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REVIEW

Glycemic Profile and Clinical Treatment in Patients with Diabetes Mellitus-Tuberculosis: An Update Scoping Review

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Background: Type 2 diabetes mellitus (T2DM), characterized by chronic hyperglycemia, leads to a decreased immune system and increased susceptibility to infections, such as tuberculosis (TB). However, there are gaps in comprehensive reviews on the relationship between TB and the severity of glycemic control in patients with T2DM, characteristics of glycemic levels, and clinical treatment among patients with DM-TB.

Purpose: The primary aim of this study is to explore the association of DM-TB and glycemic control. The secondary aim of this study was to explore the association between DM-TB, successful treatment, and TB severity.

Methods: This study used a scoping review following the Arksey and O'Malley framework to provide an overview of glycemic control and clinical treatment of DM-TB. A literature search was performed using three databases, PubMed, Scopus, and Medline, with inclusion criteria for the population of patients with diabetes mellitus and tuberculosis who discuss glycemic control and clinical treatment. Critical appraisal in this study was assessed using the Joanna-Briggs Institute (JBI) critical appraisal tools.

Results: We included 16 studies from a total of 741 articles in the initial search. The results of this study showed that patients with DM-TB were more likely to have poor glycemic control than those with diabetes mellitus (DM) without TB. Severe hyperglycemia in patients with DM-TB is associated with an increased risk of TB treatment failure, a long recovery time, and the likelihood of developing multi-drug-resistant tuberculosis (MDR-TB). In addition, patients with DM-TB who did not start TB treatment were more likely to have poorer glycemic control than patients with DM-TB who underwent active TB treatment.

Conclusion: Patients with DM-TB, such as MDR-TB, are at a higher risk of poor glycemic control, treatment failure, and clinical severity. Adequate treatment, such as a continuum of glycemic monitoring and early detection and intervention for TB, is needed to improve treatment outcomes.

Keywords: diabetes mellitus, DM-TB, glycemic control, tuberculosis

Introduction

Diabetes mellitus (DM) is a chronic disease where the pancreas cannot produce enough insulin or cells do not respond appropriately.[1] According to the International Diabetes Federation (IDF), there is expected to be an increase in diabetes cases worldwide from 2021 to 2045.[2] In 2021, approximately 536.6 million cases of diabetes were reported in the 20–79 age group. It is predicted to grow to 642.8 million by 2030, with a prevalence of 10.8% and 783.7 million in 2045.[2]

Type 2 DM (T2DM) is the most common type of DM, accounting for approximately 90% of all diabetes cases. Uncontrolled glycemia in DM patients can lead to various disease complications.[3] Patients with DM are at high risk of developing chronic infections such as immunocompromised tuberculosis (TB).[4] Hyperglycemia in T2DM can suppress the immune system by reducing the production of cytokines, such as interleukin-1 beta (IL-1β) and IL-6 that function against the infection.[5] TB in DM is present due to uncontrolled diabetes management, thus increasing susceptibility to infection with mycobacterium tuberculosis.[6] Evidence showed that people with diabetes have a 2 to 4 times higher risk of

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developing tuberculosis.[7] According to a meta-analysis, the estimated prevalence of DM-TB comorbidities globally was 13.73% and is highest in Asian and North American countries.[8] North America has a prevalence rate of 19.7%, and Asia has a prevalence rate of 19.0%.[9] Hence, the prevalence of DM-TB comorbidities is 1.8 to 9.5 times higher compared to the general population in developing countries.[10]

Patients with DM-TB had higher glycemic levels than those with DM alone. Previous studies have shown that TB infection can worsen glycemic levels due to chronic inflammation. Increased glucose concentrations can trigger the chronic production of advanced glycation end products (AGEs).[6,11] Moreover, TB is associated with an increased risk of hyperglycemia-related complications.[4] There is a reciprocal relationship between DM and TB, where DM can increase the severity of the TB infection process, while TB worsens blood glucose levels and increases the risk of complications in patients with DM.[12]

