

THE EFFECT OF TYPE II DIABETES MELLITUS TO TUBERCULOSIS TREATMENT OUTCOME : A SYSTEMATIC REVIEW

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ABSTRACT

Background: The converging epidemics of non-communicable disease like DM (DM) and an infectious disease like tuberculosis (TB) is a double burden. DM is increasing in the same population that is at high risk for developing TB.

Methods: By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

Result: In the PubMed database, the results of our search brought up 1199 articles, whereas the results of our search on SagePub brought up 892 articles. The results of the search conducted for the last year of 2013 yielded a total 30 articles for PubMed and 13 articles for SagePub. In the end, we compiled a total of 5 papers, 2 of which came from PubMed and 2 of which came from SagePub. We included five research that met the criteria.

Conclusion: In summary, DM plays a salient role among TBDM patients. Our results showed that even a doubling risk for poor treatment outcome would have substantial population impact—up to 25% of deaths in TB patients could be attributable to DM. These findings are not only important for lowmiddle income countries that have high TB incidence and high DM prevalence, but also important for high income countries with sub-populations that have higher risks of both conditions. Screening programmes for DM among TB patients should be implemented in primary care especially in regions that have high-incidence of TB. Further studies are needed to explore the optimal treatment plan and glycaemic control among TB-DM.

Keyword: Type II Diabetes Mellitus, Tuberculosis, Treatment, Efficacy

INTRODUCTION

Tuberculosis (TB) and diabetes mellitus (DM) are two diverse conditions of immense public health importance existing for centuries. TB was traditionally identified with poverty while DM was considered as an entity associated with prosperity. TB is today one of the commonest and widespread communicable infectious diseases largely but not necessarily confined to low-economic groups. DM on the other hand spearheads the group of chronic non-communicable diseases affecting people across all socio-economic strata. Contrary to previous beliefs, a larger number of people with DM are living in middle- and low-income countries. Unfortunately, these are the countries where DM is expected to increase in the near future. Both DM and TB have been associated with significant morbidity and mortality from time immemorial. Advancements in modern medical science over the years has definitely improved the outcome in both these conditions. But the magnitude of these two diseases has not waned and both are collaborative in worsening each other. In fact, the increase in the population affected with DM is sustaining the TB epidemic.¹

There is a two-to-four-fold higher risk of active TB in individuals with DM and up to 30% of individuals with TB are likely to have DM. Immune deficiency either in absolute or relative quantities are sufficient for re-activation of latent TB. From a 10% risk of reactivation over the whole lifetime of an immunocompetent individual, the risk of reactivation increases to 10% every year in immune-deficient individuals. DM impairs cell mediated immunity and poor glycemic control affects cytokine response and alters the defenses in the alveolar macrophages. Fever, hemoptysis, extensive parenchymal lesions, and lung cavities are more common in those with DM particularly heavier and older males.

The global increase in type 2 diabetes mellitus (DM) is a recognized re-emerging risk and challenge to tuberculosis (TB) control. Individuals with DM have three times the risk of developing TB and there are now more individuals with TB-DM co-morbidity than TB-HIV co-infection. The association between DM and TB was first described by centuries ago by Avicenna, a persian philosopher, and the co-morbidity was a frequent topic in the medical literature from the first half of the XXth century. But this literature dwindled as the association reduced notoriety with the introduction of insulin for diabetes patients and antibiotics for TB. In the 1980s the publications on joint TB-DM began to re-emerge in parallel with the DM 'pandemic': The global prevalence of DM among adults has increased by 20% in less than 30 years, and DM is predicted to reach 642 million worldwide by 2040 with most (80%) of the patients living in low and middle-income countries where TB is also endemic. Consequently, the World Health Organization has identified DM as a neglected, important and re-emerging risk factor for TB (1). In this chapter 'DM' will refer mostly to type 2 DM since it is the most prevalent form, but type 1 DM in children has also been associated with TB. This chapter describes the epidemiology of TB-DM, the impact of DM on the clinical presentation and outcomes of TB, the underlying biology that favors the co-occurrence of both diseases, and the public health implications for TB control and DM management.²

