Screening of Tuberculosis patients for possible diabetes mellitus in India: a systematic review

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Background Tuberculosis (TB) and diabetes mellitus (DM) are both the greatest public health problems in the world. Although India ranks fourth in TB burden, the incidence of diabetes in the country is also rising. The bidirectional association between TB and DM is established by many epidemiological studies elsewhere in the world.

Objective The aim of this study was to understand the utility and importance of screening patients with TB for possible DM in Indian settings through systematic literature review.

Methodology For the search of articles, PubMed and Google Scholar search engines were primarily used. Few articles were also obtained from the cross-references of the selected articles. Of 108 articles obtained by the end of this search process, eight full-texts articles were finally selected for the purpose of this review.

Results Of the eight titles, six articles focused on screening of patients with TB for DM (unidirectional screening), whereas two articles focused on bidirectional screening, that is, screening of patients with TB for DM and vice versa. Of the eight studies obtained, six studies are from South Indian states (Andhra Pradesh, Tamil Nadu, and Karnataka), one from West Indian state (Gujarat), and one covers pan-India sample. The prevalence of DM among patients with TB ranged from 2.9% (lowest) to 21.2% (highest). Similarly, the number needed to screen ranged from 16 (lowest) to 40 (highest) as reported by various studies conducted in India.

Conclusion Screening of patients with TB for DM is feasible at the level of existing health system without any additional resources as demonstrated by the studies conducted in different parts of India.

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Introduction

The association between tuberculosis (TB) and diabetes mellitus (DM) is a known fact since thousand years. The association between these two clinical entities was first reported by Avicenna in 980–1027 AD. Many of the epidemiological studies during these days have established their association. Moreover, their association in many different perspectives has been studied extensively. During the earlier part of 20th century, the significance of their association was a matter of great concern; however, with the emergence of drugs for the treatment of these two clinical entities, the concern took a back seat [1,2]. During the recent decade with the increasing incidence of TB, especially the multidrug-resistant TB and the simultaneous prevalence of DM, the interaction is emerging as a global public health challenge. The situation is worse in developing world where TB is an endemic disease and the prevalence of DM is rising [3]. It is estimated that 70% of the diabetics live in the TB endemic countries in the world. The prevalence of DM in general population ranges from 2 to 9% in 22 countries with highest burden of TB. Furthermore, eight of the 10 countries with highest incidence of DM have also been classified as high TB burden countries by the WHO [2]. Several of the countries need special focus, which include China, India, Peru, and Russia, owing to high burden of such diseases [4]. DM becomes a pivotal risk factor among population with higher incidence of TB [5]. DM accounts for a small proportion of TB cases in settings such as Australia with a low incidence of TB [6]. This number is 14.8% in India and 25% in the Mexican setting [7]. Therefore, it becomes an established fact that the population attributed to risk for TB from DM is dependent on the prevalence of DM [3]. The range of prevalence of DM among patients with TB is wide and is reported from 1.9 to 35% in different study settings. The regions with high prevalence of DM report highest number of TB cases. Many of these patients were newly diagnosed owing to expanded medical attention related to TB treatment [8–12]. In this paper, the public health importance and the utility of screening patients with TB for DM have been reviewed with a special focus on India-centric policy implications.

Objective

The aim of this study was to understand the public health importance and the utility of screening patients with TB for possible DM in Indian settings through systematic literature review.

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Methodology

Search strategy

For the search of articles, PubMed and Google Scholar search engines were primarily used. Few articles were also obtained from the cross-references of the selected articles. The key words used for the purpose of search included 'Screening; Tuberculosis; Diabetes; and India'. Of 108 articles obtained by the end of this search process; eight full-texts articles were finally selected for the purpose of this review. Figure 1 shows the flowchart of selection of articles for this review.