Healthcare providers face challenges in treating DM-TB comorbidities due to associated suboptimal retention in TB medication and lower efficacy of TB treatment.[13] Also, DM patients with TB also face the challenge of achieving optimal glycemic control while undergoing TB treatment, due to interactions between one of the main drugs for TB (eg rifampicin) and some oral antidiabetic drugs that affect diabetes-therapy efficacy.[14] Another alternative used is the use of insulin to treat severe hyperglycemia, but this insulin requires a continuum of monitoring to prevent the risk of hypoglycemia.[14] Hyperglycemia in TB patients is a predictor of treatment failure in TB, sputum positivity, and fewer cavitary lesions.[15] These challenges may lead to multi-drug-resistance (MDR). Therefore, maintaining glycemic control and adjusting appropriate therapeutics into clinical practices can optimize treatment outcomes for DM-TB comorbidities.[16] Understanding glycemic control and its implications to treatment outcomes in TB-DM treatment clinical practice can inform health policies throughout TB treatment guidelines, ensuring comprehensive care and better outcomes for patients with DM-TB.

There is still a gap in comprehensive reviews describing the association between tuberculosis and glycemic control severity in patients with T2DM. To date, no review studies have thoroughly summarized the characteristics of glycemic control and clinical treatment in patients with DM-TB. Previous reviews have only addressed the correlation between DM and susceptibility to TB,[17,18] and their studies did not specifically highlight the characteristics and correlation of DM-TB with clinical progression, especially glycemic control. Therefore, the current review was conducted to describe the characteristics of glycemic levels and clinical treatment among patients with DM-TB. This review aimed to provide glycemic and clinical characteristic features that can inform future clinical practice and research.

Materials and Method

Design

This study used a scoping review following the PRISMA Extension for Scoping Reviews (PRISMA-ScR) Arksey and O'Malley (2005).[19,20] The broad review question of this study is how to characterize glycemic levels and clinical treatment in patients with DM-TB. The narrow question of this review is what the correlation of TB-DM comorbidity with glycemic control and clinical treatment.

Eligibility Criteria

The search strategy followed the PRISMA-ScR guidelines. Article selection was based on the inclusion and exclusion criteria. In this study, the PCC framework is used as a guide.

Population: Patients with diabetes mellitus

Concept: Comorbid of tuberculosis

Context: Glycemic control and clinical treatment

Additionally, we included primary observational studies (cross-sectional, cohort, and case–control studies) and research subjects with type 2 diabetes mellitus who experienced tuberculosis. We also included articles published within the last 10 years (2014–2024) to reduce variability in treatment due to updates in the treatment guidelines for DM-TB. The exclusion criteria include conference papers, non-peer-reviewed articles, and articles with only abstracts available.

Search Strategy and Study Selection

PubMed, Scopus, and Medline were selected to search for articles in this scoping review. We used a keyword-adjusted MeSH term that included diabetes mellitus (DM)-TB and glycemic control (see Supplementary File 1). The literature search process was conducted in August 2024. Two independent authors (S. R. and N. N.) screened the titles and abstracts. The full text was read and extracted by two independent authors. In case of disagreement between the authors, a discussion was held to reach an agreement. Two independent reviewers conducted a study assessment and consulted another author (T. P.) for finalization. The Joanna Briggs Institute (JBI) critical appraisal tool was used for the quality assessment. Articles were considered to meet the quality criteria if they obtained a minimum score of 75%, calculated based on the total score of all statements. The quality assessment score of the JBI varied between 75% and 90.9%. As many as eight articles had a quality above 85%,[21–29] and as many as four had a quality between 75% and 85%.[16,30–35] More details about the study characteristics can be found in Supplementary File 2.

Data Extraction and Analysis

Data extraction was performed by the first author (S. R.) and rechecked by other authors (N. N. and T. P.). We collected important information from the articles reviewed in the next stage. The results of this review are summarized in Table 1 containing information on the author, year of publication, research location, research design, sample, and findings. The authors then compared this information with the existing findings. Once the articles were collected, the next step was thorough reading and in-depth analysis by all authors. Once the analysis was complete, the discussions from the review were categorized based on similarities and described in detail. Thematic analysis with a qualitative approach was used.

