control programme needs to pay more attention to regular screening of TB patients for diabetes and providing good-quality care for diabetes to those with dual disease.

Keywords: CENTRAL ASIA, DIABETES MELLITUS, OPERATIONAL RESEARCH, SORT IT, TREATMENT OUTCOMES, TUBERCULOSIS

INTRODUCTION

There is a close adverse relationship between diabetes mellitus and tuberculosis (TB). Systematic reviews, meta-analyses and formal reviews have shown that people with diabetes have a two to three times higher risk of developing active TB compared with those who do not have diabetes *(1–5)*. This is of concern, as the global burden of diabetes is already large and expected to increase. In 2013, an estimated 382 million people

worldwide had diabetes, with 90% or more having type 2 disease *(6)*. About 80% of these people lived in low- and middle-income countries, and, if the trends of the past 10–15 years continue with 10 million new cases occurring every year, an estimated 592 million people will have diabetes by 2035 *(6)*. Over half of these patients are undiagnosed, and complications due to diabetes cause disability, reduced quality of life and death. Patients with diabetes and TB also experience more adverse TB treatment outcomes, with possible delays in sputum culture conversion and a higher risk of failure or death during TB treatment *(7, 8)*. The risk of recurrent TB disease after successful completion of treatment is also higher in those with diabetes compared with those who do not have diabetes *(7, 8)*. For these reasons, in 2011 the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease launched a collaborative framework for the care and control of dual disease, particularly emphasizing the need to undertake bidirectional screening for TB and diabetes and the need to enhance joint management strategies for the two diseases *(9)*.

Uzbekistan is a country in central Asia where there has been an increase over the years in both TB and diabetes. Between 2011 and 2013, the Bukhara region of the country experienced an increase in the total number of TB cases registered per year from 37.3 to 38.6 per 100 000 population, with an increase in destructive forms of the disease (with cavity in the lungs) from 21.7 to 25.0 per 100 000 population *(10)*. Similarly, notification rates for diabetes rose from 61.8 to 69.9 per 100 000 population per year *(11)*. Owing to the interaction between the two diseases, all individuals with diabetes in Uzbekistan are required to undergo annual chest radiography for possible TB *(12)*. In addition, all TB inpatient dispensaries are required to clinically screen all newly diagnosed TB patients for diabetes.

Recent studies from India, China and Iran have shown a high prevalence of diabetes in patients with TB, which varied from 13% to 17% *(13–16)*. To the authors' knowledge, there is no published information from Uzbekistan on the prevalence of diabetes among TB patients and on whether TB/diabetes comorbidity influences treatment outcomes. The current WHO international recommendation is to use blood screening, either fasting blood glucose or glycated haemoglobin, for diagnosing diabetes in TB patients *(17)*, while in Uzbekistan diagnosis is currently based on clinical screening for symptoms and signs, which may underestimate detection of diabetes. More information on these issues would be useful to guide screening and management strategies within the framework of the TB programme in the region and beyond.

The aim of this study, therefore, was to determine the prevalence, characteristics and treatment outcomes of all newly registered TB patients with diabetes in Bukhara, Uzbekistan. Specific objectives among patients newly registered with pulmonary TB during the period 2011–2013 were to determine: (i) the trend in annual numbers diagnosed with diabetes; (ii) the sociodemographic and clinical characteristics of those with and without diabetes; (iii) the proportion achieving sputum smear conversion at 2, 3 and 4 months of treatment; and (iv) the final treatment outcomes for those with and without diabetes.

METHODS

STUDY DESIGN

This was a retrospective cohort study of all new TB patients with and without diabetes registered in the Bukhara oblast TB hospital, Uzbekistan, from January 2011 to December 2013.

SETTING

General setting

Uzbekistan is a central Asian country with an estimated population of approximately 30 million. Uzbekistan comprises 12 provinces (oblasts), one autonomous republic (Republic of Karakalpakstan) and the capital city Tashkent. Bukhara is one of these 12 provinces, with a population of 1 758 173. Bukhara province also includes the cities of Bukhara and Kagan, as well as 11 districts.

