Symptom reporting among prevalent tuberculosis cases who smoke, are HIV-positive or have hyperglycaemia

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Data from a tuberculosis (TB) prevalence survey conducted in 24 communities in Zambia and the Western Cape, South Africa, January–December 2010, were analysed to determine the influence of smoking, hyperglycaemia and human immunodeficiency virus (HIV) infection on TB symptom reporting in culture-confirmed TB cases. Of 123 790 adults eligible for enrolment, 90 601 (73%) consented and 64 463 had evaluable sputum samples. ORs and 95% CIs were calculated using a robust standard errors logistic regression model adjusting for clustering at community level. HIV-positive TB cases were more likely to report cough, weight loss, night sweats and chest pain than non-HIV-positive TB cases. TB cases who smoked or had hyperglycaemia did not report symptoms differently from cases without these comorbidities.

The risk of developing tuberculosis (TB) is higher among smokers,¹ subjects with diabetes mellitus (DM)² and/or those with human immunodeficiency virus (HIV)³ infection than in the general population, making TB screening among these high-risk groups important.^{1–4} However, people who smoke, have diabetes or are HIV-positive may have symptoms that they attribute to these comorbidities and not recognise them as TB symptoms.⁵ The World Health Organization (WHO) developed guidelines for TB screening specifically for HIV-positive individuals that are implemented in national TB programmes. However, no such evidence-based guidelines for TB symptom screening exist for patients with DM or those who smoke.^{1,6,7}

To further investigate evidence for TB screening guidelines in other risk groups, our report aims to evaluate whether prevalent TB cases who smoke, have hyperglycaemia or who are HIV-positive are equally likely to report TB symptoms compared to prevalent TB cases without these comorbidities.

METHODS

Data from a population-based TB prevalence survey conducted from January to December 2010 in eight communities in the Western Cape, South Africa, and 16 communities in Zambia were analysed. The prevalence survey measured the primary outcome (prevalence of culture-positive TB) of the Zambia South Africa TB and AIDS Reduction (ZAMSTAR) Trial⁸ after 4 years of two interventions randomised in high TB-HIV burden communities.

For the prevalence survey, enumerator areas in the communities were randomly selected, from which all adults aged ≥ 18 years in all houses were asked to provide written informed consent for data collection using a questionnaire. The questionnaire captured information regarding TB symptoms (cough of any duration, chest pain, night sweats, fever, weight loss and shortness of breath) as well as whether the participants were currently smoking or had smoked previously, or had ever been diagnosed with DM. Research assistants trained in eliciting appropriate information read the questions to the participants and recorded answers using a handheld electronic capturing device. All subjects were asked to provide a finger-prick blood sample for a rapid random blood glucose test with a glucometer. If blood glucose levels were >11.1 mmol/l, the participant was considered hyperglycaemic. All participants were offered an HIV test with counselling (two rapid HIV tests: Alere Determine™ HIV-1/2 [Waltham, MA, USA] and Uni-Gold™ [Trinity Biotech, Wicklow, Ireland]). Sputum samples were collected and inoculated into MGIT™ (manual mycobacterial growth indicator tubes, BD, Sparks, MD, USA) and *Mycobacterium tuberculosis* confirmed by 16SrRNA sequencing.⁸ The study population comprised all adults with culture-confirmed TB.

Ethics

Ethics approval was obtained from the Human Research Ethics Committees of Stellenbosch University, Cape Town, South Africa; the University of Zambia, Lusaka, Zambia; London School of Hygiene & Tropical Medicine, London, UK; the University of Cape Town, Cape Town, South Africa; and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France. The analysis was performed on the locked ZAMSTAR database which contained unique study numbers but no names.

Statistical analysis

Data were analysed using STATA 12 for Windows (Stata Corp, College Station, TX, USA). Odds ratios (ORs) were calculated as the measure of the association between HIV co-infection, smoking and hyperglycaemia (as individual exposures) in the study population of TB cases, and any or each symptom (as individual outcomes) using a robust standard errors logistic regression model adjusting for clustering at community level.

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TABLE 1 Distribution of demographics and reported symptoms among confirmed tuberculosis cases

	Total participants included n (%)
All	894 (100)
Female sex	469 (52)
Age group, years	
15–24	214 (24)
25–34	279 (31)
35–44	183 (20)
45–54	119 (13)
≥55	99 (11)
Education	
None	52 (6)
Primary	264 (30)
Secondary	554 (62)
Tertiary	24 (3)
Unemployed	
Yes	614 (69)
Symptoms	
None	365 (41)
Cough	319 (36)
Fever	227 (25)
Shortness of breath	165 (18)
Weight loss	279 (31)
Night sweats	260 (29)
Chest pain	195 (22)
Comorbidity	
HIV*	223/611 (36.5)
Hyperglycaemia*	58/456 (12.7)
Current smoker	121 (13.5)

*Denominator indicates number of participants with results.

HIV = human immunodeficiency virus.