Results

Study Selection

Based on search results from several databases, 741 articles were found, 73 articles were detected as duplications, and 668 articles remained. The selection of articles from several databases was then adjusted according to the previously determined inclusion and exclusion criteria. The articles were then selected based on their title and abstract, which followed the research objectives. A total of 92 articles were obtained. We then assessed the eligibility of the full-text articles and found that 16 articles were included and analyzed in this review. A total of eight articles were excluded because they met the JBI article assessment criteria below 75%, and only ten articles were obtained in the database search. Then, 10 more articles were obtained from manual hand searching, and two articles were excluded because they were not relevant to the specified objectives and population; two other articles were excluded because the JBI was below 75%, and eight articles remained. Therefore, the total number of articles included in this scoping review was 16 (Figure 1). Several themes were related to the impact of tuberculosis comorbidity on glycemic control in patients with type 2 diabetes mellitus (Table 1). These themes include a description of the characteristics of patients with DM-TB, glycemic control in patients with DM-TB, and treatment patterns in patients with DM-TB.

Demographic Characteristics of Patients with DM-TB

The included studies were cross-sectional (n = 5), retrospective (n = 5), prospective (n = 4), and case–control (n = 2) cohorts. The total sample size of all the articles included 145.094 people. The articles reviewed in this scoping consisted of 16 articles, of which four were from China, one from Tanzania, one from Spain, one from the United States, one from the Philippines, one from South Africa, one from Pakistan, four from India, and two from Taiwan. Based on the ten articles reviewed, most patients with DM-TB coexistence or those who experienced hyperglycemia during the TB treatment phase were male. The percentage of male patients varied between 56.2% and 81.57%.[21,24–26,28,29,31,32,34,35] The mean age of patients varied between 40 and over 60 years, with the majority being in the 50–59 years range.[16,21,24,26,29,30,32] See details in Table 2.

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Table 1 Data Extraction

Study	Outcome	Country	Design	Sample	Results
[25]	To determine the severity of hyperglycemia at the time of TB diagnosis.	Tanzania	Cross-Sectional	105 DM patients with tuberculosis	• A total of 39% (41 people) experienced severe hyperglycemia characterized by HbA1c (≥86 mmol/mol). • A previous history of DM (OR: 3.71, P = 0.013) and a predominantly female gender (OR: 3.55, P = 0.040) are factors that influence the condition of hyperglycemia.
[24]	To determine whether poor blood sugar control is associated with an increased risk of TB in patients with DM.	Spain	Retrospective Cohort Study	8.004 patients with DM	• Poor glycemic control with HbA1c levels ≥9% in patients with DM increases the risk of TB. • Patients with poor glycemic control had a 4.36 times higher risk of developing TB.
[31]	To identify risk factors that can potentially develop Multidrug Resistance (MDR) in patients with DM-TB.	China	Retrospective Cohort Study	200 patients (156 non-MDR TB patients and 44 MDR TB patients)	The results showed that age below 65 years, high HbA1c levels, and having failed previous TB treatment were factors that increased the risk of developing MDR in patients with DM-TB.
[22]	To explore the relationship between diabetes and tuberculosis (TB) infection risk and see how glycemic control affects this relationship.	United States	Retrospective Cohort Study	4.215 participants	• Patients with DM have a higher risk of TB infection, with a prevalence of 7.6%. • Poor glycemic control significantly increases the risk of TB infection in patients with DM. • Every 1 mg/dL increase in FPG and PG and every 1% increase in HbA1C increased the risk of TB infection.
[33]	To analyze whether hyperglycemia (diabetes and pre-diabetes) causes delays in detecting TB disease.	China	Cross-Sectional	2.280 TB patients	• Hyperglycemia, including DM and Pre-DM, can significantly increase the likelihood of a patient's delay in detecting TB disease. • Hyperglycemia increases the likelihood of such delays by twofold.
[21]	To analyze glycemic control in patients with DM who are undergoing TB treatment.	Philippines	Prospective Cohort Study	188 patients with DM-TB	• A total of 40% (177 patients) with DM-TB who were undergoing TB treatment had glycemic levels above 8%. • Patients who were already diagnosed with DM before starting TB treatment tended to have poorer glycemic control compared to patients who were diagnosed with DM at the time of TB treatment.
[32]	To explore the impact of DM on diabetes and glycemic control status in TB patients.	China	Retrospective Cohort Study	3.393 TB patients with DM	• From the study's results, TB patients with DM were 11.3%, and those with reasonable glycemic control were 15.8%, while 68.2% had poor glycemic control. • Poor glycemic control is associated with the risk of lung cavities formation and the spread of lesions in patients with DM-TB.

