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Bi-directional screening for tuberculosis and diabetes: a systematic review

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Summary

OBJECTIVE To assess the yield of finding additional TB or diabetes mellitus (DM) cases through systematic screening and to determine the effectiveness of preventive TB therapy in people with DM.

METHODS We systematically reviewed studies that had screened for active TB or implemented preventive therapy for TB among people with DM, and those that screened for DM among patients with TB. We searched published literature through PubMed and EMBASE and included studies that reported the number of TB cases identified among people with DM; the number of DM cases identified among patients with TB, or the relative incidence of TB between people with DM who received a TB prophylaxis and those who did not. We assessed the yield of screening by estimating the prevalence of TB or DM in each study, the prevalence ratio and difference where comparison populations were available, and the number of persons to screen to detect an additional case of TB or DM.

RESULTS Twelve studies on screening for TB in people with DM and 18 studies on screening for DM in patients with TB met our inclusion criteria. Screening for TB in persons with DM demonstrated that TB prevalence in this population is high, ranging from 1.7% to 36%, and increasing with rising TB prevalence in the underlying population as well as with DM severity. Screening patients with TB for DM also yielded high prevalences of DM ranging from 1.9% to 35%. Two studies examining the role of TB preventive therapy in people with DM did not provide sufficient details for clear evidence of the effectiveness.

CONCLUSION Active screening leads to the detection of more TB and DM with varying yield. This review highlights the need for further research in screening and preventive therapy.

keywords tuberculosis, diabetes, screening

Introduction

Currently, an estimated 285 million people live with diabetes mellitus (DM), a number which is expected to grow to at least 439 million by the year 2030 (IDF, 2010). At the same time, 9.6–13.6 million people live with tuberculosis [TB] disease and 1.1–1.7 million people die from the disease every year (WHO, 2009). Previous studies have demonstrated that DM not only increases the risk of active tuberculosis but also puts co-affected patients at increased risk for poor outcomes (Alisjahbana *et al.* 2007; Stevenson *et al.* 2007; Wu *et al.* 2007; Jeon & Murray 2008; Leung *et al.* 2008; Dooley *et al.* 2009). With the rising prevalence of DM, a greater proportion of TC disease will be attributable to DM in the future (Ruslami *et al.* 2010). The potential for 'syndemics' of DM and TB in countries with high burdens of both diseases raises the question of how best to integrate management of these diseases (Restrepo 2007; Dooley & Chaisson 2009; Harries *et al.* 2009).

Over the past two decades, TB control efforts have focused on the strategy of Directly Observed Therapy Short-Course (DOTS), a package of interventions, including diagnosis by sputum smear microscopy and supervised chemotherapy. While this strategy has improved both the detection rate of smear-positive cases and the outcomes of

treatment, its impact on TB prevalence is less clear (Dye *et al.* 2005). Experts suggest that TB control would be further improved by intervening patients with known determinants of TB, including those with diabetes (Lonnroth *et al.* 2009, 2010). This entails both TB prevention through actions to diminish the prevalence of risk factors and targeted diagnostic and treatment interventions in risk groups, such as people with DM. Screening for active TB in people with DM could hasten case detection, which could lead to earlier therapy and prevention of transmission; the administration of preventive TB therapy in TB-infected people with DM could avert progression to TB. Conversely, screening for DM in patients with TB could improve case detection, early treatment and tertiary prevention of DM, and indirectly lead to better TB-specific treatment outcomes.

Recognizing the opportunities offered by screening and preventive therapy, we systematically reviewed studies that had implemented screening or preventive therapy for TB among people with DM and those that screened for DM among patients with TB to assess the yield of finding additional TB or DM cases through active screening and to determine the effectiveness of preventive TB therapy in patients with diabetes.

Methods

Selection of studies

We conducted this systematic review to address three distinct aims: (1) to assess the yield of screening people with DM for the detection of TB in various settings, (2) to assess the yield of screening the patients with TB for the detection of DM in various settings and (3) to measure the effectiveness of TB preventive therapy in people with DM. For these aims, we conducted a literature search in PubMed from 1965 to May 2009 and in EMBASE from 1974 to May 2009 using the search strategy outlined below with no language restriction.

For the PubMed search, we used the MeSH Terms: 1. 'diabetes mellitus' and 2. 'tuberculosis' [majr] and the Text terms 3. 'prevent*' OR 'isoniazid*' OR 'chemoproph*'; 4. 'detect*' OR 'screen*' OR 'diagnos*' with the search string: 1 AND 2 AND (3 OR 4 in abstract). For the EMBASE search, we used the subject terms 1. 'diabetes mellitus' and 2. 'tuberculosis' [majr] and the text terms 3. 'prevent*' OR 'isoniazid*' OR 'chemoproph*'; 4. 'detect*' OR 'screen*' OR 'diagnos*', with the search string: 1 AND 2 AND (3 OR 4 in abstract).

We chose the root terms 'detect*', 'screen*' and 'diagnos*' to find articles that described a screening programme for people with DM. We also employed the root terms 'prevent*', 'isoniazid*' and 'chemoproph*' to find articles that described preventive therapy against TB among people with DM. We specifically included 'isoniazid*' as one of the search terms, given that isoniazid is the most commonly used preventive therapeutic drug against TB. We also searched the bibliographies of relevant literature and the abstracts of World Lung Conferences held in 2007 and 2008, limiting the search to these years because we expected high-quality studies reported in prior years to be published by May 2009. Among the retrieved citations, we examined the full texts of articles with abstracts that described or mentioned (1) the screening of people with DM for TB, (2) the screening of patients with TB for DM or glucose intolerance, (3) the effectiveness of preventive therapy in people with DM or (4) 'diabetes' and 'tuberculosis' but did not provide enough detail on the methods to determine if screening or preventive therapy were implemented.

