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Type 2 diabetes and tuberculosis in a dynamic bi-national border population

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SUMMARY

The epidemic of type 2 diabetes in the United States prompted us to explore the association between diabetes and tuberculosis (TB) on the South Texas–Mexico border, in a large population of mostly non-hospitalized TB patients. We examined 6 years of retrospective data from all TB patients ($n=5049$) in South Texas and northeastern Mexico and found diabetes self-reported by 27·8% of Texan and 17·8% of Mexican TB patients, significantly exceeding national self-reported diabetes rates for both countries. Diabetes comorbidity substantially exceeded that of HIV/AIDS. Patients with TB and diabetes were older, more likely to have haemoptysis, pulmonary cavitations, be smear positive at diagnosis, and remain positive at the end of the first (Texas) or second (Mexico) month of treatment. The impact of type 2 diabetes on TB is underappreciated, and in the light of its epidemic status in many countries, it should be actively considered by TB control programmes, particularly in older patients.

INTRODUCTION

Approximately one third of the world's population is latently infected with *Mycobacterium tuberculosis*. Progression of latent infection to active tuberculosis (TB) is a major public health problem, particularly in developing countries where 8 million new cases and 2–3 million deaths occur annually. The major risk factors for TB in developing countries are HIV infection and/or poverty [1]. In contrast, in developed countries such as the United States, TB control is mostly limited to well-defined risk groups that also include the poor and/or HIV patients, but extend to chiefly young males with history of homelessness, substance or alcohol abuse, incarceration, recent immigration and HIV infection [2]. The Texas border with Mexico has one of the highest incidences of TB in the United States (12·2/100 000) [3], with rates rising up to 44·6/100 000 south of the Rio Grande river, in Mexico (G. Crespo, unpublished data).

There has been a growing impression among TB control programme staff both sides of the South Texas/Mexico border that the risk of TB is aggravated by type 2 diabetes mellitus (DM). In Texas the prevalence of self-reported DM increased from 4·8% in the period 1988–1994 to 6·6% between 1999 and 2000 [4]. The prevalence was even higher among the population from South Texas (Region 11) where self-reported DM was 7·9% in 2002 [5]. In Mexico the prevalence of DM is 5·8% by self-reporting and 7·5% based on

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self-reporting and blood glucose testing. The State of Tamaulipas in northeastern Mexico, adjacent to the Texas border, has one of the highest prevalences of DM in that country, with a 9·5% prevalence estimate based on self-reporting and blood glucose testing [6]. Self-reporting of DM in these national surveys is a well-accepted measure of the disease, with prevalences generally considered to be underestimated by 23–30% [6, 7]. Self-reporting of DM is used by TB control programmes in both countries to record DM co-morbidity in their patients. Hitherto, however, these data have not been analysed to determine the extent and potential significance of the association.

The association between DM and TB was first suggested in Roman times [8]. With decreased TB in developed countries and improved treatment for DM, the numbers with this comorbidity fell dramatically between the 1920s and 1970s. Nevertheless, large surveys in the 1950s suggested a relative risk of TB in individuals with DM, mostly type 1, between 2 and 3·6 times that of those without DM [9–11]. With the recent increase in type 2 DM, the association appears to be re-emerging along the US/Mexico border (California), and in Mexico [12, 13]. A major concern about the association is that type 2 DM may profoundly affect the clinical presentation of TB, including higher frequency of cavitation, mortality and multidrug resistance [14–16]. However, it is unclear if these studies are overestimating the frequency of severe clinical disease in patients with type 2 DM since most were conducted in relatively few, hospitalized patients.

We analysed two large datasets from South Texas and northeastern Mexico comprising the entire population of TB patients for these regions for the previous 5–6 years, in each of which self-reported DM was recorded. Our analysis identified DM as the major comorbidity, with patients presenting distinctive clinical and microbiological features of TB.

