





SYSTEMATIC REVIEW

Effect of hyperglycemia on lung microbiota and treatment outcome in pulmonary tuberculosis: A scoping review

[version 1; peer review: 1 approved, 2 approved with reservations]

Victor Moses Musyoki ¹⁻³, Marianne Mureithi^{1,2}, Annamari Heikinheimo^{1,4}, Elizabeth Maleche-Obimbo^{3,5}, Dennis Kithinji ^{6,7}, Susan Musau^{1,3}, Kariuki Njaanake^{1,2}, Omu Anzala^{1,2}

¹Department of Medical Microbiology and Immunology, University of Nairobi, Nairobi, Nairobi County, 00202, Kenya

²KAVI-Institute of Clinical Research, University of Nairobi, Nairobi, Nairobi County, 00202, Kenya

³Tuberculosis and HIV co-infection Training Program in Kenya, Fogarty International Center, Bethesda, Maryland, 2220, USA

⁴Department of Veterinary Medicine, University of Helsinki, Helsinki, Uusimaa, 00014, Finland

⁵Department of Paediatrics and Child Health, University of Nairobi, Nairobi, Nairobi County, 00202, Kenya

⁶Department of Medical Laboratory Sciences, Meru University of Science and Technology, Meru, Meru County, 60200, Kenya

⁷Research Methodology, Medright Consulting LTD, Maua, Meru, 60600, Kenya

V1 First published: 20 Dec 2024, 13:1543
<https://doi.org/10.12688/f1000research.159555.1>
Latest published: 20 Dec 2024, 13:1543
<https://doi.org/10.12688/f1000research.159555.1>

Abstract






Abstract

The comorbidity due to pulmonary tuberculosis (TB) and diabetes mellitus (DM) is a global health problem, but its mechanism remains unclear. It is suspected that hyperglycemic alteration of the immune response to TB and the composition of the lung microbiota play an important role. This scoping review aimed to contribute to the understanding of the mechanisms by mapping evidence on the effect of hyperglycemia on physical health indicators, immune cell counts, cytokine levels, and the composition of lung microbiota in patients with the DM-TB comorbidity.

A systematic search for research articles about the relationship between hyperglycemia and physical health, immune cells, and cytokine levels in humans was conducted in MEDLINE, Scopus, and CINAHL Plus. Then, articles on the interactions between the immune cells, cytokines, and lung microbiota were identified through Google Scholar and Google search engines. Characteristics of the studies focusing on effects of hyperglycemia, the findings of the articles relevant to the research objectives, and strengths and weaknesses of the selected articles were charted in a data extraction tool.

Open Peer Review

Approval Status   

| | 1 | 2 | 3 |
|--|---|---|---|
| version 1 |  |  |  |
| 20 Dec 2024 | view | view | view |
| 1. Foluke Adenike Ayeni  , University of Lagos, Akoka, Nigeria | | | |
| 2. Tahziba Hussain , ICMR-Regional Medical Research Centre, Bhubaneswar, India | | | |
| 3. Sonal Sekhar Miraj  , Manipal Academy of High Education, Manipal, India | | | |
| Any reports and responses or comments on the article can be found at the end of the article. | | | |

Twenty-one articles on the effects of hyperglycemia on immune mediators and health outcomes of patients with DM-TB were included. The evidence showed hyperglycemia to be associated with unfavorable treatment outcomes; altered counts and functioning of dendritic cells, monocytes, and CD4+ T cells; and changes in cytokine levels (mainly INF- γ , IL-17, IL-1 β , IL-2, IL-6, IL-10, and TNF- α) in patients with DM-TB. The composition of the lung microbiota changed in correlation with changes in physical health outcomes, counts of immune cells, and cytokine levels.

Thus, hyperglycemia, immune responses, and dysbiosis of the lung microbiota are integral in the pathogenesis of DM-TB and TB treatment outcomes. A prospective cohort study, especially in individuals with newly diagnosed DM versus known DM and concomitant latent TB versus active TB, is recommended to define causal relationships.

Keywords

Diabetes, Tuberculosis, Comorbidity, Lung microbiome, Immune response, Cytokines, Pathogenesis, Scoping review

Corresponding author: Victor Moses Musyoki (vmusyoki@uonbi.ac.ke)

Author roles: **Musyoki VM:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Mureithi M:** Supervision, Validation; **Heikinheimo A:** Supervision, Validation; **Maleche-Obimbo E:** Conceptualization, Methodology, Supervision, Validation; **Kithinji D:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Musau S:** Methodology, Writing – Review & Editing; **Njaanake K:** Conceptualization, Methodology, Supervision, Validation, Writing – Review & Editing; **Anzala O:** Conceptualization, Supervision, Validation

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2024 Musyoki VM *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Musyoki VM, Mureithi M, Heikinheimo A *et al.* **Effect of hyperglycemia on lung microbiota and treatment outcome in pulmonary tuberculosis: A scoping review [version 1; peer review: 1 approved, 2 approved with reservations]** F1000Research 2024, 13:1543 <https://doi.org/10.12688/f1000research.159555.1>

First published: 20 Dec 2024, 13:1543 <https://doi.org/10.12688/f1000research.159555.1>

Introduction

Pulmonary tuberculosis (PTB) is caused by *Mycobacterium tuberculosis* (MTB), which is a leading infectious agent cause of death globally (Fukunaga *et al.*, 2021). PTB, more common than extra-pulmonary TB, affects about 80% of the patients with TB. Although the incidence of PTB has been declining over the years, it is still high with about 10 million people developing the disease in 2019 and approximately 1.4 million and 1.3 million people dying of TB in 2019 and 2022, respectively (Fukunaga *et al.*, 2021; Menon *et al.*, 2020; World Health Organization, 2023).

The increasing prevalence of DM globally complicates the efforts to eradicate TB since DM-TB comorbidity makes patients non-responsive to conventional TB treatment regimen (Menon *et al.*, 2020). Based on studies published between 1999 and 2017, the pooled prevalence of DM-TB in Sub-saharan Africa is 9% (95% CI: 6.0, 12.0%) (Alebel *et al.*, 2019). The odds of multi-drug resistant TB (MDR-TB) in patients with DM can be twice the odds of MDR-TB in non-diabetic patients (Ngo, Bartlett and Ronacher, 2021). In addition, patients with the DM-TB comorbidity are more MTB-infectious than patients with other comorbidities (Ngo, Bartlett and Ronacher, 2021). Thus, the comorbidity derails efforts to reduce the incidence rate of TB and complicates the treatment of PTB based on the existing guidelines.

Infection with *M. tuberculosis* disturbs hormone and cytokine production to make the liver produce excess glucose and induce insulin resistance (Bisht *et al.*, 2023; Rao *et al.*, 2019). MTB infection alters insulin activity, thus deranging carbohydrate metabolism, which impairs glucose tolerance and consequently increases blood glucose levels. Insulin resistance often occurs during active tuberculosis due to increase in pro-inflammatory cytokine levels and the dysregulation of lipid metabolism secondary to MTB infection (Bisht *et al.*, 2023).

About 10% of patients with TB and who have embarked on TB treatment have hyperglycemia at 3 – 6 month follow-up, which could be predisposing the patients to complications and drug resistance (Menon *et al.*, 2020). Half of the patients among whom hyperglycemia is detected at baseline have persistent hyperglycemia at 3 – 6 month follow-up. Patients with DM-TB comorbidity are more likely to have lower concentrations of antibiotics during treatment of MTB, which further complicates management (Ngo, Bartlett and Ronacher, 2021). Therefore, hyperglycemia threatens the achievement of treatment outcomes in TB patients.