Our initial aim was to identify studies that assessed the effectiveness of TB screening in people with DM for preventing TB-related morbidity or mortality, but because of the lack of such studies, we focused on assessing the yield of screening for TB disease among people with DM. For this aim, we included studies that screened people with DM for TB using any of the following methods of identification: X-ray consistent with TB, positive sputum smear microscopy, positive mycobacterial culture and clinical evaluation. We excluded studies that did not allow computation of TB prevalence or TB incidence in the screened population and those that did not describe the age distribution of the screened population. Because our focus was on summarizing the yield of screening for TB in people with DM, we included studies even if they did not provide a non-diabetic control group; in the latter case, we searched for published estimates of TB prevalence in a comparable population based on surveys conducted within ±5 years in the same population that gave rise to the screened DM patients and conducted with the same screening methods as the screening study.

To assess the yield of screening for DM among patients diagnosed with active TB, we included studies that screened for DM using the following types of blood glucose tests: random blood glucose, fasting blood glucose and oral glucose tolerance test. We excluded studies that did not describe the age distribution of the screened population and studies that only diagnosed impaired glucose tolerance. Here again, we did not require that studies include a control group but used an external estimation of the population prevalence of DM as a comparator if the prevalence was estimated from a survey conducted within ±5 years in the same population that gave rise to the screened TB cases and employed the same definition of DM as the study.

To assess the efficacy of TB preventive therapy in people with DM, we included studies that had compared the incidence of TB in a diabetic population receiving any form of preventive therapy to a control population with DM. We included studies whether or not TB infection was confirmed to consider evidence on the potential effect of preventive therapy in people with DM even in settings where TB infection is not a prerequisite for preventive therapy.

Data Extraction

Two investigators (CYJ, SG) independently extracted data from the studies using standardized extraction forms. Evaluation and data extraction of non-English papers was carried out in conjunction with translators fluent in the language of the paper. For all studies, we extracted information on the study population, location, study period and method of recruitment of the screened population.

For the studies on screening for TB among people with DM, we extracted information on the proportion of people with DM that were insulin dependent, the method of TB diagnosis, the sample size, the number of patients with TB identified in the screened populations (and control population, if available), as well as the age and sex distribution of the screened DM patients and identified TB patients. We noted whether studies included prevalent or incident TB cases and if incident TB, we extracted information on the period during which patients were followed for TB.

For the studies on screening for DM among patients with TB, we extracted information on the method of DM diagnosis, the timing of DM diagnosis relative to the onset of TB treatment, the sample size, the number of people with DM identified in the studied TB population (and control population, if available), as well as the age and sex distribution of the screened TB patients and DM patients identified through screening. For studies on preventive therapy, we extracted information on the duration and type of regimen, the follow-up period, the incidence of TB in the intervention group and control groups, and the criteria by which intervention was assigned.

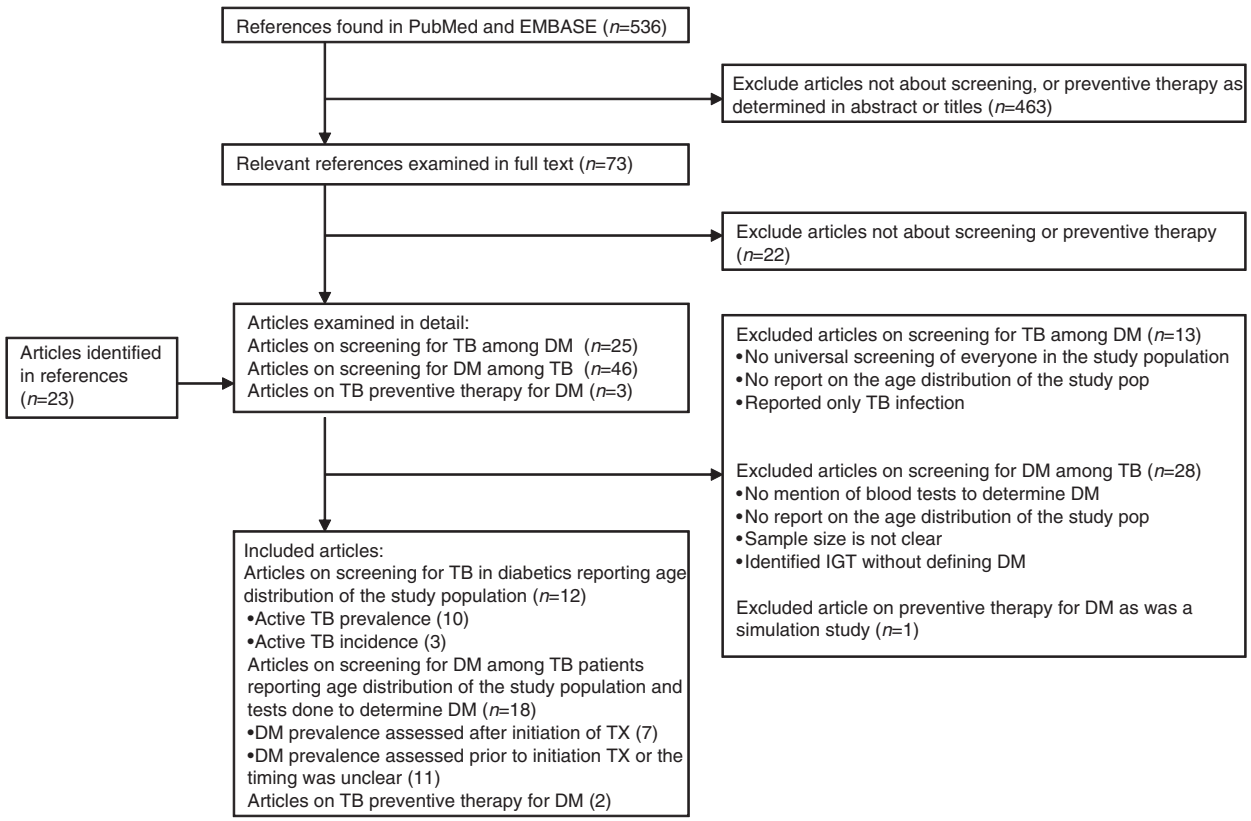

Figure 1 Flow chart of selection of studies.

