Int J Diabetes Dev Ctries (October–December 2017) 37(4):379–399
DOI 10.1007/s13410-017-0577-y

GUIDELINES

RSSDI clinical practice recommendations for diagnosis, prevention, and control of the diabetes mellitus-tuberculosis double burden

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Published online: 16 September 2017
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Background

The International Diabetes Federation (IDF) estimates for 2015 revealed that 8.8% of the world's population had diabetes mellitus (DM) and with 69.2 million people with DM, India ranked second in the world [1]. Globally, 10.4 million new cases of tuberculosis (TB) were estimated to have occurred in 2015 with India,

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Indonesia, China, Nigeria, Pakistan, and South Africa accounting for 60% of them [2]. There exists a strong epidemiological evidence base demonstrating the coexistence of DM and TB [3–8]. This association between a globally prevalent non-communicable disease such as DM and a serious infectious disease (TB), endemic in developing nations is known to adversely impact the course of progression and treatment outcome for both diseases and is transforming into a "syndemic" necessitating synergistic management [4, 5, 9, 10]. A recently published systematic review identified several risk factors associated with the DM-TB comorbidity that included older age, sedentary occupation, cigarette smoking, alcohol consumption, both lower and higher body mass index (BMI), human immunodeficiency virus (HIV) co-infection, weight loss, hypertension, and familial history of DM or TB [11].

Epidemiology

As per the WHO estimates for TB and DM double burden, 15% TB cases worldwide are associated with DM, and India and China account for more than 40% of these cases. India alone accounts for the highest number of adult TB cases associated with DM followed by China [12, 13]. Although the prevalence of DM and TB coexistence in India is not yet determined, prevalence studies have been conducted and reported from different regions. In a survey from five randomly selected TB units in Tamil Nadu, around 25% of TB patients had DM of which 9.3% were newly detected cases of DM. A similar percentage of TB patients had prediabetes. Common risk factors including age, BMI, family history of DM, and sedentary lifestyle were identified as possible risk factors for DM in TB patients [14]. Further, the prevalence of DM was significantly higher in men compared to women which was attributed to smoking, tobacco consumption, and alcohol use that are known risk factors for both TB and DM [14]. In the state of Kerala, the prevalence of DM in patients with TB was nearly double than that observed in Tamil Nadu. Among the total patients with TB in this study, 44% had DM, of which, 21% patients had newly diagnosed DM. The demographic characteristics of the investigated population was in line with those observed in Tamil Nadu and had a preponderance of men and patient aged above 50 years [15]. The risk of DM in TB patients was relatively higher in sputum positive TB patients in both Kerala and Tamil Nadu [14, 15]. In a recent cross-sectional study from Odisha, 13.9% tribal patients with TB had DM and 8.9% had impaired fasting glucose (IFG) [16]. In another retrospective study, among 1000 patients with respiratory diseases from Punjab, 11.6% had DM and TB coexistence, majority of which were men (56.5%), in the age group of 51 to 60 years and belonging to rural areas (68.4%) [17]. From studies conducted in patients with TB from urban centers, 29.0% (8.3%, newly diagnosed DM) from Puducherry and 15.3% (8.23%, newly diagnosed DM) from Ahmedabad had diabetes [18, 19]. A recent study conducted among patients with established TB and registered under the national program in Gwalior district of Madhya Pradesh reported the prevalence of DM as 15.5%, comparable to most reports from India [20]. Overall, the prevalence of DM among Indian patients with active TB appears to be at least two to three times higher than the national average or comparative regional data in the general population [21].

Biological links

Numerous plausible biological links between TB and DM have been elucidated. Chronic hyperglycemia in DM is known to increase the susceptibility of patients to infections by direct suppression of the innate and adaptive immunity [4, 7]. Compromised cell-mediated immunity has been particularly shown to facilitate *Mycobacterium tuberculosis* infection via disruption of key defense mechanisms such as monocyte chemotaxis, neutrophil recruitment, phagocytosis by alveolar macrophages, and antigen-specific cytokine responses (interferon-gamma release) due to depressed T helper cell activation [22, 23]. This immunosuppression in poorly controlled DM increases susceptibility to infections such as TB along with an increased baseline load of the mycobacilli and protracted time for sputum culture conversion in response to antibiotics, thus adversely impacting treatment outcomes [24]. The presence of DM also threatens TB control by worsening the outcomes of TB treatment and increasing the risk of treatment failure, deaths during treatment, recurrences, and development of resistance, highlighting the severity of this association [10, 25].

Further, studies reporting the development of glucose intolerance in patients with active TB implicate the two-way association between TB and DM [26, 27]. An endocrine-linked metabolic response to stress such as an acute infection has been postulated to severely hamper glycemic control; however, the underlying mechanism specific to TB infection is uncertain [7, 27, 28].

Need for clinical practice recommendations

In the light of this surging danger, the World Health Organization (WHO) along with the International Union against

Tuberculosis and Lung Disease (the Union) proposed the *Collaborative Framework for Care and Control of Tuberculosis and Diabetes* that emphasizes the need for collaborative control efforts through bi-directional screening and efficient co-management of both diseases [29, 30]. The "National Framework for Joint TB-Diabetes Collaborative Activities," released in March 2017 highlights the need and measures for strengthening operational consensus and integration of services between the two national programs for DM (National Program For Prevention and Control of Cancer, Diabetes, Cardiovascular Disease and Stroke [NPCDCS]) and TB (Revised National Tuberculosis Control Program [RNTCP]) [31]. Although these documents outline a systematic approach for bi-directional screening within routine health care settings, the guidance for clinical management of TB and DM at the individual patient level is missing.

The current article aims to fill this gap and provide evidence-based recommendations to clinicians, researchers, policy makers, patients, and all other stakeholders' for the screening, diagnosis, and management of the double burden. These recommendations are convened to facilitate clinical decision making and should be appropriately adjusted when required for individual patient needs, comorbidities, and other factors based on good clinical judgment and practice.

Diagnosis and management of tuberculosis in patients with diabetes mellitus

Diagnosing tuberculosis in patients with diabetes mellitus

Diabetes mellitus increases the risk of developing TB by 2.5- to 3-fold underscoring the need for effective screening and diagnosis of TB in patients with DM [3, 4, 7, 32]. In general, the approach of screening activities should focus on the early detection of TB, prevention, and control of the transmission with an ultimate goal of improving overall treatment outcome and lowering associated morbidity and mortality [5]. Results from a systematic review that evaluated the studies implementing a bi-directional screening of DM-TB conducted before the release of the WHO framework assert the significance of such a screening approach [29, 33]. The high risk of TB affliction in patients with DM was observed in all of the 12 studies that screened patients with DM for TB despite heterogeneity in geographic area, baseline disease burden, and techniques of screening and diagnosis. Most often, the diagnosis was a combination of screening of clinical signs and symptoms, radiological changes in chest, and positive smear and/or culture of *M. tuberculosis* complex [33].

A pilot project describing the implementation of TB screening in patients with DM within tertiary healthcare setting in India outlines the systematic screening work-up for TB [34]. The diagnosis of active TB followed the national guidelines (RNTCP) and was carried out at every patient visit [35]. Patients with a history of TB and/or having common symptoms of TB were referred for sputum smear microscopy (Ziehl-Neelsen staining followed by examination for acid fast bacilli) and chest radiography. Diagnostically sensitive techniques such as mycobacterial culture tests or nucleic acid amplification were not used. Despite several operational limitations of this study the findings demonstrated the higher incidence of TB in DM patients and more importantly the feasibility of TB screening in routine DM clinics [34, 35]. Subsequently, several studies reporting the double burden conducted across India screened patients based on the presence of clinical symptoms of TB and diagnostic investigations (chest X-ray, sputum smear microscopy) in different patient populations and healthcare settings [16, 17].

More recently, under the expanding laboratory services strategy, the RNTCP has widely implemented state-of-the-art diagnostic methods such as the cartridge based nucleic acid amplification test (CB-NAAT) and line probe assay (LPA) at TB units nationally [36]. The RNTCP technical and operational guidelines for TB control advocate the use of CB-NAAT in high-risk groups that include patients with DM [37]. The Gene Xpert MTB/RIF assay or CB-NAAT is a WHO-endorsed assay to detect TB infection along with resistance to rifampicin [38, 39]. The assay has a high degree of accuracy and sensitivity with a single direct sputum sample and offers rapid diagnosis with a turnaround time of less than 2 h. In contrast to conventional solid culture techniques that need a minimum of three sputum samples and a turnaround time of several weeks, the CB-NAAT offers significant operational benefits for employment at a program level [40, 41].

Although the national TB program mandates screening of TB in patients with DM at every visit, this approach may not be possible and pragmatic in a program setting. It is recommended that patients should be screened for TB as soon as the diagnosis of DM is made. Thereafter, a symptom screen should be undertaken annually. In addition, patients with DM should be screened for TB when metabolic control worsens and cannot to be explained by other known causes.

