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Global prevalence of diabetes mellitus in patients with tuberculosis: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Diabetes mellitus (DM) is an important risk factor for active tuberculosis (TB), which also adversely affect TB treatment outcomes. The escalating global DM epidemic is fuelling the burden of TB and should therefore be a major target in the strategy for ending TB. This review aims to estimate the global prevalence of DM in patients with TB.

Methods and analysis This systematic review will include cross-sectional, case–control or cohort studies of populations including patients diagnosed with TB that have reported the prevalence of DM using one of the fourth standard recommendations for screening and diagnosis. This protocol is written in accordance with recommendations from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement. Relevant abstracts published in English/French from inception to 31 December 2016 will be searched in PubMed, Excerpta Medica Database and online journals. Two investigators will independently screen, select studies, extract data and assess the risk of bias in each study. The study-specific estimates will be pooled through a random-effects meta-analysis model to obtain an overall summary estimate of the prevalence of diabetes across the studies. Heterogeneity will be assessed, and we will pool studies judged to be clinically homogenous. On the other hand, statistical heterogeneity will be evaluated by the χ^2 test on Cochrane's Q statistic. Funnel-plots analysis and Egger's test will be used to investigate publication bias. Results will be presented by continent or geographic regions.

Ethics and dissemination This study is based on published data. An ethical approval is therefore not required. This systematic review and meta-analysis is expected to inform healthcare providers as well as general population on the co-occurrence of DM and TB. The final report will be published as an original article in a peer-reviewed journal, and will also be presented at conferences and submitted to relevant health authorities. We also plan to update the review every 5 years.

Protocolregistration number PROSPERO International Prospective Register of Systematic Reviews (CRD42016049901).

Strengths and limitations of this study

- This will be the first systematic review and meta-analysis aiming to estimate the global prevalence of diabetes mellitus in patients suffering from tuberculosis.
- Methodological and statistical procedures that will be used to derive accurate estimates are powerful and reliable.
- This review would be limited by difficulties related to the accurate diagnosis of tuberculosis infection in some regions.
- Some studies could also be missed due to language restriction.
- Another possible limitation could be the heterogeneity.

INTRODUCTION

Rationale

Despite the laudable progress registered in the control of tuberculosis (TB), it remains a huge global health threat.[1] In 2014, an estimated 9.6 million people developed new active TB and 1.5 million people died from the disease.[2] Although HIV is still the greatest risk factor for TB, there are several other important determinants of the TB epidemic, among which diabetes mellitus (DM) is of growing interest.[3] Indeed, there is overwhelming evidence that DM represents a major impediment in bending the TB epidemic. DM and poor glycaemic control triple the risk of TB and adversely affect TB treatment outcomes such as prolongation of culture conversion, treatment failure, relapse and death. Much more, the world is currently facing a surge in DM prevalence with 1 adult on 11 who has DM, and this will increase to 1/10 adults by 2040. The DM epidemic is therefore fuelling the TB epidemic.[4–6] The vital need to address the escalating global DM

epidemic as part of the strategy for ending TB has led to the creation of Collaborative Framework for Care and Control of Tuberculosis and Diabetes which provides guidance on bidirectional screening and treatment of the two diseases.[7–9] The framework recommends as one major key points the screening and management of DM in patients with TB.[3 10] Systematic screening has shown prevalence rates of DM in patients with TB up to 15%, especially in countries with high prevalence of DM at the population level.[7–11] However, to the best of our knowledge there is no previous review which evaluated the burden of DM in patients with TB at the global level. We present here a protocol for a systematic review and meta-analysis to summarise the existing data on the prevalence of DM in patients with TB, with the aim of providing accurate data for monitoring of future trends.

OBJECTIVES

This systematic review aims to determine the global prevalence of DM among patients with TB.

Review question

This review of studies published in the past 30 years, from 1 January 1986 to 31 August 2016, should answer the following question:

What is the global prevalence of DM among patients with TB?

CRITERIA FOR CONSIDERING STUDIES FOR THE REVIEW

Inclusion criteria

We will include cross-sectional, case–control or cohort studies conducted in patients suffering from pulmonary drug-sensitive or resistant TB and reporting on the prevalence of DM or providing enough data to compute this estimate. We will consider extrapulmonary TB diagnosed by culture of *Mycobacterium tuberculosis* and also those which will have been treated as such despite the absence of culture of *M. tuberculosis*. However, this second group will not be considered for the meta-analysis but will be used for the narrative part review. The diagnosis of diabetes will have to have been made by a physician or defined based on measured fasting plasma glucose, oral glucose tolerance test or self-report, according to WHO criteria.[12] TB cases must have been diagnosed based on WHO criteria.[13]

Exclusion criteria

We will exclude:

1. Commentaries, editorials and cases series with less than 50 patients.
2. Duplicates: for studies published in more than one paper, the most comprehensive one reporting the largest sample size will be considered.
3. Studies whose key data will not be accessible even after request from the authors.