[23]	To identify risk factors for TB in patients with DM.	China	Case-Control Study	315 patients	Major risk factors associated with increased risk of TB in patients with DM include poor glycemic control, history of contact with TB patients, smoking, and low frequency of DM rechecks.
[16]	To explore the link between glycemic control in diabetes patients and the likelihood of developing active TB.	Taiwan	Prospective Cohort Study	123.546 patients`	• During the follow-up period of an average of 4.6 years, 327 TB cases were recorded. • This study showed that diabetic patients with poor blood sugar control (FPG > 130 mg/dl) had more than double the risk of developing TB compared to non-diabetic individuals. • The study also estimated that about 7.5% of TB cases in diabetic patients were due to poor blood sugar control.
[34]	To determine how poor glycemic control affects newly diagnoses smear-positive pulmonary tuberculosis patients with type 2 diabetes.	India	Prospective Study	630 individual	• The study found that 423 patients had poor glycemic control (PGC), while 207 had optimal glycemic control (OGC). • Specifically, 76.6% of PGC patients had lung cavities, compared to 43.48% in the OGC group. Treatment outcomes were also worse for the PGC group, with higher rates of treatment failure (23.4% vs 4.35%) and relapse (16.5% vs 2.3%).
[35]	To examine how poor glycemic control affects the X-ray findings in newly diagnosed smear-positive PTB patients with type 2 diabetes.	India	Cross Sectional	70 patients diabetes with TB	• Among 70 patients, 67.1% had poor blood sugar control (HbA1c ≥7%). • The study also found that patients with poor glycemic control had more cavities in their lungs, with 76.6% showing cavitary lesions compared to 43.5% in those with better control.
[26]	To study how glycemic control affects the clinical outcomes of smear-positive PTB patients with diabetes.	Pakistan	Prospective Study	280 patients	• Out of 280 patients, 173 had poor blood sugar control, while 107 had good control. • At the end of the intensive treatment phase, 50.3% of patients with poor control were still smear-positive, while only 12.1% of those with good control remained smear-positive.
[27]	To understand how blood sugar control affects tuberculosis symptoms, which can help improve the detection and treatment of both conditions.	India	Cross Sectional	50 patients	• This study showed that glycemic control has a significant impact on the clinical and radiological manifestations of pulmonary tuberculosis (TB) in patients with diabetes mellitus (DM). Of the total 50 patients studied, 90% had poor glycemic control (HbA1c >7%) and only 10% had good control (HbA1c ≤7%). • In terms of radiological findings, right lung lesions were more common in the group with HbA1c >12%, while left lung lesions were more common in the group with good glycemic control.

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Table 1 (Continued).

Study	Outcome	Country	Design	Sample	Results
[28]	To evaluate the impact of glycemic status on radiological findings of PTB in diabetic patients.	Taiwan	Retrospective Study	214 patients	• Diabetic patients were more likely to have unusual X-ray results, such as signs of primary tuberculosis and more severe lung disease, compared to non-diabetic patients. • Specifically, those with HbA1c levels over 8% were more likely to have abnormal findings and advanced disease. • The study also showed that these unusual X-ray findings were more common in diabetic patients, especially in those with poor blood sugar control.
[29]	To examine whether metformin helps protect against tuberculosis in diabetic patients and to explore the link between poor blood sugar control and tuberculosis.	India	Case Control	451 patients	• The study found that poor blood sugar control (HbA1c >8) was more common in the study group (51.7%) than in the control group (31.4%). • The use of metformin was strongly linked to a lower risk of tuberculosis, with an odds ratio of 0.256, meaning it reduced the risk by 3.9 times.
[30]	To assess how common active tuberculosis is in diabetic patients.	South Africa	Cross Sectional	135 patients	• The results showed that there was no significant difference in blood glucose levels between diabetic patients diagnosed with TB and those without TB. • The mean HbA1c level in patients with TB was 9.5% (IQR 8.20–9.90), while that in patients without TB was 9.1% (IQR 7.30–11.00), with a p value of 0.897, indicating this difference was not statistically significant. • Although there was no significant difference in diabetes control between TB and non-TB patients, approximately 80% of diabetic patients had poor blood sugar control.

Abbreviation: DM, Diabetes Mellitus; IGT, Impaired Glucose Tolerance; MDR, Multidrug Resistance; PTB, Pulmonary Tuberculosis; TB, Tuberculosis.