At the outset, screening of active TB in all patients with DM should be based on the identification of any one of the recognized symptoms (cough of any duration, fever, unexplained weight loss, night sweats, hemoptysis) or suggestive chest X-ray in patients not currently receiving anti-TB medications (Fig. 1) [37]. It must be noted that patients with DM and having autonomic neuropathy may not manifest cough; on the other hand, DM patients receiving angiotensin-converting-enzyme (ACE) inhibitors may manifest cough as side effect of the medication. The initial screening of TB

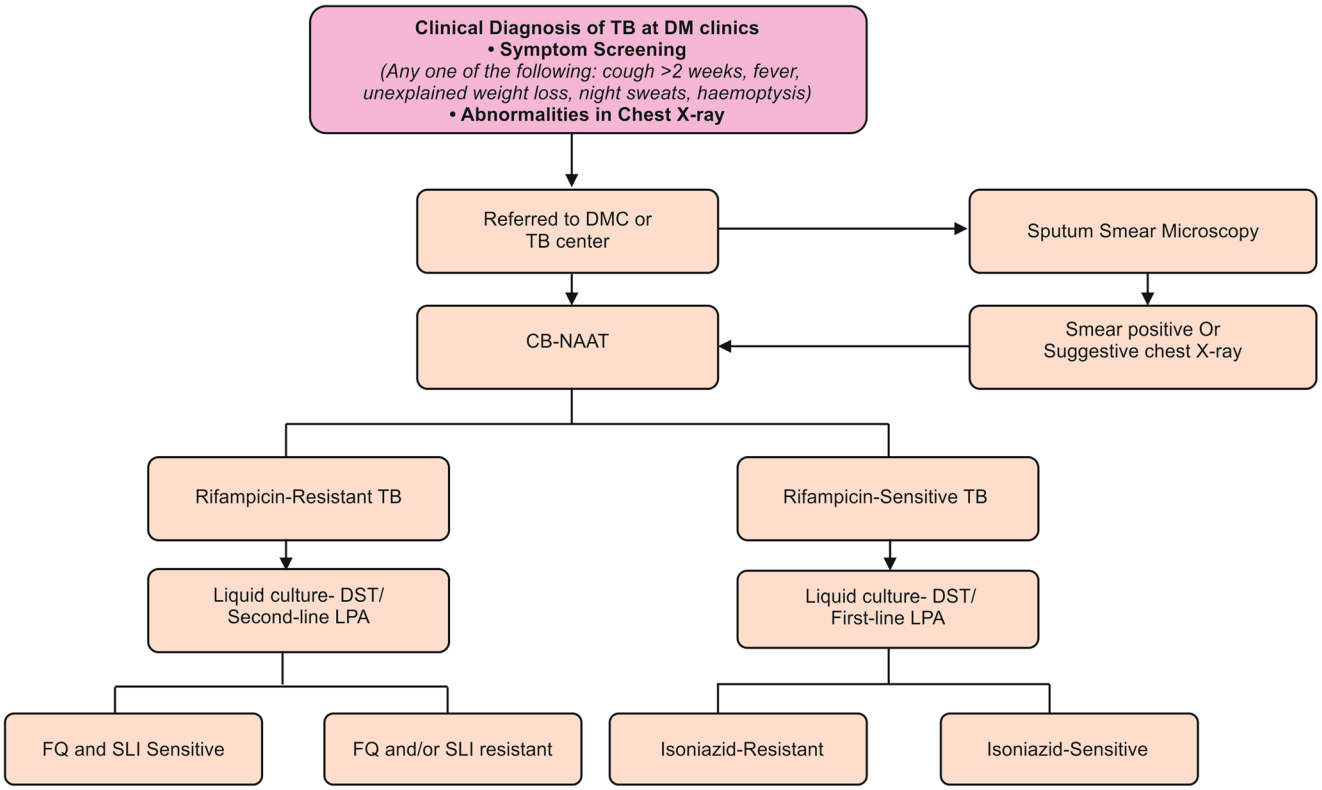

Fig. 1 Diagnostic algorithm for tuberculosis in patients with diabetes mellitus. CB-NAAT, cartridge-based nucleic acid amplification test; DM, diabetes mellitus; DMC, designated microscopy center; FQ, fluoroquinolone; LPA line probe assay; SLI, second-line injectables; TB, tuberculosis

should also involve identification of presumptive cases to facilitate diagnostic strategy and better clinical management (Box 1) [37].

Box.1: Presumptive Tuberculosis

1. Presumptive Pulmonary TB
   Patients with any of the following symptoms
   - Cough >2 weeks
   - Fever >2 weeks
   - Significant weight loss
   - Haemoptysis
   - Abnormal chest radiography
2. Presumptive extra pulmonary TB
   Organ-specific symptoms in addition to constitutional symptoms of pulmonary TB
   - Swelling of lymph nodes
   - Pain and swelling in joints
   - Neck stiffness
   - Disorientation etc.
3. Presumptive paediatric TB
   - Persistent cough for >2 weeks
   - Weight loss or no weight gain
   - Contact with TB-infected individuals
4. Presumptive drug resistant TB
   - First-line treatment failure previously
   - Pediatric non-responders
   - Contact with drug resistant TB patients
   - Culture positive during first-line treatment
   - TB-HIV co-infected

Patients with clinically diagnosed TB should be referred to a designated microscopy center (DMC) or testing laboratory for microbiological confirmation of TB, if such a facility is not available within the clinic/hospital. Microbiological confirmation of TB infection is essential in all suspected cases. In patients tested as screening positive, the RNTCP endorses the use of sputum smear microscopy, culture-based drug susceptibility testing or rapid molecular assays that involve different levels of infrastructural sophistication and technical complexities (Box 2) [37].

Box.2: RNTCP endorsed TB diagnostic tools

1. **Sputum Smear microscopy (AFB)**
   - Zeihl-Neelson staining
   - Fluorescence staining

   Most commonly used
   Limited sensitivity in children and HIV-co-infected patients
2. **Culture**
   - Solid culture (Lowenstein Jensen [LJ])
   - Automated liquid culture system (e.g. BACTEC MGIT-960, BacT/ALERT, VersaTREK etc.)
   - Modified LJ and MGIT-960 systems

   Highly specific and sensitive
   Turnaround time of 2 to 8 weeks
   Useful for assessing response to treatment during follow-up of MDR-TB
3. **Rapid Molecular Diagnostic Testing**
   - Line probe assay for MTB complex and detection of RIF and INH resistance
   - Gene Xpert MTB/RIF assay or CB-NAAT

   High specificity and sensitivity
   Rapid diagnosis
   Recommended for diagnosis of TB in key population such as children, HIV co-infected patients and for extra-pulmonary TB and DR-TB

Positive conventional sputum smear microscopy (for AFB) or CB-NAAT or growth of MTB on culture may be sufficient for the diagnosis of TB. Patients unable to produce a good sputum sample for testing may need sputum induction using nebulized hypertonic saline. In patients with RIF-resistant strains detected by CB-NAAT (Fig. 1), and in those suspected to have drug resistance, liquid culture (BACTEC MGIT 960)-

based drug susceptibility testing (DST) should be employed for rapid detection of MDR-TB in resource-limited settings where LPA may not be feasible [42–44]. A solid culture-based DST may be used if liquid culture is not available, although the turnaround time to yield results will be increased by several additional weeks [45].

Plain chest radiograph is recommended in all patients with presumptive pulmonary TB [46]. Although there is a lack of consensus among TB experts over the differences in the radiological manifestations of TB in patients with DM as compared to the general population, conflicting manifestations specific to this population have been observed [47–51]. The differences reported include the presence of greater frequency of pulmonary lesions in the lower lung field in contrast to the typical upper lobe lesions observed in normoglycemic patients with pulmonary TB. A significantly higher occurrence of cavitary lesions have also been noted in patients with TB having uncontrolled DM [50, 52, 53]. These atypical radiographic presentations of TB in patients with DM pose a problem of misdiagnosis of the mycobacterial infection for community-acquired pneumonia or lung cancer [54]. Similar uncommon presentation of pulmonary TB has also been observed in chest computer tomography (CT) assessments in patients with DM [55]. A bilateral and multilobar pulmonary involvement was noted along with substantially greater lymphadenopathy in patients with TB having underlying DM [52, 55, 56]. Observations of aggressive pulmonary manifestations, greater parenchymal lesions, and multiple cavities have been potentially linked to higher bacillary load in sputa, leading to higher positive smear rates at diagnosis in patients with poor glycemic control [14, 48, 51, 57, 58].