Table 1 Search strategy for PubMed

Search	Search terms
1	'Tuberculosis' OR 'TB' OR 'Mycobacterium' OR 'Pleuresy'
2	'Diabetes' OR 'diabetes mellitus' OR 'hyperglycemia' OR 'diabetic patients' OR 'diabetic' OR dysglycemia OR glucose abnormalities OR glucose intolerance
3	# 1 AND # 2
4	Studies published in English/French

SEARCH STRATEGY FOR IDENTIFYING RELEVANT STUDIES

The search strategy will be implemented in two stages:

Bibliographic database searches

A. We will search PubMed, Excerpta Medica Database (Embase), Index Medicus and African online journals to identify relevant abstracts on the prevalence of DM among patients with TB published from inception to 31 December 2016. Key search terms will include: 'tuberculosis', 'TB', 'mycobacterium', 'diabetes', 'diabetic patients' and 'hyperglycemia'. The PubMed search strategy is shown in table 1, and will be adapted for other databases.

B. Abstracts of all eligible papers will be reviewed and their full articles in the second time. To supplement the bibliographic database searches and identify potential additional data sources. Where relevant data will not be available, we will directly contact the authors to request supplementary information or the full texts of their articles.

Selection of studies deemed relevant for inclusion in the review

Assessment of eligible papers will be independently run by two authors using an assessment guide to ensure that the selection criteria are reliably applied by them all (ATT and JJB). Two investigators (ATT and JJB) will independently screen titles and abstracts obtained from the searches and retrieve all full texts of potentially eligible papers. These full texts will be screened using a standardised form for final inclusion in the review. Disagreements between assessors will be resolved by consensus, with consultation of a third investigator (JJN) for arbitration if needed. Level of agreement between review authors will be measured using the Cohen's Kappa statistic.[14]

Assessment of methodological quality and reporting of data

The methodological quality of included studies will be assessed using the Newcastle-Ottawa Scale.[15]

Data extraction and management

A data extraction sheet will be used to collect information relating to the country, the region, year of publication, type of study, period of the study, study design, study setting, number of participants, mean/median age or

age range of the population, diagnostic criteria for each condition, the presence of another important comorbidity like HIV and the prevalence of DM. Authors will be contacted to request lacking or additional data. We will conduct a subgroup analysis using comorbidities, different diagnosis criteria and period of the study. In case of multinational studies, we will disaggregate the results to present the prevalence of DM among patients with TB in each country. If it is not possible to separate the data by country, the study will be presented as one and the countries in which the studies was conducted will be shown.

Statistical analysis

A meta-analysis will be conducted for data from studies in which DM will have been diagnosed using the same diagnosis criteria. We will first determine SEs for the study-specific estimates from the point estimate and the appropriate denominators, assuming a binominal distribution. After stabilising the variance of individual studies with the Freeman-Tukey double arc-sine transformation,[16] we will then pool the study-specific estimates through a random-effects meta-analysis model to obtain an overall summary estimate of the prevalence across studies. Assessment of publication bias will be performed by using funnel plots and the Egger's test. Heterogeneity will be evaluated by the χ^2 test on Cochrane's Q statistic and quantified by the I^2. I^2 values of 25%, 50% and 75% will be considered as representing low, medium and high heterogeneity, respectively.[17] In the case of substantial heterogeneity, we will perform a subgroup analysis to detect possible sources of heterogeneity using the following grouping variables: age group, the period of diagnosis (beginning or ending of treatment), positivity of sputum culture at microscopy, relapse or recurrence, association to others comorbid conditions such as HIV, continent or geographical area and study quality. Statistical analyses will be performed using Stata V.14 software.

Results reporting and presentation

The proposed systematic review will be reported following the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies.[17] The study selection process will be summarised using a Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols flow diagram including reasons for studies' exclusion. Tables and forest plots will serve to summarise quantitative data where appropriate. Prevalence data will be presented by continent, time period of diagnosis, presence of others comorbid conditions and classification of TB infection depending on available data. The methodological quality of included studies will be presented in a table and narratively summarised.

CONCLUSION

TB remains a major global health problem. The prevalence of DM which is known as an important risk factor for patients with TB is escalating worldwide and is thought to contribute significantly in the burden of TB. According to the rising figures of DM worldwide, we hypothesised that the global prevalence of DM among patients with TB is elevated and we are conducting this review to estimate its magnitude. We expect to provide accurate data for effective policies making and for monitoring of future trends. Much more, this review may identify the research gaps and remaining challenges that may form the basis of future studies to improve our understanding of the prevalence and impact of DM in patients with TB.

The major limitation of this study could be the heterogeneity generated by the variability in DM diagnostic criteria for, especially as the definition of DM has changed over time. In addition, since we will only include studies that full text or abstracts are published in French/English, we could missed some studies published in another language. However, most of papers are now published in English even from researchers in countries where English is not the official language. Therefore, most of the studies on the topic are expected to be in English. Despite these potential limitations, this review will be, to the best of our knowledge, the first study aiming to estimate the global prevalence of DM among patients with TB.

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Contributors JJN, ATT, FTAE and GW conceived and designed the protocol. ATT drafted the manuscript. ATT, JJB, JRN, FTAE, GSW, ADK and JJN critically revised the manuscript for methodological and intellectual content. JJN is the guarantor of the review. All authors approved the final version of this manuscript.

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