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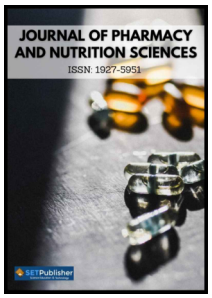

Treatment Strategies and Challenges in the Co-Management of Type 2 Diabetes and Tuberculosis

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Abstract:

Despite rapid advances in the healthcare field, diabetes mellitus (DM) and tuberculosis (TB) continues to be a global burden that affects millions of people every year. The association between DM and TB has been known for an extended period. The last 15 years, however, have seen an increased number of studies showing that diabetes (both type 1 and type 2) increases the risk of tuberculosis because of impaired immune defences and likewise, TB may induce hyperglycemia and therefore increase the risk of DM. When DM and TB co-exist as dual diseases, it complicates management strategies as treatment outcomes are affected. In developing countries where the epidemic of DM and TB is rapidly growing, the presence of a concomitant disease becomes a challenge to the affected nation and could also impact DM and TB control on a global scale. This review brings together information on what is currently known about T2DM and TB as a double epidemic, the recommended treatment strategies, and the challenges involved in disease management. Furthermore, we address the future perspectives of the co-management of T2DM and TB and what can be done to overcome the shortcomings of currently available guidelines.

INTRODUCTION

The management of diabetes mellitus (DM) remains a formidable challenge. In 2017, approximately 425 million DM cases have been reported, and this figure is expected to increase annually [1]. The number of people suffering from type 2 diabetes mellitus (T2DM) is also increasing in various countries as T2DM is responsible for up to 95% of DM cases [2]. On the other hand, tuberculosis (TB) is a global epidemic that produces a significant disease burden. According to the World Health Organization (WHO) global tuberculosis report 2018, in 2017, TB had caused approximately 1.6 million deaths globally across all age, ethnicity and gender [3]. Their association with one another further complicates the management of these diseases. DM raises the risk of TB by 2 to 3 folds and increases the risk of adverse events in anti-TB therapy [3]. Therefore, it has been a challenge to treat TB and DM as a concomitant disease because TB is known to cause stress-induced hyperglycemia, which may complicate the management of DM [2]. Here, we provide a review on T2DM and TB as comorbidity and the treatment strategies and challenges of managing this concomitant disease.

MATERIALS AND METHOD

The main sources of data used were PubMed, Nvivo, Mendeley, Evernote, CiteUlike, Biohunter, Delvehealth, Scicurve, and Google Scholar, etc. Articles on the prevalence of tuberculosis in diabetes mellitus patients or vice versa in the recent 5 years were used. The search terms used in this study were: ("Tuberculosis"[Mesh] AND "Diabetes Mellitus, Type 2"[Mesh]) AND "Prevalence"[Mesh] AND ("2014/02/24"[PDat]: "2019/02/22"[PDat]). There were 796 articles published during the search duration, however, only free full-text articles were included in this review, which includes 530. Among these 530 articles, only randomised controlled trials, clinical trials, systematic review articles on human subjects were only included finally for the analysis. The preclinical studies on animals, formal review, book chapters, abstracts were excluded from the analysis. Finally, 28 articles that met the study criteria were included for analysis. The articles were further segregated based on the subsections for analysis. All the authors independently extracted the relevant information from the published studies that fulfilled our inclusion criteria, and any disagreements were resolved with consensus.

The search strategy included in this review is (("tuberculosi"[All Fields] OR "tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields] OR "tuberculoses"[All Fields] OR "tuberculosis s"[All Fields]) AND ("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND