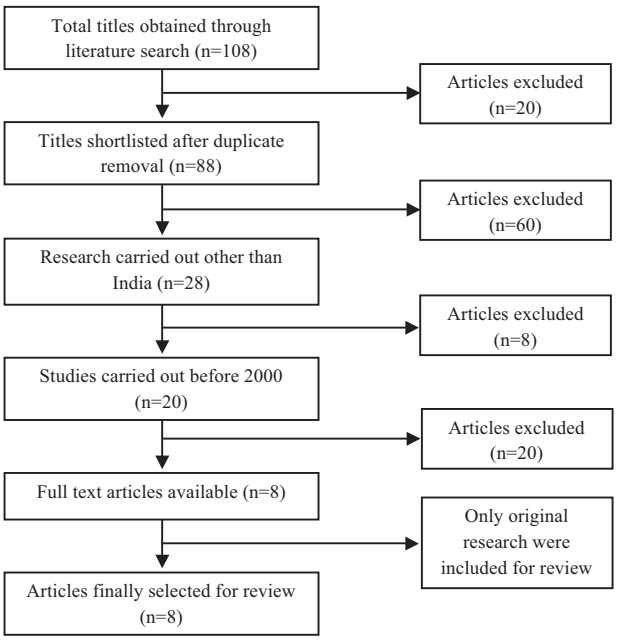
Inclusion and exclusion criteria

The studies that fall under the category of inclusion criteria include those researches that have been carried out in India only. Articles published in English language only were included in the review. Furthermore, articles published after the year 2000 till 2015 were included in this review. The studies that did not fall under these categories were excluded from review. In addition, this review categorically included original research carried out at health facilities and/or communities in various Indian states and precluded the review articles, commentaries, and editorials in the said subject.

Data extraction and analysis

In the first phase, the articles were identified based on the objectives of the study. In the second phase, the articles identified based on study objectives were pooled together for the purpose of screening by reading the titles and thereafter the abstracts. Articles were excluded at this stage if they did not satisfy the inclusion criteria. After this, the eligible articles were further screened by reading the full texts, and those not meeting the inclusion criteria were excluded. By the end of this process, the eligible full-text articles meeting the inclusion criteria were included in the study. Figure 1 gives an idea about the flow of information through different phases of this systematic review as per PRISMA (Preferred Reporting Items for Systematic review and Mata Analysis) guidelines (http://www.prisma-statement.org/).

Figure 1



Flowchart showing the selection of articles for review.

Methodological quality of reviewed articles

In total, four important indicators were used to assess the methodological quality of the published articles reviewed in this study. These four important indicators are as follows: was the study original? Who were the study participants? Was the bias in the study design avoided? Was the sample and duration of study credible enough? [13] The first study was an original study conducted among a sample of 650 presumed patients with TB over a period of 1 year. The second, third, fourth, and eighth studies were original studies conducted among 374, 362, 556, and 8109 patients with TB, respectively, over a period of 9 months. Similarly, the fifth and sixth studies were also the original studies conducted among 510 and 983 patients with TB, respectively, over a period of 7 months. The seventh study was an original study which was carried out among 307 patients with TB over a period of 8 months. All the studies delineated that potential bias was avoided while conducting these studies [14–21].

Results

Of the 108 titles obtained during the search process, eight articles were finally selected for this review. Of the eight titles, six articles focused on screening of patients with TB for DM (unidirectional screening), whereas two articles focused on bidirectional screening, that is, screening of patients with TB for DM and vice versa. Of the eight studies obtained, six studies are from South Indian states (Andhra Pradesh, Tamil Nadu, Karnataka), one from West Indian state (Gujarat), and one covers pan-India sample. Most of the studies adopted descriptive cross-sectional study design. Moreover, one study focused on the screening of patients with TB for DM among the tribal population in South India, which the authors believe as the first study in India on tribal population. Table 1 delineates about the studies conducted in different Indian states on screening patients with TB for possible DM.