Table 1 Summary of studies on screening for tuberculosis among people with diabetes and selected comparison population

Study	Region, Country	Study Period	Diabetes diagnosis methods	TB identification method	% insulin dependent	% male	Age distribution	Comparison population
Studies on screening for prevalent TB in DM								
Boucot *et al.* 1952	Philadelphia, United States	1946	Diabetics referred by clinics (FBG ≥ 130 mg/dl; Random BG ≥ 170 mg/dl with glycosuria)	PTB by chest X-ray	74%	Among DM 31%; Among TB 45%	Among DM 14% <40 years; Among TB 13% <40 years	Non-diabetic industrial workers of Philadelphia in 1942
Oscarsson & Silwer 1958	County of Kristianstad, Sweden	March 1954	Diabetics identified by medical records	PTB by chest X-ray	64%	Among DM 45%; Among TB 52%	Among DM 18% <40 years; Among TB 26% <40 years	Residents of county of Kristianstad in 1953
Opsahl *et al.* 1961	Korea	N/R	Patients with diabetes at The National Medical Center	PTB by chest X-ray	43%	Among DM 63%; Among TB N/R	Among DM 35% <40 years; Among TB N/A	Patients applying to the surgical outpatients department for diseases other than TB
Davidovich *et al.* 1963	Rosario, Argentina	N/R	Patients with diabetes at the clinic identified by medical records	PTB by chest X-ray	N/R	Among DM 22%; Among TB 25%	Among DM 12% <45 year; Among TB 25% <45 years	No comparison
Marton *et al.* 1963	Hungary	Summer 1960	Patients with diabetes of hospital; and non-diabetic controls	PTB by chest X-ray, followed by sputum culture	N/R	Among DM 44%; Among TB 58%	Among DM: Mean 59; Among TB: Mean 60	Non-diabetics of similar age and sex distribution from the same hospital
Golli *et al.* 1975	Germany	N/R	Patients with diabetes registered in the diabetes centre in Berlin	PTB by chest X-ray	38%	Among DM 62%, Among TB 92%	Among DM 11% ≤ 40; Among TB 17% ≤40	No comparison
Gill *et al.* 1984	Soweto, South Africa	N/R	Diabetics <30 years with insulin dependence by medical records	PTB by chest X-ray	100%	Among DM 50%; Among TB N/R	Among DM Mean 21.7,SD 4.8; 100% <30 years; Among TB N/R	No comparison

Table 1 Continued

Study	Region, Country	Study Period	Diabetes diagnosis methods	TB identification method	% insulin dependent	% male	Age distribution	Comparison population
Tripathy *et al.* 1984	Adra, India	N/R	Diabetics identified by medical records	PTB by sputum smear on three consecutive days	N/R	Among DM N/R; Among TB 78%	Among DM 24% <40 years; Among TB 12% <40 years	No comparison
Ezung *et al.* 2002	Imphal, India	N/R	Diabetics at diabetic clinic; DM established by clinical symptoms and by WHO criteria	PTB by chest X-ray, and sputum smear	N/R	Among DM 65%, Among TB 74%	Among DM 12% ≤40 years; Among TB 15% ≤40	No comparison
Webb *et al.* 2009	Western Cape, South Africa	Sept 2006–Jan 2007	Type 1 diabetics diagnosed by paediatric endocrinologist	TB by chest X-ray, suggestive symptoms, and positive Mantoux test	100%	Among DM 42%, Among TB 67%	100% <21 years for DM and TB	No comparison
Studies on screening for incident TB in DM								
Lester 1984	Ethiopia	Apr 1976–Jul 1983	Patients with diabetes at a hospital diagnosed by FBG > 140 mg/dl, Random BG > 200 mg/dl OR history of diabetes treatment	PTB by chest X-ray, sputum smears; OR positive Mantoux test with suggestive clinical presentation	40%	Among DM 50%, Among TB 69%	Among DM 53% <40 years; Among TB 79% < 40 years	No comparison
Kim *et al.* 1995	South Korea	1988–1990	Civil servants with DM diagnosed by random ≥ 119 mg/dl, FBG ≥150 mg/dl and ≥180 mg/dl post-meal	PTB by chest X-ray, smear microscopy and culture	N/R	Among DM 96%, Among TB 98%	≥20	Korean civil servants without diabetes

N/R, not reported; PTB, pulmonary tuberculosis; DM, diabetes mellitus; FBG, fasting blood glucose.