METHODS

In 2002 we formed a consortium for TB control both sides of the South Texas/northeastern Mexico border (Nuevo Santander Tuberculosis Trackers, NSTT). An agreement was established to share and analyse existing databases from all patients reported to the respective TB control programmes. The Texas database included patients identified between 1996 and 2002 in the 19 South Texas counties comprising Public Health Region 11 (see Supplementary Fig. S1 on the Journal's website). The Mexican data comprised all TB patients in the border Sanitary Jurisdictions 3 (Matamoros), 4 (Reynosa) and 5 (Nuevo Laredo) from the State of Tamaulipas, from 1998 to 2003 (Fig. S1). For simplicity we will refer to data from each side of the border as from 'Texas' or 'Mexico'. In Texas, TB diagnosis is based on clinical findings, supported by routine smear and culture. Self-reported demographic data and multiple entries for social and medical risk factors are recorded for each patient. HIV infection is confirmed by blood test. All other risk factors are self-reported, including DM, alcohol and drug use. Texas data were collected using the TB400A and B forms. These are first filled in by health officials at each clinic, and then sent to the central DSHS Tuberculosis Elimination Division in Austin, Texas, where data are entered into the state database. The TB400A contains risk factors for TB, and data extracted from the clinical and microbiological records of each health department, including: (i) signs and symptoms recorded at clinical examination, (ii) chest X-ray results, (iii) *M. tuberculosis* culture and sensitivity, (iv) tuberculin skin test results, (v) direct sputum smear stained for acid fast bacilli taken at the time of diagnosis and at monthly follow-up for as long as the patient has a productive cough (for pulmonary TB) or other specimens in the case of extra-pulmonary TB), (vi) treatment follow-up, type of schedule (including directly observed treatment, short course supervision), and outcome. Each patient is entered once even when treatment fails or the patient seen intermittently.

In Mexico, TB diagnosis is supported in most cases by direct smear alone. Culture and drug-sensitivity testing is performed mostly, but not exclusively, on patients not responding to treatment. Patient data is electronically entered, including self-reported socio-demographic characteristics (age and sex), and one or two entries for comorbidities such as DM, HIV, drug and alcohol use, among others. In Mexico, all TB patients identified at public and private institutions are reported to the appropriate sanitary jurisdictions. Their data are electronically entered into the state EPI-TB form at each local sanitary jurisdiction, and then submitted to the central state Tuberculosis Program Control office in Ciudad Victoria, as part of the State of Tamaulipas database. Patients are entered as: (i) new case, (ii) re-entry when patient has abandoned treatment, (iii) referred from another sanitary jurisdiction, (iv) relapse after patient completed treatment, or (v) failed previous treatment and needs to start a new regimen. Thus, a given patient

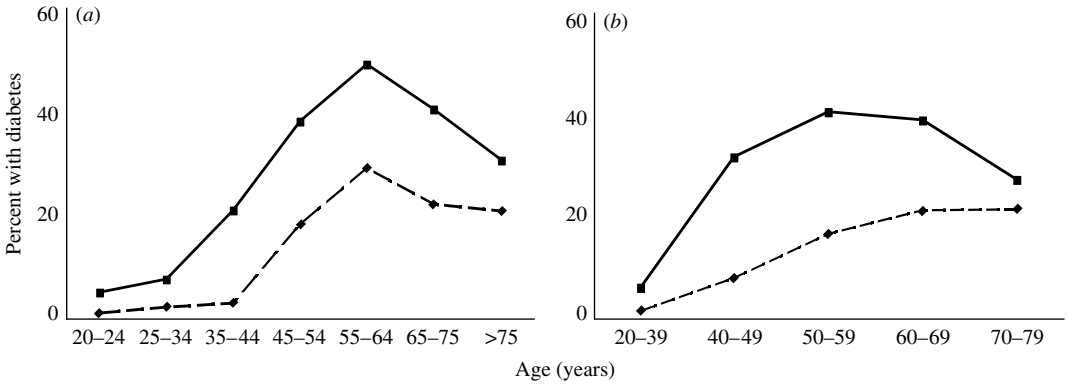

Fig. 1. Self-reported DM is more frequent among TB patients than in the general population, stratified by age. (*a*) Texas. –■–, Patients with self-reported DM and TB (1996–2002); - -◆- -, randomly selected participants with self-reported DM in a survey of a subset (Lower Rio Grande Valley) from the same population [5]. (*b*) Mexico. –■–, Patients with self-reported DM and TB in Tamaulipas, Mexico (1998–2003); - -◆- -, randomly selected participants in a population survey in Mexico (2000) [6].