Table 1 Studies conducted in different Indian states on screening patients with tuberculosis for possible diabetes mellitus (*n*=8)

References	Methodology/type of study Study tool/sample size	Time frame and place of study	Important findings
Shidam *et al.* [14]	Cross-sectional study. The study was carried out among 650 presumed patients with TB attending the DMC. Capillary blood glucose was measured using fasting blood sugar and/or oral glucose tolerance test and evaluated according to the WHO criteria	DMC attached to a tertiary care center in Pondicherry, India	Of 570 presumed patients with TB evaluated for DM, 121 (21.2%) were found to be diabetic. Of these, 69 were previously known diabetics, whereas 52 were newly diagnosed. The NNS to detect a new case of DM was 11; among those aged >40 years, the NNS was 9.3, and among patients with smear-positive TB, it was 4.6
Achanta *et al.* [15]	Cross-sectional study. In total, 374 patients with TB were screened for DM using a screening questionnaire and RBS, followed by FBG measurements using a glucometer. DM was diagnosed if FBG was ≥126 mg/dl	From January to September 2012. A total of 10 PHIs of a tribal TU, Saluru, Vizianagaram District, South India	In total, 374 patients with TB were assessed for DM and 19 (5%) were found to have DM (12 were newly diagnosed and 7 had a previous diagnosis of DM). The only characteristic associated with DM was age ≥40 years. The NNS to detect a new case of DM among all patients with TB was 31; among those aged ≥40 years, the NNS was 20, and among current smokers, it was 21
Naik *et al.* [16]	Overall, 362 patients with TB were assessed for DM using a glucometer supplied by the national program on a capillary blood sample. Those with fasting blood glucose (FBG) level ≥126 mg/dl (≥7 mmol/l) were diagnosed as DM positive	From January to September 2012. 17 PHIs in Kolar district (population: 0.5 million), South India	Overall, 358 were assessed for DM and 62 (17.1%) had the diseases – 53 (14.6%) had a previous history of DM and 9 (2.9%) were newly diagnosed. Higher DM prevalence was found among patients with TB aged ≥40 years, smokers and those with smear-positive pulmonary TB. To detect a new case of DM, the NNS among patients with TB was 40
Dave *et al.* [17]	Descriptive study. Overall, 556 patients with TB were asked whether they had a history of DM. Those with unknown DM were tested for RBS and FBG. FBG levels of ≥126 and 110–125 mg/dl were considered indicative of DM and IFG, respectively	January and September 2012. Anklav Tuberculosis Unit, Anand, Gujarat, India	Of 553 patients with TB assessed, 36 (6.5%) had diabetes (14 had been previously diagnosed DM and 22 were newly diagnosed) and 39 (7%) had IFG. The median (interquartile range) time to DM diagnosis was 5 (1–17) days. Age ≥35 years was associated with DM. The NNS was 25 and 14 for one new case of DM and IFG, respectively, with a lower NNS in males, those aged ≥35 years, those with smear-positive pulmonary TB, retreatment patients, and smokers
Prakash *et al.* [18]	A descriptive study in which 510 patients with TB were assessed for DM and vice versa. Fasting blood glucose values of ≥126 mg/dl and 110–125 mg/dl were considered as DM and prediabetes, respectively	From 1 March to 30 September 2012. TB and DM clinics at Bowring and Lady Curzon Hospital, a tertiary care center in Bangalore, India	Of 510 patients with TB, 32 (6.3%) had been previously known DM. Screening among 478 patients yielded 15 (2.9%) with prediabetes and 15 (2.9%) newly diagnosed cases of DM. A higher prevalence of DM was found among patients aged ≥40 years, patients with PTB, and smokers
Kumpatla *et al.* [19]	A total of 983 patients. Screening for DM was carried out by 2-h 75 g OGTT. HbA1c ≥47.5 mmol/l was used for diagnosis of diabetes. The performance of A1c and FPG tests was evaluated against the results of OGTT using receiver operating characteristic curve analysis	In total, 7 TB units – 4 urban, 2 rural, and 1 semiurban areas of Tamil Nadu, India, during August 2010–March 2011	Prevalence of NDD was 10.8%. The areas under the curve were 0.754 [95% confidence interval (CI) 0.68–0.83] (P<0.001) for A1c and 0.662 (95% CI 0.58–0.74) for FPG (*P*<0.001) in NDD patients. The HbA1c cutoff point of ≥47.5 mmol/l gave a sensitivity of 59.1% and specificity of 91.7%, and the respective values were 34.8% and 97.5% for FPG in patients with NDD
Jali *et al*. [20]	Prospective observational study. 307 TB patients were screened. The screening for active TB in DM is	The study was carried out within the Diabetes Centre and Pulmonary Medicine Department from February 2012 to September 2012	Among the patients with TB, 9.77% were smokers, 19.54% were known cases of diabetes, and 15.96% were NDDs. A total of 4118 patients with