In euglycemic individuals, the lung microbiota play a significant role in health and disease including innate protection against pathogenic microorganisms. In patients with TB, hyperglycemia may contribute to dysbiosis of the lung microbiota, thus increasing the risk of disease progression (Dumas *et al.*, 2018; Wang *et al.*, 2022). Lung microbiota is connected to the gut microbiota through the bidirectional gut-airway axis, which is a system for information exchange to modulate microorganism-immune interactions (Özçam and Lynch, 2024). Wang *et al.* (2022) reported that the bacterial types and species diversity of the gut microbiota were low in a PTB group compared to a healthy group. The populations of the predominant beneficial bacteria in the intestinal microbiota, such as Firmicutes, were also significantly low (Wang *et al.*, 2022; Comberiat *et al.*, 2021). Considering the gut-lung axis, hyperglycemia may also play a role in the disruption of the pulmonary microbial community (Dumas *et al.*, 2018). Evidence on the effect of the hyperglycemia in causing lung dysbiosis and the microbiome-immune crosstalk among patients with TB is necessary to understand its implications in the pathophysiology of TB, effects of therapeutic interventions, and treatment outcomes (Comberiat *et al.*, 2021).

The specific objectives of this scoping review include identifying the effects of hyperglycemia on cytokine levels, immune cells, and physical health of patients with TB, and exploring how the changes influence the lung microbiome to affect health outcomes in TB. The scoping review will clarify the implications of hyperglycemia in adult patients with MTB infection by synthesizing evidence on the immunological effects of the hyperglycemia on the lung microbiome. This evidence will be useful in elucidating the need to investigate the value of hyperglycemia screening and DM management in the care plan for patients with pulmonary TB.

Methods

Protocol design

This scoping review adhered to the The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension for scoping reviews (PRISMA-ScR) checklist (Kithinji *et al.*, 2024). A scoping review methodology was appropriate since evidence on the relationships between PTB, hyperglycemia, and the lung microbiome is scarce and published in research articles with heterogeneous methods. A review protocol does not exist.

Literature search

Eligibility criteria

Peer-reviewed primary articles that explored the relationship between PTB, hyperglycemia, and lung dysbiosis were included in the study. The participants in the studies must have been aged over 18 years and diagnosed with PTB based on chest X-ray and bacteriological confirmation of the MTB infection. They must also have had hyperglycemia defined as fasting blood glucose >5.6 mmol/L, 2-hour oral glucose tolerance >7.8 mmol/L, or HbA1c >5.7%. The exclusion criteria eliminated studies whose outcomes were not objectively measured due to their susceptibility to bias. Studies published in non-English language and without English translations were also excluded because all the authors are English speakers.

Information sources

The MEDLINE, Scopus, and CINAHL Plus databases were searched to identify research studies that explored the relationship between MTB infection and hyperglycemia. The reference lists of the systematic reviews and meta-analyses retrieved from the search were screened to identify additional articles that would be included in this study. Google Scholar and Google were used to search and identify articles on the relationships between the significant changes in measured outcomes in the PTB - hyperglycemia publications with lung microbiota. [Table 1](#) outlines the details of the searches conducted and the full search strategy for each source. The key search terms were tuberculosis, hyperglycemia, and lung microbiome. The key terms and their synonyms were combined using Boolean operators (AND, OR) to improve the sensitivity of the search ([Table 1](#)).

Selection of sources of evidence

Titles and abstracts of the identified articles were screened to identify articles that met the inclusion and exclusion criteria. The full-texts of the relevant records were read to assess suitability for the study objectives. The study population, outcome measures, and results of the data analysis were examined to only select articles that explored the changes in physical health, immune cells, and cytokine levels in the interplay between pulmonary TB and hyperglycemia. Two reviewers, VMM and DK, a medical microbiologist and a research methodologist, respectively, scrutinized each article to identify relevant data regarding the effect of hyperglycemia on physical health, immune cell counts, and cytokine levels in patients with PTB. The remarkable changes in outcomes observed in the included TB-hyperglycemia studies informed the search for articles on the relationship between the changes and dysbiosis in the lung microbiota.

Data charting process

The researchers charted the data using a Microsoft excel data abstraction tool that captured information on the sample characteristics and the variables on the interaction between pulmonary TB and hyperglycemia. The two reviewers, VMM

Table 1. Search strategies for MEDLINE, Scopus, and CINAHL Plus databases.

| Database | Date searched | Filters and limits | Search query | Hits |
|-------------|---------------|--|---|------|
| MEDLINE | 13/06/2024 | Limiters - Peer Reviewed; English Language; Human; Age Related: All Adult: 18+ years; Language: English Expanders - Apply equivalent subjects Search modes - Boolean/Phrase | AB (tuberculosis or tb) AND TX (hyperglycemia or high blood sugar or high blood glucose) | 71 |
| Scopus | 14/06/2024 | Refine search Subject area: immunology and microbiology Document type: article Language: English Source type: journal | (tuberculosis AND hyperglycemia) AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (EXACTKEYWORD, "Human") OR LIMIT-TO (EXACTKEYWORD, "Humans")) | 381 |
| CINAHL Plus | 14/06/2024 | Expanders: Apply related words, apply equivalent subjects Source types: academic journals Language: English | TI (tuberculosis or tb) AND AB hyperglycemia | 31 |

Table 2. Data items extracted from the selected articles.

| Variable | Definition | Assumption |
|-----------------------------|--|--|
| Hyperglycemia | Fasting blood glucose (FBG) >5.6mmol/L, impaired glucose tolerance – 2-hour Oral glucose tolerance test result of >7.8mmol/L or HbA1c levels of 5.7% – 6.4% | Hyperglycemia could be due to DM or other causes such as stress or TB-induced |
| Diabetes mellitus (DM) | A chronic condition characterized by hyperglycemia (FBS > 7 mmol/L, random blood sugar (RBS) or 2-hr postprandial glucose levels of 11 mmol/L, or HbA1c > 6.5%) due to impaired glucose metabolism | DM contributed to the hyperglycemia that affected the prognosis of TB |
| Prediabetes | A precursor of DM characterized by hyperglycemia (FBG = 5.5 – 6.9 mmol/L, 2-hour postprandial glucose 7.8-11 mmol/L, or HbA1c of 5.7% and 6.4%) | Even hyperglycemia that is yet to be DM can influence the pathogenesis of TB |
| Pulmonary tuberculosis (TB) | A lung infection caused by <i>Mycobacterium tuberculosis</i> diagnosed via chest X-ray and/or bacteriological sputum analysis (microscopy or culture) | Newly diagnosed TB, relapse and recurrent TB differ in prognosis and pathogenesis |
| PreDM or DM-TB comorbidity | The coexistence of hyperglycemia and TB diagnosis | The hyperglycemia worsened the course of TB |
| Cytokines | Signaling molecules that facilitate communication between cells particularly during inflammation | Hyperglycemia influences changes in cytokine levels, which disrupt lung microbiota to worsen the course of TB. |
| Lung microbiota | The pulmonary microbial community in the lower respiratory tract. | Hyperglycemia disrupts lung microbiota to cause poor health outcomes in patients with TB |

and DK, discussed any disagreements in their charting, which they resolved by engaging the co-authors to arrive at a majority decision.

Data items

The main data items included hyperglycemia in both pre-DM and DM, and PTB diagnosed through imaging or bacteriology as independent variables. The other data items included indicators of physical health in PTB and changes in immune cell counts and cytokine levels attributable to hyperglycemia. Changes in lung microbiota associated with changes in physical health, immune cell counts, and cytokine levels were the relevant data items in the second round of the search process. Details of the data items are provided in [Table 2](#).

Synthesis of results

VMM and DK synthesized evidence on the effect of hyperglycemia on TB prognosis by grouping related evidence. The effects of hyperglycemia on physical indicators of health such as TB treatment failure and cavitation in the lungs upon chest X-ray; immune cells; and cytokines extracted from each of the sources were synthesized to elucidate the mechanism. The main strengths and weaknesses of the individual studies were considered during the synthesis to reduce the risk of bias.