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we review published literature of studies to identify studies that reported efficacy of tuberculosis treatment in patient with diabetes mellitus type II. This is done to provide an explanation and improve the handling of treatment at the patient. As the main purpose of this paper, to show the relevance of the difficulties that have been identified as a whole.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "type II diabetes mellitus", "tuberculosis treatment" and "efficacy" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: (*"effect"[All Fields] OR "effecting"[All Fields] OR "effective"[All Fields] OR "effectively"[All Fields] OR "effectiveness"[All Fields] OR "effectivenesses"[All Fields] OR "effectives"[All Fields] OR "effectivities"[All Fields] OR "effectivity"[All Fields] OR "effects"[All Fields]*) AND (*"diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR "diabetes"[All Fields] AND "mellitus"[All Fields]*) OR *"diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]*) AND (*"therapeutics"[MeSH*

Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]) AND ("tuberculosi"[All Fields] OR "tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields] OR "tuberculoses"[All Fields] OR "tuberculosis s"[All Fields])) AND ((clinicaltrial[Filter]) AND (2013:2023[pdat])) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

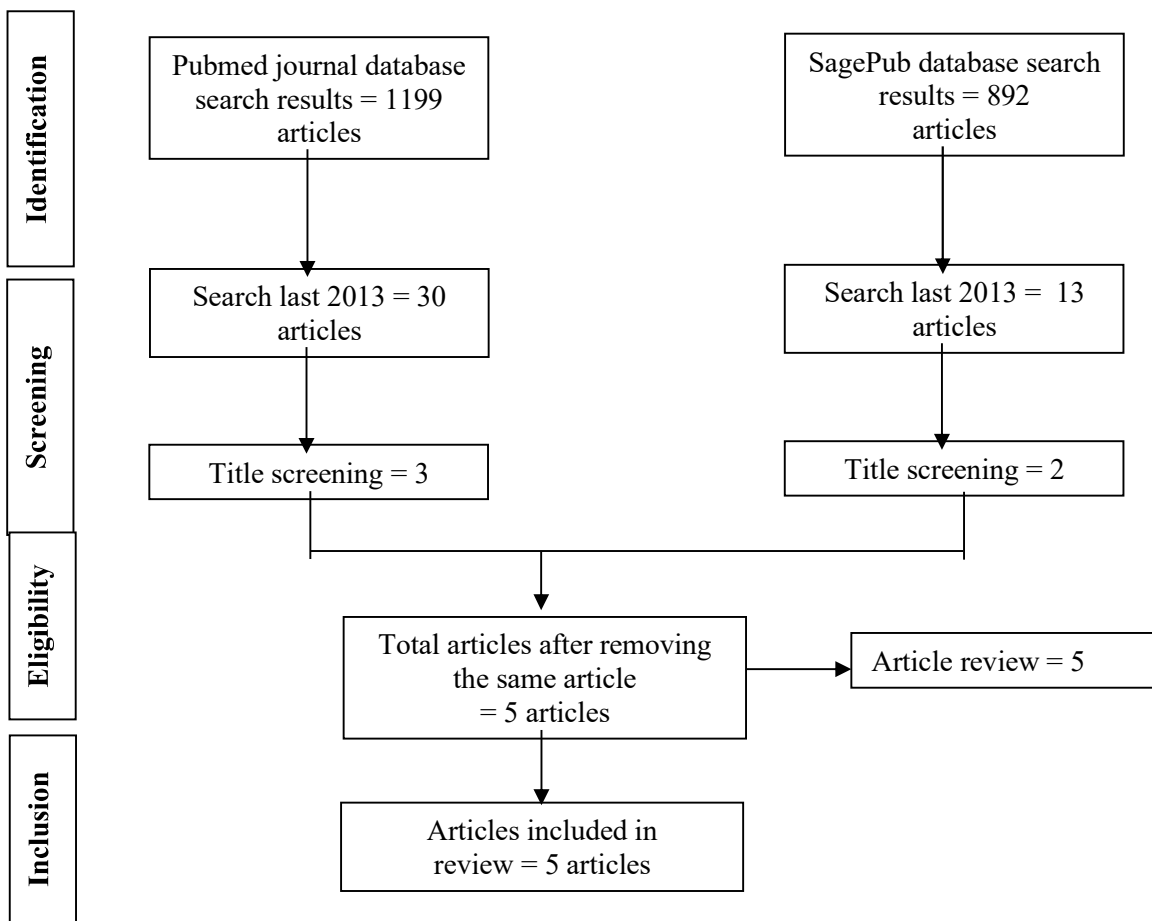


Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 1199 articles, whereas the results of our search on SagePub brought up 892 articles. The results of the search conducted for the last year of 2013 yielded a total 30 articles for PubMed and 13 articles for SagePub. In the end, we compiled a total of 5 papers, 2 of which came from PubMed and 2 of which came from SagePub. We included five research that met the criteria.

Faurholt-Jepsen, et al³ (2013) showed that diabetes considerably increases risk of early mortality during TB treatment. The effect may not be explained by increased severity of TB, but could be due to impaired TB treatment response. Research is needed to clarify the mechanism and to assess whether glycaemic control improves survival.