(*Continued*)

Table 1 (***Continued***)

References	Methodology/type of study Study tool/sample size	Time frame and place of study	Important findings
	followed as per the guidelines of the RNTCP in India		diabetes were screened for TB; in which, 111 patients were found to have TB
India Tuberculosis-Diabetes Study Group [21]	In total, 8109 patients with TB were screened for DM. Agreement on how to screen, monitor, and record was reached in October 2011 at a stakeholders' meeting, and training was carried out for staff in the facilities in December 2011 and January 2012	Implementation started from January 2012, and we report on activities up to 30 September 2012	A total of 8109 individuals were assessed for DM and 1084 (13%) were found to have DM; of these, 682 (8%) had a previously known diagnosis of DM and 402 (5%) were newly diagnosed. There was a higher prevalence of DM in patients with TB diagnosed in tertiary care hospitals (16%) than in those diagnosed in TUs (9%) ($P<0.001$) and among those from South India (20%) than from North India (10%) ($P<0.001$)

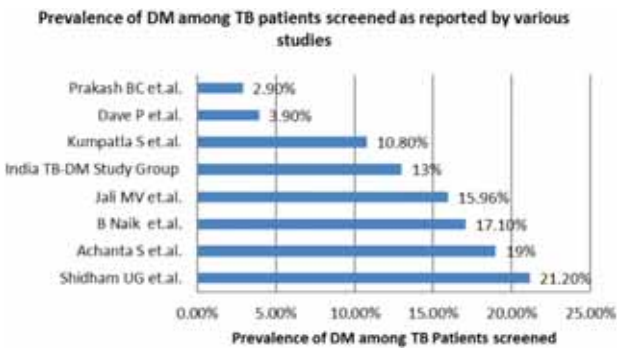
DM, diabetes mellitus; DMC, designated microscopy center; FBG, fasting blood sugar; IFG, impaired fasting glucose; NDD, newly diagnosed diabetes; NNS, number needed to screen; OGTT, oral glucose tolerance test; PHI, peripheral health institutions; PTB, pulmonary tuberculosis; RBS, random blood sugar; TB, tuberculosis; TU, tuberculosis unit; RNTCP, Revised National Tuberculosis Control Programme.

Discussion

All the studies revealed that screening of patients with TB for DM is feasible with the existing resources at the disposal of peripheral health institutions; however, for the treatment of these diagnosed patients, referral to higher center is required [14–21]. Figure 2 shows the prevalence of DM among patients with TB per different studies conducted in different parts of India [14–21]. In a similar manner, Fig. 3 delineates the number needed to screen as reported by different studies conducted in different parts of India [15–18]. In all the studies reviewed, it was observed that all the patients with TB screened for DM were ready for the testing with no resistance at all [14–21]. Furthermore, the implementation of National Programme for Prevention and Control of Cancer, Diabetes and Stroke (NPCDCS) has eased this process by making available all the resources required for this purpose; however, the same is a pilot project and has been implemented only in 100 selected districts of India [22].