Table 2 Summary of results of screening for tuberculosis in people with diabetes and selected comparisons

Study	Pop Size of diabetics	Number of TB	Number of TB diagnosed prior to screening	TB prevalence or incidence in diabetics (per 100 000)	TB prevalence or incidence for comparison (per 100 000)	Prevalence or incidence ratio	Prevalence or incidence difference (per 100 000)	Number needed to screen to detect 1 TB case
Studies on screening for prevalent TB in DM								
Boucot *et al.* 1952	3106	261	87	8403*	4300*	2.0	4103	24
Oscarsson & Silwer 1958	1270	46	N/R	3622*	880*	4.1	2742	36
Opsahl *et al.* 1961	116	42	13	36206*	10359*	3.5	25848	4
Davidovich *et al.* 1963	100	4	N/R	4000*	–	–	–	–
Marton *et al.* 1963	802	16	8	1995	997	2.0	998	100
Golli *et al.* 1975	304	12	N/R	3947*	–	–	–	–
Gill *et al.* 1984	66	7	3	10606*	–	–	–	–
Tripathy *et al.* 1984	219	9	N/R	4110	–	–	–	–
Ezung *et al.* 2002	100	6	N/R	6000	–	–	–	–
Webb *et al.* 2009	258	9	2	3488	–	–	–	–
Studies on screening for incident TB in DM								
Lester 1984	849	29	N/R	488†	–	–	–	–
Kim *et al.* 1995	8015	45	Excluded at baseline	281†	55	5.1	226	442

–, No appropriate comparison could be identified; N/R, not reported; DM, diabetes mellitus.
*The TB cases were determined only by X-ray, thus TB prevalence may be overestimated.
†The cumulative incidence in the diabetic was divided by the number of years of follow-up.

Table 3 Relative detection of TB by severity of diabetes in studies that stratified by insulin dependence

Study	Diabetes severity (quantity of insulin required)			Prevalence or incidence ratio (compared to mild diabetes)			*P*-value (severe *vs* mild)
	Mild	Moderate	Severe	Mild	Moderate	Severe	
Boucot *et al.* 1952	No insulin	1–39 u/day of insulin	≥40 u/day of insulin	1.0	1.3	3.9	<0.0001
Oscarsson & Silwer 1958	No insulin – 20 u/day of insulin	20–39 u/day of insulin	≥40 u/day of insulin	1.0	4.2	20.9	<0.0001
Golli *et al.* 1975	No insulin	10–20 u/day of insulin	>20 u/day of insulin	1.0	0.6	2.8	0.07
Lester 1984	No insulin	–	Insulin-dependent	1.0	–	7.2	<0.0001

Differences in the extracted information were resolved by discussion between the two data extractors; for non-English articles, any ambiguous information on extracted data was asked to be reviewed by the same translator.

Data analysis

We grouped studies on screening for TB among people with DM into those that assessed TB prevalence and those that assessed TB incidence through longitudinal follow-up. We calculated the prevalence or the incidence rates of TB found in people with DM and controls where data were available. For follow-up studies, we summarized the annual TB incidences by dividing the cumulative incidence by the number of years of follow-up. For studies that provided the number of TB cases diagnosed by X-ray separately from those diagnosed by bacteriology, we used the latter definition to calculate TB prevalence. We computed prevalence or incidence ratios and prevalence or incidence differences to assess the relative and absolute contrast in yield of finding TB cases between the screened diabetic populations and the comparison populations where available. Additionally, we calculated the number of people needed to screen to detect one additional case of TB in a diabetic population by taking the inverse of the prevalence or incidence difference for each study.

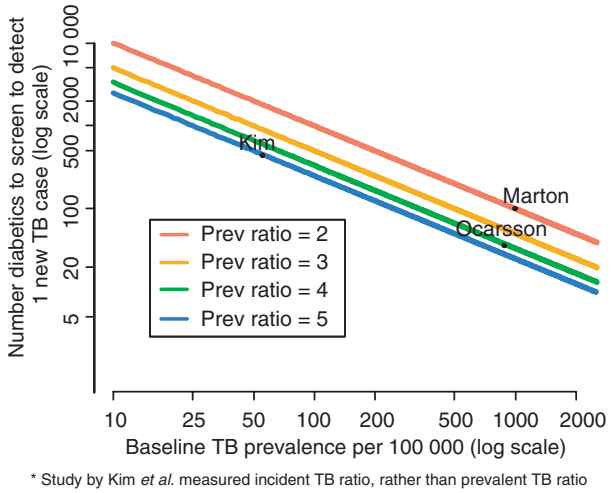

Figure 2 Number of people with diabetes to screen to detect one additional case of tuberculosis by varying baseline tuberculosis prevalence, given prevalence ratios found in screening studies.

To illustrate the potential yield in screening for TB in people with DM residing in various settings, we plotted how many patients with DM would need to be screened to detect one additional case of TB, under baseline TB prevalence ranging from 1 to 2000 per 100 000 persons, for prevalence ratios estimated from the screened populations and their comparisons.

Because DM may be over-diagnosed in patients with TB experiencing a transient infection-related hyperglycaemia at the beginning of treatment, we grouped studies on screening for DM among people with TB into (1) those that administered screening after TB treatment initiation, (2) those that had screened the population prior to TB treatment and (3) those in which the timing of screening relative to the initiation of TB treatment was not clear. We computed the DM prevalence for the screened diabetic populations and controls. We computed the prevalence ratios and differences to assess the relative and absolute contrast between the screened TB populations and the comparison populations where available. We also calculated the number of people needed to screen to detect one additional case of DM in a TB population by taking the inverse of the prevalence or incidence difference for each study.

To illustrate the potential yield in screening for DM in patients with TB in various settings, we plotted how many patients with TB would need to be screened to detect one additional case of DM, under baseline DM prevalence ranging from 1% to 25%, for prevalence ratios estimated from the screened populations and their comparisons.

