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The Analysis Study of Effects of Oral Antidiabetic Drugs on Tuberculosis Risk and Treatment Outcomes : A Comprehensive Systematic Review

^{1,2} Rachmad Alsy Setiafadi, ³ Nor Anisatun Nida, ³ Muhammad Naufal
Marom

¹ General Practitioner, PKU Muhammadiyah Mayong General Hospital,
Jepara Regency, Central Java, Indonesia

² Faculty of Medicine, Muhammadiyah University of Surakarta, Surakarta
City, Central Java, Indonesia

³ Faculty of Medicine, Sultan Agung Islamic University, Semarang City,
Central Java, Indonesia

Correspondence : alsysetiafadi47@gmail.com

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ABSTRACT

Background: Diabetes mellitus triples the risk of infection, leading to poor clinical outcomes. Hyperglycemia suppresses immune responses, affecting TB and diabetes patients. Modulation of host cell responses and targeting pathogens could improve treatment outcomes and reduce drug resistance.

Methods: Following PRISMA 2020 guidelines, this systematic review focused exclusively on full-text articles published in English between 2014 and 2024.

Result: The study conducted a comprehensive review of over 600 publications sourced from reputable databases, including ScienceDirect, SagePub, and PubMed. Following an initial screening, eight publications were identified as warranting more in-depth analysis. Consequently, a thorough review of these selected studies was performed to ensure a detailed and rigorous evaluation. **Conclusion:** Metformin, an oral antidiabetic (OAD) agent, is associated with reduced incidence and mortality from active tuberculosis in patients with diabetes. In contrast, saxagliptin, another oral antidiabetic drug, is linked to an increased risk of active tuberculosis. The continuing examination of the association between metformin and tuberculosis risk highlights the need for further research to better elucidate and validate these associations.

Keyword: Diabetes mellitus, tuberculosis, metformin, OAD

INTRODUCTION

Tuberculosis (TB) is a global health threat due to its ability to evade the host's immune responses, causing persistent infections. Initially causing lung infections, it can spread throughout the body, leading to severe health consequences.¹ The World Health Organization reports that nearly 2 billion people worldwide are infected with *Mycobacterium tuberculosis*, equivalent to about a quarter of the world's population.² Risk factors such as HIV, diabetes, smoking, alcohol consumption, and malnutrition increase the likelihood of developing active infection. In 2020, an estimated 9.9 million people worldwide developed tuberculosis, with 1.3 million dying. Southeast Asia, Africa, the Western Pacific, Eastern Mediterranean, Americas, and Europe have the highest burden of incident cases.^{1,3}

Diabetes mellitus (DM) triples the risk of tuberculous infection, leading to increased disease severity and mortality. Poor clinical outcomes in patients with diabetes and tuberculosis can be attributed to hyperglycemia's suppressive effects on innate and adaptive immune

responses.^{4,5} Diabetes affects 422 million people globally, with an increasing number of overweight and obese individuals at risk. Metabolic abnormalities in type 2 diabetes, such as hyperglycemia, elevated pro-inflammatory cytokine levels, and increased oxidative stress, may adversely affect host defense responses to tuberculosis.⁶ Modulation of host cell responses and direct targeting of the pathogen could improve treatment outcomes and reduce drug resistance.⁷

TB and DM interact in a way that complicates their management due to their synergistic effects. Recent preclinical and clinical studies have suggested that certain oral antidiabetic drugs (OADs) might benefit TB management. Specifically, metformin has been highlighted for its potential to decrease the risk of latent TB infection (LTBI), active TB, adverse treatment outcomes, including mortality, and to improve health-related quality of life in TB patients with DM.^{8,9} Nevertheless, the evidence remains inconsistent. For instance, recent randomized controlled trials have not demonstrated that metformin

accelerates sputum culture conversion or provides protection against the onset of TB.^{7,10}

Determining whether OADs have definitive beneficial effects on TB is essential, as these drugs could potentially be incorporated into the therapeutic arsenal against TB, advancing global eradication efforts. Therefore, our objective was to evaluate the influence of OADs on the risk of developing tuberculosis and their impact on treatment outcomes.