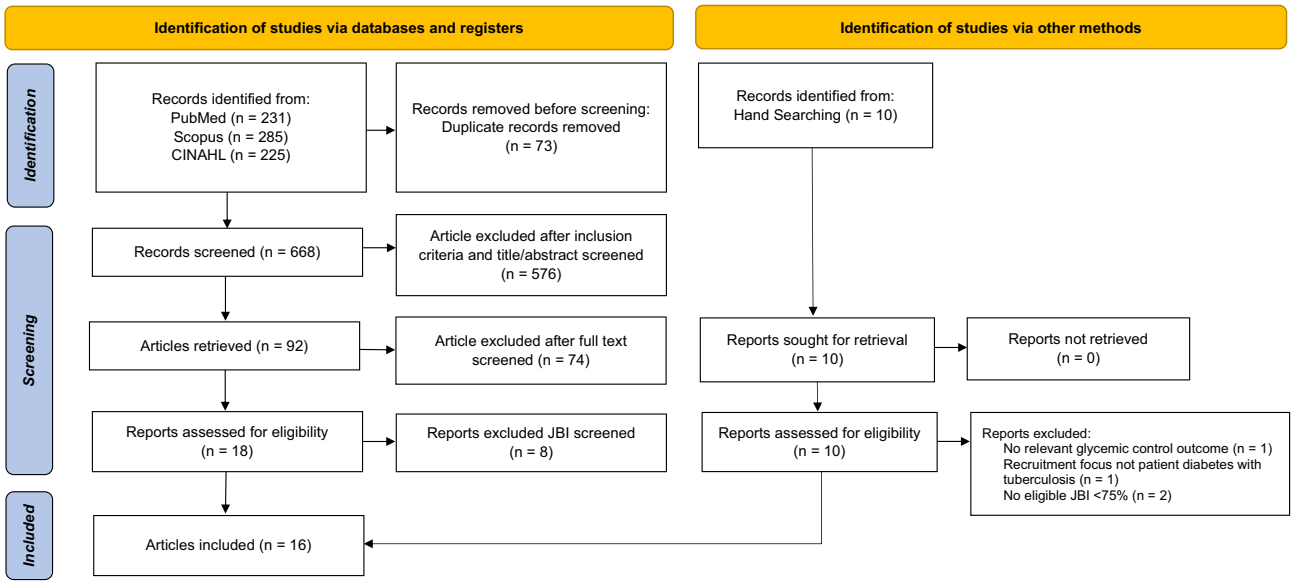

Figure 1 PRISMA flow diagram adapted from Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:71. Creative Commons.[36]

Clinical Characteristics of Patients with DM-TB

There were variations in the nutritional status of patients with DM-TB (Table 2). The proportion of underweight patients with a body mass index (BMI) of less than 18.5 was 61%.[21] Patients with BMI in the normal category (18.5 to 23.9) reached 73.9%[22,23] among patients in the DM-TB range of 1.4 years and 3.6 years following DM diagnosis.[23,24,31] Comorbidities in patients with DM-TB, including hypertension (0.24%) and macrovascular complications (8.33%).[24] There was also specific data showing 47 patients with stage 1 hypertension.[21]

Table 2 Characteristics of Patients With DM-TB

Category	Study	Details
Gender (%)	[25]	Male (56.2%)
	[24]	Male (68.8%)
	[32]	Male (81.55%)
	[21]	Male (65.7%)
	[31]	Male (59.0%)
	[34]	Male (68%)
	[35]	Male (68%)
	[26]	Male (64.7%)
	[28]	Male (80.3%)
	[29]	Male (81.57%)
Age (years)	[25,34,35]	40–49 years
	[16,21,24,26,29,30,32]	50–59 years
	[22,23,28,31]	>60 years

(*Continued*)

Table 2 (Continued).

Category	Study	Details
BMI (Body Mass Index) (%)	[21]	Underweight (BMI < 18.5): 61%
	[23]	Normal Range (BMI 18.5–23.9): 73.9%
	[22]	Normal Range (BMI 18.5–23.9): 73.9%
Duration of DM (years)	[23]	1.4 years
	[24]	2.59 years
	[31]	3.6 years
Other Comorbidities (%)	[24]	Macrovascular (8.33%)
	[31]	Hypertension (0.24%)
	[21]	Stage 1 Hypertension (47 people)

Abbreviation: BMI, Body Mass Index.