TB control

TB control throughout the Bukhara province is coordinated by the regional TB dispensary. Case finding, diagnosis, treatment regimens, treatment outcomes, and monitoring and evaluation follow WHO TB treatment guidelines *(18)*. Patients with a confirmed diagnosis of TB undergo the intensive phase of treatment through hospital inpatient care according to the guidelines of the National TB Programme *(19)*.

All districts of Bukhara province also have TB clinics that provide counselling, treatment and clinical examinations for TB patients during the continuation phase of treatment. General health services also play a role in the early detection of patients with TB and their treatment during the continuation phase of treatment. Laboratories in the province are equipped with modern binocular microscopes for sputum smear microscopy for both diagnosis and follow-up of patients on treatment. In mid-2012, the regional TB clinic launched an interregional bacteriological laboratory. The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) supplies all first-line anti-TB drugs throughout the country, and, as of 2013, also supplies second-line drugs for the treatment of patients with multidrug-resistant TB. According to the national protocol, patients with diabetes are tested once a year for early detection of TB, by chest radiographic screening in general health-care facilities. In addition, hospitalized patients with active TB who are suspected of having diabetes are tested for diabetes.

STUDY POPULATION

The study population included all new TB patients registered in the Bukhara oblast TB hospital, from January 2011 to December 2013.

Data variables, sources of data and data collection

Data variables included baseline data of TB registration number, date of starting treatment, type of TB, residence status, age, sex, education, employment status, marital status, HIV status, smoking history and alcohol use and a past history of diabetes or a new diagnosis of diabetes based on results of fasting blood glucose. Sputum smear status (positive, negative or not done) was determined at 2 months, 3 months and 4 months into treatment. Treatment outcomes were based on standardized definitions of cured, treatment completed, died, failed, lost to follow-up and transferred out. The sources of data for the study were the TB patient registers and individual TB patient cards from the Bukhara oblast TB hospital. Data were collected from July to December 2014 using a paper-based questionnaire.

DATA ANALYSIS

The data were single entered and analysed in EpiData 3.1 (EpiData Association, Odense, Denmark) and Stata (Version 12; Stata Corporation, College Station, Texas, United States of America). The data were summarized into frequencies and proportions, using descriptive statistics. Characteristics of patients with diabetes in the registry were compared with those of patients without diabetes, using the chi-square test (unadjusted) odds ratios (OR) and their 95% confidence intervals (CIs), and, wherever appropriate, adjusted ORs. Sputum smear conversion and final treatment outcomes were compared using the chi-square test, with relative risks (RRs) and 95% CIs calculated as appropriate. Significance levels were set at 5%, using two-tailed *P* values.

ETHICS

Permission to conduct this study was obtained from the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan. Ethical approval was additionally sought from the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease in Paris, France.

RESULTS

The number of patients newly registered with TB between 2011 and 2013 and the number and proportion of these patients with diabetes are shown in Table 1. In each of the years, between 9% and 10% of newly diagnosed patients were found to have diabetes, while 8% of all newly registered TB patients had previously diagnosed diabetes.

Sociodemographic characteristics of newly diagnosed TB patients with and without diabetes are shown in Table 2. Among those with diabetes, there were significantly more women (57% versus 43%, $P < 0.01$)

TABLE 1. ANNUAL PREVALENCE OF DIABETES MELLITUS IN NEW TUBERCULOSIS PATIENTS REGISTERED IN BUKHARA REGION, UZBEKISTAN, 2011–2013

Characteristics	2011		2012		2013		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
All new TB patients	575		642		602		1819	
TB patients with diabetes mellitus	57	(10)	55	(9)	64	(10)	176	(10)
TB patients with a previous diagnosis of diabetes mellitus	45	(8)	49	(8)	50	(8)	144	(8)
TB patients with a new diagnosis of diabetes mellitus	12	(2)	6	(1)	14	(2)	32	(2)

TB: tuberculosis.