Lee, et al⁴ (2017) showed that the prevalence of diabetes was markedly higher in patients with PTB than in a sample of the general South Korean population. Diabetes may delay sputum conversion and adversely affect treatment outcomes; detection and management of diabetes in patients with PTB is crucial.

Koesoemadinata, et al⁵ (2023) showed that DM in TB-DM patients is characterised by poor glycaemic control, high CVD risk, and nephropathy. TB treatment provides opportunities for better DM management, but effort is needed to improve long-term care.

Table 1. The literature include in this study

Author	Origin	Method	Sample	Result
Faurholt-Jepsen et al, 2013 ³	Tanzania	Retrospective study	1250 patients	There were no differences between participants with and without diabetes regarding the proportion of positive cultures at 2 (3.8% vs. 5.8%) and 5 (1.3% vs. 0.9%) months ($P > 0.46$). However, among patients with a positive TB culture, relatively more patients with diabetes died before the 5-month follow-up. Within the initial 100 days of TB treatment, diabetes was associated with a fivefold increased risk of mortality (RR 5.09, 95% CI 2.36; 11.02, $P < 0.001$) among HIV uninfected, and a twofold increase among HIV co-infected patient (RR 2.33 95% CI 1.20; 4.53, $P = 0.012$), while diabetes was not associated with long-term mortality. Further adjustment with AGP did not change the estimates.
Lee et al, 2017 ⁴	South Korea	Retrospective study	1044 patients	Diabetes prevalence was 24.2% (252/1044) among patients with PTB and 11.6% (1700/14,655) among controls. Diabetes [odds ratios (OR) 2.56, 95% confidence interval (CI) 1.56-4.21, $P < 0.001$], male sex (OR 1.93, 95% CI 1.08-3.44, $P = 0.027$), and cavitory disease (OR 2.08, 95% CI 1.29-3.35, $P = 0.003$) were significant risk factors for 2-month culture positivity. Diabetes was the only factor associated with unsuccessful treatment outcomes (OR 1.67, 95% CI 1.03-2.70, $P = 0.039$).