Results

Selection of sources of evidence

A total of 31 primary research articles were synthesized in this scoping review. Twenty-one were on the effects of hyperglycemia on various indicators of health in TB while 10 were on the effect of the changes in the indicators on the lung microbiota. [Figure 1](#) shows the sources of evidence selected, screened, assessed for eligibility, and included in the review regarding the relationship between TB and hyperglycemia.

Characteristics and results of individual sources of evidence

Table 3 (Extended data; [Kithinji et al., 2024](#)) summarizes the details of the primary articles that were included in this scoping review. In instances where the study design was not identified in the article, it was deciphered from the description of the recruitment of participants and data collection processes.

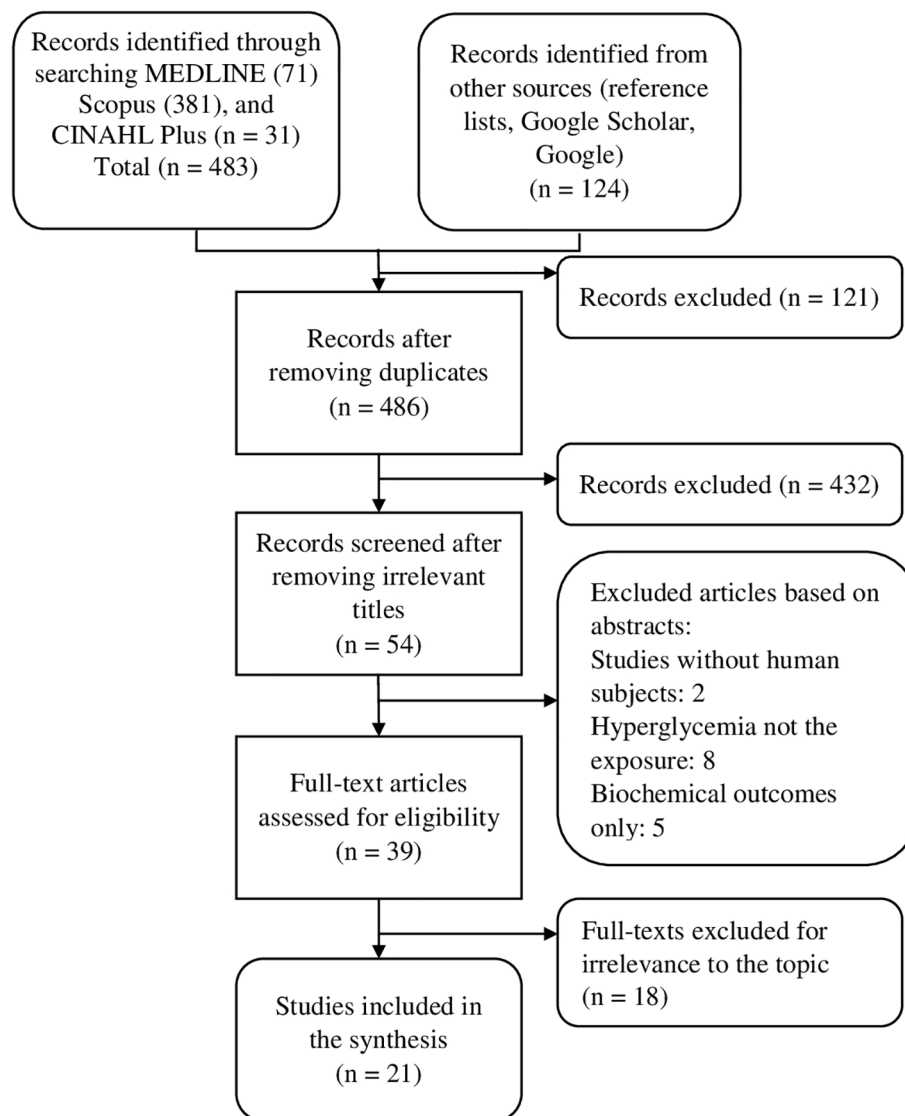


Figure 1. PRISMA flow diagram showing the selection of sources of evidence for the relationship between TB and hyperglycemia.

Synthesis of results

Effects of hyperglycemia on overall TB treatment outcomes

The results on the effects of hyperglycemia on overall TB treatment outcomes are shown in Table 4 (Extended data; [Kithinji *et al.*, 2024](#)). The findings show that hyperglycemia contributed to poor treatment outcomes among patients with TB ([Lin *et al.*, 2020](#); [Liu *et al.*, 2021](#); [Meng *et al.*, 2023](#); [Pardeshi *et al.*, 2024](#); [Faurholt-Jepsen *et al.*, 2013](#)). A prospective cohort study in six clinics in Jilin province, China reported a statistically significant association between persistent hyperglycemia of any duration and unfavorable treatment outcomes among patients with TB ([Lin *et al.*, 2020](#)). However, the study relied on clinical presentation of patients to classify them as TB-negative, thus giving rise to a risk of overdiagnosis. [Pardeshi *et al.*, 2024](#)) and [Liu *et al.*, 2021](#)) also found that patients with TB and transient hyperglycemia had 2-4 times the odds of treatment failure compared to euglycemic patients. Although the estimates of the incidence rates of events were imprecise based on the wide confidence intervals, they were significant and showed a temporal relationship between hyperglycemia and poor TB treatment outcomes. Similarly, [Faurholt-Jepsen *et al.*, 2013](#)) reported that the risk of mortality among patients with DM-TB in Mwanza, Tanzania was five times the risk of mortality among patients with TB only within the first 100 days after initiation of TB treatment. Considering the large sample size and the cohort study design, the evidence presented by [Faurholt-Jepsen *et al.*, 2013](#)) cements the relationship observed between hyperglycemia and poor treatment outcomes in the various studies.

Poor treatment outcomes co-occurred with dysbiosis of the lung microbiota (Tiella *et al.*, 2021; Wu *et al.*, 2013). Wu *et al.* (2013) found that dysbiosis in the lung microbiota is associated with poor TB treatment outcomes, treatment failure, and recurrence. Although Wu *et al.* (2013) analyzed sputum rather than bronchoalveolar lavage to characterize the lung microbiota, their findings suggest dysbiosis as a significant determinant of TB treatment outcomes. Tiella *et al.* (2021), who sought to identify the bacteria that constitute lung microbiota in TB by analyzing the bronchoalveolar lavage fluid obtained from both lungs of patients with unilateral TB lesions, found that *Cupriavidus* spp. rather than *Streptococcus* spp. was the most dominant bacterial genus in the lower respiratory tract of patients with TB.

The form of dysbiosis in the lung microbiota is dependent on the pulmonary TB status. Wu *et al.* (2013) compared sputum microbiota across patients with three types of TB: new, recurrent and treatment-failure TB among 25, 30, and 20 patients, respectively. Higher abundance of *Bulleidia* spp. and *Atopobium* spp. was observed in patients with recurrent TB compared to newly diagnosed patients. The *Pseudomonas* / *Mycobacterium* and *Treponema* / *Mycobacterium* ratios were higher and lower, respectively, in patients with recurrent TB than in newly diagnosed TB patients. Similarly, in treatment failure TB, the *Pseudomonas* / *Mycobacterium* ratio was higher than in newly diagnosed cases (Wu *et al.*, 2013). Patients with recurrent TB had more abundant *Corynebacterium* spp. compared to patients with treatment failure TB. On the other hand, the more abundant genera in the patients with treatment-failure TB compared to patients with recurrent TB included *Campylobacter*, *Prevotella*, *Atopobium*, *Blastobacter*, and *Treponema* (Wu *et al.*, 2013).