Results

Screening for TB among DM

The PubMed and EMBASE search yielded 536 citations; we examined the full text of 73 articles and excluded 22 studies as they did not describe a screening study. A hand-search of the bibliographies yielded 23 additional studies for full text review (Figure 1).

Of these, we included 12 studies that reported the presence of TB among people with DM: 10 of these reported TB prevalence (Boucot *et al.* 1952; Davidovich *et al.* 1963; Ezung *et al.* 2002; Gill *et al.* 1984; Golli *et al.* 1975; Marton *et al.* 1963, Opsahl *et al.* 1961, Oscarsson & Silwer 1958, Tripathy *et al.* 1984; Webb *et al.* 2009) and 2 TB incidence (Lester 1984; Kim *et al.* 1995). Population characteristics and the methods of screening are summarized in Table 1. The prevalence of active TB among people with DM ranged from 1.7% in Sweden in 1954 to 36% in Korea in 1961; the annual incidence ranged from 280/100 000 people with DM in Korea to 488/100 000 people with DM in Ethiopia (Table 2).

Five of the 12 studies either screened a non-diabetic control group or provided an estimate of the TB prevalence in the population that gave rise to the study group within 5 years of the study. In these, prevalence ratios ranged from 2.0 in Hungary and United States to 5.1 in Korea (Table 2). Among the four studies that were stratified by the severity of diabetes, TB was more common in those with insulin dependence compared to those with milder diabetes with prevalence ratios from 2.8 to 20.9 (insulin-dependent *vs* non-insulin-dependent) (Table 3).

Figure 2 plots the number of people with DM that would need to be screened to detect one additional case of TB based on prevalence ratios from 2 to 5, for varying levels of baseline TB prevalence. In settings in which TB prevalence is <25 per 100 000 persons, at least 1000 people with DM would need to be screened to find a single additional case of TB. In contrast, in places with higher TB burden, such as India, where TB prevalence is estimated at 283/100 000, screening 90–350 people with DM would yield one or more cases of TB.

Screening for DM among TB

We identified 18 studies that met our inclusion criteria on screening for DM among patients with TB; seven studies conducted screening after TB treatment initiation (Goyal *et al.* 1978, Kishore *et al.* 1973; Oluboyo & Erasmus 1990; Singh *et al.* 1984; Balde *et al.* 2006; Kovaleva *et al.* 1975; Nichols 1957) with four of these screening for DM

at multiple time points during TB therapy (Goyal, 1978, Kishore *et al.* 1973; Oluboyo & Erasmus 1990; Singh *et al.* 1984); four screened for DM only before treatment began (Nanda & Tripathy 1968; Jawad *et al.* 1995; Basoglu *et al.* 1999; Alisjahbana *et al.* 2006); and seven did not specify when screening had occurred (Higashi 1967; Roy-chowdhury & Sen 1980; Deshmukh & Shaw 1984; Tripathy *et al.* 1984; Mugusi *et al.* 1990; Ponce-de-Leon *et al.* 2004; Golsha *et al.* 2009). Population characteristics and methods of screening are summarized in Table 4. Five of the 18 studies also reported the results of screening for DM in a population without TB. In addition, we were able to find DM prevalence estimates for a comparison population based on prevalence surveys using the same method of screening for three of the studies that did not employ a control group (Shera *et al.* 1999; Ponce-de-Leon *et al.* 2004; Esteghamati *et al.* 2008).

DM prevalence reported in studies that screened after TB treatment initiation ranged from 1.9% in Nigeria in 1990 to 10% in India in 1968. The prevalence of DM was higher in patients with TB than in controls, with prevalence ratios of 2.78 and 8.00 calculated from studies with a control population that had a non-zero count for people with DM (Table 5).

Among studies that conducted screening prior to TB treatment, the prevalence of DM ranged from 8.6% in Turkey to 19.8% in Pakistan. Among those that did not report the timing of DM screening relative to TB treatment, estimates ranged from 2.1% in India to 35.2% in Mexico. In these latter two groups of studies, diabetes prevalence was higher in patients with TB than in the comparisons where available, with prevalence ratios >1, ranging from 1.83 in Pakistan to 7.81 in Tanzania (Table 5).

Data from the four studies that screened for DM at multiple points in the course of TB treatment are presented in Figure 3 (Goyal, 1978, Kishore *et al.* 1973; Oluboyo & Erasmus 1990; Singh *et al.* 1984). In each, the prevalence of hyperglycaemia decreases over time since the initiation of TB treatment.

Figure 4 plots the number of TB patients that would need to be screened to detect one additional case of DM, under varying assumptions about baseline DM prevalence and prevalence ratios. In settings like Mexico with a baseline DM prevalence of 10% (IDF, 2010), screening as few as 2–10 patients with TB would lead to the detection of at least one additional case of DM.

Chemoprophylaxis for prevention of TB among people with DM

We identified two observational studies in which people with DM had been administered chemopropylaxis for prevention of TB. In a study conducted in Germany (Pfaffenberg & Jahler 1958) in the 1950s, 63 patients with diabetes who had completed a course of treatment for active TB were subsequently treated with isoniazid for 6–24 months, while a comparison group of 164 people with DM completing treatment for active TB was not treated. While the comparison group accrued 18 cases of recurrent TB over a mean of 2.3 years of follow-up time, the intervention group experienced no recurrent TB over 1.6 years of follow-up time. In a second study conducted in Russia in the 1960s (Lesnichii & Karpina 1969), investigators administered ftivazid, a Russian analogue of isoniazid, to 2006 patients with diabetes and compared their course to 387 controls who were not treated. Treated patients were reported to experience 2–3 times lower incidence of TB compared to controls who did not receive any ftivazid during a follow-up period of 5 years. The study did not report raw numbers of TB cases, specify whether the follow-up period occurred during intervention or afterwards, nor indicate the reasons for not administering ftivazid in the control group.