METHODS

Protocol

The study was conducted with strict adherence to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines, underscoring a commitment to methodological excellence. This adherence to PRISMA 2020 principles ensures enhanced transparency, reproducibility, and rigor throughout the review process. The approach involved thorough strategies for literature search, data extraction, and synthesis, systematically applied to minimize biases and strengthen the reliability of the findings and conclusions.

Criteria for Eligibility

This study delivers a comprehensive analysis of research conducted over the past decade on the impact of oral antidiabetic drugs (OADs) in patients with tuberculosis. Through a systematic review and synthesis of data from a variety of studies, this research aims to identify patterns and refine patient care strategies for individuals with this comorbidity.

The primary goal of this thesis is to highlight significant themes from a diverse range of academic literature, thus enhancing the understanding of how OADs affect tuberculosis patients. To ensure the robustness and precision of the analysis, strict inclusion and exclusion criteria were employed. Only peer-reviewed studies published in English between 2014 and 2024 with a valid DOI were considered. Non-research materials such as reviews, editorials, and duplicate entries from the same journal were excluded to maintain the focus and integrity of the dataset. This methodical approach ensures that the data utilized in the analysis is both relevant and reliable, providing a robust foundation for drawing

meaningful conclusions and advancing clinical practice.

Search Strategy

We used "oral antidiabetic drug OR tuberculosis risk OR effects." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

Data retrieval

The authors conducted a thorough preliminary review of each article by examining its abstract and title to assess relevance before advancing to a more detailed investigation. Only studies that met the study's objectives and adhered to the predefined inclusion criteria were selected for further analysis. This method allowed for identifying consistent and clear patterns across the research.

Full-text articles were restricted to those published in English to ensure consistency in the language of the studies reviewed. A rigorous screening process was applied to select content that was directly relevant to the study's focus

and met all established inclusion criteria. Studies that did not meet these criteria were systematically excluded from further analysis and were not considered in the final evaluation.

The evaluation process covered a wide array of data, including study factors, titles, authors, publication dates, research locations, and methodologies. This comprehensive approach ensured that the content included in the analysis was of the highest relevance and quality, thereby strengthening the reliability and validity of the study's findings.

Quality Assessment and Data Synthesis

The writers did a thorough examination of the abstract and title of each publication to identify those that need further inquiry. After the initial screening, each document that was considered relevant underwent a thorough review. The evaluation results influenced the selection process for review papers, ensuring that only those with the utmost significance were chosen for in-depth analysis. The stringent standard

facilitated the selection process, enabling a comprehensive and nuanced consideration of previous research and its evaluation context.

Table 1. Search Strategy

<i>Database</i>	<i>Search Strategy</i>	<i>Hits</i>
Pubmed	<i>("oral antidiabetic drug" OR "tuberculosis risk" AND "effects")</i>	328
Science Direct	<i>("oral antidiabetic drug" OR "tuberculosis risk" AND "effects")</i>	406
Sagepub	<i>("oral antidiabetic drug" OR "tuberculosis risk" AND "effects")</i>	215