<p>Koesoemadin ata et al, 2023⁵</p>	<p>United Kingdom</p>	<p>Randomized trial</p>	<p>218 patients</p>	<p>Of 218 TB-DM patients identified, 170 (78%) were followed up. Half were males, the mean age was 53 years, 26.5% were newly diagnosed DM. High glycated haemoglobin at TB diagnosis (median 11.2%) decreased during TB treatment (to 7.4% with intensified management and 8.4% with standard care), but this effect was lost 6 months later (9.3%). Hypertension and dyslipidemia contributed to a high 10-year CVD risk (32.9% at month 6 and 35.5% at month 12). Neuropathy (33.8%) and albuminuria (61.3%) were common. After TB treatment, few patients used CVD-mitigating drugs</p>
<p>Du et al, 2015⁶</p>	<p>China</p>	<p>Cohort study</p>	<p>178 patients</p>	<p>The treatment success rates of the optimized group 1 and the retreatment group 1 were 83.3%(25/30) and 60.0%(18/30), respectively, and the difference was statistically significant ($\chi^2=4.02$, $P=0.045<0.05$). The treatment failure rate of the optimized group 1 (6.7%, 2/30) and the retreatment group 1(30.0%, 9/30) was statistically different ($\chi^2=5.46$, $P=0.02<0.05$). The outcome difference between the optimized group 2 and the retreatment group 2 showed no statistical significance. Multi-factor analysis showed that treatment regimen, DM, gender and drug resistance were the significant factors related with treatment outcome. The probability of treatment success using the individualized treatment regimen was 2.7 times higher than that using the standard regimen ($P=0.025$). The risk of treatment failure of the drug resistance cases was 2.8 times higher than that of the drug sensitive cases ($P=0.038$). The probability of treatment success in DM cases was 0.4 times that in non-DM cases ($P<0.05$).</p>
<p>Chiang et al, 2015⁷</p>	<p>China</p>	<p>Randomized control study</p>	<p>1473 patients</p>	<p>Glycemic control was assessed by glycated haemoglobin A1C (HbA1C) and diabetic patients</p>

				<p>were categorized into 3 groups: HbA1C<7%, HbA1C 7-9%, HbA1C>9%. 1,473 (705 with DM and 768 without DM) patients were enrolled. The proportions of patients with any symptom, cough, hemoptysis, tiredness and weight loss were all highest in diabetic patients with HbA1C>9%. In multivariate analysis adjusted for age, sex, smoking, and drug resistance, diabetic patients with HbA1C>9% (adjOR 3.55, 95% CI 2.40-5.25) and HbA1C 7-9% (adjOR 1.62, 95% CI 1.07-2.44) were significantly more likely to be smear positive as compared with non-diabetic patients, but not those with HbA1C<7% (adjOR 1.16, 95% CI 0.70-1.92). The influence of DM on outcome of TB treatment was not proportionately related to HbA1C, but mainly mediated through diabetes-related comorbidities. Patients with diabetes-related comorbidities had an increased risk of unfavorable outcome (adjOR 3.38, 95% CI 2.19-5.22, p<0.001) and one year mortality (adjOR 2.80, 95% CI 1.89-4.16). However, diabetes was not associated with amplification of resistance to isoniazid (p = 0.363) or to rifampicin (p = 0.344).</p>
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Du, et al⁶ (2015) showed that the outcome of the optimized regimen group was better than that of the standard regimen group, and retreatment TB patients complicated with DM faced a higher risk of treatment failure, which should receive more attention.

Chiang, et al⁷ (2015) showed that poor glycemic control is associated with poor TB treatment outcome and improved glycemic control may reduce the influence of diabetes on TB.

DISCUSSION

This systematic review involved a total of 4.163 patients who received combined heart surgery and lung tumor resection in 5 observational studies. Diabetes prevalence has increased worldwide as a result of population ageing, urbanisation, changes in diet and reduced physical activity patterns resulting in increasing obesity. About 80% of the 415 million estimated DM cases globally are from low and middle income countries and the DM prevalence is projected to rise most steeply in regions with high TB incidence over the next 30 years.⁸

At the population level, the contribution of DM to TB is generally between 10-20%, but can vary substantially, even within a country. For example, in the UK the general population attributable risk is 10%, but rises to 20% in Asian males.² The profile of TB-DM patients versus TB only is strikingly different, with TB-DM patients being older, obese and more likely to be females who are not likely to present behaviors classically associated with TB such as alcohol abuse, consumption of illicit drugs, incarceration or HIV-AIDS. Thus, physicians need to be trained in contemporary times to “think TB” when examining patients with pulmonary infections and a “non-classical” socio-demographic profile for TB, in order to avoid delays in TB diagnosis. TB-DM patients (versus TB only) are also more likely to have lower education

and higher unemployment, which complicates TB and DM management given that these sociodemographic factors are associated with less access to healthcare and poorer glucose control.⁹