TABLE 2. SOCIODEMOGRAPHIC CHARACTERISTICS OF NEW TUBERCULOSIS PATIENTS DIAGNOSED WITH AND WITHOUT DIABETES MELLITUS, BUKHARA REGION, UZBEKISTAN, 2011–2013

Characteristics	TB patients with diabetes mellitus		TB patients with no diabetes mellitus		OR	95%CI	*P* value
	n	(%)	n	(%)			
All patients	176		1643				
Sex							
Male	75	(43)	889	(54)	Reference		
Female	101	(57)	754	(46)	1.6	1.2–2.2	<0.01
Age, years							
<20	8	(<1)	386	(23)	0.1	0.1–0.99	0.04
21–40	8	(5)	381	(23)	Reference		
41–60	77	(44)	408	(25)	9.0	4.2–18.9	<0.001
≥61	90	(51)	468	(29)	9.2	4.4–19.1	<0.001
Residence							
Urban	41	(23)	342	(21)	Reference		
Rural	135	(77)	1300	(79)	0.9	0.6–1.3	0.45
No data	0		1	(<1)			
Education							
None	10	(6)	135	(8)	Reference		
Primary	3	(2)	229	(14)	0.18	0.05–0.66	<0.01
Secondary	121	(68)	1046	(64)	1.6	0.8–3.1	0.2
Higher	20	(11)	61	(4)	4.4	2.0–10.0	<0.001
No data	22	(13)	172	(10)	1.7	0.8–3.8	0.2
Marital status							
Married	174	(99)	1169	(71)	Reference		
Single	2	(1)	473	(29)	0.03	0.01–0.1	<0.001
No data	0		1	(<1)			
Employment status							
Unemployed	23	(13)	610	(37)	0.5	0.3–1.1	0.08
Employed	11	(6)	153	(9)	Reference		
Student	1	(<1)	291	(18)	0.05	0.01–0.4	<0.001
Pensioner	116	(66)	546	(33)	3.0	1.6–5.6	<0.001
Invalid/disabled	25	(15)	43	(3)	8.0	3.7–17.7	<0.001
Alcohol use							
No	159	(90)	1380	(84)	Reference		
Yes	14	(8)	197	(12)	0.62	0.35–1.1	0.09
No data	3	(2)	66	(4)			
Current smoking status							
No	154	(87)	1375	(84)	Reference		
Yes	19	(11)	204	(12)	0.8	0.5–1.4	0.5
No data	3	(2)	64	(4)			

CI: confidence interval; OR: odds ratio; TB: tuberculosis.

and significantly more in the older age groups of 41–60 years and 61 years and above (44% and 51% respectively, $P < 0.001$), compared with those who did not have diabetes. More patients with diabetes were married (99%, $P < 0.001$) and a higher proportion of patients with diabetes were pensioners (66%, $P < 0.001$) or persons classified as invalids or disabled (15%, $P < 0.001$). There was no difference between the two groups with respect to urban or rural residence or in relation to the district of residence. The proportions of patients who drank alcohol or smoked cigarettes were in the range 8–12%, and were similar between those with and without diabetes.

Clinical characteristics of newly diagnosed TB patients with and without diabetes are shown in Table 3 . A significantly higher proportion of patients with diabetes had pulmonary TB, sputum smear-positive disease and cavities on chest radiography, compared with those who had no diabetes. No patient with diabetes-associated TB was HIV infected and among those with no diabetes there were only 21 (1%) with HIV infection.

The time of sputum smear conversion during treatment in patients with new smear-positive pulmonary TB is shown in Table 4 . Significantly fewer patients with diabetes smear converted at 2 months compared with those who did not have diabetes, while a significantly higher proportion of those with diabetes smear converted after 4 months.