Studies on lung microbiome have reported different compositions of the microbiota concurrent with variations in TB treatment outcomes; hence the TB's pathogenesis could be due to the interplay of both hyperglycemia and lung dysbiosis. Species in the phylum firmicutes including *Staphylococcus* and *Selenomonas* were more abundant in the lung microbiota of patients with TB compared to patients without TB (Ding *et al.*, 2021; Tiella *et al.*, 2021). Abundance of members of phylum Actinobacteria such as *Mycobacteria* was also evident in the lung microbiota of patients with TB compared to those without it (Tiella *et al.*, 2021). *Porphyromonas* in the phylum Bacteroidetes and *Fusobacterium* in the phylum Fusobacteria were more common compared to *Streptococcus* in the phylum Firmicutes in the sputum of patients with TB (Ding *et al.*, 2021).

Poor physical health outcomes in TB were more common in hyperglycemic patients than in euglycemic patients (Barreda *et al.*, 2020; Meng *et al.*, 2023; Meng *et al.*, 2022). Both the retrospective cross-sectional study by Barreda *et al.* (2020) and the cohort study by Meng *et al.* (2023) reported that hyperglycemic patients with TB were more likely to have various types of pulmonary lesions such as cavities, alveolar infiltrates, and fibrous tracts compared to euglycemic patients. The two-year follow-up period in the study by Meng *et al.* (2023) allowed the identification of hyperglycemia as a risk factor of poor health outcomes. The poorer the glycemic control, the higher the rates of pulmonary lesions. Byashalira *et al.* (2022) improved health outcomes of patients with DM-TB by integrating glycemic control into a TB and HIV care programme.

Effects of hyperglycemia on TB immunity

Results on the effects of hyperglycemia on the immunological markers of health in TB (Table 5 (Extended data; Kithinji *et al.*, 2024)) show that hyperglycemia reduced the population and functioning of dendritic cells and macrophages in patients with DM-TB (Gomez *et al.*, 2013; Kumar *et al.*, 2017). Kumar *et al.* (2017) observed a negative correlation between hyperglycemia and the frequencies of monocytes, plasmacytoid, and myeloid dendritic cells, as well as intermediate and classical monocytes, upon phenotyping monocytes and dendritic cells *ex vivo* from patients with DM-TB comorbidity and others with only TB under standard TB treatment. Although the correlations were borderline, perhaps due to the small sample size and the cross-sectional study design, the results pointed to hyperglycemia's downregulation of the functioning of monocytes and dendritic cells in patients with TB (Kumar *et al.*, 2017). Another *ex vivo* study revealed lower attachment and phagocytosis of MTB in monocytes from patients with DM, especially upon heat inactivation of serum in the case of poorly controlled hyperglycemia (Gomez *et al.*, 2013). This suggests that hyperglycemia could impair the functioning of monocytes against MTB by inhibiting their activation through the complement system. Similarly, multiple *ex-vivo* experiments showed that patients with DM-TB have significantly low complement receptor 3 or CD11b and MARCO levels compared to patients with TB, which translated to low capacity for phagocytosis in macrophages (Panda *et al.*, 2022).

Hyperglycemia variedly affected the populations of different types of T-cells. A prospective comparative study demonstrated that within two months of TB treatment and follow-up, patients with DM-TB had lower CD4+ T cell counts compared to patients with TB only, DM only, and healthy controls (Rendón Ramírez *et al.*, 2023). Although the study could have been underpowered and ungeneralizable due to a small sample recruited from a single hospital, its findings indicate the possibility of DM contributing to a decrease in CD4+ T cells count. On the other hand, a prospective

observational cohort study reported that increased HbA1c in the course of TB treatment is associated with elevated Th1 and Th17 CD4+ responses (Krause *et al.*, 2023). In an experimental study, the numbers of Th17 CD4+ T cells and a regulatory T cell subset, ROR γ ⁺ Tregs, changed depending on the presence of *Lactobacillus murinus* (*Lagilactobacillus murinus*) strain (CNCM I-5314), which is a pulmonary *Lactobacillus* strain (Bernard-Raichon *et al.*, 2021). Intranasal introduction of the CNCM I-5314 and not intragastrically in mice infected with MTB increased the expansion of lung leukocytes, particularly Th17 CD4+ T cells and ROR γ ⁺ Tregs locally in the lungs and airways (Bernard-Raichon *et al.*, 2021). Upon administering the CNCM I-5314, the proportion of ROR γ ⁺ Tregs increased most prominently since they changed from 14% to 50% of all the lung Foxp3⁺ CD41 T cells in MTB-infected mice.

In an experiment that tested the activation of immune cells from patients with active and latent TB by stimulating the peripheral blood mononuclear cells with *Mycobacterium bovis* BCG, an inverse correlation was observed between the level of glycemia and IFN- γ - and TNF- α - CD4+ T cell productions (Boillat-Blanco *et al.*, 2018). This suggested that hyperglycemia could be downregulating antigen processing and presentation of the whole MTB, thus stalling the production of cytokines that promote TB immunity. Although the study did not include patients with transient hyperglycemia, the findings among patients with DM empirically suggest the effect of hyperglycemia on TB immunity.

Findings from different studies show that hyperglycemia could be disrupting cytokine responses in favor of TB immunopathology. An *ex-vivo* experimental study on the mRNA expression of pro-inflammatory and anti-inflammatory cytokines in monocyte-derived macrophages reported a positive correlation between IL-1 β expression and HbA1c levels (Panda *et al.*, 2024). Levels of IL-1 β were also elevated among patients with DM-TB compared to patients with DM only or TB only (Kumar *et al.*, 2020). In contrast, lower levels of IL-1 β were reported in patients with DM- TB comorbidity compared to patients with TB only (Chao *et al.*, 2015).

IFN- γ levels were low in newly diagnosed DM and TB comorbidity cases. Patients with newly diagnosed DM (NDM) were characterized by significantly diminished unstimulated levels of INF- γ (Kumar *et al.*, 2020; Panda *et al.*, 2024). Additionally, INF- γ levels were positively correlated with IL- β levels (Panda *et al.*, 2024). Earlier, Kumar *et al.* (2014) reported that latent TB in treatment-naïve patients with DM or pre-DM was associated with diminished circulating levels of INF- γ .

IFN- γ levels were elevated in patients with known DM-TB comorbidity compared to patients with DM only (Chen *et al.*, 2022; Kumar *et al.*, 2020). Although the power of the study by Chen *et al.* (2022) was low due to a small sample size, the observed differences between the compared age- and sex-matched groups suggest a possible effect of the hyperglycemia on the cytokine levels. Similar findings have been reported from a cross-sectional study indicating that INF- γ levels were more raised in patients with DM but with controlled hyperglycemia and latent TB than in healthy endemic controls upon purified protein derivative antigen (PPD) stimulation (Masood *et al.*, 2022).

Alteration of the lung microbiota affected the production of INF- γ (Bernard-Raichon *et al.*, 2021; Palma Alborno *et al.*, 2021; Xia *et al.*, 2022). The introduction of CNCM I-5314 into the lung microbiota significantly decreased the production of INF- γ (Bernard-Raichon *et al.*, 2021). Dysbiosis characterized by increased *Bacteroides* and *Firmicutes* in the lungs decreased the number of IFN- γ -producing CD4+ cells and consequently IFN- γ levels (Palma Alborno *et al.*, 2021). Xia *et al.* (2022) reported a positive correlation between IFN- γ and *Leptotrichia* and *Gemella*, which are members of the lung microbiota in healthy control populations.