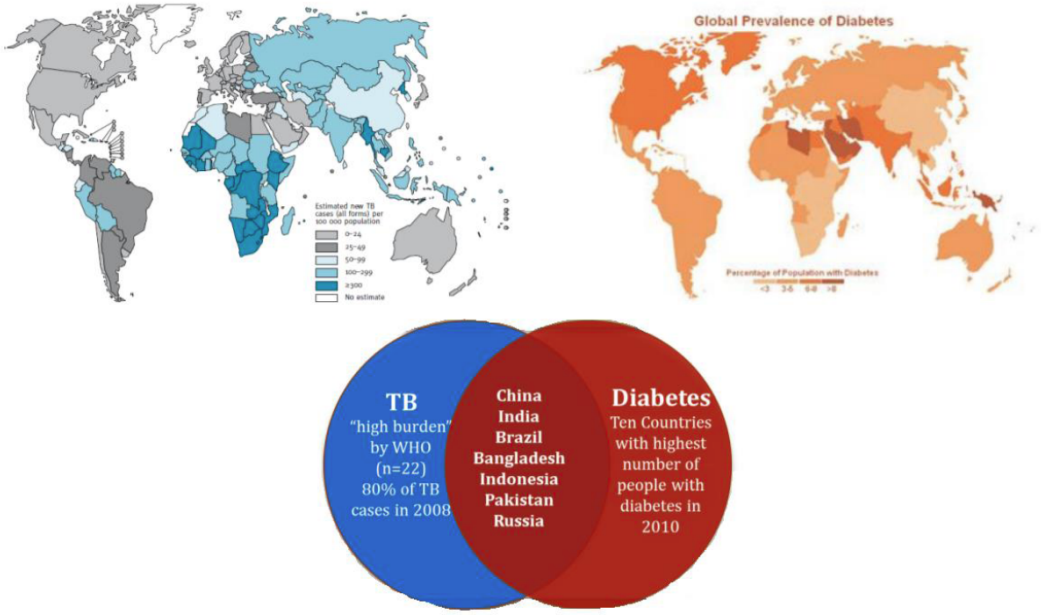

Figure 1: World diabetes foundation prevalence report on diabetes and tuberculosis.

(Source: https://www.worlddiabetesfoundation.org/sites/default/files/TB-diabetes%20co-epidemic%20fact%20sheet_March2014%20update.pdf

"insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ("epidemiology" [MeSH Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms] OR "prevalance"[All Fields] OR "prevalences"[All Fields] OR "prevalence s"[All Fields] OR "prevalent"[All Fields] OR "prevalently"[All Fields] OR "prevalents"[All Fields])) AND ((ffrft[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview [Filter]) AND (humans[Filter]) AND (2014:2019[pdat])).

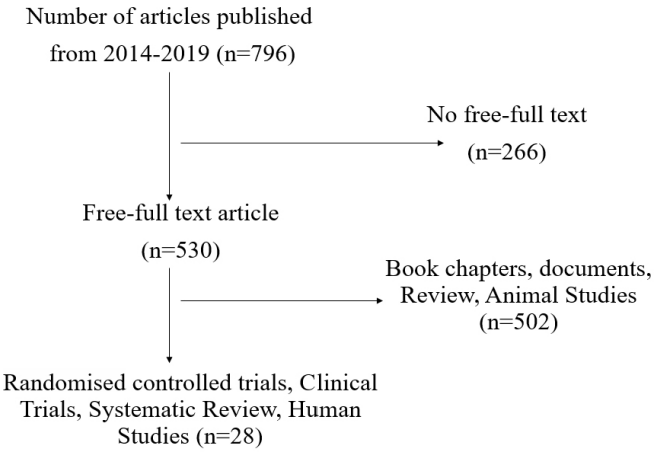

Figure 2: Schematic diagram of the article collection for the review.

The articles used for information on the prevalence of TB among diabetes patients is summarized in the following Table **1**.

RESULTS AND DISCUSSION

Analysis of the treatment strategies and challenges in the co-management of type 2 diabetes and tuberculosis are summarised in a different section of this article.

Association of Type 2 Diabetes and Tuberculosis

Diabetic patients possess a higher risk of developing tuberculosis, and similarly, a patient with tuberculosis is associated with an increased risk of developing diabetes [4-6]. The bidirectional relationship between T2DM and TB orchestrates the importance of pathogenesis and the association between these medical conditions. Several potential underlying pathophysiological mechanisms regarding the interaction of diabetes and tuberculosis have been proposed [7-10]. Diabetic patients have a higher susceptibility towards microbial Mycobacterium tuberculosis infection due to their altered and impaired immune system, thus resulting in a greater risk of developing TB [11-13].