RESULTS

Of the 123 790 adults eligible for enrolment in the prevalence survey, 90 601 (73%) gave consent and 64 463 (71%) had evaluable sputum samples, of whom 41 528 (64%) were female. Of these, 5540 (9%) smoked. Of the 47 404 participants who underwent HIV testing, 7939 (17%) were HIV-positive; 31.9% (130/407) already knew their HIV-positive status and 39.6% (153/386) tested positive for HIV. Of the 40 552 with a blood glucose test result, 3337 (8%) had hyperglycaemia, 45.4% (45/894) knew they had diabetes and 3.5% (15/429) had glucose readings >11.1 mmol/l. Of the 894 (1%) participants with prevalent culture-confirmed pulmonary TB, 469 (52%) were female. Of the patients with known HIV status, 35% (223/621) were HIV-positive; 13% (58/456) of those whose hyperglycaemic status was known were hyperglycaemic, and 13.5% (121/894) were smokers; 365 (41%) of the culture-confirmed pulmonary TB cases were asymptomatic, while 319 (36%) complained of cough (Table 1).

Controlling for age, sex and country, prevalent HIV-positive TB cases were more likely to report cough (44% vs. 35%, OR 1.5, 95% confidence interval [CI] 1.0–2.3), weight loss (43% vs. 30%, OR 1.7, 95%CI 1.1–2.7), night sweats and chest pain (32% vs. 30%, OR 1.4, 95%CI 1.0–2.0) than those who were HIV-negative (Table 2). Those with hyperglycaemia reported shortness of breath less often than those with normal blood sugar (14% vs. 21%, OR 0.5, 95%CI 0.3–0.9), and smokers reported weight loss less often than non-smokers (26% vs. 32%, OR 0.7, 95%CI 0.5–0.9).

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TABLE 2 Association between smoking, HIV co-infection, hyperglycaemia and TB symptoms among confirmed TB cases

	Symptom present n/N (%)	OR (95%CI)	OR (95%CI)*
HIV			
Any symptom			
HIV–	231/388 (60)		
HIV+	153/223 (69)	1.5 (0.9–2.4)	1.5 (0.9–2.5)
Data missing	145/283 (51)		
Cough			
HIV–	135/388 (35)		
HIV+	99/223 (44)	1.5 (1–2.1)	1.5 (1–2.3)
Data missing	85/283 (30)		
Fever			
HIV–	94/388 (24)		
HIV+	69/223 (31)	1.4 (0.9–2.2)	1.3 (0.9–2.1)
Data missing	64/283 (23)		
Shortness of breath			
HIV–	72/388 (19)		
HIV+	54/223 (24)	1.4 (1–2)	1.3 (0.9–2.1)
Data missing	39/283 (14)		
Weight loss			
HIV–	115/388 (30)		
HIV+	95/223 (43)	1.8 (1.2–2.7)	1.7 (1.1–2.7)
Data missing	69/283 (24)		

(continued over)

TABLE 2 (continued)

	Symptom present <i>n/N (%)</i>	OR (95%CI)	OR (95%CI)*
Night sweats			
HIV–	115/388 (30)		
HIV+	71/223 (32)	1.1 (0.8–1.5)	1.4 (1–2)
Data missing	74/283 (26)		
Chest pain			
HIV–	115/388 (30)		
HIV+	71/223 (32)	1.1 (0.8–1.5)	1.4 (1–2)
Data missing	74/283 (26)		
Hyperglycaemia†			
Any symptom			
Not hyperglycaemic	254/398 (64)		
Hyperglycaemic	35/58 (60)	0.9 (0.5–1.6)	0.7 (0.4–1.3)
Data missing	240/438 (55)		
Cough			
Not hyperglycaemic	161/398 (40)		
Hyperglycaemic	17/58 (29)	0.6 (0.4–1)	0.7 (0.4–1.1)
Data missing	141/438 (32)		
Fever			
Not hyperglycaemic	101/398 (25)		
Hyperglycaemic	18/58 (31)	1.3 (0.8–2.2)	1.2 (0.7–2.2)
Data missing	108/438 (25)		
Shortness of breath			
Not hyperglycaemic	85/398 (21)		
Hyperglycaemic	8/58 (14)	0.6 (0.4–1)	0.5 (0.3–0.9)
Data missing	72/438 (16)		
Weight loss			
Not hyperglycaemic	138/398 (35)		
Hyperglycaemic	18/58 (31)	0.8 (0.5–1.4)	0.8 (0.5–1.3)
Data missing	123/438 (28)		
Night sweats			
Not hyperglycaemic	118/398 (30)		
Hyperglycaemic	20/58 (34)	1.2 (0.7–2.1)	0.8 (0.5–1.5)
Data missing	122/438 (28)		
Chest pain			
Not hyperglycaemic	118/398 (30)		
Hyperglycaemic	20/58 (34)	1.2 (0.7–2.1)	0.8 (0.5–1.5)
Data missing	122/438 (28)		
Smoker‡			
Any symptom			
Non-smoker	462/773 (60)		
Smoker	67/121 (55)	0.8 (0.6–1.2)	0.7 (0.5–1.1)
Cough			
Non-smoker	273/773 (35)		
Smoker	46/121 (38)	1.1 (0.8–1.5)	1.1 (0.7–1.5)
Fever			
Non-smoker	195/773 (25)		
Smoker	32/121 (26)	1.1 (0.6–1.8)	1.1 (0.6–1.9)
Shortness of breath			
Non-smoker	148/773 (19)		
Smoker	17/121 (14)	0.7 (0.3–1.5)	0.6 (0.3–1.3)
Weight loss			
Non-smoker	138/398 (35)		
Smoker	18/58 (31)	0.8 (0.5–1.4)	0.8 (0.5–1.3)
Night sweats			
Non-smoker	248/773 (32)		
Smoker	31/121 (26)	0.7 (0.5–1)	0.7 (0.5–0.9)
Chest pain			
Not smoking	223/773 (29)		
Smoker	37/121 (31)	1.1 (0.8–1.5)	0.8 (0.5–1.2)