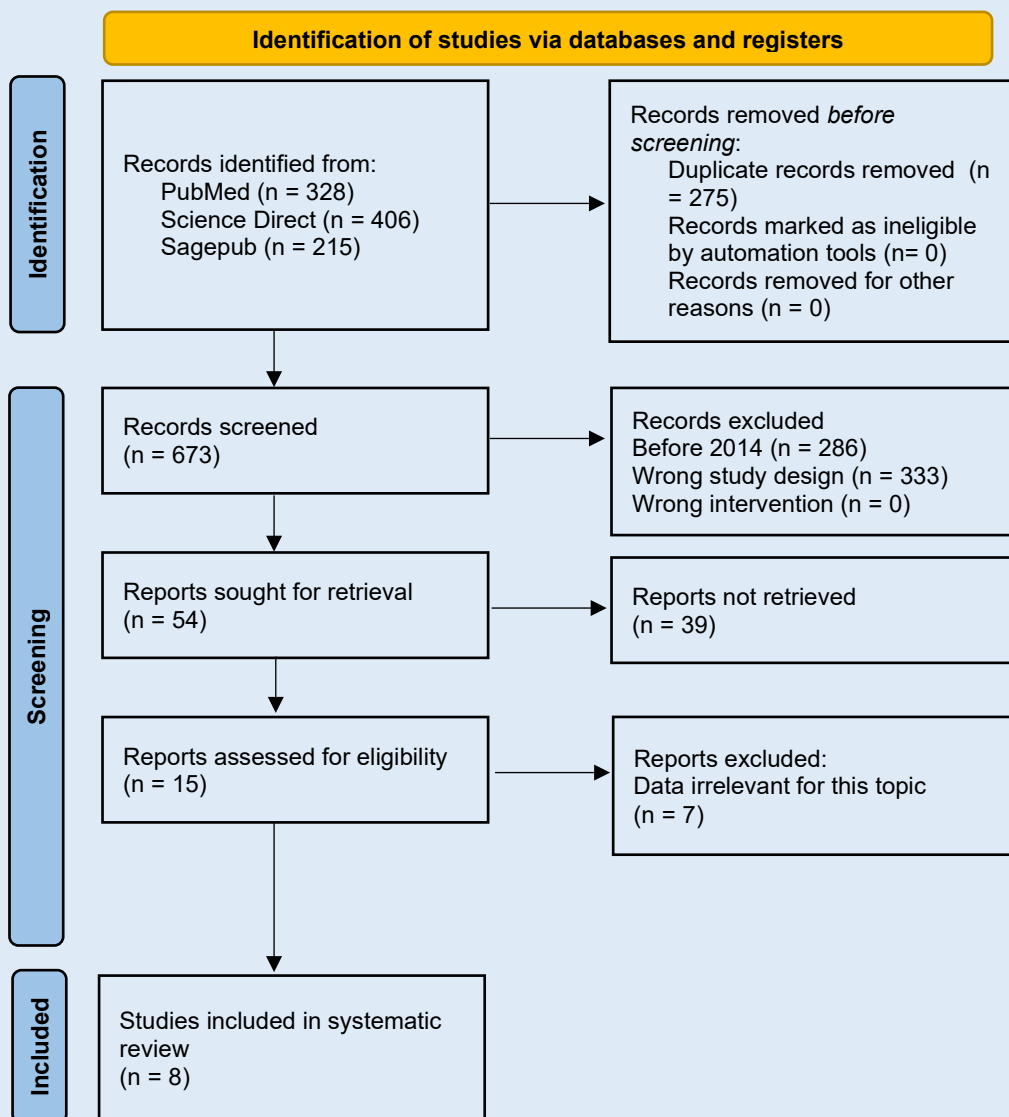


Figure 1. Article search flow chart

Table 2. Critical appraisal of Study

Parameters	(Perez - Nava rro et al., 2017)	(Wor kneh et al., 2017)	(Yu et al., 2019)	(Mere gildo-Rodri guez et al., 2022)	(Mish ra et al., 2022)	(Sutter et al., 2022)	(Vyas et al., 2022)	(Al-Bari et al., 2024)
1. Bias related to temporal precedence								
Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation								
Was there a control group?	No	No	No	No	No	No	No	No
3. Bias related to confounding factors								
Were participants included in any comparisons similar?	No	Yes	Yes	Yes	No	No	No	No
4. Bias related to administration of intervention/exposure								
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No.	Yes.	Yes.	Yes.	No.	No.	No.	No.
5. Bias related to assessment, detection, and measurement of the outcome								
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	No	Yes	Yes	Yes	Yes	No	No	No
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes	No	No	No
6. Bias related to participant retention								
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	No	No	No
7. Statistical conclusion validity								
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	No	No	No

RESULT

We began the investigation by systematically collecting a substantial array of papers from reputable sources, including ScienceDirect, PubMed, and SagePub. After a comprehensive three-stage screening process, we identified eight highly relevant studies for in-depth analysis. Each selected paper was meticulously reviewed and evaluated based on specific criteria. To facilitate our study, a concise summary of the evaluated information has been included in Table 3.