This could be attributed to the reduction in T-lymphocytes' number and function, which results in a weakened cellular innate immunity [14-16]. Disturbances in innate humoral immunity also majorly contribute to the increased prevalence of infections in DM patients. Specifically, the levels of diabetic T-helper 1 cytokine [5], tumor necrosis factor [17-19], interleukin-1 [20-23], and interleukin-6 are lowered, and thus the immune system is weakened [24, 25]. Besides, the poor cellular innate immune system also plays a crucial role as the diminished function of macrophages leads to the impairment of phagocytic and chemotactic function [26, 27]. Plus, it leads to low production of reactive oxygen species [5, 20, 28]. In short, the reduced cellular and humoral immunity in diabetics contribute to an increased risk of developing TB. Intriguingly, in a diabetic patient with tuberculosis, specific cytokines associated with the humoral innate response are consistently up-regulated along with the elevation of HBA1c [19, 20]. The elevated levels of glucose and advanced glycation end products (AGEs) which are the products of glucose and lysine, or

Table 1: Prevalence of TB in Participants with Existing DM or Vice Versa

Author(s)	Year	Location	Study participants (N)	Results (%)
Koesoemadinata RC *et al.* [5]	2017	Bandung, Indonesia	651 DM patients	38.9% tested positive for TB
Swarna Nantha Y *et al.* [6]	2017	Seremban, Malaysia	404 DM patients	28.5% tested positive for TB
Caraffa E *et al.* [10]	2016	Rome, Italy	971 TB patients	12.7% have DM
Lin Y *et al.* [7]	2015	Kunming, China	2942 DM patients	9.5% tested positive for TB
Martínez-Aguilar G *et al.* [8]	2015	Mexico	600 DM patients	51.3% tested positive for TB
Lin YH *et al.* [9]	2015	Taiwan	3,087 DM patients	2.4% tested positive for TB
Magee MJ *et al.* [11]	2014	Georgia	1325 TB patients	11.4% have DM

DM = Diabetes Mellitus; TB = tuberculosis.

arginine residues are responsible for the enhanced cytokine production [5]. The basal cytokines up-regulated in diabetic patients include IFN-γ, IL-1β, IL-17, and TNF-α. Despite the increased presence of protective cytokines, suppression of the downstream responses and accumulation of dysfunctional cytokines result in poor resolution of tuberculosis [19, 20]. Apart from that, the ciliary function of the lungs in a diabetic patient is hindered, which affects the force of respiratory burst in eliminating pathogens. Another inevitable mechanism is the increasing adherence of the microorganism to diabetic cells [5, 29].

On the other hand, not much is known about the cause of the increased risk of T2DM in TB patients, but several mechanisms have been proposed. In TB patients, the stress response to infection leads to poor glycaemic control and impaired glucose tolerance. This stress response is mediated by increased IL-1, IL-6, and TNF-α. Tuberculosis pancreatitis and pancreatic endocrine hypofunction may also worsen glucose control and the new onset of diabetes [30, 31].

Clinical Presentation

The results of a few retrospective analysis of TB-DM cases have shown an increasing trend in developing TB in DM patients as age increases [5-7]. Hence, most TB cases occur in the older age group of diabetic [8, 9]. These cases have also shown male predominance up to age 40 and female predominance from age 50 [10]. Pulmonary tuberculosis is more likely to develop in diabetes patients than extra-pulmonary tuberculosis, which is more common in non-diabetics [10-12]. The clinical presentation of the tuberculosis-diabetes patient may be atypical with altered signs and symptoms. Compared to non-diabetic patients, symptoms of anorexia, dyspnoea, and haemoptysis are presented more frequently in people with diabetes while no significant differences have been found with other symptoms such as cough and fever [10, 11]. Among patients with DM, TB may progress faster with more chest and systemic symptoms [4, 13]. Also, an increase in lower lobe involvement and consolidation is presented among TB-DM patients [10, 11]. However, frequent and higher-grade smear and culture positivity are not associated with diabetes [13, 14].

Patient Screening

In 2018, International Union against Tuberculosis and Lung Disease (The union) and WHO published a guideline on TB-DM management, particularly addressing the treatment algorithm on screening TB-DM patients [2].