For patients who have pulmonary lesions and fail to produce sputum even with induction or in cases where the suspicion of pulmonary TB persists despite a negative sputum test, more complex diagnostic methods using the flexible bronchoscope such as bronchoalveolar lavage and transbroncheal lung biopsy should be considered [54].

Management of tuberculosis in patients with diabetes mellitus

Tuberculosis, an immunopathological complication of DM should not be underestimated and managed with equal rigor as the management of other complications of DM (neuropathy, nephropathy, and retinopathy). Patients with DM and TB (RIF-sensitive as confirmed by Gene Xpert MTB/RIF assay) must be initiated on the standard directly observed treatment (DOT) with the four-drug regimen similar to the treatment presented to the general TB population [29, 37]. The standard therapy for tuberculosis includes the daily dosing of anti-TB drugs that include isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) (Box 3 outlines the regimen) [37]. It should be noted that patients who have previously failed or defaulted the first-line TB regimen or relapsed after treatment are at a greater risk of lodging drug-resistant or MDR strains and have reported lower success rates with the retreatment TB regimen (Box 3) [59–62]. Therefore, in accordance with the recent WHO update on the guidelines for retreatment of TB in drug-susceptible cases, it is highly recommended that patients with TB being retreated after a previously failed anti-TB regimen should first undergo DST to determine the appropriate choice of drug regimen [63].

Owing to the established vulnerability and treatment challenges in patients with DM, WHO recommends optimization of the standard algorithm depending on the pharmacokinetic alterations and metabolic differences in patients with the twin burden [29].

Box.3: Treatment of tuberculosis in patients with diabetes mellitus

1. **Newly diagnosed tuberculosis**
   - **Intensive phase (8 weeks)**
     Isoniazid, Rifampicin, Pyrazinamide, Ethambutol
   - **Continuation phase (16 weeks)**
     Isoniazid, Rifampicin, Ethambutol
2. **Previously treated tuberculosis**
   - **Intensive phase (12 weeks)**
     Isoniazid, Rifampicin, Pyrazinamide, Ethambutol + Streptomycin (8 weeks)
   - **Continuation phase (20 weeks)**
     Isoniazid, Rifampicin, Ethambutol

Diabetes is often associated with numerous complications such as peripheral neuropathy, retinopathy, and compromised kidney function [64]. Therefore, management of concurring toxicities such as INH-induced peripheral neuropathy, EMB-induced optic neuritis, and EMB-induced impaired kidney function must be kept in mind during treatment of TB in patients with DM [65]. The use of pyridoxine (vitamin B6) along with INH is therefore mandatory in patients with DM [7, 66].

Changes in drug absorption due to DM can lead to inadequate blood level of first-line anti-TB drugs in these patients that can eventually culminate into drug resistance. It has been observed that patients with DM exhibit suboptimal response to anti-TB agents particularly RIF due to lower serum concentrations [67]. In a cross-sectional study conducted in South India, a significantly higher proportion of patients with DM demonstrated resistance to RIF (27%) as compared to patients without diabetes (8.8%, $p < 0.01$) [68]. A Turkish study reported that plasma INH and RIF concentrations in TB patients with diabetes were 50% lower than those observed in TB patients without DM [69]. Rifampicin serum concentrations were 53% lower in patients with DM as compared to

normoglycemic TB patients in a study from Indonesia [67]. In a recent study from India, TB patients with DM had lower serum concentration of INH and PZA as compared to patients without DM and the effect was linked to hyperglycemia [70].

Reduced exposure to anti-TB drugs is also attributed to the higher body weight observed in patients with concomitant TB and DM and is regarded as a serious impediment to clinical recovery and contributing to therapeutic failure and acquired drug resistance [67, 69]. Therefore, appropriate dose adjustments based on body weight is recommended while prescribing anti-TB drugs and should be in accordance with good clinical sense [71]. Routine monitoring of therapeutic drug responses and fortification of TB regimen such as use of higher doses or extended treatment duration is advocated especially in patients at risk of inferior treatment outcome [10, 72].

Drug interactions with anti-TB drugs

Caution should be exercised when prescribing anti-TB drugs in patients receiving oral anti-diabetic drugs (OADs). Most commonly prescribed OADs (sulfonylureas and thiazolidinedione) are mainly metabolized by enzymes of the cytochrome P450 system. Rifampicin is a potent inducer of the several isoenzymes of the cytochrome P450 system and by activating these enzymes, RIF accelerates the systemic elimination of concomitantly administered drugs significantly reducing their therapeutic efficacy [73]. Initiation of RIF in patients receiving sulfonylureas—glipizide and glyburide (CYP2C-mediated metabolism)—has been associated with 39 and 22% lower serum concentration, respectively, hampering their hypoglycemic effects [74]. Among thiazolidinediones, RIF decreased plasma concentrations of rosiglitazone by 54 to 65% and induced a 54% decrease in levels of pioglitazone via increased CYP2C8-catalyzed metabolism [75–77]. Modest reductions in plasma levels of nateglinide and substantial decrease in repaglinide concentrations have been observed following co-administration with RIF with potential effects on hypoglycemic effects of these drugs [78, 79]. Isoniazid on the other hand is an inhibitor of the cytochrome system and delays the biotransformation of glimepiride, a CYP2C9 substrate, and increases the risk of hypoglycemia due to accumulation of the sulfonylurea [80].

Diagnosis and management of MDR-TB in patients with DM

Delays in mycobacterium TB clearance during treatment and treatment failures predispose patients with DM to an increased risk of primary multidrug-resistant TB (MDR-TB) [81]. Numerous studies have identified a 2- to 9-fold increase in the risk of MDR-TB among patients with DM as compared to normoglycemic individuals [82–85]. A recent meta-analysis addressing the comorbid relationship between DM and MDR-TB reported significantly higher odds of MDR-TB in patients with DM (OR = 1.71, 95% CI = 1.32; 2.22) [86]. Concurrent DM was significantly associated with MDR-TB in both Caucasians and Asian subgroups and was identified as an independent risk factor especially for primary MDR-TB [86].

As recommended for the general population with TB, patients with DM and receiving treatment for TB should also be monitored through the time course of treatment for the development of drug resistance [82, 87, 88]. Chest CT with pulmonary lobe consolidation and multiple mouth-eaten cavities and bronchial damage are characteristic of MDR in patients with DM and TB [89]. Rapid molecular techniques (CB-NAAT and LPA) or liquid and culture DST should be employed for prompt diagnosis of resistance (Fig. 1) [35, 90]. Patients already receiving first-line anti-TB therapy and who continue to be smear positive at the end of the intensive treatment phase (first 2 months) should be assessed for drug resistance. It is imperative that confirmed cases of MDR-TB be referred to specialized centers (under respiratory physicians, infectious disease specialists or TB specialists with experience in the management of MDR-TB) for treatment [35].

The treatment of MDR-TB comprises an extensive 24- to 27-month chemotherapy [35, 91]. The WHO and RNTCP prescribed treatment for MDR-TB or RIF-resistant TB includes the use of at least five effective anti-TB drugs. The RNTCP-recommended regimen for MDR-TB is as shown in Box 4 [37].

Box.4: Treatment of multi-drug resistant tuberculosis in patients with diabetes mellitus

Intensive phase (6 to 9 months)	Continuation phase (18 months)
Fluoroquinolone • Levofloxacin Second-line injectable • Kanamycin Core second-line agents • Ethionamide • Cycloserine Add-on agents • Pyrazinamide • Ethambutol	• Levofloxacin • Ethionamide • Ethambutol • Cycloserine

In RIF-resistant and isoniazid-sensitive cases, isoniazid should be added to the regimen (Box 4). Screening using liquid culture DST or second-line LPA (Fig. 1) should be carried out for all cases at baseline to detect sensitivity to kanamycin and levofloxacin. Appropriate alterations in second-line drug regimen may be considered if resistance is detected. In routine clinical practice, standardization of second-line regimen based on individual patient's drug resistance (using DST) and tolerance profile has been adopted to improve treatment success rates [92, 93]. In cases of additional drug resistance, the inclusion of clofazimine, linezolid, and paraaminosalicylic acid may be considered [37]. Although potential drug interactions with most prescribed second-line

drugs are minimal, consideration of DM-related changes in pharmacokinetics that can influence therapeutic outcome should be considered in patients with DM.

Bedaquiline and delamanid are recent additions to the MDR-TB therapy. The use of bedaquiline has been indicated as a part of MDR-TB regimen by the RNTCP [37]. Therapeutic drug monitoring is advised in patients on anti-diabetic therapy and receiving bedaquiline owing to CYP450-mediated pharmacokinetic alterations, drug-drug interactions, and adverse events. Concerns of electrolyte imbalance, QTc prolongation, and gastrointestinal toxicity following concurrent use of bedaquiline with sulfonylureas, insulin analogs, and meglitinides have been reported [94]. Overall, metformin has a favorable pharmacokinetic and safety profile for use with bedaquiline. Metformin is also known to restrict intracellular replication of MDR strains and can therefore be a potentially viable option for the co-management of DM and MDR-TB [95].