may be registered more than once when re-entered, has had a relapse or has failed the current treatment. We created single files on these patients to ensure they are only analysed once. That is, re-entries following abandoned treatment, relapses/reinfections and failed treatments were not included in our data. The EPI-TB form includes target organ of TB infection, sputum direct smear results at diagnosis, and smear data at monthly intervals. Culture and sensitivity data are only available for selected patients, frequently but not exclusively patients failing to respond to regular therapy, through the bi-national initiative 'Grupo Sin Fronteras' (http://www.tdh.state.tx.us/news/acc0323.htm). There are currently no routine culture facilities in the three Mexican *jurisdicciones*. Treatment outcome is classified as: completed, failed, died or abandoned. Ethical approval was obtained from all the participating institutions.

The Mexico database contained 3935 patients (1998–2003) and the Texas database 1788 patients (1996–2002). Given the variations between the two sites in data collection methods, diagnostic criteria for TB, time of data collection, and variables recorded, each dataset was analysed individually and results compared only where relevant. The specific role of type 2 DM was determined by comparison of patients with TB and self-reported DM (TB-DM cases) with those not reporting DM (TB controls). Data analysis was performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA). Explanatory variables related to TB-DM were identified using univariate logistic regression analysis. Clinical signs and symptoms were entered in a multiple logistic regression analysis to evaluate degree of association with cases and controls.

Role of the funding source

The funding institutions had no role in the study design, data collection, data analysis, interpretation nor preparation of the manuscript. The corresponding author had full access to all data and takes responsibility for the integrity of the data and accuracy of the data analysis.

RESULTS

Self-reported DM is the most common risk factor for TB

Analysis was confined to patients aged ⩾20 years to minimize the contribution of type 1 DM. The final datasets contained 3506 patients for Mexico and 1543 for Texas (see Supplementary Table S1 and Text S2). DM was by far the most common co-morbidity with a prevalence of 17·8% in Mexico and 27·8% in Texas. These prevalences far exceeded those in the general populations of both countries: 7·9% self-reported in Texas region 11 [5] and exceeded even the 9·5% blood-glucose confirmed rates reported from Tamaulipas [6]. Further examination of the data by age stratification used South Texas–Lower Rio Grande Valley data (database provided by R. J. Dutton, Texas Department of State and Health Services) and the entire country of Mexico as a reference (age-stratified data not available for Tamaulipas) [6]. For most age groups, self-reported DM was higher among TB patients than in the general population (range 1·5- to 6·8-fold in Texas and 0·7- to 3·9-fold in Mexico; Fig. 1).

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Table 1. *Sociodemographic characteristics and risk factors for TB patients with and without diabetes in Texas and Mexico**

	Mexico ($n=3411$)			Texas ($n=1441$)		
	Diabetic ($n=607$)	Not diabetic ($n=2804$)	aOR (95% CI)†	Diabetic ($n=401$)	Not diabetic ($n=1040$)	aOR (95% CI)†
Mean number of patients/year	101	467		57	148	
Female	213 (35%)	826 (29·5%)	1·2 (1–1·5)	148 (36·9%)	305 (29·3%)	1 (0·7–1·4)
Median age (IQR)	51 (17)	36 (24)		56 (21)	43 (29)	
Age groups (yr)						
20–39	96 (15·8%)	1625 (58%)	1	54 (13·5%)	465 (44·7%)	1
40–69	460 (75·8%)	972 (34·6%)	7·8 (6·2–9·9)	260 (64·8%)	409 (39·3%)	5 (3·4–7·5)
⩾70	51 (8·4%)	207 (7·4%)	3·9 (2·7–5·7)	87 (21·7%)	166 (16%)	3·4 (2·1–5·3)
Hispanic	n.a.	n.a.		382 (95·3%)	922 (88·7%)	3 (1·5–5·7)
Mexican origin	n.a.	n.a.		212 (53·7%)	478 (47·2%)	1·2 (0·9–1·7)
Jail/prison inmate	n.a.	n.a.		7 (2·2%)	119 (16·3%)	0·2 (0·1–0·4)
Homeless shelter	n.a.	n.a.		3 (0·8%)	37 (3·6%)	0·2 (0·1–0·7)
AIDS	n.a.	69 (2·5%)		10 (2·5%)	75 (7·2%)	0·4 (0·2–0·9)
Alcohol abuse	n.a.	60 (2·1%)		51 (12·7%)	241 (23·2%)	0·4 (0·2–0·6)
Drug abuse	n.a.	83 (3%)		18 (4·5%)	134 (12·9%)	1·1 (0·5–2·1)