Screening People with TB for DM

TB patients should be screened for DM at the time of TB diagnosis, and it is recommended first to perform a blood testing to test for Random Blood Glucose (RBG) [2]. it indicates that the patient is at risk of DM, This involves testing for glycosylated haemoglobin (HbA1c) level or fasting blood glucose level (FBG). A confirmed diagnosis of DM is when patients have an FBG ≥ 7 mmol/l (≥ 126 mg/dl) or HbA1c ≥ 6.5% (≥ 48 mmol/l). If the blood glucose is ≥ 6.1 mmol/l (≥ 110 mg/dl), then it indicates that the patient is at risk of having DM it indicates that the patient is at risk of DM, and a subsequent test should be performed.

The gold standard for diagnosing TB-DM patients is FBG and HbA1c but not oral glucose tolerance tests (OGTT) [2]. This is because OGTT is not feasible to be carried out in hectic TB clinics with a high flow of patients.

Screening People with DM for TB

According to the guideline [2], testing DM patients for TB is recommended. For countries with a high TB epidemic where the prevalence rate is 100 per 100000 population, a systematic TB screening should be performed for DM patients because they are at a higher risk of developing TB. The mainstay of diagnosis is sputum testing. First, patients will be assessed for TB symptoms such as persistent coughing for more than two weeks, weight loss, fever, or night sweats. If the patient is presented with positive symptoms, they will be arranged for TB screening. The patient should have their sputum collected and sent to a TB clinic to test for Mycobacterium Tuberculosis. THE Xpert MTB/RIF assay is recommended by WHO and the union for TB screening. Once the diagnosis is confirmed, the patient should be appropriately treated for TB.

Treatment Strategy for Concurrent Tuberculosis and Diabetes

Many studies regarding the incidence and screening of TB and DM have been published but when it comes to managing these diseases concurrently, several strategies without established evidence have been proposed, including prolonging the duration of TB treatment [32] and increasing the dose of anti-TB drugs [33, 34]. However, higher drug doses raise the risk of toxic exposure to TB drugs and this consequently

Table 2: Recommended Doses of First-Line TB Drugs for Adults with DM [37]

Drug	Recommended Daily Doses	
	Dose (range) In mg/kg body weight	Maximum Dose in mg
Isoniazid (H)	5 (4 - 6)	300
Rifampicin (R)	10 (8 - 12)	600
Pyrazinamide (Z)	25 (20 - 30)	2000
Ethambutol (E)	15 (15 - 20)	1600

complicates diabetes management, especially in the elderly and patients with liver or kidney dysfunction [35]. As a result of the possible complications arising from the proposed treatment strategies, to date, there are no optimal treatment regimens for the co-management of TB and DM. Current treatment plans follow individual treatment guidelines [36].

According to WHO [37], TB treatment consists of two drugs (rifampicin and isoniazid) taken for 6 months, combined with two other drugs (pyrazinamide and ethambutol) for the first 2 months at the recommended doses as shown in Table **2**.

Fixed-dose combinations (FDCs) of TB drugs are preferred over separate drug formulations. The use of FDCs can facilitate drug administration and assist in medication adherence with fewer tablets taken daily [38]. The recommended number of FDC tablets given daily is determined based on the weight bands as shown in Table **3**.

Diabetes Control in Patients with Active Tuberculosis

Treatment supervision has been suggested to help reduce treatment failure and prevent recurrence of TB in diabetic patients. However, the effectiveness of this strategy remains doubtful [30, 39]. Therefore, optimal glycaemic control may improve the outcome of TB treatment and avoid complications such as nephropathy, retinopathy, neuropathy as well as improve the outcome of TB treatment and avoid complications such as nephropathy, retinopathy, neuropathy, and cardiovascular diseases.

The management of DM in TB patients consists of pharmacological and non-pharmacological treatments. Pharmacological treatment involves blood glucose-lowering agents such as insulin and metformin. In contrast, the non-pharmacological aspect involves lifestyle modifications such as adopting an optimal diet plan, losing weight, increasing physical activity, smoking cessation, and avoiding excess alcohol. When it comes to choosing diabetic drugs in treating TB-DM, not only do drug-drug interactions need to be considered, drug availability, treatment cost, ease of administration and the safety of drugs also need to be taken into account. Therefore, the use of modern insulin or insulin analogues at the beginning of treatment has been suggested as they do not interact with anti-TB drugs, have more predictable actions, and cause less hypoglycemia [30, 40]. However, insulin has