Diagnosis and management of diabetes mellitus in patients with tuberculosis

Diagnosis of diabetes mellitus in patients with tuberculosis

Diabetes mellitus is associated with greater risk of treatment failure, morbidity, death, and relapse in TB [6, 7, 10]. The higher mycobacterial load at diagnosis and delayed sputum culture conversion during the initial intensive treatment phase (first 2 months) are regarded as strong determinants of this increased risk [24]. A study from India that assessed sputum conversion rate reported positive sputum smear in about 14.7% of patients with TB and DM at the end of the intensive phase of DOTS therapy. The relative risk to remain sputum smear positive at the end of intensive phase was estimated to be 3.9 (95% CI = 1.5; 10.6) in patients with DM [96].

Other confounding factors associated with coexisting DM include the development of adverse events that negatively influence treatment adherence hampering treatment success [25, 97]. Detection of overt DM, previously undiagnosed DM or inadequate glycemic control in patients with TB is crucial for achieving optimal treatment outcomes. Convergence of active screening and monitoring of DM with routine TB screening at national-level programs can greatly aid current TB control efforts [29]. This approach of routine DM screening at the time of TB registration has been implemented at national-level TB programs in China and India [98, 99].

The systematic screening and diagnosis approach suggested here is based on the experiences from the pilot project that implemented a standardized procedure for DM screening at TB units in India and is in accordance with the RSSDI recommendations (Fig. 2) [99–101]. Patients with TB are first interviewed and those with known DM should be referred to diabetes care centers for the management of glucose control. For patients without a history of DM, RSSDI-endorsed screening methods such as random blood glucose (RBG), oral glucose tolerance test (OGTT), or estimation of glycated hemoglobin (HbA1c) can be employed. RBG and fasting blood glucose (FBG) using capillary (using glucometer) or venous sampling are the common, widely accepted and convenient diagnostic methods that are adopted for the mass screening of DM among patients with TB [29]. A FBG $\geq$ 126 mg/dL is diagnosed as DM; FBG 110 to 125 mg/dL is considered as impaired fasting glucose. Patients with RBG $\geq$ 200 mg/dL should be diagnosed as diabetes and referred for management of DM [101]. RBG between $\geq$ 100 and < 200 mg/dL is suggestive of retesting and FBG should be utilized for screening in the next patient visit and a FBG $\geq$ 126 mg/dL should be regarded as diabetes [101, 102]. Confirmatory assays such as OGTT and estimation of HbA1c can be used for cases primarily diagnosed using glucometers [29]. A recent interim report from South India studying the effect of DM on TB severity (EDOTS) reported high prevalence of DM and prediabetes in adults with pulmonary TB and also noted considerable heterogeneity in the severity of DM among patients with TB. This heterogeneity has implications for clinically relevant TB-DM interaction and the interpretation of DM diagnosis in TB studies [103].

Although both OGTT and HbA1c are expensive diagnostic methods that involve tedious procedures limiting their feasibility for community-based screening activities, they offer a higher degree of sensitivity compared to FBG and RBG [29, 104]. The OGTT, a WHO recommended measure for DM is particularly of value for the detection of previously undiagnosed cases and patients with impaired glucose tolerance [100]. OGTT was used for patients without a history of DM in a study conducted across TB units of the RNTCP in Tamil Nadu that reported a prevalence of 24.7% prediabetes among TB patients in South India [14]. A study from South India that compared the performance of HbA1c and FPG evaluated HbA1c as a better diagnostic tool for the identification of newly diagnosed DM among patients with TB [104].

HbA1c has been used for screening newly diagnosed cases of DM among patients with TB in India [15, 104] and few other resource-limited countries [105, 106]. In more recent studies, the severity of hyperglycemia measured using HbA1c has been associated with risk of TB occurrence. HbA1c > 7.0 has been associated with a three times increased risk of active TB (Hazard ratio: 3.11) [51] whereas HbA1c < 7.0 is associated with protective effects

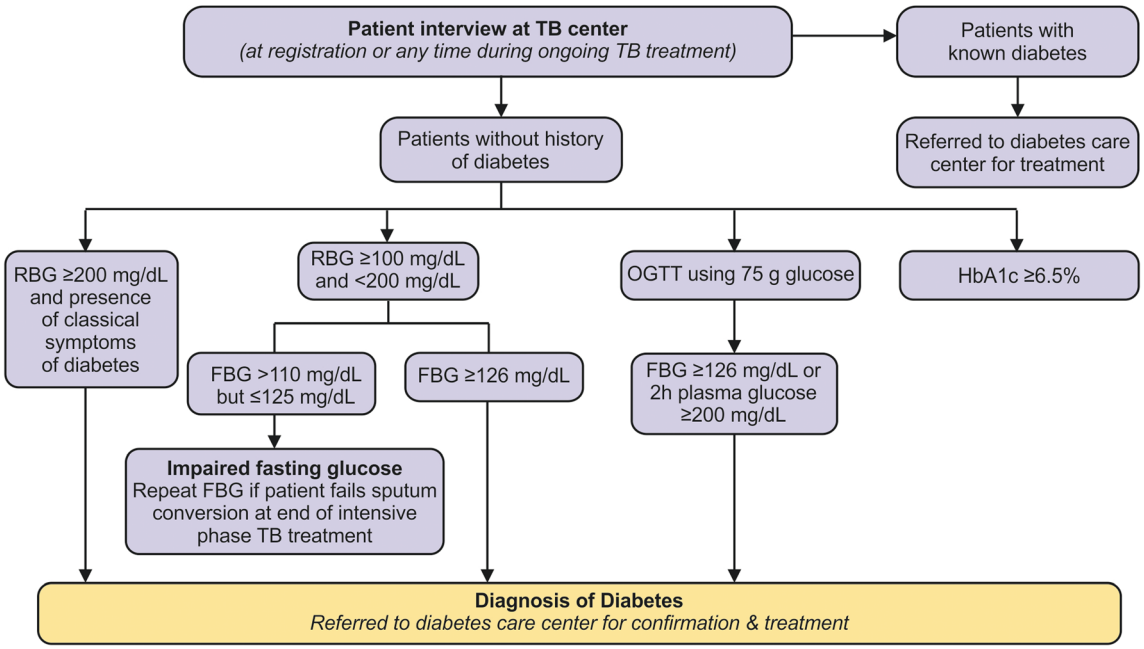

Fig. 2 Diagnostic algorithm for diabetes mellitus in patients with tuberculosis. CB-NAAT, cartridge-based nucleic acid amplification test; DM, diabetes mellitus; DMC, designated microscopy center; FQ, fluoroquinolone; LPA line probe assay; SLI, second-line injectables; TB, tuberculosis

against TB (odds ratio 0.52) [107]. HbA1c value of ≥ 6.5% is recognized as the clinical cut-off for the diagnosis of DM by the RSSDI [101]. The HbA1c gives a cumulative index of the blood glucose profile over a period of 2 to 3 months in contrast to time point FBG and RBG measures and therefore eliminates risk of possible false diagnosis of stress-induced hyperglycemia [15, 104]. In addition, it can be measured irrespective of the patient's fasting state and is devoid of rapid fluctuations that are common with RBG and FBG estimations. The absence of a prerequisite fasting state is major advantage of HbA1c measure especially in a country like India where most patients with TB visiting community centers are unlikely to visit the centers in a fasting state and may not come back when asked to return for the test. On the other hand, there are issues interpreting the results in presence of concomitant anemia, likely in patients with TB. Both methods, OGTT and HbA1c, are recognized as standard screening techniques for DM by the RSSDI and have clinical cut-off for diagnosis (Figs. 2 and 3) [101].

The time of screening of DM in patients with TB may impact the result of diagnosis, however, clinical management of DM is imperative and should be regardless of the severity or stage (diabetes, prediabetes) of glucose abnormality [15, 29]. Transient hyperglycemia possibly induced by infection-related inflammation is commonly detected at the time of TB diagnosis and is linked with adverse outcomes of TB treatment [102]. Although normalization of this temporary glucose elevation is largely achieved during TB treatment, it may be suggestive of a reverse causality and may precede clinical onset of DM [102, 108]. Therefore, multiple glucose measurements during the course of TB treatment and a repeat investigation towards completion of treatment is recommended [15]. Frequent follow-ups after resolution of TB are advised especially in patients on single-drug anti-diabetic therapy [102].

Management of diabetes mellitus in patients with tuberculosis

Infections tend to deteriorate glucose regulation and poor glucose regulation worsens infection in patients with DM and TB is no exception; hence, intensive management of DM in patients concomitantly suffering from TB is critical [66].