* Only variables significant by univariate analysis are shown.
† aOR, Odds ratio adjusted for all significant variables by univariate analysis for either Texas (age, sex, ethnicity, Mexican origin, jail or prison inmate, homeless, HIV-AIDS, alcohol abuse and drug abuse) or Mexico (age and sex).
n.a., Data not available.

Sociodemographic profile and risk factors for DM patients with TB

Information on self-reported DM was available for 3411 patients from Mexico (97·3%) and 1441 (93·4%) in Texas. Most TB patients were males, but there were a significantly higher proportion of females among those with TB-DM comorbidity (Table 1). TB-DM cases were significantly older (mostly over 40 years) than TB controls (Fig. 2, Table 1). Univariate analysis showed Texan TB-DM cases (data not available for Mexico) were more likely to be Hispanics of Mexican origin, and less likely to have the typical social risk factors associated with TB alone, such as incarceration, or homelessness. TB-DM Texans were significantly less likely than TB controls to be HIV-positive, use alcohol or drugs. After adjusting for each significant variable in the univariate analysis (Table 1), Mexican TB-DM cases were more likely to be older females than TB controls. Among Texans, being Hispanic and >40 years remained a risk factor for TB-DM cases. In contrast, being $\leqslant 40$ years and having a history of incarceration, homelessness, HIV-AIDS or alcohol use was more likely among TB controls (Table 1).

DM comorbidity may be associated with more severe and contagious TB

The clinical and laboratory manifestations of TB that were more severe (or common) in TB-DM cases when compared to TB controls by univariate analysis are shown in Table 2. These included higher frequency of pulmonary TB (in contrast to extra-pulmonary disease), positive direct sputum smears at the time of diagnosis, and for Texas, presentation with fever, cough, haemoptysis, cavitations detected by chest X-ray and false-negative tuberculin skin test results (data unavailable for Mexico). Smear positivity remained significantly higher in TB-DM cases up to the first month of anti-mycobacterial treatment for Texans, and up to the second month for Mexicans (Fig. 3). After adjusting each variable for age and sex, TB-DM cases were more likely to present with pulmonary (in contrast to extra-pulmonary) TB in both countries, and with positive smear upon diagnosis, fever, cough, haemoptysis and cavitations in Texas (Table 2).

DISCUSSION

We report the first large study of the role of type 2 DM in a population comprising all patients identified

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Table 2. *Differences in microbiological, radiological and clinical findings between TB patients with diabetes vs. those with no diabetes**†*

	Mexico			Texas		
	Diabetics ($n=607$)	Non-diabetics ($n=2804$)	aOR (95% CI)‡	Diabetics ($n=401$)	Non-diabetics ($n=1040$)	aOR (95% CI) ‡
Pulmonary disease	605 (99·7%)	2698 (96·2%)	12·7 (3·1–52·2)	376 (97·8%)	941 (91%)	1·7 (1·1–2·8)
Positive smear at diagnosis	572 (96·8%)	2542 (94·9%)	1·4 (0·8–2·4)	170 (64·9%)	358 (50·9%)	1·8 (1·3–2·4)
Fever	n.a.	n.a.		191 (57%)	377 (49·4%)	1·5 (1·1–1·9)
Cough	n.a.	n.a.		289 (86·3%)	612 (80·1%)	1·7 (1·1–2·4)
Haemoptysis	n.a.	n.a.		79 (23·6%)	146 (19·1%)	1·4 (1–1·9)
Cavitations	n.a.	n.a.		180 (60·4%)	315 (47·9%)	1·1 (1·1–1·2)
Negative skin test	n.a.	n.a.		72 (27·9%)	141 (20·5%)	0·8 (0·5–1·1)

* Percent is based on the total number of cases with available information for each variable.
† Shown variables were significantly associated with cases ($P \leqslant 0{\cdot}05$) by univariate analysis (see text).
‡ aOR, Odds ratio adjusted for age and sex.
n.a., Data not available.