Table 3: Number of FDC Tablets given Daily for Adults Based on the Weight Bands [37]

Month of Treatment	Drugs	Number of FDC tablets taken daily			
		30-37 kg	38-54 kg	55-70 kg	>70 kg
1-2 Intensive phase	HRZE combined tablets	2	3	4	5
3 – 6 Continuation phase	HR combined tablets	2	3	4	5

H = isoniazid (75 mg); R = rifampicin (150 mg); Z = pyrazinamide (400 mg); E = ethambutol (275 mg).

various disadvantages when used in under-resourced settings in terms of cost, availability, storage, and route of administration. In these settings, insulin is indicated as the third line option in treating TB-DM except for hospitalised patients or patients who have used insulin before diagnosing TB [35].

Evidence regarding the use of metformin in treating diabetic patients with TB shas been contradictory. CytochromeP450 enzymes (CYP450 enzymes) do not metabolise metformin, the serum concentration will therefore not be affected by the inductive effect of rifampicin and thus it does not usually lead to hypoglycemia. Furthermore, metformin has also been linked to decreased mortality during TB treatment, suggesting the important role of metformin as adjunctive therapy [41, 42]. However, the use of metformin may increase toxicity in patients with renal impairment [43]. Thus, the dose of metformin should be adjusted when estimated glomerular filtration rate (eGFR) <50 ml/min, and if eGFR <30 ml/min, use is contraindicated.

As recommended by the American Diabetes Association, the HbA1c target should be <7% (53 mmol/mol) [44]. However, this target may be difficult to achieve during anti-TB treatment, especially in the first two months due to several reasons such as the worsening of hyperglycaemia due to active TB, patient's long history of DM, drug-drug interaction of rifampicin, and diabetic drugs [39]. Although this is not evidence-based, a more practical target for HbA1c and random/fasting blood glucose will therefore be < 8% and < 11.1 mmol/l (200 mg/dl) respectively during the treatment of TB [35].

Supplement for Co-Management of TB and T2DM

Compared to TB patients without DM, diabetic patients have been shown to have lower levels of vitamin D, where the serum levels are 16.1 ng/mL and 12.1 ng/mL respectively [45]. This indicates the possible role of vitamin D in managing TB and DM. Vitamin D is considered an immune system enhancer. It assists the cathelicidin production and the conversion of 25-hydroxycholecalciferol (25-(OH)-D3) to 1,25-dihydroxycholecalciferol (1,25-(OH)2-D3) which results from the interactions between macrophages and M. tuberculosis antigens. 1,25-dihydroxycholecalciferol is the active form of vitamin D that helps in suppressing intracellular growth of Mycobacterium tuberculosis after initial infection [45, 46]. Other than boosting immunity, vitamin D may also stimulate the expression of the insulin receptor and enhance insulin responsiveness for glucose transport [47]. It does this by affecting the absorption of calcium into the body. The calcium flux through the cell membrane will affect the insulin production from β-cell in the pancreas. In terms of treatment outcomes, vitamin D may shorten the duration of sputum conversion and result in radiological improvements [48, 49]. Therefore, vitamin D supplements may be given to diabetic patients with TB as an adjuvant therapy to decrease treatment duration and improve disease prognosis. However, due to the limited number of available studies, more high-quality trials are needed to be carried out to conclude these findings.

Challenges in the Management of TB in Diabetic Patients

On top of having a higher risk of TB, diabetic patients may also suffer from less than desirable treatment outcomes. The success of TB treatment can be determined by a few endpoints: sputum culture conversion after 2 to 3 months of therapy, failure or death during treatment, and relapse rate. Based on a systematic review on the impact of diabetes on tuberculosis treatment outcome [50], DM patients are 1.7 times more likely to be associated with failure or death during the treatment of tuberculosis. In these patients, the risk of relapse is also 4 times greater than patients without DM. On the other hand, studies that investigated the effect of DM on positive sputum culture show varying results, with some reporting delay in sputum culture conversion in individuals with DM and therefore suggesting an association between these factors. However, in patients with recurrent TB, there is no clear relationship between drug resistance and DM. The poor TB treatment outcomes in diabetic patients may be attributed to impairment of cellular immunity due to DM, therefore causing a delay in infection control [17, 51, 52].