Glycemic Profile in Patients with DM-TB

Among patients with DM-TB, patients with previous DM had poorer glycemic control during TB treatment compared to those with newly diagnosed DM.[21] Figure 2 and Table 1 show that most HBA1C among patients with DM TB is ≥7%, and a few patients with HBA1C >10%. Only one study reported HBA1C levels of <7%.

Correlation of Glycemic Control and Tuberculosis Treatment

The management and use of treatment in patients with DM-TB require more attention. Poor glycemic control often defined as HbA1c levels of ≥7% control can increase the risk of complications during TB treatment, including prolonged

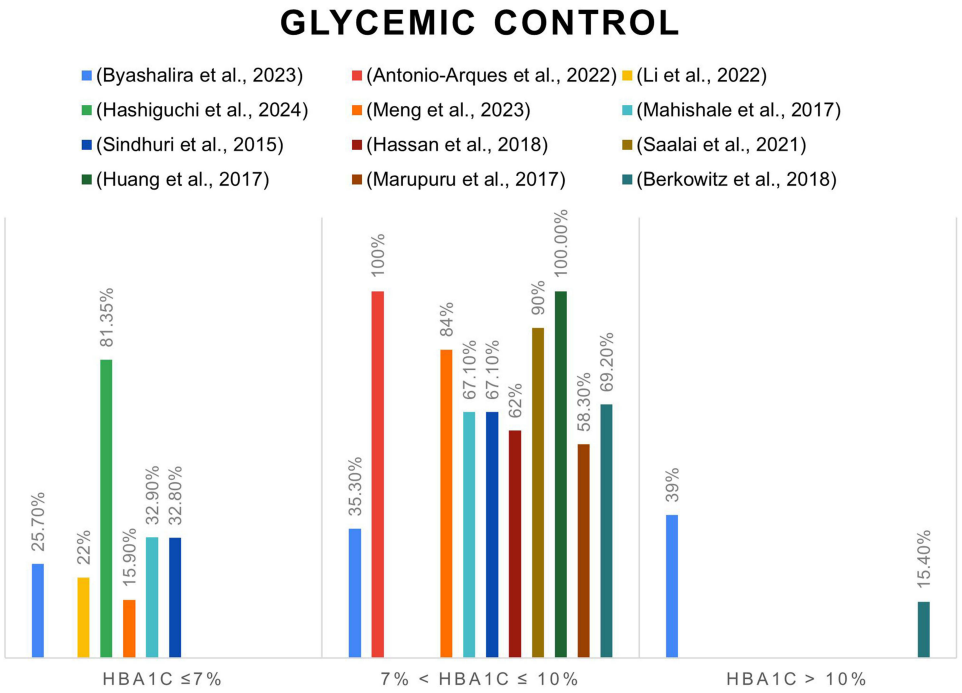

Figure 2 Distribution of HbA1c levels in DM-TB patients.

recovery time and recurrence of TB.[25,34] The frequency of active TB drug treatment failure is being presented in 2330% among patients who had poor glycemic control during active TB treatment.[23,25,26,33,34] Suboptimal glycemic control correlated with multidrug resistance (MDR). Patients with MDR presented in 11–21.8% of patients who had poor glycemic control.[21,34] There is a significant difference between MDR and non-MDR patients in glycemic control, whereas the MDR group was more likely to have poor glycemic control compared to those without MDR.[31] See details of the correlation between glycemic control and tuberculosis treatment in Table 1.

Characteristic of Treatment in Patients with DM-TB

Table 1 shows the treatment characteristics of patients with DM-TB. Treatment therapy to control blood glucose levels in patients with DM-TB most likely uses insulin, oral hypoglycemic agents (OHA) such as metformin, sulfonylureas, and biguanides, as well as the use of combined oral medication and insulin treatment.[16,23,29,32] Poor glycemic control and poor metformin use may influence the risk of treatment failure and increase the risk of inflammation in patients with DM-TB.[21]

Discussion

Diabetic patients are more susceptible to TB infection, with the risk of TB infection increasing with every 1 mg/dL increase in GDP and every 1% increase in HbA1c.[22] This scoping review overviews the characteristics of glycemic control among patients with DM-TB. The findings showed that the glycemic profile of patients with DM-TB was ≥7%. Poor glycemic control in patients with DM-TB increases the risk of TB treatment failure and the development of MDR. Moreover, medication for DM-TB is standard care, including diabetic management and active TB treatment. These findings suggest that patients with DM-TB face significant challenges in controlling their glycemic and active TB treatments.