Insulin

Insulin is the most preferred treatment in patients with severe TB because of its anabolic actions, regulation of appetite, promotion of weight gain, low potential for drug interactions with the anti-TB agents, and effect on producing a general sense of well-being [47, 66, 109]. In addition, it provides the practical advantage of reducing the pill burden thereby improving chances of treatment adherence to the TB regimen. Insulin is recommended for the management of DM in all TB patients and should be used wherever feasible. As recommended by the RSSDI, insulin must be used in newly diagnosed DM patients with

HbA1c > 9.0%, FBG > 250 mg/dL, ketone bodies, symptoms of hyperosmolar state, and for those in a catabolic state. In patients already on OADs, insulin may be added to ongoing therapy if the patient is poorly controlled and has a low BMI. Regular monitoring of glycemia and adoption of lifestyle interventions are advised to complement ongoing insulin treatment for better management of DM. Appropriate dose adjustments for insulin are critical as requirements vary during the course of treatment: after attainment of glucose control, reduction in infection load, and improvements in appetite [66, 110]. As in the general cases of DM (without TB), postponement of insulin therapy should be avoided in patients with concomitant DM-TB.

Metformin

The use of OADs is permissible in less severe cases of TB especially when insulin treatment is not available or acceptable to the patient [66]. Among the OADs, the current first-line of treatment for patients with DM is the use of biguanide agent metformin [111, 112]. Metformin is not metabolized by the CYP450 enzymes and thus its exposure is not influenced by RIF or any anti-TB agents making it a viable treatment option for patients with concurrent DM-TB [109]. Owing to its additional immunomodulatory properties described below, metformin is the preferred therapy for DM in patients with TB either alone (as a first-line OAD) or in combination with insulin or other OADs and in the absence of specific contraindications. Dose adjustments to minimize gastrointestinal intolerance and regular monitoring of renal and hepatic functions are recommended during metformin treatment [101]. Metformin should be discontinued in patients with abnormal liver function tests (> 3 times upper limit of normal [ULN]) and patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2. Signs of metformin-associated lactic acidosis (MALA) should be observed especially in hypoxic conditions [109, 113].

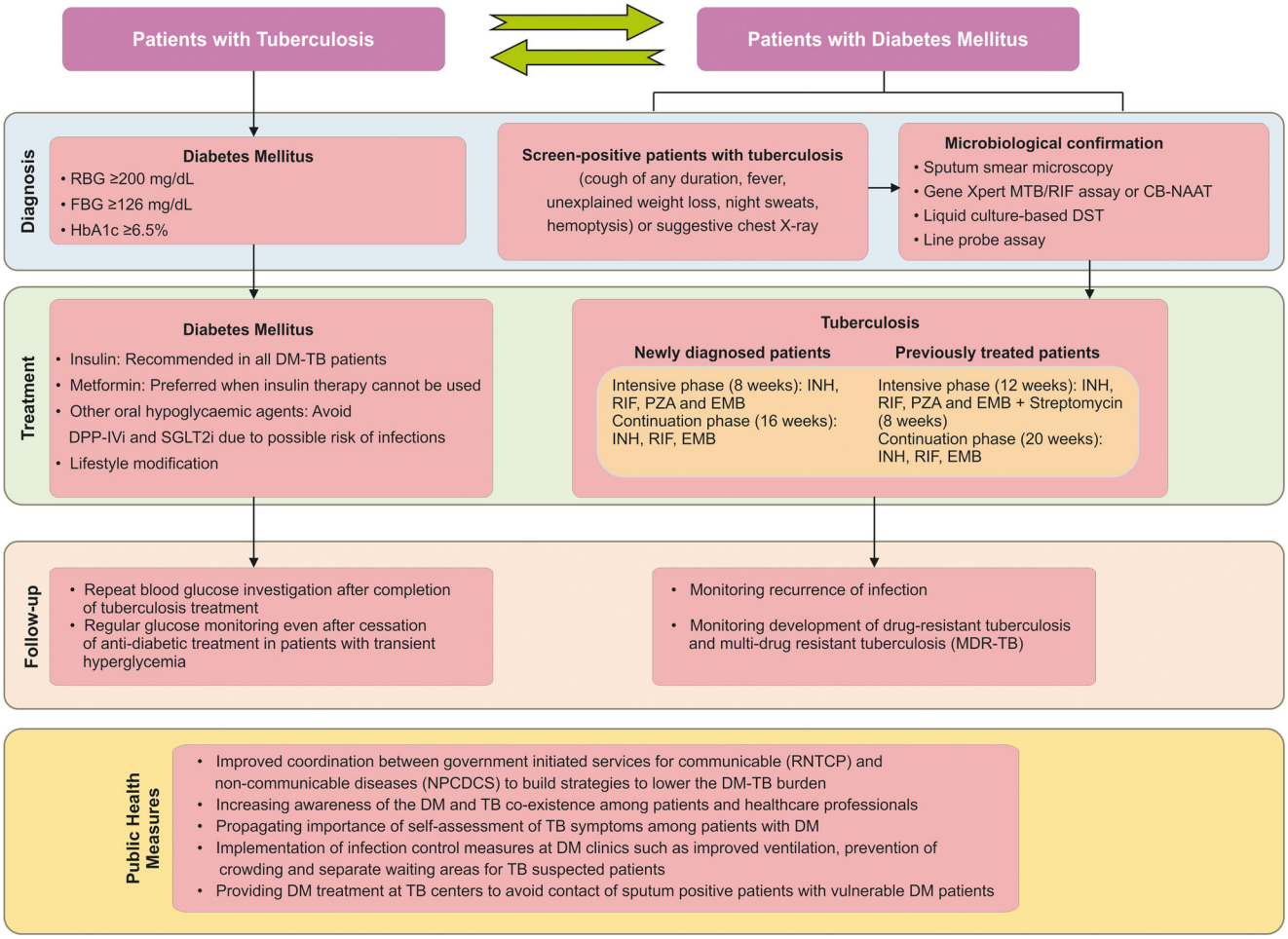

Fig. 3 Algorithm for bi-directional management of DM-TB. CB-NAAT, cartridge based nucleic acid amplification test; DM, diabetes mellitus; DPP-IVi, dipeptidyl peptidase-IV inhibitor; DST, drug susceptibility testing; EMB, ethambutol; FBG, fasting blood glucose; INH, isoniazid; PZA, pyrazinamide; RBG, random blood glucose; RIF, rifampicin; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TB, tuberculosis

In addition to its antihyperglycemic effects, metformin is also a mitochondrial toxin and this effect has been recently researched as a clinical benefit in the treatment of TB. By blocking the NDH-1 complex, an intermediate in the respiratory chain, metformin inhibits important metabolic mechanisms that have shown to induce antibiotic tolerance in *M. tuberculosis* [114]. Metformin also reduces the activation of inflammatory genes and enhances host immunity against *M. tuberculosis* and has been proposed as an adjunct to improve anti-TB treatment outcomes [95]. Activation of adenosine monophosphate-activated protein kinase (AMPK)-mediated phagolyses of *M. tuberculosis* by the host cell is regarded as one of the underlying mechanisms for metformin-induced modulation of host immunity [95, 107]. In a retrospective case-control study, the protective effect of metformin at doses 500 and 1000 mg was 3.9-fold as compared to OADs [107]. Thus, metformin has a favorable pharmacokinetic, has safety and efficacy profile, and should be included in the co-management of DM-TB if not contraindicated and tolerated by patients.

Other oral anti-diabetic drugs

As for the choice of OADs, it is imperative to consider the possible drug-drug interactions with anti-TB drugs to avoid toxicity and potential clinical failure of either therapy [30, 66, 74, 77, 79, 80]. Sulfonylureas may be used as the second-line treatment for DM in patients with TB when metformin is contraindicated. These agents may be used to rapidly achieve glucose targets in patients with high blood glucose and in patients who cannot tolerate metformin [101]. Shorter acting sulfonylureas such as gliclazide and glipizide may be used owing to the lower magnitude of adverse events as compared to longer acting molecules of this class [115]. As with the other OADs, there exists inadequate data for use of dipeptidyl peptidase-4 (DPP-4) inhibitors, alpha glucosidase inhibitors (acarbose), thiazolidinediones, and sodium-glucose co-transporter 2 inhibitors (SGLT2i) in patients with concurrent TB. The immunomodulating effect of DPP-4 inhibitors (e.g., sitagliptin, vildagliptin, saxagliptin) and associated risk of infections, mainly respiratory, raises concerns over their use in patients with DM-TB; although recent reports do not indicate significant risk [116, 117]. Appearance of clinical features of drug-induced hepatotoxicity should be monitored during concurrent use of thiazolidinediones or acarbose with anti-TB drugs [118–120]. The higher risk of infections and diabetic ketoacidosis associated with SGLT2i therapy poses a major challenge in the use of these newer glucose-lowering agents in patients with DM-TB (Box 5) [121, 122].