IL-10 levels in DM-TB are inconsistent across various studies. For instance, IL-10 levels were significantly low in patients with increased HbA1c (Krause *et al.*, 2023). In contrast, findings from a study by Chen and colleagues showed that the levels in DM-TB patients were double those in patients with DM only or TB only (Chen *et al.*, 2022). In another *in vitro* study, IL-10 levels were significantly enhanced in the mice infected with the MS1987 protein (the virulence protein for MTB) especially after intranasal infection with anaerobic *Escherichia coli* and *Delftia acidovorans* (Fraser-pitt *et al.*, 2023).

Significantly high IL-6 levels were reported among patients with DM-TB compared to patients with TB only or DM only, even in cases with latent TB (Chen *et al.*, 2022; Kumar *et al.*, 2020; Masood *et al.*, 2022). This upregulation was mainly in patients with HbA1c levels greater than 8 g/dL. Contrary to these findings, an *in vitro* study reported a significant decrease in IL-6 in mice at day 9 post-infection with a model containing the MS1987 protein (Fraser-pitt *et al.*, 2023). Intranasally introducing *E. coli* into mice increased the production of IL-6 while exposure to *D. acidovorans* inhibited IL-6 production. Xia *et al.* (2022) also reported a negative correlation between IL-6 levels and *Corynebacterium* in patients with TB.

IL-17 levels were elevated among DM-TB patients (Chen *et al.*, 2022). Similarly, IL-17A levels were high in patients with DM-TB but diminished in patients with newly diagnosed DM and TB comorbidity (Kumar *et al.*, 2020). Kumar *et al.* (2014) also reported diminished levels of IL-17F in patients with latent TB and DM or pre-DM. Fraser-pitt *et al.* (2023) found that models of MTB with the pathogenic protein MS1987 caused a decrease in levels of IL-17 in the lungs at day nine post-infection. Administering *E. coli* intranasally into mice led to increased production of IL-17. Administering CNM-I-5314 caused the lung CD4+ T cells to produce more IL-17 and express more IL-17a mRNA (Bernard-Raichon *et al.*, 2021). Xia *et al.* (2022) reported that IL-17 was positively correlated with *Gemella* and *Streptococcus* of the lung microbiota.

TNF- α levels varied depending on the status of the DM and TB. They were elevated in DM-latent TB cases upon PPD stimulation (Masood *et al.*, 2022). Kumar *et al.* (2020) also reported increased levels of TNF- α in patients with DM-TB but the unstimulated levels were diminished in patients with newly diagnosed DM and TB comorbidity. Similarly, the circulating levels of TNF- α were diminished in patients with DM and pre-DM, and latent TB (Masood *et al.*, 2022; Chen *et al.*, 2022). Bernard-Raichon *et al.* (2021) reported significantly decreased production of TNF- α in lung exudates upon CMCM I-5314 treatment. Intranasal administration of *D. acidovorans* was shown to inhibit TNF- α production (Fraser-pitt *et al.*, 2023).

IL-2 levels also varied depending on the status of the DM-TB. They were elevated in DM-latent TB cases compared to healthy endemic controls upon PPD-stimulation (Masood *et al.*, 2022; Kumar *et al.*, 2020). Unstimulated levels were significantly low in patients with newly diagnosed DM and TB comorbidity (Kumar *et al.*, 2020). Similarly, diminished circulating levels of IL-2 were associated with latent TB infection in DM or pre-DM patients (Kumar *et al.*, 2014).

Discussion

This scoping review sought to identify the effects of hyperglycemia on cytokine levels, immune cells, and physical health of patients with TB and explore how the changes influence the lung microbiome to affect health outcomes in TB.

Overall, we found that hyperglycemia is associated with poor health outcomes, and changes in cytokine levels, altered counts and functioning of dendritic cells, monocytes, and CD4+ T cells in patients with DM-TB. The microbial lung composition changes in correlation with changes in physical health outcomes, counts of immune cells, and cytokine levels. Cavities, fibrous tracts, and alveolar infiltrates among other pulmonary lesions commonly occur in patients with DM-TB. These patients experience treatment failure, recurrence, and death (Kornfeld *et al.*, 2020).

Effects of hyperglycemia on immune responses of patients with DM-TB

Dendritic cells and monocytes are central in the presentation of MTB antigens to the naïve T-cells in order to activate the adaptive immune response but their numbers are decreased in DM (Comberiati *et al.*, 2021). T-cell-mediated adaptive immune responses are integral in controlling MTB infections in humans (Jasenosky *et al.*, 2015). For instance, the availability of polyfunctional T cells, which are desirable in the fight against TB due to their capacity for effector and proliferative abilities considering their trifunctional production of TNF, IFN- γ , and IL-2 determines TB progression (Jasenosky *et al.*, 2015). Therefore, a decrease in CD4+ T cells during DM-TB comorbidity may impede the induction and maintenance of the adaptive immunity against TB.

The contrasting findings on IL-1 β levels in similar studies among patients with DM-TB suggests that the production of IL-1 β may be influenced by other factors such as the status of DM or TB. MTB decreases the activation of pyrin and AIM2- domain containing 3 (NLRP3)-inflammasomes, which induces the production of INF- β that subsequently reduces the secretion of IL-1 β (Etna *et al.*, 2014). A prospective cohort study that follows up patients with TB and hyperglycemia in the course of disease and treatment is essential to define the factors behind varying patterns of IL-1 β levels among patients with DM-TB.

IFN- γ levels are low in newly diagnosed DM-TB and high in known DM-TB cases. When diabetes status is known, treatment is often initiated, hence hyperglycemia is controlled (Li *et al.*, 2020). It is therefore important to control hyperglycemia in DM-TB to reduce the blunting of IFN- γ production. However, this is a double edged sword as the reduction of the pro-inflammatory IFN- γ in hyperglycemia not only slows down the inflammation-based pathology of TB but also hinders killing of the bacteria, induction of nitric oxide synthesis, and macrophage activation that depend on IFN- γ (Etna *et al.*, 2014).

In newly diagnosed DM-TB, IL-2, IL-17, and TNF- α levels are low, while in known DM-TB, IL-2, IL-17, and TNF- α levels are high. Chronic hyperglycemia rather than acute hyperglycemia is important in inducing inflammation in the lungs through cytokines such as IL-2, IL-17, and TNF- α (Ngo, Bartlett and Ronacher, 2021). IL-17 is involved in the

immune defense against bacteria, including MTB. As a pluripotent pro-inflammatory cytokine, it recruits neutrophils, induces chemokines' and cytokines' production, modifies the differentiation of T-helper cells, and prompts the release of antimicrobial proteins that mediate inflammation in TB (Chung, Ye and Iwakura, 2021). Similarly, TNF- α , which induces bactericidal effects in macrophages and has pro-inflammatory effects (Yuk *et al.*, 2024), is low in newly diagnosed DM-TB but high in known DM-TB. Its levels are also high in active TB (Suzukawa *et al.*, 2020), which may explain why they are elevated in DM-TB but suppressed in newly diagnosed DM and TB comorbidity. IL-2 is central in adaptive immune responses and immune tolerance (Damoiseaux, 2020), hence alterations of its levels by hyperglycemia may have adverse health implications.