Discussion

In this systematic review, we summarized the published experiences of screening for TB in people with DM and screening for DM in patients with TB over a wide temporal and geographical range. We found that the prevalence of TB in screened people with DM was exceptionally high, commensurate with estimates for populations in which active case finding is implemented, such as HIV-infected individuals (Reid & Shah 2009), gold miners (Lewis *et al.* 2009) and prisoners in developing countries (Banda *et al.* 2009). The yield of screening for TB in people with DM increases with the prevalence of TB in the region as well as with the severity of individual's diabetes, as determined by insulin dependence. Studies that screened for DM among patients with TB also reported a wide range of DM prevalence ranging from 1.9% to as high as 35%, with the highest values reported for regions in which DM prevalence is high. For example, in Veracruz Mexico, where the baseline DM prevalence is relatively high at 7.6%, 35% of the screened TB patients were found to have DM (Ponce-de-Leon *et al.* 2004).

The studies reviewed here shed light on how to target screening efforts in people with DM and patients with TB; however, they were limited in several aspects. First, none of the studies followed an unscreened population to measure the effectiveness of screening in preventing TB or in improving disease outcomes. Second, many studies did not employ a control group and lacked an appropriate comparison. This restricted the computation of prevalence

Table 4 Summary of studies on screening for diabetes among patients with tuberculosis and selected comparison populations

Study	Region, country	Study period	TB diagnosis method	Diabetes mellitus (DM) diagnosis method	Timing of DM diagnosis	% Male	Age distribution	Comparison population
Studies in which DM was screened for all study participants after TB Tx initiation								
Nichols 1957	Denver, Colorado, U.S.	N/R	TB inpatients seen at the Fitzsimons Army Hospital	DM defined by following criteria (1) OGTT peak sugar > 180 mg/dl, (2) OGTT > 130 mg/dl at 2 h and (3) More than a trace of glycosuria	7–9 months post-Tx start	Among TB 100%; Among DM 100%	Among TB: Mean 27.9, Range 18–53; Among DM: Mean 33.4	No comparison
Kishore *et al.* 1973	Agra, India	Apr 1971–Oct 1971	Patients with PTB diagnosed by clinical examination, sputum smear, or X-ray	DM defined by WHO 1965 criteria, OGTT(100 g) 2 h > 130 mg/dl	3 months post-Tx start	Among TB 66%; Among DM 74%	Among TB: Mean 29.4, Range 13–61, 84% <40; Among DM: N/R	Health subjects of comparable age and sex, without family history of diabetes and tuberculosis
Kovaleva *et al.* 1975	Moscow, Russia	N/R	TB inpatients	DM defined by FBG > 120 mg/dl, OGTT(50 g) > 200 m/dl at 1 h, >160 mg/dl at 2 h; exclude previous diagnosed DM	post-Tx start (unspecified time)	Among TB 76%; Among DM N/R	Among TB: 60% ≤50; Among DM: 33% ≤50	No comparison
Goyal *et al.* 1978	Uttar Pradesh, India	N/R	Patients with PTB diagnosed by clinical examination, sputum smear and X-ray	DM defined by WHO 1965 criteria, OGTT and cortisone primed GTT	3 months post-Tx start	Among TB 85%; Among DM N/R	Among TB: 69% ≤40; Among DM: N/R	Healthy individuals of comparable age and sex without family history of diabetes and pulmonary tuberculosis
Singh *et al.* 1984	Delhi, India	N/R	PTB outpatients, diagnosed by X-ray and bacteriologically confirmed	DM defined by WHO 1980 criteria, FBG ≥120 mg/dl, OGTT (75 g) 0.5–2 h ≥ 180 mg/dl after eating	12 weeks post-Tx start	Among TB 65%; Among DM N/R	Among TB: Mean 30.5, Range 19–60; Among DM: N/R	No comparison
Oluboyo & Erasmus 1990	Ilorin, Nigeria	N/R	Newly diagnosed patients with PTB diagnosed by sputum smear and X-ray	DM defined by WHO 1980 criteria, OGTT (75 g), FBG	3 months post-Tx start	Among TB 56%; Among DM N/R	Among TB: Mean 34.9, SD 14.4; Among DM: N/R	Health individuals matched by age, sex and BMI