*Controlling for age, sex and country.

†Those with a blood glucose result of ≥ 11.1 mmol/l and/or had been diagnosed with diabetes were classified as hyperglycaemic.

‡Current smokers at the time of the survey were determined using the questionnaire. Participants who answered 'yes' to the question 'have you ever smoked?' and who answered that they had not stopped smoking were defined as current smokers.

HIV = human immunodeficiency virus; TB = tuberculosis; OR = odds ratio; CI = confidence interval; – = negative; + = positive.

DISCUSSION AND CONCLUSIONS

This study had a number of limitations: the ZAMSTAR study was not designed to answer this subanalysis, we were unable to confirm a formal diagnosis of DM based on a single random glucose level and we had limited data regarding duration of smoking, HIV and DM disease spectrums, and were therefore unable to stratify according to these variables. Some data on HIV and hyperglycaemia were missing, and a sensitivity analysis showed that those with missing hyperglycaemia data were less likely to report symptoms, although the difference was not statistically significant. Those with missing HIV results were less likely to report TB symptoms; this difference was significant for most symptoms.

A major strength of the study is that these data provide a large sample of bacteriologically confirmed TB cases who had information about TB symptoms, smoking, hyperglycaemia and HIV before TB diagnosis.

We found that, in confirmed TB cases from a population-based prevalence survey, there were few differences in symptom reporting between those who smoked, had hyperglycaemia or HIV infection and those who did not. HIV-positive TB cases reported cough, weight loss, night sweats and chest pain more often than HIV-negative TB cases. This supports the use of the current WHO symptom screening algorithm for TB cases among adults and adolescents living with HIV for the reliable exclusion of TB.⁶

Smoking or hyperglycaemia had very little effect on symptom reporting among TB cases. While a higher degree of sputum positivity grading has been reported in people who smoke,⁹ indicating possible differences in clinical manifestations of TB in this risk group, further studies are needed to investigate whether a different symptom screening algorithm for TB should be used

among smokers. Despite the rapid rise in DM in TB-endemic areas, our data do not indicate that the screening algorithm for TB should be adapted in people with hyperglycemia.^{7,10}

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Des données émanant d'une enquête de prévalence de la tuberculose (TB), réalisées dans 24 communautés de Zambie et de la province du Cap Ouest en Afrique du Sud de janvier à décembre 2010, ont été analysées afin de déterminer l'influence du tabagisme, de l'hyperglycémie et de l'infection par le virus de l'immunodéficience humaine (VIH) sur l'expression des symptômes de TB dans des cas de TB confirmés par la culture. Sur 123 790 adultes éligibles, 90 601 (73%) ont consenti et 64 463 ont produit des échantillons de crachats

utilisables. Les OR et les IC à 95% ont été calculés grâce à un modèle de régression logistique des erreurs standard robustes en ajustant le regroupement au niveau des communautés. Les patients atteints de TB et VIH positifs rapportaient plus volontiers de la toux, une perte de poids, des sueurs nocturnes et des douleurs thoraciques que les patients non VIH positifs. Par contre, les cas de TB qui fumaient ou présentaient une hyperglycémie ne signalaient pas de symptômes différents des patients qui n'avaient pas ces co-morbidités.

En el presente estudio se analizaron los datos de una encuesta reciente sobre la prevalencia de tuberculosis (TB), que se había llevado a cabo en 24 comunidades en Zambia y en el Cabo Occidental de Suráfrica de enero a diciembre del 2010, con el fin de determinar la influencia del tabaquismo, la hiperglucemia y la infección por el virus de la inmunodeficiencia humana (VIH) sobre los síntomas de TB que refieren los pacientes con diagnóstico de TB confirmada por cultivo. De los 123 790 adultos aptos para el estudio, 90 601 dieron su consentimiento (73%) y 64 463 aportaron muestras de esputo

adecuadas. Se calculó el cociente de posibilidades y el intervalo de confianza del 95% mediante un modelo consistente de regresión logística y errores estándar, tras corregir la agregación de los datos por comunidad. Fue más frecuente que los pacientes con TB que eran positivos frente al VIH refirieran tos, pérdida de peso, sudoración nocturna y dolor torácico que los pacientes sin esta coinfección. No hubo diferencia en los síntomas comunicados por los pacientes tuberculosos que fumaban o que presentaban hiperglucemia, en comparación con los pacientes sin estas enfermedades concurrentes.