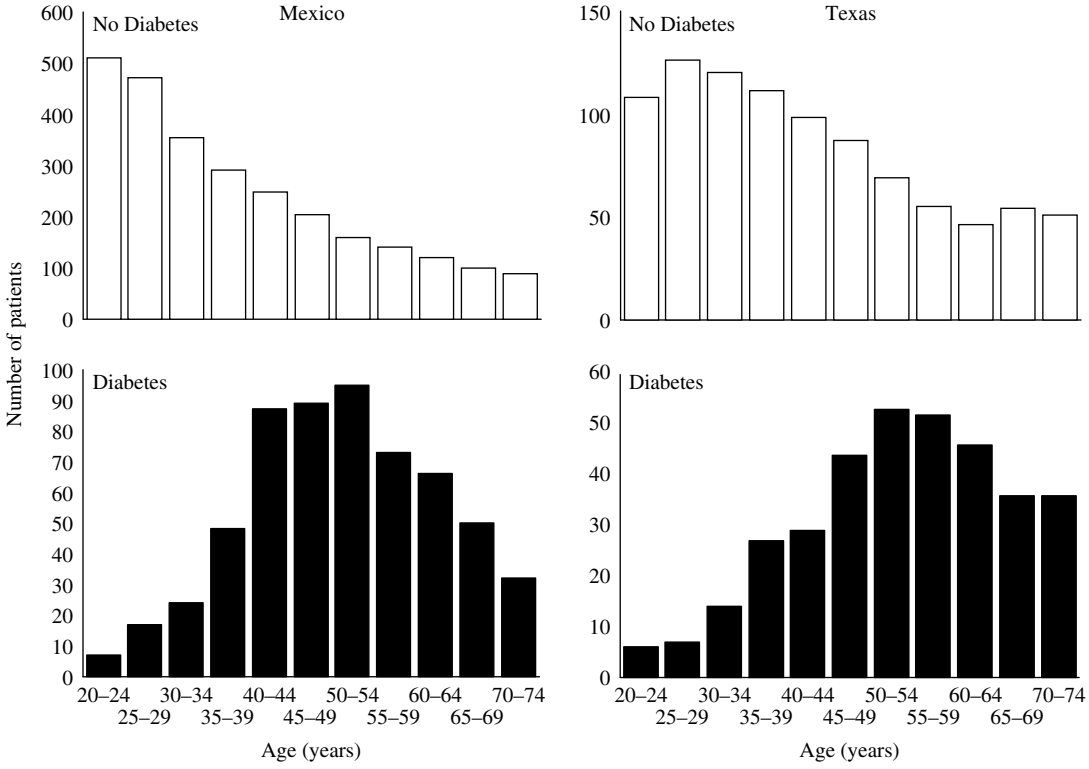

Fig. 2. Differences in age distribution between diabetic and non-diabetic TB patients from Mexico and Texas. Bar graphs illustrate the number of TB patients by 5-year age intervals in Mexico and Texas with DM (■) and without DM (□).

with TB in the control programmes on both sides of the Lower Rio Grande River in Texas and Mexico. We show type 2 DM as the major risk associated with TB among Mexicans and Hispanic Americans. This is despite the considerable underestimation of true prevalence associated with self-reporting of DM. Unlike most recent studies of very much smaller populations, our study included the entire population of TB patients in a defined region, regardless of hospitalization [12–15, 17]. Although the risk of TB in DM has been long recognized, particularly type 1 DM [8–10], our observations now demonstrate the