Table 3. The literature included in this study

Author	Origin	Method	Sample	Result
Perez-Navarro et al.¹¹ (2015)	Mexico	Cohort	507 participants	Patients with TB-T2DM are more likely to remain positive for acid-fast bacilli after two months of anti-TB treatment, have drug resistant (DR) and multi-drug resistant (MDR) TB, and have higher odds of resistance to isoniazid, rifampicin, and pyrazinamide. They are also more likely to present with MDR TB, treatment failure, and relapse, with effect sizes ≥ 0.34 compared to non-DM subjects.
Workneh et al.¹² (2017)	Norway	Systematic Review	94 studies	The prevalence of diabetes mellitus (DM) among TB patients ranged from 1.9% to 45%, with a global median of 16%. TB prevalence was higher in Asia, North America, and Oceania, while low globally. Risk factors for TBDM comorbidity included sex, older age, urban residence, tobacco smoking, sedentary lifestyle, poor glycemic control, family history of DM, and TB illness.
Yu et al.¹³ (2019)	China	Systematic Review	12 studies	A study of 6980 cases from 12 observational studies found that metformin prescription could decrease the risk of tuberculosis (TB) in diabetics. However, it was not associated with a lower risk of LTBI. Metformin medication during anti-TB treatment was associated with smaller TB mortality and higher probability of sputum culture conversion at 2 months of TB disease. Metformin prescription did not significantly reduce TB relapse in diabetics.
Meregildo-Rodriguez et al.¹⁴ (2022)	Peru	Systematic Review	18 studies	Metformin significantly reduces active tuberculosis risk in diabetic patients by 40%, with a dose-response gradient. However, DPP IV inhibitors increase this risk by 43%. The study found that study design and metformin dose account for heterogeneity, with medium doses reducing the risk by 45% and high doses by 52%.

Mishra et al.¹⁵ (2022)	India	Prosspective Study	120 participants	The study found that metformin users had larger T-Cells, Helper T-Cells, and Cytotoxic T Cells levels at the second visit compared to non-users. Additionally, metformin significantly impacted the conversion of sputum smear compared to non-users, with a p-value of 0.0318, unpaired t-test.
Sutter et al.³ (2022)	USA	Review	-	Metformin has been shown to reduce the establishment of LTBI, progression of LTBI to active disease, modulate active pulmonary disease, and improve health-related quality of life in patients with tuberculous disease, particularly those with diabetes. However, further studies are needed to evaluate its immunomodulatory effects in humans, especially when used as adjunctive therapy with first-line anti-tuberculous medication. Randomized control trials are essential for further research.
Vyas et al.¹⁶ (2022)	India	Review	-	The bidirectional relationship between tuberculosis (TB) and diabetes mellitus (DM) is a significant concern, as DM affects TB severity, progress, and outcomes. TB patients have higher morbidity, treatment failure, and mortality rates, while DM triples TB risk. Addressing both diseases is crucial, and immunomodulatory drugs like Metformin can enhance TB immunity in diabetic patients.
Al-Bari et al.¹⁷ (2024)	Bangladesh	Review	-	Tuberculosis (TB) is a leading cause of death, especially in poor countries. Its coexistence with chronic illnesses like diabetes mellitus (DM) makes control challenging. TB-DM is a syndemic, with T2DM increasing the risk of severe TB recurrence. Joint management of TB and DM is necessary due to drug-drug interactions and autophagy. To manage TB-DM, multidisciplinary collaboration, screening, suitable drugs, and improved treatment strategies are needed.

DISCUSSION

Yu X et al. investigated the impact of metformin on tuberculosis (TB), latent TB infection (LTBI), and treatment outcomes in patients with diabetes. Their findings indicated that metformin significantly lowered the risk of developing TB (OR 0.38; 95% CI, 0.21–0.66). In contrast, metformin did not demonstrate a significant effect on reducing the risk of LTBI (OR 0.73; 95% CI, 0.30–1.79) among diabetic individuals.¹³ During anti-tuberculosis treatment (ATT), metformin was associated with decreased TB mortality and a higher rate of sputum culture conversion within two months. However, it did not significantly affect the incidence of TB relapse in diabetic patients.^{13,14}