Most studies on TB-DM are observational with few cohorts (all retrospective based on medical records) so strict inference of directionality in the association is not possible. However, most data provides support for DM preceding TB. Many studies suggest that DM is associated with the clinical presentation of TB. Namely, TB-DM patients (versus TB-no DM) are more likely to present with pulmonary (versus extra-pulmonary), cavitary (versus non-cavitary) and sputum smear-positive TB at diagnosis. During the course of TB treatment, TB-DM patients take longer to convert from sputum smear-positive to -negative.²

There is growing evidence from observational studies that TB-DM is associated with an increase in adverse TB treatment outcomes, specifically for delays in mycobacterial clearance, treatment failures, death, relapse and re-infection.

TB-DM versus TB-no DM patients are more likely to remain sputum smear-positive after completion of the intensive phase of treatment, and this outcome is an early predictor of treatment failure (sputum smear or culture positivity at five months or later during treatment), which is also more likely in TB-DM versus TB-no DM. Death was a hallmark of the co-morbidity in the 1950s with studies reporting that patients with DM were likely to die from a diabetic comma or TB. TB-DM patients also appear to have a higher risk of relapse.¹⁰

The clinical findings and higher risk of adverse outcomes in TB-DM patients indicate the need for prospective cohort studies aimed at confirming these observations and identifying the underlying factors leading to treatment failures in DM. Two underlying factors are prime suspects. The first is poor glucose control. Chronic hyperglycemia is associated with the dysfunctional immunity to Mtb in DM patients, and hence, likely to reduce the efficiency of anti-mycobacterial treatment. Hyperglycemia may also compromise Mtb killing by affecting the microvasculature and reducing lung tissue perfusion for optimal immune surveillance. However, the need for intervention studies to assess the effect of glucose control on TB treatment outcomes is questionable, and the WHO considers that the available data is sufficient to recommend optimized glucose control as part of the management of TB-DM patients for improved TB outcomes. The second suspect is possible suboptimal plasma levels of anti-mycobacterial antibiotics in the DM versus non-DM patients.¹¹

This may not only lead to treatment failure, but can favor the development of MDR-TB as discussed above. With the available information, a joint group of expert clinicians have provided recent guidelines for treatment of drug-susceptible TB with specific recommendations for DM patients. First, depending on the resources and epidemiology of the community, screening for DM should be performed on all new TB patients with age > 45 years, body mass index > 25, first-degree relative with diabetes and race/ethnicity of African American, Asian, Hispanic, American Indian/Alaska Native or Hawaiian Native/Pacific Islander. Second, pyridoxine (vitamin B6) should be given with INH to DM patients, given their higher risk of neuropathy. Third, given that DM patients are more likely to present cavitations, smear-positivity at diagnosis and/or remain culture-positive at 2 months of treatment, a continuation phase of seven months duration is recommended, for a total of 9 months of therapy. Fourth, consideration should be given to measuring their drug concentrations in serum (therapeutic drug monitoring) to gain insights into the adequacy of drug dosing and need for tailored adjustments. If the DM patient has end stage renal disease, then therapeutic drug monitoring may be necessary to adjust drug levels in the context of dialysis, assess interactions with other medications for their co-morbid condition, and monitor toxicity.¹²

CONCLUSION

This systematic review showed that DM plays a salient role among TBDM patients. Our results showed that even a doubling risk for poor treatment outcome would have substantial population impact—up to 25% of deaths in TB patients could be attributable to DM. These findings are not only important for low/middle income countries that have high TB incidence and high DM prevalence, but also important for high income countries with sub-populations that have higher risks of both conditions. Screening programmes for DM among TB patients should be implemented in primary care especially in regions that have high-incidence of TB. Further studies are needed to explore the optimal treatment plan and glycaemic control among TB-DM.

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