Effects of hyperglycemia-instigated changes on the lung microbiome in TB

The lungs are not sterile since bacteria and fungi dominate the lower airways. *Mycobacteria* spp. are present in the lower airways of both individuals with and without TB, although they are dominant among patients with TB (Hu *et al.*, 2020). This scoping review demonstrates that patients with TB have different compositions of lung microbiota with varying patterns. *Pseudomonas*, *Acinetobacter*, *Porphyromonas*, *Bulleidia*, and *Seimonas* were abundant while *Treponema*, *Streptococcus*, and *Prevotella* were scanty in patients with TB compared to healthy controls. Other studies have reported the abundance of *Gramulicatella* and *Pseudomonas* in the lung microbiota of patients with TB (Wu *et al.*, 2013). *Sharpea* and *Bergeyella* were distinctively detected in the sputum of patients with TB. The dominant genera in healthy subjects include *Streptococcus*, *Selenomonas*, *Prevotella*, *Bifidobacterium*, and *Neisseria*. Others include *Leptotrichia*, *Catonella*, *Treponema*, and *Coprococcus* (Wu *et al.*, 2013). The fungal members of the lung microbiome belong to the phyla Ascomycota and Basidiomycota (Hu *et al.*, 2020). Patients with treatment failure TB had more abundant *Pseudomonas* than patients with newly diagnosed TB while *Corynebacterium* was more common in recurrent TB compared to treatment failure TB (Wu *et al.*, 2013). Therefore, there is varying lung dysbiosis in patients with different TB status, which implies that patients with DM-TB comorbidity may have a distinct composition of lung microbiome.

The lung microbiome remains vital in determining pulmonary health and disease. The poor treatment outcomes evident in patients with both TB and hyperglycemia indicate the possibility of hyperglycemia contributing to the lung dysbiosis. Since studies on lung microbiome have also reported variations in composition of the microbiota based on TB treatment outcomes, TB pathogenesis could be due to the interplay of both hyperglycemia and lung microbial dysbiosis. Hyperglycemia is commonly associated with dysbiosis in the gut (Darra *et al.*, 2023), it is therefore likely to be associated with dysbiosis in the lungs given the gut-lung axis. Thus, there is a need to determine the relationship between hyperglycemia and dysbiosis in the lung microbiota among patients with TB.

Changes in T-cells populations such as regulatory T cells, which the composition of lung microbiota licenses, are central in the control of pathogenesis of TB (Mori, Morrison and Blumenthal, 2021). As a result, in patients with DM-TB, hyperglycemia could influence lung dysbiosis, subsequently reducing the production of polyfunctional T cells and compromising the adaptive immune response against TB.

The present review of literature did not find evidence on the interactions between lung microbiota and dendritic cells in patients with TB. However, some members of the microbiota may interact with the dendritic cells to produce cytokines that promote type 1 immunity (Koizumi *et al.*, 2008). Similarly, the interaction between commensal bacteria through their metabolites and the immune system can contribute to the differentiation of monocytes to macrophages and boost the host innate defense against MTB (Schulthess *et al.*, 2019). Thus, dendritic cells and monocytes may mediate the interactions between the lung microbiome and hyperglycemia, thus influencing the course of TB in patients with DM-TB comorbidity.

Changes in the levels of IFN- γ , IL-17, and TNF- α , which are associated with both hyperglycemia and lung dysbiosis, are key players in the inflammatory circuits that control the progression of TB (Mori, Morrison and Blumenthal, 2021). For instance, less IFN- γ is produced in TB disease states when Bacteroidetes and Firmicutes are dominant in the lung microbiome. On the other hand, more IFN- γ is produced in health state when *Gemella* and *Leptotrichia* dominate the lung microbiota in healthy individuals. IL-10, which is produced to modulate the pathogenesis of TB, acts by dampening excess inflammation (Etna *et al.*, 2014). The increase in IL-10 levels with the intranasal administration of *E. coli* and *D. acidovorans* implies that lung dysbiosis contributes to IL-10 levels variation in enhancing or dampening inflammation. Similarly, lung dysbiosis affects IL-17 levels as evident in upsurge in IL-17 when dysbiosis was altered via intranasal exposure to *E. coli*, *Gemella*, *Lactobacillus*, and *Streptococcus*. This scoping review also shows that TNF- α levels were diminished upon intranasal introduction of *Lactobacillus* and *D. acidovorans* in the lungs. Thus, hyperglycemia may contribute to the pathogenesis of TB by altering the lung microbiota, which then disorients the immune response to TB through changes in cytokine levels.

Increase in IL-6 levels, common in patients with DM-TB, could be due to alterations in the composition of the lung microbiome. In this scoping review, we found that, IL-6 levels in mice infected with TB could be increased by intranasally introducing *E. coli* or reduced by administering *D. acidovorans*. *Corynebacterium*, whose low population in the lung microbiota is associated with increased IL-6 levels, is a major immunomodulatory bacterium in the lung microbiota (Liu *et al.*, 2022). IL-6 is in the pro-inflammatory cytokine family and a major player in the human cytokine network (Uciechowski and Dempke, 2020), hence variations in its levels should be explored when studying the relationship between hyperglycemia and lung microbiota in TB pathogenesis.

The main weakness of this scoping review is that majority of the included studies analyzed sputum samples to assess lung microbiome. There was, therefore, a possibility of specimen contamination with bacterial genera that are common in the oropharynx such as *Prevotella*, *Atopobium*, and *Bulleidia*. As a result, it is likely that the oropharynx microbiota would be misclassified for lung microbiota (Mori, Morrison and Blumenthal, 2021; Goddard *et al.*, 2012). This underlines the need to consider bronchoalveolar lavage (BAL) specimen for an accurate depiction of the lower respiratory system microbiota.

Conclusion

In conclusion, hyperglycemia and lung microbiota are involved in the pathogenesis of DM-TB, which culminates in poor treatment outcomes. They mediate their effects through changes in counts of dendritic cells, monocytes, CD4+ T cells, and cytokine levels. The interactions between hyperglycemia and the immune cells, cytokines, and lung microbiota vary depending on whether the DM is newly diagnosed or its a known case and whether TB is latent or active. A prospective study is necessary to determine the causal relationships in the interactions between hyperglycemia, immune cells, cytokines, and lung microbiota that result in poor TB treatment outcomes.

Ethics and consent

Ethical approval and consent were not required.

Author contributions

Conceptualization: Victor MM, Dennis K, Kariuki N, Elizabeth MO, Omu A

Data curation, formal analysis, investigation: Victor MM, Dennis K

Methodology: Victor MM, Dennis K, Susan M, Kariuki N, Elizabeth MO

Supervision, validation: Elizabeth MO, Kariuki N, Omu A, Marianne M, Annamari H

Writing – original draft preparation: Victor MM, Dennis K

Writing - review and editing: Victor MM, Dennis K, Elizabeth MO, Susan M, Kariuki N

Data availability

Underlying data

No data are associated with this article.

Extended data

Open Science Framework: Materials and data for the DM-TB immunopathology and lung dysbiosis scoping review. <https://doi.org/10.17605/OSF.IO/WM82P> (Kithinji *et al.*, 2024).

This project contains the following extended data:

- The filled PRISMA-ScR checklist.
- Table 3 showing characteristics of the selected studies.
- Table 4 with data on physical health outcomes in patients with TB extracted from selected sources.
- Table 5 with data on immunological markers of health in patients with TB extracted from the included articles.

Data are available under a Creative Commons (CC0 1.0 Universal) license.

Acknowledgements

We would like to acknowledge the University of Nairobi Library staff for their assistance with initial planning and development of our search strategy.