Box.5: Pharmacotherapy of Diabetes in Patients with Tuberculosis

Insulin

- Recommended in all patients with TB
- Potential benefits in patients with DM-TB
  - Anabolic actions
  - Low potential for drug interactions with the anti-TB agents
- Use of insulin is advised in newly diagnosed DM patients with
  - HbA1c >9.0%
  - FBG > 250 mg/dL
  - Presence of ketone bodies, symptoms of hyperosmolar state and for those in a catabolic state
- Dose adjustments may be needed during the course of treatment

Metformin

- Recommended in less severe cases of TB especially when insulin treatment is not available or acceptable to the patient
- Potential benefits in patients with DM-TB
  - Low potential for drug interactions with the anti-TB agents
  - Immunomodulatory effects: Enhances host immunity against *M. tuberculosis*
- Discontinue metformin in patients with
  - Abnormal liver function tests (>3 times upper limit of normal)
  - Estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2

Other Oral Antidiabetic Agents

- Avoid possible drug–drug interactions
- Shorter acting sulfonylureas such as gliclazide and glipizide may be used
- Possible risks of infections with DPP-4 inhibitors and SGLT2 inhibitors should be considered

Adjunctive lifestyle therapy

Lifestyle modifications (LSM) along with ongoing DM treatment can greatly aid treatment outcomes in patients with the DM-TB double burden. Assessment of quality and quantity of nutrition is important. Evidence for correlation of nutritional deficiency with lower immunity and increasing susceptibility to TB is of metabolic significance in patients with DM [123, 124]. Protein malnutrition and depletion of protein reserves in DM is known to increase risk of recurrent TB infections [125]. Further, by triggering malabsorption of TB drugs, protein insufficiency negatively affects treatment outcomes in TB [126]. Therefore, emphasis on nutrition management is highly recommended in patients with concomitant DM and TB. The RSSDI recommends a protein intake accounting for a minimum of 15% of total daily calorie consumption in patients with DM [101]. Although a calorie intake threshold is not established for patients with DM and concomitant TB, it is recommended that a major portion of calorie intake should come from proteins in patients without any renal or hepatic comorbidity. In hyper catabolic patients with DM-TB and experiencing weight loss of > 10% within 3 to 6 months, addition of 500 calories essentially from protein sources is recommended. Inclusion of complex carbohydrates and moderate fats in diet is also advised in patients with the double burden. Among micronutrients, appropriate intake of minerals and vitamins should be maintained especially throughout the course of TB treatment in patients with DM [127]. Vitamin D supplementation may be initiated in patients with TB and underlying DM to resolve immunopathological inflammatory responses and improve outcome of ongoing TB treatment [128–130]. In addition, supplementation with vitamin B6 and B12 for management of neuropathy is strongly recommended in patients with DM and receiving TB treatment. Use of vitamin A for improving immune cell responses to mycobacterial infection may also be considered [131, 132].

In obese people with DM and concomitant TB, weight reduction may be considered as an adjunctive measure; however, this should be secondary to achieving optimal glycemic control, preventing infections and ensuring macro- and micronutrient adequacy.

Mild to moderate physical activity as per the patient's ability and tolerance is also advised in patients with DM-TB. Outdoor activity is preferred to increase skin exposure to sunlight and increase vitamin D synthesis. The intensity of physical activity should be increased gradually as the patient's condition improves.

Attenuation of immune responses due to direct or indirect effects of alcohol is known to substantially increase the risk of acquiring TB infections, reactivation of latent TB infections, and a higher risk of TB recurrence [133, 134]. Cessation of alcohol intake is therefore recommended during treatment of TB as well as post treatment [135].

Tobacco use in patients with DM has been associated with an increased risk of TB occurrence and transmission; hence, permanent discontinuation of tobacco use in all forms (smoking, chewing, etc.) is considered critical (Box 6) [136].

The impact of LSM on treatment outcome should be monitored and tailored as per individual patient needs. It is important that patients are educated about the benefits of continued LSM and timely and regular blood glucose measurements. Regular blood glucose monitoring should be emphasized even after TB is cured and upon completion of TB treatment and reversal to normoglycemic state along with cessation of antidiabetic treatment. Even if hyperglycemia was transitory due to stress of infection, patients manifesting hyperglycemia under stress are extremely vulnerable for future diabetes and integrated lifestyle measures may delay the onset of diabetes in these cases.

Box 6. Recommended Lifestyle Modifications

- Lifestyle measures should be tailored to individual patient needs
- Improvement of nutrition
  - Increase protein intake in patients with significant weight loss
  - Weight reduction may be considered in obese patients
  - Ensure appropriate intake of minerals and vitamins
  - Vitamin D supplementation: for improved TB outcomes
  - Vitamin B6 and B12 supplementation: for management of neuropathy
  - Vitamin A supplementation: for improved immune cell responses
- Mild to moderate physical activity
- Cessation of alcohol intake
- Permanent discontinuation of tobacco use in all forms
- Continue lifestyle modifications and regular blood glucose monitoring even after completion of TB treatment and attainment of normoglycemic status.

Management of TB in patients with diabetes complications

Chronic kidney disease

Chronic kidney disease (CKD) is a common comorbidity and complication of DM with high morbidity and mortality [137]. CKD is known to adversely impact multiple immune functions (phagocytosis, B cell and T cell response) and substantially increase the risk of acute and chronic infections such as TB, HIV, and hepatitis B virus (HBV) [138, 139]. Several studies report the high incidences of TB in high-risk renal patients and patients with end-stage renal disease (ESRD) and advocate periodic screening of TB in these patients [139–144]. The compounded effect of CKD and DM not only increases the risk and severity of TB but also complicates its treatment.

Although there is dearth of studies reporting the prevalence of TB-DM and comorbid CKD, the occurrence of TB has been found to be higher in patients with DM undergoing dialysis [145, 146]. In a nationwide, 10-year study from Taiwan, patients with TB having chronic kidney or liver diseases were observed to have a higher chance of developing DM underlining the two-way association between the comorbidities [147]. The same study reported a high prevalence of DM among patients with TB and the prevalence of CKD among patients with TB and DM was 11.7% [147]. A study conducted in a tertiary care hospital from North India showed that patients with type 1 DM had high rates of positive *M. tuberculosis* culture and a significant number of patients among these had CKD (31.2%; $p < 0.001$) [148].

The standard quadruple regimen for active TB (RIF, INH, PZA, and EMB) is recommended in patients with CKD [149]. Dose reduction of up to 50% for drugs EMB and PZA that are majorly metabolized and eliminated by the kidneys is recommended in patients with compromised renal function and advanced renal impairment having creatinine clearance < 10 mL/min [150, 151]. The risk of under-dosing can jeopardize TB outcomes and regular monitoring of treatment outcomes and adverse events is therefore essential to achieve optimal therapy [144, 149]. To reduce cross-interactions of RIF with common concomitant drugs such as OADs, immunosuppressants, and antihypertensives, substitution of RIF with rifabutin may be considered.

Among interventions for DM, insulin is the preferred therapy and the use of metformin should be avoided in patients with eGFR < 30 mL/min/1.73 m^2 [152]. Insulin dose must be carefully titrated as the risk of hypoglycemia is increased due to prolonged insulin half-life in patients with DM and concurrent CKD. Diagnostic difficulties may be encountered in patients with CKD and chronic liver disease (CLD) that include misdiagnosis due to exaggerated symptoms of the comorbid conditions. False-positive elevation in HbA1c as a result of analytical interference due to high concentration of urea in patients with ESRD attenuates the reliability of HbA1c for glucose monitoring in these patients (Box 7) [153]. Also, a false-positive diagnosis of ketoacidosis due to INH or PZA treatment may also interfere with the management. Monitoring of renal adverse events including hyperuricemia

is recommended in patients with compromised renal function and receiving treatment for concurrent DM-TB. Assessment of calorie intake and restrictions in protein intake (instead of the usually recommended high protein intake) is advised in patients with DM-TB and comorbid CKD. Vitamin B6 supplementation is recommended in these patients.