Pharmacological issues are also a part of the challenges of co-managing diabetes and tuberculosis. The drugs used to treat TB may affect glycaemic control by interacting with anti-diabetic drugs. Rifampicin, the primary anti-TB drug, is a strong inducer of various metabolizing enzymes including cytochrome P450 (CYP) 3A4 enzymes [53]. One of the most commonly used classes of oral hypoglycemic agents (OHAs) in T2DM is a sulfonylurea. Glyburide and glipizide are both metabolised by CYP2C9, and when combined with rifampicin, their plasma concentrations are lowered by 39% and 22%,

respectively. Pharmacodynamics results also show that the efficacy of glyburide in lowering blood glucose is reduced when taken with rifampicin [54]. Similarly, rifampicin affects the pharmacokinetics of other types of OHAs, such as thiazolidinediones and meglitinides, which are metabolised by CYP 2C8 and CYP 2C9, resulting in a lower concentration. When taking rifampicin, it is recommended to monitor blood glucose levels and alter anti-diabetic drugs accordingly. Rifampicin is inefficient in improving treatment outcomes due to considerable pharmacokinetic variability across individuals, making dose modifications challenging [39, 55-57]. Moreover, the use of neurotoxic isoniazid and ocular toxic ethambutol may worsen diabetes complications, causing a higher incidence of peripheral neuropathy and retinopathy in diabetic patients. Biguanides such as metformin are not recommended to give for glycaemic control in TB-DM patients due to the high risk of hepatotoxicity when taken with anti-TB drugs. While taking anti-TB drugs with metformin, patients may also present with gastrointestinal complaints and lactic acidosis in rare cases [58].

Diabetes and tuberculosis as a concomitant disease is a double epidemic burden, especially in developing countries where health systems are limited and fragmented. In these countries, high cost is a considerable impediment in expanding diabetes care [59]. The cost of diabetes management not only includes the expenses linked to anti-diabetic medications, but it also involves visits to outpatient clinics, inpatient admissions, and the management of disease complications. By integrating healthcare services for tuberculosis and diabetes, it might overwhelm disease management programmes that are already overburdened and understaffed with limited resources [60]. Based on the estimated incidence of tuberculosis, the additional funding required for the care of diabetes ranges from US$3 million to US$55 million per year in Africa and US$5 million to US$92 million per year in Southeast Asia [59]. The cost-effectiveness of the integration of treatment for these diseases has also not been assessed.

Unfortunately, healthcare management in developing countries usually does not meet evidence-based standards and it is often more oriented towards treating acute issues rather than chronic diseases [60, 61]. This poses a challenge in the management of TB in diabetic patients as optimal glycaemic control is dependent on the quality of the healthcare system. Poor glycaemic control in T2DM is associated with more severe TB symptoms where patients experience more dyspnoea and weight loss. Cavitary lesions of the lungs were also more frequently reported when blood glucose levels are not controlled well. In terms of treatment outcomes, poorly controlled T2DM may lead to higher treatment failure and relapse [62, 63].

LIMITATION

The search duration of the article is one of the limitations as the articles published from 2014-2019 only were included. There were only a few studies published in 2020 and 2021, however, they may not fit into the aim of this review.

CONCLUSION

Despite various efforts, international guidelines and protocols to manage TB and DM as comorbidity are still unavailable, apart from a collaborative framework for care and control of these diseases developed by WHO and the International Union against Tuberculosis and Lung Disease. An optimal clinical algorithm for the co-management of TB and DM has not been established as many questions regarding TB and DM as comorbidity remain unanswered. While TB screening in DM patients is recommended, this could increase costs and further burden healthcare systems. Therefore, future research will have to address the cost-effectiveness of screening procedures and assess the feasibility of integrating clinical management of TB and DM, especially in low- and middle-income countries. Furthermore, evidence regarding the role of glycaemic control in the treatment outcome of TB is also scarce and this calls for more clinical trials to be conducted. More pharmacokinetic studies will also have to be carried out to study the interaction between anti-TB and anti-diabetic drugs to generate an ideal drug combination to better combat this dual disease. In short, a vast amount of work needs to be done to improve the co-management of TB and DM so that better treatment outcomes can be achieved.

CONFLICT OF INTEREST

Nil.

FUNDING

Not applicable.

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