References

- Alebel A, *et al.*: Prevalence of diabetes mellitus among tuberculosis patients in Sub-Saharan Africa: A systematic review and meta-analysis of observational studies. *BMC Infect. Dis.* 2019; **19**: 254. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Barreda NN, *et al.*: Severe pulmonary radiological manifestations are associated with a distinct biochemical profile in blood of tuberculosis patients with dysglycemia. *BMC Infect. Dis.* 2020; **20**: 139. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bernard-Raichon L, *et al.*: A Pulmonary Lactobacillus murinus Strain Induces Th17 and ROR γ t+ Regulatory T Cells and Reduces Lung Inflammation in Tuberculosis. *J. Immunol.* 2021; **207**(7): 1857–1870. [PubMed Abstract](#) | [Publisher Full Text](#)
- Bisht MK, *et al.*: The cause–effect relation of tuberculosis on incidence of diabetes mellitus. *Front. Cell. Infect. Microbiol.* 2023; **13**: 1134036. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Boillat-Blanco N, *et al.*: Hyperglycaemia is inversely correlated with live *M. bovis* BCG-specific CD4 β T cell responses in Tanzanian adults with latent or active tuberculosis. *Immun. Inflamm. Dis.* 2018; **6**(2): 345–353. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Byashalira KC, *et al.*: Impact of early diagnosis of impaired glucose regulation in tuberculosis: Comparison of clinical outcomes in people with tuberculosis in Tanzania. *Trop. Med. Int. Health.* 2022; **27**(9): 815–822. [PubMed Abstract](#) | [Publisher Full Text](#)
- Chao WC, *et al.*: Increased resistin may suppress reactive oxygen species production and inflammasome activation in type 2 diabetic patients with pulmonary tuberculosis infection. *Microbes Infect.* 2015; **17**(3): 195–204. [PubMed Abstract](#) | [Publisher Full Text](#)
- Chen H, *et al.*: The impact of pulmonary tuberculosis on immunological and metabolic features of diabetic patients. *Front. Immunol.* 2022; **13**(August): 973991. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Chung SH, Ye XQ, Iwakura Y: Interleukin-17 family members in health and disease. *Int. Immunol.* 2021; **33**(12): 723–729. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Comberlati P, *et al.*: The role of gut and lung microbiota in susceptibility to tuberculosis. *Int. J. Environ. Res. Public Health.* 2021; **18**: 12220. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Damoiseau J: The IL-2 – IL-2 receptor pathway in health and disease: The role of the soluble IL-2 receptor. *Clin. Immunol.* 2020; **218**(June): 108515. [PubMed Abstract](#) | [Publisher Full Text](#)
- Darra A, *et al.*: Hyperglycemia is associated with duodenal dysbiosis and altered duodenal microenvironment. *Sci. Rep.* 2023; **13**: 11038. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ding L, *et al.*: Pathogen Metagenomics Reveals Distinct Lung Microbiota Signatures Between Bacteriologically Confirmed and Negative Tuberculosis Patients. *Front. Cell. Infect. Microbiol.* 2021; **11**(September): 708827. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Dumas A, *et al.*: The role of the lung microbiota and the gut–lung axis in respiratory infectious diseases. *Cell. Microbiol.* 2018; **20**(12): 1–9. [Publisher Full Text](#)
- Etna MP, *et al.*: Pro-and anti-inflammatory cytokines in tuberculosis: A two-edged sword in TB pathogenesis. *Semin. Immunol.* 2014; **26**(6): 543–551. [PubMed Abstract](#) | [Publisher Full Text](#)
- Faurholt-Jepsen D, *et al.*: Diabetes is a strong predictor of mortality during tuberculosis treatment: A prospective cohort study among tuberculosis patients from Mwanza, Tanzania. *Trop. Med. Int. Health.* 2013; **18**(7): 822–829. [PubMed Abstract](#) | [Publisher Full Text](#)
- Fraser-pitt DJ, *et al.*: Mycobacterium tuberculosis Rv1987 protein attenuates inflammatory response and consequently alters microbiota in mouse lung. *Front. Cell. Infect. Microbiol.* 2023; **13**: 1256866. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Fukunaga R, *et al.*: Epidemiology of Tuberculosis and Progress Toward Meeting Global Targets — Worldwide, 2019. *Morb. Mortal. Wkly Rep.* 2021; **70**(12): 427–430. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [Reference Source](#)
- Goddard AF, *et al.*: Direct sampling of cystic fibrosis lungs indicates that DNA-based analyses of upper-airway specimens can misrepresent lung microbiota. *Proc. Natl. Acad. Sci. USA.* 2012; **109**(34): 13769–13774. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Gomez D, *et al.*: Reduced association of mycobacteria with monocytes from diabetes patients with poor glucose control. *Tuberculosis.* 2013; **93**(2): 192–197. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Hu Y, *et al.*: Metagenomic analysis of the lung microbiome in pulmonary tuberculosis - a pilot study. *Emerg. Microbes Infect.* 2020; **9**(1): 1444–1452. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Jasenosky LD, *et al.*: T cells and adaptive immunity to Mycobacterium tuberculosis in humans. *Immunol. Rev.* 2015; **264**(1): 74–87. [PubMed Abstract](#) | [Publisher Full Text](#)
- Kithinji D, *et al.*: Open Science Framework: Materials and data for the DM-TB immunopathology and lung dysbiosis scoping review. 2024. [Publisher Full Text](#)
- Koizumi S, *et al.*: Essential role of Toll-like receptors for dendritic cell and NK1. 1 + cell-dependent activation of type 1 immunity by Lactobacillus pentosus strain S-PT84. *Immunol. Lett.* 2008; **120**(2008): 14–19. [PubMed Abstract](#) | [Publisher Full Text](#)
- Kornfeld H, *et al.*: Impact of Diabetes and Low Body Mass Index on Tuberculosis Treatment Outcomes. *Clin. Infect. Dis.* 2020; **71**(9): E392–E398. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Krause R, *et al.*: Failure to decrease HbA1c levels following TB treatment is associated with elevated Th1/Th17 CD4+ responses. *Front. Immunol.* 2023; **14**: 1151528. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kumar NP, *et al.*: Diminished systemic and antigen-specific type 1, type 17, and other proinflammatory cytokines in diabetic and prediabetic individuals with latent mycobacterium tuberculosis infection. *J. Infect. Dis.* 2014; **210**(10): 1670–1678. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kumar NP, *et al.*: Modulation of dendritic cell and monocyte subsets in tuberculosis-diabetes co morbidity upon standard tuberculosis treatment. *Tuberculosis.* 2017; **101**: 191–200. [Publisher Full Text](#)
- Kumar NP, *et al.*: Heterogeneity in the cytokine profile of tuberculosis – diabetes co-morbidity. *Cytokine.* 2020; **125**: 154824. [PubMed Abstract](#) | [Publisher Full Text](#)
- Li H, *et al.*: Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. *Diabetes. Obes. Metab.* 2020; **22**(10): 1897–1906. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lin Y, *et al.*: Unfavourable treatment outcomes in tuberculosis patients with different vitamin D status and blood glucose levels in a programme setting in China. *Trop. Med. Int. Health.* 2020; **25**(3): 373–379. [PubMed Abstract](#) | [Publisher Full Text](#)
- Liu B, *et al.*: Correlation Analysis of the Microbiome and Immune Function in the Lung-Gut Axis of Critically Ill Patients in the ICU. *Front. Med.* 2022; **9**: 808302. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Liu Q, *et al.*: Glycemic Trajectories and Treatment Outcomes of Patients with Newly Diagnosed Tuberculosis A Prospective Study in Eastern China. *Am. J. Respir. Crit. Care Med.* 2021; **204**(3): 347–356. [PubMed Abstract](#) | [Publisher Full Text](#)
- Masood KI, *et al.*: Latent *M. tuberculosis* infection is associated with increased inflammatory cytokine and decreased suppressor of cytokine signalling (SOCS)-3 in the diabetic host. *Scand. J. Immunol.*

2022; **95**: e13134.