TABLE 3. CLINICAL CHARACTERISTICS OF NEW TUBERCULOSIS PATIENTS DIAGNOSED WITH AND WITHOUT DIABETES MELLITUS, BUKHARA REGION, UZBEKISTAN, 2011–2013

Baseline characteristics	TB patients with diabetes mellitus		TB patients with no diabetes mellitus		OR	95% CI	*P* value
	n	(%)	n	(%)			
All patients	176		1643				
Type of TB							
Pulmonary	165	(94)	1090	(66)	7.6	4.1–14.1	<0.001
Extra-pulmonary	11	(6)	553	(34)		Reference	
Sputum smear status							
Smear-positive for AFB	100	(57)	466	(28)	2.3	1.7–3.2	<0.001
Smear-negative for AFB	67	(38)	723	(44)		Reference	
No data	9	(5)	454	(28)			
Cavities on chest X-ray							
Yes	49	(28)	263	(16)	2.0	1.4–2.9	<0.001
No	127	(72)	1374	(84)		Reference	
No data	0		6	(<1)			
HIV status							
HIV positive	0		21	(1)	Not applicable		
HIV negative	172	(98)	1587	(97)			
No data	4	(2)	35	(2)			

AFB : acid-fast bacilli; CI: confidence interval; OR: odds ratio; TB: tuberculosis.

TABLE 4. MONTH OF SPUTUM SMEAR CONVERSION IN NEW PATIENTS WITH SMEAR-POSITIVE PULMONARY TUBERCULOSIS DIAGNOSED WITH AND WITHOUT DIABETES MELLITUS, BUKHARA REGION, UZBEKISTAN, 2011–2013

Time of sputum smear conversion	TB patients with diabetes mellitus		TB patients with no diabetes mellitus		RR	(95%CI)	*P* value
	n	(%)	n	(%)			
New patients registered with smear-positive pulmonary TB	100		466				
Month of sputum smear conversion							
2 months	75	(75)	392	(84)	0.9	(0.8–1.0)	0.03
3 months	12	(12)	43	(9)	1.3	(0.7–2.2)	0.4
4 months	4	(4)	17	(4)	1.1	(0.4–3.0)	0.9
>4 months	9	(9)	14	(3)	2.3	(1.4–4.0)	<0.01

CI: confidence interval; OR: odds ratio; RR: relative risk; TB: tuberculosis.

TABLE 5. TREATMENT OUTCOMES IN NEW PATIENTS WITH TUBERCULOSIS DIAGNOSED WITH AND WITHOUT DIABETES MELLITUS, BUKHARA REGION, UZBEKISTAN, 2011–2013

Treatment outcome	TB patients with diabetes mellitus		TB patients with no diabetes mellitus		RR	(95%CI)	*P* value
	n	(%)	n	(%)			
All patients enrolled for treatment	176		1643				
Treatment success[a]	118	(71)	1270	(80)	0.88	(0.8–0.98)	<0.01
Unfavourable outcome	49	(29)	317	(20)	1.5	(1.1–1.9)	<0.01
Died	17	(10)	49	(3)	3.2	(1.9–5.5)	<0.001
Treatment failure	14	(8)	35	(2)	3.7	(2.0–6.8)	<0.001
Lost to follow-up	18	(11)	233	(15)	0.7	(0.5–1.1)	0.15

CI: confidence interval; OR: odds ratio; RR: relative risk; TB: tuberculosis.
[a] Patients who were cured and patients who completed treatment with no smear result.

Final TB treatment outcomes for all TB patients with and without diabetes are shown in Table 5. The success of treatment for TB was significantly lower in patients with diabetes compared with those who did not have diabetes (71% and 80% respectively, $P < 0.01$), and this was largely a result of a higher rate of death and a higher rate of failure during treatment (10% and 8% versus 3% and 2% respectively, $P < 0.001$).

DISCUSSION

This is the first published study from the Bukhara oblast in Uzbekistan assessing the association between TB and diabetes. About 10% of TB patients were identified with diabetes, with most having a previous diagnosis. Amongst patients with TB and diabetes, there were more women, more people in the older age groups and more who were pensioners or recorded as invalids or disabled. Patients with TB and diabetes had a higher prevalence of pulmonary disease, smear-positive sputum and radiographic cavities, compared with patients who had TB alone. Despite receiving the same treatment regimen, patients with diabetes and TB took a longer time to smear convert and had worse treatment outcomes, mainly because of higher rates of death and treatment failure.