Box 7. Recommendations for DM-TB in Patients with Comorbid Chronic Kidney Disease

- Management of TB
  - Standard quadruple regimen (RIF, INH, PZA and EMB) is recommended in patients with CKD
  - Up to 50% dose reduction for EMB and PZA may be needed in patients with creatinine clearance <10 ml/min
  - Regular monitoring of treatment outcomes and adverse events is advised to ensure optimal therapy
- Management of DM
  - Insulin is the most preferred therapy
    - Careful dose titration is advised to avoid risk of hypoglycaemia
  - Use of metformin should be avoided in patients with eGFR <30 mL/min/1.73 m^2
- Regular monitoring of renal function is advised during ongoing DM-TB therapy
- Restricted protein intake is recommended

Chronic liver disease

As with CKD, there are limited studies reporting the coexistence of DM-TB in patients with CLD. The treatment of TB in patients with CLD is challenging due to the lower threshold of drug-induced hepatitis and hepatotoxic events in these patients with preexisting liver impairment [154, 155]. The three core first-line anti-TB drugs, INH, RIF, and PZA, are associated with hepatotoxicity with RIF being least and PZA having the highest potential. Most second-line anti-TB drugs are safe and associated with mild and reversible hepatic adverse events [156–158]. The time of initiation and cut-off for cessation of anti-TB treatment are pivotal factors in the management of DM-TB in patients with CLD. It is recommended that the treatment for TB be delayed and deferred until acute hepatitis is resolved. If acute hepatitis develops during TB treatment, all potentially hepatotoxic drugs (INH, RIF, and PZA) should be discontinued till complete clinical and biochemical resolution of hepatotoxicity. Non-hepatotoxic anti-TB drugs such as EMB, streptomycin, ofloxacin, and levofloxacin may be used in the interim period along with periodic monitoring of renal and hepatic function. Both HBV and hepatitis C virus (HCV) infections are significant risk factors for TB treatment-induced hepatotoxicity. Monotherapy with INH is advised and multidrug TB therapy should be avoided in patients with HBV or HCV infection [159–162], Antiviral therapy for HBV (entecavir and tenofovir) and HCV (pegylated interferon and ribavirin) may be initiated to lower viral load in patients who need anti-TB treatment [156]. Monthly monitoring of liver function is recommended in these patients upon reintroduction of anti-TB treatment. Anti-TB regimen in patients with cirrhosis should be introduced with caution keeping in mind the elevated risk of liver failure in these patients [156, 163]. Treatment with most anti-TB dugs may be restarted upon normalization of elevated transaminases (AST concentration < 2 times ULN) [156]. It is recommended that the therapy should be restarted with RIF due to its lower potential for hepatotoxicity. Reintroduction of anti-TB therapy should be implemented in a phased manner starting with lower doses of INH (50 mg) and RIF (150 mg) and up-titrated every 3 to 4 days to the recommended therapeutic doses. Pyrazinamide should be permanently discontinued in patients with liver dysfunction. The treatment should be reassessed upon recurrence of symptoms [156].

Insulin is the drug of choice for treatment of DM in patients with TB and comorbid CLD, more so in patients with cirrhosis [164]. Insulin requirements are higher in patients with impaired hepatic function due to insulin resistance and may be lower in patients with decompensated liver disease due to reduced breakdown of insulin [165]. Close monitoring of blood glucose and frequent dose adjustments are recommended during insulin therapy [166]. Metformin can be used in patients with stable liver disease (Child-Pugh score < 7) and should be avoided in patients with cirrhosis due to higher risk of MALA [167]. Use of metformin may be beneficial in treatment of simple hepatic steatosis and non-alcoholic steatohepatitis (NASH) and has been associated with normalization of transaminases [168, 169]. Reductions in hepatocellular carcinoma and hepatic complications in patients with DM and cirrhosis have been observed. Sulfonylureas have limited benefits in patients with CLD due to their pharmacodynamic and pharmacokinetic profile and should be avoided in patients with CLD [164]. Alpha-glucosidase inhibitors effectively lower both fasting and postprandial hyperglycemia and have an acceptable safety profile in patients with CLD [170]. Thiazolidinediones should be administered with caution in patients with elevated transaminases (> 2.5 times ULN) and periodic monitoring is advised [164, 171]. Treatment with pioglitazone and rosiglitazone has been associated with lowering of serum transaminases and insulin resistance and may also be useful in non-alcoholic fatty liver disease (NAFLD) [164, 172–174]. Regardless of the therapy, drug-drug interactions should be monitored and dose titrations should be reassessed in patients receiving concomitant treatment for DM-TB. Assessment of calorie intake is important in patients with DM-TB and coexisting CLD. Higher protein intake is recommended in cases of protein malnutrition that is common in patients with liver disease. In cases of NAFLD, calorie restriction and weight loss is advised although weight loss due to TB should also be taken into account. Cessation of alcohol consumption is strongly recommended due to toxic liver effects. Although beneficial,

physical exercise may not be advisable in patients with active liver disease [164, 175].

As with CKD, inconsistencies in HbA1c measure pose diagnostic challenges that further confound management of DM-TB in patients with CLD. Falsely elevated HbA1c levels due to nutritional anemia and increased RBC survival and misleading reductions due to bleeding and hemolysis hamper accuracy of results (Box 8) [176].

Box 8. Recommendations for DM-TB in Patients with Comorbid Chronic Liver Disease

- Management of TB
  - Delay and defer TB treatment until acute hepatitis is resolved
  - Discontinue hepatotoxic drugs (INH, RIF, and PZA) if acute hepatitis develops during TB treatment. Non-hepatotoxic anti-TB drugs such as EMB, streptomycin, ofloxacin, levofloxacin may be used in the interim period
  - Use INH monotherapy and avoid multidrug TB therapy in patients co-affected with hepatitis B and C virus infections
  - Restart TB treatment upon normalization of elevated transaminases (AST concentration <2 times upper limit of normal)
    - Start TB treatment with lower doses of INH (50 mg) and RIF (150 mg) and up-titrate every three to four days to the recommended therapeutic doses
  - Discontinue pyrazinamide in patients with liver dysfunction
- Management of DM
  - Use of insulin is recommended for treatment of DM
  - Insulin requirements may be higher in patients with impaired hepatic function and lower in patients with decompensated liver disease. Monitoring of blood glucose and frequent dose adjustments are therefore recommended during insulin therapy.
  - Metformin can be used in patients with stable liver disease (Child-Pugh score <7) and should be avoided in patients with cirrhosis
- Cessation of alcohol consumption is strongly recommended

Human immunodeficiency virus

The confluence of HIV and TB is a recognized global syndemic and TB is regarded as the second leading cause of death due to infectious diseases among patients with HIV [177, 178]. Several studies from India have also acknowledged the high prevalence of TB-HIV co-infection [179]. Estimates for DM-TB and HIV coexistence is currently not reported. A study examining comorbidities in TB patients from South India identified the preponderance of DM coexistence over HIV [179]. The WHO recommends symptom screening (persistent cough or fever, weight loss, night sweats, and lymphadenopathy) for TB in all patients with HIV followed by a confirmatory assessment using Gene Xpert MTB/RIF assay in suspected cases. It has been observed that TB-HIV co-infection confounds the clinical diagnosis of TB and typical chest radiographic presentations may be absent in sputum culture-positive patients with HIV and low $CD4^+$ count [180]. Screening of latent TB using methods such as interferon-gamma release assays (IGRA) and skin tuberculin are also advised to facilitate preventive care in vulnerable cases. On the other hand, HIV testing is advocated in all patients with presumptive TB. The feasibility of HIV testing was demonstrated in India through a joint effort by RNTCP and the National AIDS Control Organization (NACO) in two districts from India where the HIV status was ascertained in 70% patients with TB [181].

Anti-retroviral therapy (ART) is strongly recommended in all patients with TB and HIV irrespective of the $CD4^+$ count. It is recommended that TB treatment should be started first followed by the initiation of ART as soon as possible and preferably within the first 8 weeks of TB treatment [63]. In co-affected patients with severe immunosuppression ($CD4^+$ count < 50 cells/mm^3) ART should be started within the first 2 weeks of TB treatment [63]. A paradoxical worsening of TB symptom shortly after initiation of ART may be suggestive of the development of TB-immune reconstitution inflammatory syndrome (TB-IRIS) and should be monitored closely [182, 183]. The symptoms of TB-IRIS commonly include lymphadenopathy, recurrent fever, worsening respiratory symptoms, and radiological manifestations of TB. The possible misclassification of TB-IRIS as a superinfection, TB treatment failure, and development of drug resistance or TB relapse should be eliminated before confirming diagnosis. The management of TB-IRIS usually involves systemic administration of corticosteroids and anti-inflammatory drugs [182, 183].

Anti-retroviral therapy, the mainstay in the treatment of HIV, has been associated with increased risk of metabolic derailments that include hyperglycemia. The presence of coexisting TB and poor nutrition may further stress the compensatory mechanisms and overwhelm the ability to increase insulin production in the face of rising insulin resistance resulting in a fully decompensated diabetic state. Alternatively, DM induced by ARTs can further enhance the risk of TB in these patients and complicate management of comorbidities [184, 185]. It is recommended that patients with HIV should be screened for DM at the onset of ART and at an interval of 3 to 6 months. The use of venous sampling is advised as opposed to finger prick for blood glucose estimations and HbA1c is not recommended in patients with HIV (Box 9) [186]. By virtue of its anabolic effects, favorable effects on inflammatory markers and limited effects on renal and hepatic functions, insulin is recommended for treatment of DM in patients with HIV and TB [186]. The use of metformin should be avoided in cachexic patients with TB and concurrent DM. Metformin-related incidences of diarrhea, reductions in subcutaneous fat, and subsequent worsening of lipodystrophy can complicate management of comorbidities [187]. Among other OADs, meglitinides and sulfonylureas may be used for rapid improvements in cases of severe insulin resistance. Close supervision of adverse events is essential during treatment with thiazolidinediones; however, poor responses to these agents have been reported in patients with HIV limiting their use. LSM including adoption of healthy balanced diet, regular physical activity, and restricted tobacco use is recommended for improved management of comorbidities [186].