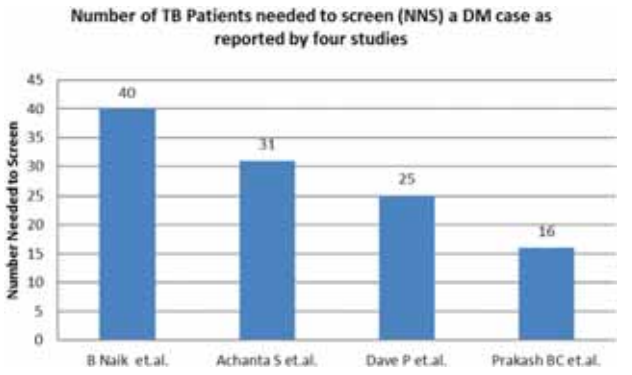
Another important advantage of screening patients with TB for DM is that it can identify the prediabetics (impaired fasting glucose=110–125) who are potential diabetics, who can develop DM at the later part of their life, hence these cohort could be trapped properly and should be kept on close monitoring. These patients can be targeted for counseling and preventive services. In a similar manner, the integration of DM and TB management services must be considered as scale-up takes place, and this could mark the beginning of a strong cooperation and collaboration between communicable and noncommunicable disease control programs [15]. Studies also suggest that patients with TB may have an elevated fasting blood glucose owing to infection-induced hyperglycemia, hence periodic blood glucose monitoring is necessary among patients with TB to establish this fact. Few of the studies also recommended the use of glycosylated hemoglobin as a confirmatory test of DM; however, the use of this test at program level is difficult as the test is very expensive [23–25].

Figure 2



Prevalence of diabetes mellitus (DM) among patients with tuberculosis (TB) per different studies conducted in different parts of India.

Figure 3



Number needed to screen (NNS) as reported by different studies conducted in different parts of India.

Of the eight articles reviewed, two focused on bidirectional screening and revealed that screening of TB for DM is cost-effective and relatively easy compared with the reverse screening [18,20]. Furthermore, screening of patients with TB for DM yielded more positive results compared with the screening of patients with DM for TB. The number needed to screen in case of patients with TB for DM is less compared with patients with DM for TB [18,20].

The study conducted by the India Tuberculosis-Diabetes Study Group reported 13% prevalence of DM among patients with TB screened for DM [21]. In addition, the prevalence of DM among screened patients with TB as reported by various studies is shown in Fig. 2. The prevalence was seen more among the South Indian states compared with North Indian states and more in tertiary care institutions than in peripheral health institutions/ tuberculosis units. The reason for higher prevalence of DM in both these cases is because of known DM cases among these two groups [21]. Furthermore, patients visiting tertiary care institutions undergo various investigations from time to time including DM [21]. The study revealed that the screening process used in India, if scaled up, could potentially identify 13% of 2.2 million patients with TB per annum with DM translating into a total of 286 000 cases of DM, if similar prevalence rates as obtained in this study were seen. The screening of those with no known diagnosis of DM could result in a yield of 5%, translating to 110 000 newly diagnosed patients with DM per year [21]. Per the International Diabetic Federation report of 2011, half of all the patients with DM are undiagnosed throughout the globe, and such screening activities among the patients with TB would increase the probability of detection of noncommunicable diseases including DM [26].

The most important concern with such screening activities is the fact that blood glucose measurement is taken on a capillary blood sample instead of a venous blood sample in the peripheral health institutions (PHI). Albeit the WHO states that venous and capillary blood thresholds for diagnosing DM are identical [27], there are issues with quality control of the glucometers and difficulty in maintaining supply chain of test strips. These problems need to be resolved if consistent and reliable testing is to be carried out at program implementation level.

Financial constraints may be a hindrance in implementing mass screening of TB cases for DM as the same requires blood glucose testing kit – glucometer and the testing strips – albeit it does not require other resources such as human resources or the infrastructure. In this context, screening should preferably be directed among patients who are 35 years of age or older and preferably 40 years old, patients with smear-positive TB, and smokers [15].

Conclusion

Screening of patients with TB for DM is feasible at the level of existing health system without any additional resources as demonstrated by the studies conducted in different parts of India. India being the fourth largest country contributing 25% of the global TB burden with the rising incidence of DM, the screening of patients with TB for DM appears rational. Specific considerations can be made in case of financial constraints, and selective screening can be carried out to detect DM among TB cases. Furthermore, as per the International Diabetic Federation report, as half of the DM cases go undiagnosed, such screening activities could be of great help in controlling the noncommunicable diseases including DM.

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J.S. conceptualized and designed the research; defined intellectual content and literature search; prepared, edited, and reviewed the manuscript; and approved the final version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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