Table 4 Continued

Study	Region, country	Study period	TB diagnosis method	Diabetes mellitus (DM) diagnosis method	Timing of DM diagnosis	% Male	Age distribution	Comparison population
Balde *et al.* 2006	Conakry, Guinea	Feb 2002–May 2002	Patients with TB from the registry	DM defined by WHO 1999 criteria; known diabetic confirmed with FBG in capillary > 1.1 g/l (corresponding to venous 126 mg/dl); random glycaemia in capillary > 2 g/l with clinical signs	post-Tx start (unspecified time)	Among TB 66%, Among DM 69%	Among TB: Mean 31, Range 14–75; Among DM: Mean 47.1, SD 13.1	No comparison
Studies in which DM was screened before TB Tx initiation								
Nanda & Tripathy 1968	Orissa, India	N/R	Patients with PTB diagnosed by clinical examination, X-ray and bacteriology	DM defined by FBG > 120 mg/dl, OR PPGTT peak sugar > 180 mg/dl, OR 2 h > 130 mg/dl	At diagnosis	Among TB 83%; Among DM N/R	Among TB: 54% ≤40; Among DM: 50% ≤40	No comparison
Jawad *et al.* 1995	Nazimabad, Pakistan	N/R	Patients with PTB diagnosed by X-ray and sputum smear	DM defined by WHO 1985 criteria, OGTT(75 g); previously known diabetics excluded	At diagnosis	Among TB 59%; Among DM N/R	Among TB: Mean 39.3; 74.6% <40; Among DM: N/R	Urban population of Baluchistan, Pakistan, 1995*
Basoglu *et al.* 1999	Izmir, Turkey	N/R	Patients with PTB diagnosed by clinical examination, X-ray and sputum smear	DM defined by OGTT(75 g) 0.5 or 1 h and 2 h > 200 mg/dl	At diagnosis	Among TB 78%; Among DM N/R	Among TB: Mean 41.9, Range 15–82; Among DM: Mean 53.9, Range 37–82	No comparison
Alisjahbana *et al.* 2006	Jakarta and Badung, Indonesia	Mar 2001–Mar 2005	Primary TB patients with clinical symptoms and suggestive X-ray, confirmed by + smear	DM defined by FBG ≥ 126 mg/dl	At diagnosis	Among TB 52%; Among DM N/R	Among TB: Median 30, Range 15–75; Among DM: Median 45	Randomly selected control of the same sex, age (±10%) from same region
Studies in which timing of DM diagnosis relative to TB Tx is unclear								
Higashi 1967	Kyushu, Japan	Jul 1966	TB inpatients in 23 TB sanatoria	DM defined by glycosuria and venous blood 2 h after meal > 120 mg/dl, or capillary blood 2 h after meal > 140 mg/dl	Unclear	Among TB 64%; Among DM 71%	Among TB: 45.3% <40; Among DM: 20.3% <40	No comparison

Table 4 Continued

Study	Region, country	Study period	TB diagnosis method	Diabetes mellitus (DM) diagnosis method	Timing of DM diagnosis	% Male	Age distribution	Comparison population
Roychowdhury & Sen 1980	Calcutta, India	Apr 1975–Mar 1976	TB inpatients diagnosed by smear, culture, X-ray or clinical symptoms suggestive of TB	DM defined by OGTT(100 g) > 140 mg/dl at 2 h, Potential DM defined by 131–140 mg/dl	Unclear	Among TB 83%; Among DM N/R	Among TB: 70% <45; Among DM: 67% <45	No comparison
Deshmukh & Shaw 1984	Jamshedpur, India	N/R	Patients with PTB diagnosed by clinical, radiological and bacteriological methods	DM defined by glucosuria and FBG > 120 mg/dl, OGTT (75 g) > 140 mg/dl	Unclear	Among TB 64%; Among DM 72%	Among TB: 60% <45; Among DM: 17% <45	No comparison
Tripathy *et al.* 1984	Adra, India	N/R	Patients with PTB diagnosed by sputum smear	DM defined by WHO 1965 criteria, OGTT (100 g)	Variable	Among TB: N/R; Among DM N/R	Among TB: 66% <40; Among DM: 52% <40	No comparison
Mugusi *et al.* 1990	Dar es Salaam, Tanzania	N/R	Patients with PTB diagnosed by sputum smear	DM defined by WHO 1985 criteria, OGTT (75 g) ≥ 10 mM or FBG > 6.7 mM	Unclear	Among TB 69%; Among DM N/R	Among TB: Mean 35, Range 14–88; Among DM: N/R	Urban community in Dar es Salaam
Ponce-de-Leon *et al.* 2004	Veracruz, Mexico	Mar 1995–Mar 2003	Patients with PTB confirmed by sputum smear or culture	DM defined by E11FBG ≥ 126 mg/dl OR ≥ 200 mg/dl for random samples	Unclear	Among TB 66%; Among DM N/R	Among TB: Mean 44, Range 19–86; Among DM: Mean 53, Range 23–82	General population of state of Veracruz (ENSA2000 diabetes survey)*
Golsha *et al.* 2009	Gorgan, Iran	2001–2005	Patients with TB with 2 + smears or 1 + smear with abnormal X-ray, OR physician's diagnosis with response to Tx	DM defined by FBG > 126 mg/dl	Unclear	Among TB 53%; Among DM 43%	Among TB: Mean 50.2, SD 19, 30% ≤40; Among DM 7% ≤40	General population of Iran (National survey of diabetes conducted in 2005)*

*Comparison data from external source.
N/R, not reported; PTB, pulmonary tuberculosis; FBG, fasting blood glucose; OGTT, oral glucose tolerance test; BMI, body mass index; PPGTT, prednisone-primed glucose tolerance test, Tx, TB treatment.

Table 5 Summary of results on screening for diabetes in patients with tuberculosis and selected comparisons