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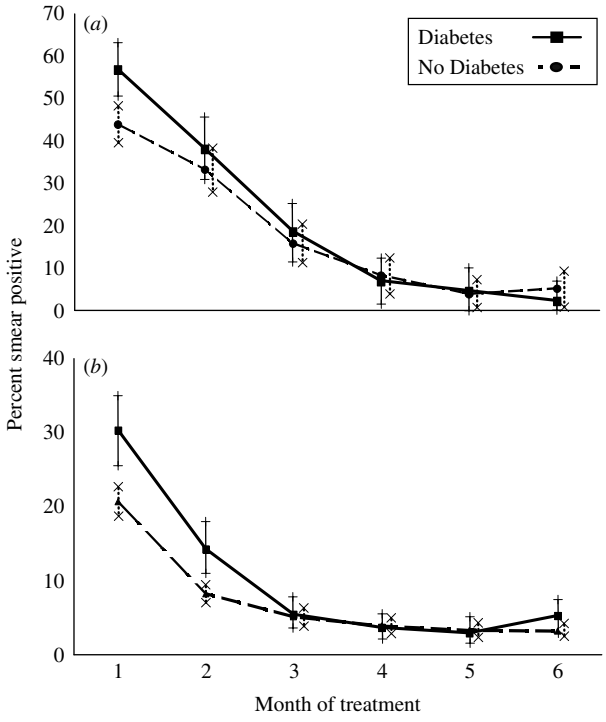

Fig. 3. Patients with DM and TB take longer to become direct smear negative upon treatment initiation. Percent of TB patients in (*a*) Texas and (*b*) Mexico whose direct smear for acid-fast bacilli by month of antimycobacterial therapy. Percentage figures are based on the total number of patients with productive cough available for direct smear evaluation for each month. Solid line, TB patients with DM. Hatched line, TB patients without DM; vertical solid/hatched lines, 95% confidence intervals.

potential magnitude of the contribution DM may make to TB in the 21st century especially among older patients with type 2 DM. We found that such patients with TB-DM had sociodemographic, behavioural and medical characteristics distinguishing them from TB controls. Further, our data indicate some clinical and microbiological manifestations suggesting that TB-DM cases may be more contagious at diagnosis and for longer periods during treatment. Our observations raise important scientific and public health questions concerning possible immunological impairment in DM, the importance of DM control in an exposed individual, and control of TB in communities with increasing prevalence of type 2 DM.

In modern times TB has become a disease of poverty and/or immunosuppression. The Texas population we studied is among the poorest in the United States [18] with increasing rates of obesity and type 2 DM [4]. The Mexican population we studied share the poverty, increasing obesity and DM, and is also medically underserved. Since TB and DM both preferentially affect the lowest socio-economic strata in all but the poorest communities, it may be argued that we may be observing a degree of coincidence rather than real association between both [19, 20]. While it is difficult to address this question directly with our data, we do know that the 2000 Census shows that our South Texas population has a very narrow range of median income between the lowest and highest quartiles of the population [21], and the range of median income in the border population in Mexico is even smaller. We consider that this narrow economic range is unlikely to be large enough to account for the differences in prevalence we observed between TB patients and the general population (Fig. 1). Even more importantly, if socio-economic status were the major explanation, then we would not expect to see the biological consequences of DM on TB observed in Table 2 and Figure 3.

Comparison of our self-reported DM numbers with national and local data showed its frequency among TB patients was significantly higher than the already high background in the same general population (Fig. 1). We can assume most of the TB-DM cases in our study have type 2 DM since absence of an association with DM in our data in TB patients under the age of 35 suggests predominantly if not exclusively type 2, not type 1 DM. In any event, over 95% of all DM patients in most contemporary studies have type 2 DM [22]. While the overall population of Mexico is younger than that of the United States, in both countries TB controls were substantially younger than TB-DM cases. Thus the message is similar in both populations: type 2 DM appears to be a substantial risk for the onset of TB particularly for adults in their 40s and early 50s, consistent with the general age of onset of type 2 DM in the general population [5, 6]. Lower frequencies of DM among TB patients by age 75 may simply reflect reduced overall survival among patients with DM [23].

Our observations have important public health implications. We show the importance of recognizing that patients aged >40 years with DM are particularly vulnerable to TB. Hitherto the dominant profile of the TB (control) patient is the younger male with a range of social risk factors, such as incarceration, homelessness, alcoholism or drug addiction, and/or HIV infection [24, 25]. While our younger population reflects many of these risks, the TB-DM cases we describe are older, may be female, and do not have these other social risks.