Patients with DM-TB tend to have poor glycemic control compared to DM patients without TB. The prevalence of poor glycemic control in patients with DM-TB reached 77.9%, which is much higher than that in DM patients without TB (56.5%).[23] Patients with previously diagnosed DM tended to exhibit poorer glycemic control compared to newly diagnosed patients during TB treatment.[21] Patients with hyperglycemic levels at the start of treatment are at a higher risk of lung damage, poorer treatment outcomes, and a higher risk of death after treatment.[37] Mild hyperglycemia is very common in tuberculosis patients and hyperglycemic levels in most patients return to normal after undergoing tuberculosis treatment.[38] Patients with normal glycemic levels in the prior show a decrease in glycemic levels back to the end of treatment.[37]

Poor glycemic control in patients with DM-TB has been associated with higher disease severity, including severe radiological manifestations.[28] Studies have demonstrated that patients with DM-TB tend to have more progressive lower lung involvement and higher incidence of cavitary lesions compared to those with better glycemic control.[34,35] It has been shown that hyperglycemia can inhibit the body's immune response to TB infection due to impairment of macrophages resulting in a worse prognosis, delayed recovery, and increased frequency of multi-drug resistance tuberculosis (MDR-TB).[22–25,28,31,32,39,40] Patients with DM-TB were more likely to have treatment failure compared to TB patients without diabetes.[31] This condition may lead to a higher risk of death during ineffective active TB treatment.[41] However, other studies have shown that the presence of DM has no significant impact on TB treatment outcomes.[42–44] These optimal outcomes of TB treatment were likely associated with adherence to glycemic control and receiving appropriate diabetes care and treatment.[13,43–45] Therefore, there still remained inconsistent findings on glycemic control and TB outcomes among people with DM-TB.

DM and TB are diseases that affect each other and can worsen both conditions. Hyperglycemia in people with DM can weaken the body's immune response to TB infection, thus inhibiting the ability of macrophages to kill Mycobacterium tuberculosis. However, TB can worsen glycemic control in people with DM because the infection causes metabolic stress that can lead to elevated blood glucose levels. This metabolic stress can trigger the release of stress hormones such as cortisol and pro-inflammatory cytokines that can worsen hyperglycemia in patients with TB.[46] Therefore, patients with DM are at higher risk of TB treatment failure if their glycemic control management is poor.[39]

Interventions include adjusting antidiabetic drugs, providing insulin therapy tailored to the patient's condition, educating patients about self-care and stress management, and tailoring the dose.[47,48] Regular glycemic monitoring is also needed to monitor and evaluate the effectiveness of the medication. As a public health strategy, the involvement of health workers and their families is important to monitor TB medication adherence and the glycemic level of patients in the community.[49,50] As such, multidisciplinary strategies can be optimized to ensure that patients not only receive

appropriate therapy but are also supported in undergoing lifestyle changes, thereby reducing the risk of further complications in patients with DM-TB. Nurses and dietitians are responsible for educating patients to adhere to healthy lifestyle changes and TB medication adherence.[51,52] If necessary, remote-based interventions are recommended to be integrated with standard treatments to ensure optimal medication adherence.[53,54]

The strength of this review is the systematic search of literature combined in several databases and manual searching, which also included quality articles that were assessed to assess bias among studies; however, this review has several limitations. The sample size used in this study needs to be increased, as related research has been limited to a few countries, particularly those with different health systems and prevalence of DM-TB. With a limited sample size and small area coverage, this study's findings may differ from those of a wider population, limiting the generalizability of the results.

Conclusion

This review concluded that patients with DM-TB face significant challenges in controlling their glycemic and active TB treatments. Patients are more likely to have hyperglycemia, which is associated with treatment failure of TB, prolonged recovery time, and death. This review suggests a tailored policy of treatment to improve treatment efficacy globally. Future research should evaluate the effectiveness of glycemic management strategies in patients with DM-TB, including medication regimens and behavioral therapy, to improve treatment adherence.

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Disclosure

The authors report no conflicts of interest in this work.

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