Study	Pop size of patients with TB	Number of diabetes mellitus (DM) in patients with TB	Diagnosed prior to screening	DM prevalence in TB	DM prevalence in comparison	Prevalence or incidence ratio	Prevalence or incidence difference	Number needed to screen to detect 1 DM case
Studies in which DM was screened for all study participants after TB Tx initiation								
Nichols 1957	178	9	N/R	5.1%	–	–	–	–
Kishore *et al.* 1973	90	5	4	5.6%	2.0%	2.78	3.6%	28
Kovaleva *et al.* 1975	771	27	0	3.5%	–	–	–	–
Goyal *et al.* 1978	110	11	10	10.0%	1.3%	8.00	8.8%	11
Singh *et al.* 1984	52	1	N/R	1.9%	–	–	–	–
Oluboyo & Erasmus 1990	54	1	N/R	1.9%	0%*	Infinity	1.9%	54
Balde *et al.* 2006	388	13	9	3.4%	–	–	–	–
Studies for which DM was screened before TB Tx initiation								
Nanda & Tripathy 1968	200	24	N/R	12.0%	–	–	–	–
Jawad *et al.* 1995	106	21	N/R	19.8%	10.8%	1.83	9.0%	11
Basoglu *et al.* 1999	58	5	N/R	8.6%	–	–	–	–
Alisjahbana *et al.* 2006	454	60	N/R	13.2%	3.2%	4.08	10.0%	10
Studies in which timing of screening of DM is unclear								
Higashi 1967	6065	222	109	3.7%	–	–	–	–
Roychowdhury & Sen 1980	961	199	N/R	20.7%	–	–	–	–
Deshmukh & Shaw 1984	2434	138	60	5.7%	–	–	–	–
Tripathy *et al.* 1984	1359	29	9	2.1%	–	–	–	–
Mugusi *et al.* 1990	506	34	N/R	6.7%	0.9%	7.81	5.9%	17
Ponce-de-Leon *et al.* 2004	525	185	172	35.2%	7.6%	4.63	27.6%	4
Golsha *et al.* 2009	243	56	N/R	23.0%	7.7%	2.99	15.3%	7

*No DM was found in a control population of 54 health individuals who were also screened for DM.
–, No appropriate comparison could be identified; Tx, TB treatment.

ratios to a few studies. Also, the studies did not provide details on the socioeconomic status of the screened population, which largely influences the chance of finding TB and DM. In future, it would be important to take socioeconomic factors into consideration when selecting populations to implement screening.

Further, DM may have been over-diagnosed in studies that tested for glucose prior to the initiation of TB treatment, as TB disease can induce an infection-related hyperglycaemia that might be misclassified as DM. Higher DM prevalence estimates were found in studies that had either screened prior to TB treatment or did not specify when screening had occurred, suggesting that glucose screening for DM diagnosis may be more appropriate after TB treatment has taken effect.

Finally, the methods of screening for TB and diabetes varied, making it challenging to compare the TB or DM prevalence across the studies. Some studies used non-specific methods (i.e. chest radiographs) to diagnose TB, which may have lead to over-diagnosis, contributing to the wider range of TB prevalence estimates (3.6–36%) than was found by more specific methods, such as culture or smear microscopy (2–6%). In those studies that reported results from both X-ray and microbiological assessment, prevalence as assessed by radiology was consistently higher than by culture (Marton *et al.* 1963; Ezung *et al.* 2002). Future TB screening studies in people with DM should focus on bacteriologically proven TB cases.

TB preventive therapy reduced the incidence of TB in two observational studies. However, the lack of details of intervention method provides little evidence for recommending TB preventive therapy in people with DM.

This systematic review supports a previous assertion that research into screening should be a high priority on the research agenda for both DM and TB (Harries *et al.* 2010). In addition, prospective observational cohort studies need to be conducted in diabetes clinics with a focus on adults,

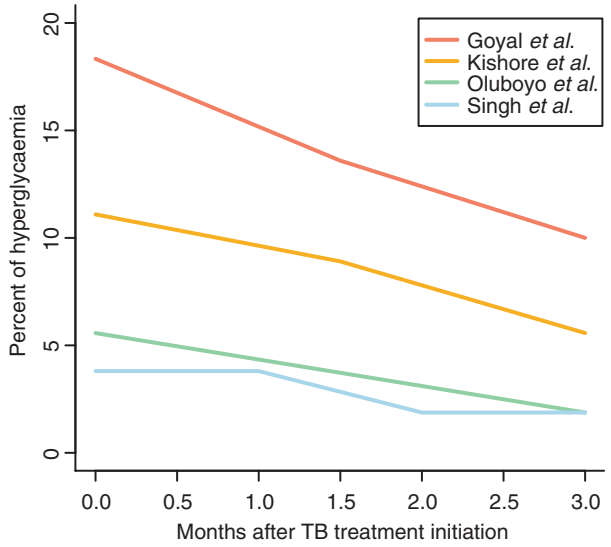

Figure 3 Decreasing trend in hyperglycaemia in patients with tuberculosis undergoing tuberculosis treatment.

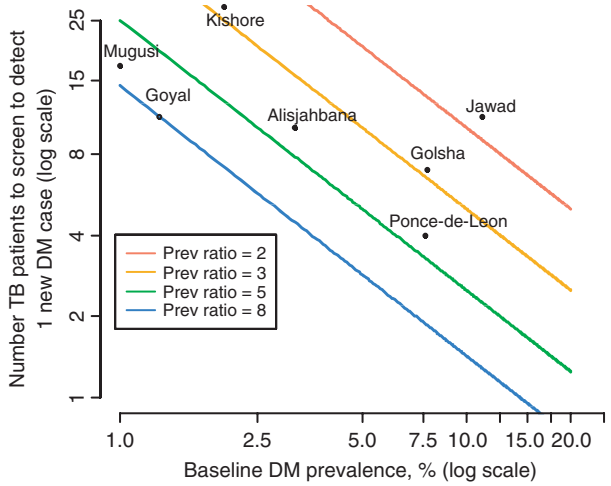

Figure 4 Number of patients with tuberculosis to screen to detect one additional case of diabetes by varying baseline diabetes prevalence, given prevalence ratios found in screening studies.

stratifying by quality of glucose control. In patients with TB, research is needed to determine the optimal time and best methods for diagnosing DM, focusing on adults and stratifying by type of TB disease. The question of TB preventive therapy may only be answered through a randomized controlled trial, which may be expensive and difficult to conduct. Screening and attention to better DM control might be a more cost-effective way of preventing TB and reducing other DM complications.

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