The strengths of this study were the large number of new TB patients registered under routine conditions in the Bukhara region over 3 years, which makes the results representative of the situation in the country. STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) and RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) guidelines and sound ethical principles were also followed for the conduct and reporting of this observational study *(20–22)*. There were some limitations, in that the data were secondary and were sometimes missing from the registers and treatment cards; sputum conversion was based on smear examination rather than culture; and data from questionnaires were only single entered to the electronic database rather than being double entered.

The patients in this study who had diabetes and TB tended to be older than patients without diabetes and this is consistent with studies carried out in other parts of the world *(23–25)*. Similarly, smear-positive disease and cavitation were more common in those TB patients in this study with diabetes compared with those who did not have diabetes, and this is in line with other studies that have found more smear-positive disease *(26)* and more cavitation in patients with diabetes, especially those with poor glycaemic control *(27)*. The reasons for these differences are unclear but may be a result of delays in patients seeking medical assistance, or incomplete screening of patients from high-risk groups, including those with diabetes comorbidity.

This study found delayed sputum smear conversion at 2 months and beyond, which is again consistent

with previous studies from India and China *(25, 26)*. Sputum culture may be a more informative way of assessing bacteriological status during follow-up but this is generally too difficult to implement routinely. Nevertheless, a systematic review of studies from 1980 to 2010 found nine studies assessing the influence of diabetes on prolonging culture positivity at 2–3 months of treatment, with six reporting relative risks of >2 and three reporting relative risks of <1 *(7)*.

The diabetes–TB patients in this study had worse treatment outcomes compared with those who did not have diabetes, with treatment failure and death being the two main adverse events; these findings are in line with other studies elsewhere *(7, 8)*. Finally, there is growing evidence that in individuals with diabetes, poor glycaemic control adversely affects TB treatment outcomes *(27, 28)*, and that smoking more than one pack of cigarettes per day significantly increases the risk of death in patients with dual disease *(29)*. Specific data on these points were not collected during the present study but these are areas that need further research in future studies. Reasons for poor treatment outcomes are also unclear but probably relate to the fact that diabetes impairs cell-mediated immunity, not by targeting the CD4-T-lymphocytes as is the case with HIV infection, but by interfering with the function and activation of macrophages, monocytes and lymphocytes *(30)*.

There are several implications to this study. First, there is a need to routinely screen TB patients for diabetes by asking about a known diagnosis of diabetes and to consider screening the remainder of patients using measurements of fasting blood glucose. Only 1–2% of patients were newly identified with diabetes through this method, so the National TB Programme in Uzbekistan will need to decide whether all patients should be screened or whether blood tests should just be offered to those in higher-risk groups, such as those aged 50 years and over. Second, having identified those with diabetes, referral and attention to good-quality diabetes care will be important to improve rates of smear conversion during treatment and final TB treatment outcomes *(28)*. Finally, lifestyle advice must be given to those who have diabetes-associated TB. Only a small proportion of the patients in this study with diabetes and TB smoked cigarettes, but smoking increases the risk of death and all patients with TB must be encouraged to quit smoking *(29)*.

In conclusion, this study in the Bukhara region of Uzbekistan found that about 10% of patients newly diagnosed with TB had diabetes, with the association particularly noted in the older age groups. Patients with dual disease tended to have smear-positive pulmonary TB with cavities on chest radiography, and during treatment had slower times to smear conversion and worse treatment outcomes compared with patients who did not have diabetes. The National TB Programme needs to pay more attention to regular screening of TB patients for diabetes and good-quality care for diabetes in those with dual disease. Diabetes is detected among TB patients after the onset of clinical symptoms associated with diabetes, but this does not exclude the possibility that there may be patients with latent diabetes among those who are not examined. In this connection, the National Tuberculosis Programme must develop a method of screening all TB patients for blood levels of glucose or glycosylated haemoglobin, regardless of clinical manifestations of diabetes, especially among persons aged 40 years and older. Timely referral to a specialist, for treatment of diabetes with proper correction of antidiabetic medication for TB patients can improve the final outcome of TB treatment. It is also necessary to improve the quality of diagnosis and monitoring of treatment.

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