[PubMed Abstract](#) | [Publisher Full Text](#)

Meng F, *et al.*: **Impact of diabetes itself and glycemic control status on tuberculosis.** *Front. Endocrinol.* 2023; **14**: 1250001.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Meng J, *et al.*: **Integration of metabolomics and transcriptomics reveals major metabolic pathways and potential biomarkers involved in aging mice with type 2 diabetes mellitus.** *Chin. Med. J.* 2022; **135**(2): 247–249.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Menon S, *et al.*: **The epidemiology of tuberculosis-associated hyperglycemia in individuals newly screened for type 2 diabetes mellitus: systematic review and meta-analysis.** *BMC Infect. Dis.* 2020; **20**: 937.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Mori G, Morrison M, Blumenthal A: **Microbiome-immune interactions in tuberculosis.** *PLoS Pathog.* 2021; **17**: e1009377.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Ngo MD, Bartlett S, Ronacher K: **Diabetes-associated susceptibility to tuberculosis: Contribution of hyperglycemia vs. dyslipidemia.** *Microorganisms.* 2021; **9**: 2282.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Özcam M, Lynch S: **The gut–airway microbiome axis in health and respiratory diseases.** *Nat. Rev. Microbiol.* 2024; **22**: 492–506.

[PubMed Abstract](#) | [Publisher Full Text](#)

Palma Albornoz SP, *et al.*: **Obesity-induced dysbiosis exacerbates ifn- γ production and pulmonary inflammation in the mycobacterium tuberculosis infection.** *Cells.* 2021; **10**: 1732.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Panda S, *et al.*: **Chronic hyperglycemia drives alterations in macrophage effector function in pulmonary tuberculosis.** *Eur. J. Immunol.* 2022; **52**(10): 1595–1609.

[PubMed Abstract](#) | [Publisher Full Text](#)

Panda S, *et al.*: **Hyperglycemia modulates M1/M2 macrophage polarization in chronic diabetic patients with pulmonary tuberculosis infection.** *Immunobiology.* 2024; **229**(2): 152787.

[PubMed Abstract](#) | [Publisher Full Text](#)

Pardeshi G, *et al.*: **Glycated Hemoglobin Trajectories and Their Association With Treatment Outcomes Among Patients With Pulmonary TB in India: A Prospective Cohort Study.** *Chest.* 2024; **165**(2): 278–287.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Rao M, *et al.*: **Immunometabolism and Pulmonary Infections: Implications for Protective Immune Responses and Host-Directed Therapies.** *Front. Microbiol.* 2019; **10**: 962.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Rendón Ramírez EJ, *et al.*: **Comparison of CD4+/CD8+ Lymphocytic Subpopulations Pre- and Post-Antituberculosis Treatment in Patients with Diabetes and Tuberculosis.** *Pathogens.* 2023; **12**: 1181.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Schulthess J, *et al.*: **The Short Chain Fatty Acid Butyrate Imprints an Antimicrobial Program in Macrophages.** *Immunity.* 2019; **50**(2): 432–445.e7.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Suzukawa M, *et al.*: **Evaluation of cytokine levels using QuantiFERON-TB Gold Plus in patients with active tuberculosis.** *J. Infect.* 2020; **80**(5): 547–553.

[PubMed Abstract](#) | [Publisher Full Text](#)

Ticlla MR, *et al.*: **The Sputum Microbiome in Pulmonary Tuberculosis and Its Association With Disease Manifestations: A Cross-Sectional Study.** *Front. Microbiol.* 2021; **12**: 633396.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Uciechowski P, Dempke WCM: **Interleukin-6: A Masterplayer in the Cytokine Network.** *Oncology.* 2020; **98**(3): 131–137.

[PubMed Abstract](#) | [Publisher Full Text](#)

Wang S, *et al.*: **Characteristic gut microbiota and metabolic changes in patients with pulmonary tuberculosis.** *Microb. Biotechnol.* 2022; **15**: 262–275.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

World Health Organization: **Global Tuberculosis Report 2023.** Geneva; 2023. [Reference Source](#)

Wu J, *et al.*: **Sputum microbiota associated with new, recurrent and treatment failure tuberculosis.** *PLoS One.* 2013; **8**(12): e83445.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Xia X, *et al.*: **Comparative analysis of the lung microbiota in patients with respiratory infections, tuberculosis, and lung cancer: A preliminary study.** *Front. Cell. Infect. Microbiol.* 2022; **12**: 1024867.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Yuk J, *et al.*: **TNF in Human Tuberculosis: A Double-Edged Sword.** *Immune Netw.* 2024; **24**(1): e4.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:   

Version 1

Reviewer Report 19 February 2025

<https://doi.org/10.5256/f1000research.175303.r362451>

© 2025 Miraj S. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Sonal Sekhar Miraj 

Manipal Academy of High Education, Manipal, India

1. In the abstract, the authors mention, "The composition of the lung microbiota changed in correlation with changes in physical health outcomes, counts of immune cells, and cytokine levels." What way composition of microbiota should be mention (phylum levels, genes level or microbial diversity)
2. Effect of the hyperglycemia on lung microbiota, the readers will expect changes in the microbial diversity and richness. These points are not discussed in the manuscript
3. How can you ensure the dysbiosis in the lung microbiota is due to hyperglycemia alone, because TB and its ATT drugs itself can cause the dysbiosis.
4. In conclusion, authors mention "hyperglycemia and lung microbiota are involved in the pathogenesis of DM-TB,"
Is it pathogenesis of DM-TB? this is not clear

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Diabetes and Tuberculosis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 12 February 2025

<https://doi.org/10.5256/f1000research.175303.r362457>

© 2025 Hussain T. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Tahziba Hussain

HIV/AIDS UNIT, ICMR-Regional Medical Research Centre, Bhubaneswar, India

I have gone through the manuscript entitled, "[*Effect of hyperglycemia on lung microbiota and treatment outcome in pulmonary tuberculosis: A scoping review*](#)" carefully.

It is a very good study and presented clearly.

Comments :

1. There are spelling mistakes at more than 4 places. Plz. correct these.
2. First of all, the authors need to adopt a uniform style of writing. The entire manuscript should be written in Times New Roman, Font 12 with double spacing. The present one is Times New Roman, Font 12 with 1.5 paragraph spacing.
3. **Abstract :** Include the place of study in Keywords. It is important.
4. The methodology, i.e., selection criteria of studies included, excluded, screened, assessed for eligibility, etc. in the review need to be represented in a figure.

If the authors can incorporate the suggested changes in the study, it would really improve the presentation.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 11 February 2025

<https://doi.org/10.5256/f1000research.175303.r360302>

© 2025 Ayeni F. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Foluke Adenike Ayeni 

Department of Clinical Pharmacy and Biopharmacy, Faculty of Pharmacy, University of Lagos, Akoka, Lagos, Nigeria

This article is a scoping review that explores the effect of hyperglycemia on lung microbiota and treatment outcomes in patients with pulmonary tuberculosis (TB) and diabetes mellitus (DM). It revealed that hyperglycemia and lung microbiota are involved in the pathogenesis of DM-TB, which culminates in poor treatment outcomes in pulmonary TB.

The objectives of the review are well-defined and relevant to the field of pulmonary tuberculosis (TB) and hyperglycemia. The study clearly aims to explore the relationship between hyperglycemia and lung microbiota, as well as its impact on TB treatment outcomes. The objectives address an important gap in the literature, and the approach is highly timely given the increasing prevalence of both TB and diabetes worldwide.

The method used in this scoping review is thorough and appropriate for the topic at hand. The systematic search strategy is comprehensive, and the inclusion/exclusion criteria are well-justified. The reviewer's approach to categorizing and summarizing the literature is rigorous, providing a clear framework for understanding the complexities of hyperglycemia's effect on lung microbiota and TB treatment outcomes.

The results are presented clearly and systematically. The synthesis of existing studies is balanced, providing a comprehensive overview of the current state of research while also identifying areas of uncertainty. The results will undoubtedly be valuable for future research and clinical applications.

The discussion section is insightful and well-rounded. The authors effectively interpret the findings, connecting them to existing literature and providing context for their implications in TB treatment. They thoughtfully highlight the importance of understanding the interplay between

hyperglycemia and the lung microbiota, particularly in diabetic TB patients. Finally, the conclusions captured and supported the results obtained in the review.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TB-DM comorbidity.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research