The systematic review and meta-analysis conducted by Yu X et al., Zhang M, and He JQ investigated the relationship between metformin use and tuberculosis (TB) in patients with diabetes. They analyzed data from five databases and 17 observational studies, all of which had a low risk of bias. The aggregated results indicated that metformin was significantly associated with a reduced incidence and mortality of

active TB in individuals with diabetes (RR 0.34; 95% CI, 0.20–0.57, $p \leq 0.001$).^{13,18} The authors concluded that metformin provides benefits in both preventing and improving treatment outcomes for TB in diabetic patients. They performed sensitivity and heterogeneity assessments, attributing the observed heterogeneity to variations in diabetes severity or complications, differing metformin dosages or treatment durations, and varying smoking behaviors. However, they did not conduct subgroup analyses or evaluate a potential dose-response relationship.^{13,18}

Metformin has been demonstrated to offer a protective effect against active tuberculosis (TB) in diabetic patients, with substantial evidence from a meta-analysis highlighting this benefit.¹⁴ This protective effect appears to be more pronounced in diabetic patients with a high prevalence of dyslipidemia, who are more frequently prescribed statins.¹⁹ The analysis revealed a dose-response relationship, indicating that higher doses of metformin are associated with a reduced risk of developing active TB. Specifically,

medium doses (>150 cumulative defined daily doses, cDDD_s) and high doses (cDDD_s > 360) of metformin were found to be effective in protecting against active TB, with medium doses reducing the risk by 45% and high doses by 52%.²⁰⁻²² These findings align with multiple primary studies²³⁻²⁵, though one study did not observe this dose-response effect.²³ Notably, no other meta-analyses have explored this dose-response relationship between metformin and active TB risk.

A meta-analysis revealed that metformin does not impact sputum culture conversion at the two-month mark. Zhang M and He JQ conducted studies that corroborated these findings, although the meta-analysis excluded three studies due to inadequate adjustment for confounding variables. Conversely, Yu X et al. found that metformin significantly enhanced sputum culture conversion at two months of tuberculosis treatment. Research on sputum culture conversion with other oral antidiabetic drugs besides metformin is lacking. Additionally, only one study has assessed the effects of metformin on tuberculosis

recurrence and mortality in diabetic patients. There is also a lack of high-quality studies investigating the relationship between metformin and the risk of latent tuberculosis infection (LTBI).^{13,18}

In contrast to metformin, other oral antidiabetic drugs (OADs) such as saxagliptin have been associated with an increased risk of active tuberculosis. This association was highlighted by the US Food and Drug Administration (FDA) in 2012, which reported saxagliptin's potential to elevate tuberculosis risk. Saxagliptin, a gliptin, possesses immunosuppressive properties and affects CD26 function, potentially leading to infections, including urinary and upper respiratory tract infections. Specifically, the FDA identified five cases of pulmonary tuberculosis and five cases of pleural tuberculosis linked to saxagliptin use.^{26,27} A meta-analysis of DPP-4 inhibitors revealed moderate heterogeneity, yet the limited number of studies precluded subgroup, sensitivity, or meta-regression analyses.²⁷ The analysis did not establish a connection between tuberculosis risk and the use of

sulfonylureas, meglitinides, thiazolidinediones, or alpha-glucosidase inhibitors. Despite its robustness compared to previous reports, the meta-analysis faced limitations such as a small study pool, potential publication bias, and the exclusion of OADs other than metformin and DPP-4 inhibitors from the analysis.¹⁴

CONCLUSION

Metformin, an oral antidiabetic drug, has been associated with a reduced incidence and mortality of active tuberculosis (TB) in diabetic patients. Several studies found that metformin is significantly associated with a reduced incidence and mortality of active TB in diabetic individuals. Higher doses of metformin are found to be effective in protecting against active TB, with medium doses reducing the risk by 45% and high doses by 52%. However, no other meta-analyses have explored this dose-response relationship between metformin and active TB risk. In contrast, saxagliptin, another oral antidiabetic drug, has been associated with an increased risk of active tuberculosis. Saxagliptin, a gliptin with

immunosuppressive properties, has been linked to infections, including urinary and upper respiratory tract infections. However, the meta-analysis of DPP-4 inhibitors revealed moderate heterogeneity, but the limited number of studies precluded subgroup, sensitivity, or meta-regression analyses. The study highlights the need for further research on the relationship between metformin and TB risk in diabetic patients.

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