Our study site is a dynamic international border with a migrating population, mostly northward. Most patients are Hispanic, originating mainly from Mexico but also from other Central and South American countries. Current TB reporting does not take into account the prevalence of DM among TB patients, and therefore, no information on the magnitude of the problem is available. We suggest DM should be strongly considered as a commonly reported risk factor for TB patients worldwide as the DM epidemic continues to grow. Further, we suggest that in regions where both diseases are endemic, glucose levels should be measured in older patients with TB, and TB suspected more readily in patients with DM.

Despite the established link between TB and DM, the reason for their association is still unclear, but is likely to depend on a number of complex factors. It is reasonable to assume that an underlying immunological state increases susceptibility, especially in poorly controlled DM [26]. Our data suggest that TB-DM cases had higher bacillary loads, and may be more infectious and for longer periods of time than TB controls. These observations support the hypothesis that TB-DM cases may be less able to effectively clear *M. tuberculosis*. Our findings suggesting an advanced and contagious stage of the disease may also be explained by delay in diagnosis because the individual does not fit the usual clinical profile of a person at risk, or in Texas, because of higher frequency of false-negative tuberculin skin tests. Thus, the high concurrent prevalence of TB and DM in a poor population may compound the problem of TB control leading to further delay in diagnosis and increased exposure of the community.

While analysis of our bi-national data has provided robust insights into the association of TB with DM, we also recognize their limitations. Data were collected to assess TB treatment and control, not for evaluating the association between both diseases. While clearly a long-term prospective study to document this more fully is needed, we believe that our data are solid and point to DM as a serious and underappreciated comorbidity of TB, which should lead to more definitive studies. As previously mentioned, data based on self-reported DM substantially underestimate the true prevalence of this disease [7]. Similarly other self-reported risk-factors such as alcohol use, drug use and incarceration are likely to be underestimates, particularly for Mexico where at most two comorbidities or risk factors could be documented per patient. Thus our data certainly represent the weakest association between the two, and prospective studies that measure appropriate glucose levels are likely to show an even stronger association. We were not able to evaluate glucose control, nor could we independently measure alcohol and drug use. Blood tests for HIV infection are only performed routinely in Texas. Nevertheless clear distinctions in the age groups and social/behavioural risk factors for TB suggest that the direction of our conclusions is valid: that is, alcohol and drug use and jail time were more frequent among younger patients, and DM in older patients. There are also differences in the identification and reporting of TB and associated risk factors in both countries. Identification of TB patients is based on the combination of clinical and microbiological data in Texas, including smear and culture, while diagnosis is based on direct smear and clinical criteria in Mexico. Separate analysis of the two datasets provided an independent evaluation for both countries. Nevertheless, results were essentially the same in the analysis of thousands of patients from both populations, each supporting the validity of the other.

The international implications of the problem of type 2 DM and TB are broad. Type 2 DM is increasing in countries with high rates of endemic TB, such as India and China, where rates of type 2 DM have in recent years increased two- to three-fold [27–29]. Projections are that by 2010 there will be 220 million people globally with DM, the majority of whom will have type 2 DM [30], and many will be in countries also endemic for TB. The increased risk of disease with *M. tuberculosis* in type 2 DM may have implications on populations analogous to that in AIDS, obviously to a lesser degree in the individual patient. However, the actual number of patients at risk from DM may become much greater than even AIDS. In addition to the impact of HIV, the global epidemic of type 2 DM has the potential to further change the face of and accelerate TB throughout the world.

Type 2 DM may well be the sleeping giant of TB. The sheer numbers of patients who have type 2 DM and exposure to TB may have significant global impact. If our observations are confirmed prospectively we may well have to revisit TB control strategies in the light of concurrent DM, identifying these patients earlier in infection, assessing and supervising the control of their DM in order to optimize anti-TB medication. Our present knowledge suggests that failure to do so will allow more infectious patients to

circulate for longer periods of time, compromising already over-extended TB control programmes.

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DECLARATION OF INTEREST

None.

NOTE

Supplementary information accompanies this paper on the Journal's website (http://journals.cambridge.org).

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