Box 9. Recommendations for DM-TB in patients with comorbid HIV

- Use Gene Xpert MTB/RIF assay for diagnosis of TB in all patients with HIV
- Use of Interferon-Gamma Release Assays and skin tuberculin is advised for screening latent TB in vulnerable patients
- HIV testing is recommended in all patients with presumptive TB
- Initiate antiretroviral therapy in all patients with TB and HIV irrespective of the CD4+ count
- Start TB treatment first followed by antiretroviral therapy preferably within the first 8 weeks of TB treatment
- In patients with CD4+ count <50 cells/mm3, antiretroviral therapy should be started within 2 weeks of TB treatment
- Patients with HIV should be screened for DM at the onset of antiretroviral therapy and every 3 to 6 months subsequently
- Treatment with insulin is recommended for DM
- Avoid use of metformin in cachexic patients

Public health implications of the co-epidemic

The escalating prevalence of both DM and TB and the syndemic association of their coexistence is a growing concern in India. Coordination between government initiated services for communicable (RNTCP) and non-communicable diseases (NPCDCS) to build a synergistic strategy to reduce the burden of TB and DM is essential. Although these independent bodies have efficiently raised awareness of TB and DM as individual issues, there is limited understanding about the DM-TB comorbidity among patients and healthcare professionals. This lack of awareness can seriously jeopardize treatment outcomes of both diseases, increasing related morbidity and mortality. It is therefore imperative to defy barriers that reduce availability, affordability, dissemination, and efficacy of optimal diagnosis and treatment of both diseases in public settings.

The efforts towards lowering the DM-TB burden start with increasing awareness of the DM and TB coexistence. It is essential to educate patients with DM about the common symptoms of TB and the importance of self-identifying the symptoms of TB. Patients should be made aware of practical indicators of weight loss such as change in clothing size and belt size, and this should be promptly communicated to health care professionals for further investigations or dose adjustments during ongoing treatment. Displaying posters of TB awareness, symptoms screening, and treatment at DM clinics and vice versa would help educate patients. Involvement of media should be promoted to disseminate health information to a wider audience and propagate the intensity of the problem as well as publicize ongoing efforts for control and management.

It is also essential to assess the awareness and level of clinical knowledge of DM among TB health workers. A study evaluating the impact of a training program on screening, diagnosis, and management of DM, designed for TB health care providers across 22 tuberculosis units in Tamil Nadu reported enhancement of knowledge and improvement in attitude and practice sense for screening and primary care for DM [188]. Similarly, health care professionals at DM clinics should be made aware of the increasing incidences of TB among patients with DM and measures to prevent transmission of infection. Implementation of key infection control strategies should be mandated at all public health facilities attended by vulnerable patients with DM. At DM clinics, measures such as installation of proper ventilation systems, improving natural ventilation and air circulation, minimizing patient waiting time, and providing separate waiting rooms for suspected patients with TB (sputum-positive patients or patients with chronic cough) should be encouraged [31, 189]. Considering the high propensity of TB infections among patients with DM and to minimize the risk of transmission, it is recommended that consultation, follow-up, and treatment for DM in sputum-positive patients be conducted at TB facilities until the patients become sputum negative.

The National Framework for Joint TB-Diabetes Collaborative Activities summarizes collaborative efforts between the two national bodies NPCDCS and RNTCP [31]. Recommendations include implementation of TB symptom screening at DM clinics and DM screening (RBG/FBG) at peripheral health institutes. Strengthening of referral systems between the two bodies and generating effective referral and feedback mechanism are important to ensure every referred patient reaches the DMC or diabetes clinic. Suggested measures include provisions in the NIKSHAY database to capture diabetes-related information for each reported and referred patient. Training and familiarization of staff members including medical officers, counselors, nurses, and data entry operators at both centers is recommended for smooth coordination and execution of screening, referrals, and treatment. Organization of state-level, district-level, and subdistrict-level workshops and trainings for collaborative activities has been proposed [31].

Promoting operational research in the prevention, diagnosis, and management of TB and diabetes co-epidemic: establishing a multicenter study on the bi-directional screening and management of DM-TB

Operational research is needed to determine the feasibility, challenges, and opportunity of bi-directional screening and management of DM-TB. Such approaches will greatly aid collaborative mechanism between the RNTCP and NPCDCS. Establishing multicenter study involving key stakeholders from both national programs (RNTCP and NPCDCS) will help to achieve consensus and wide ownership of the results, thus creating several advocates for policy change. The overall objective of the prospective research should be to identify gaps in operational activities (pertaining to screening and management) and design appropriate studies to address shortcomings and enhance understanding of the DM-TB syndemic (Table 1).

Table 1 Proposed studies to support bi-directional screening and management of diabetes mellitus-tuberculosis

Key research question	Study design and methodology	Need
• Screening patients with DM for active TB • Screening patients with active TB for DM	Prospective observational cohort studies of patients with DM routinely attending DM clinics and screened for TB, and patients with TB starting anti-TB treatment and screened for DM both in public and private setting • Testing protocols for feasibility and carrying out needs assessment and resources required for large scale program implementation • Research to determine the most effective type of screening algorithm for TB among DM patients and vice versa • Research to determine the appropriate time to perform screening/testing for diabetes: at registration, or during the course of treatment • Research to determine the most appropriate screening tool for TB among diabetes patients and for diabetes among TB patients	High
Use of the community to improve diagnosis, management, and care of patients with DM and TB	Prospective observational studies to determine feasibility and yield of screening household contacts and "at risk" individuals. These include family members of index patients with pulmonary TB and DM for TB infection, active TB, and DM	Medium
Evaluating TB treatment outcomes in patients with DM and strategies to improve outcome	Prospective observational cohort studies using standardized TB regimens and standardized treatment outcomes based on • Death in relation to start of TB treatment and cause • Duration of sputum conversion • Cure rate • Relapse and reinfection All outcomes to be analyzed in relation to DM control If improved DM control is not associated with better outcomes, studies to determine if modification to TB drug regimens, duration of therapy, and TB drug doses are required	High
Protocols for treating hyperglycemia in people with TB	Designing and testing protocols for treating hyperglycemia in people with TB through observational case cohorts and case control studies • Newly diagnosed diabetes: Initiating diabetes treatment, referrals, and follow-up. To understand if TB outcomes are better with insulin therapy or OADs. To analyze which cases need insulin • Previously known diabetes: to analyze if patients not previously on insulin be shifted to insulin • Prediabetes: need for treatment initiation RCTs to determine whether all DM patients with TB be initiated on metformin given its potential impact on improving immune functions RCT to determine the role of metformin for prevention of TB treatment failure and reinfection/relapse in DM patients with TB and prevention of DM and active TB disease in patients with prediabetes and latent TB	High
Evaluation of point-of-care diagnostic and monitoring tests for DM in primary care settings where TB treatment is delivered	Designing multicenter study to assessing the feasibility, acceptance, sensitivity, specificity and cost effectiveness of FBG, OGTT, and HbA1c to guide large scale adaptation Developmental work to produce a reliable low cost finger stick test for measuring blood glucose and HbA1c in rural areas, which then needs to be tested for efficacy and feasibility in the field	High
• Evaluating risk of MDR-TB in patients with DM • Evaluating MDR-TB in patients with poorly controlled DM	Prospective MDR-TB case cohort studies where screening for DM is done Prospective DM-TB cohort studies	High
Establishing Care Delivery Model	Developing and testing approaches to care delivery—observational cohort studies • Initial treatment—in TB center • Long-term follow-up	High
Rates of hospitalization and additional medical costs associated with diagnosis and management of dual disease	Cross-sectional and case-control studies and activity based cost analysis (ABC)	Medium
• Population attributable risk of DM on TB rates in India • Effect of the DM epidemic on the TB epidemic	Epidemiological and mathematical modeling to understand spatial spread of the epidemic	High
Evaluating strategies to improve diabetes care delivery at primary care setting Implementing and evaluating the "DOTS" model for standardized care management of DM	Operational research that includes quarterly cohort reporting of new cases and treatment outcomes of cumulative cases including frequency of comorbidities and survival analysis	High
Treatment protocols in special situations	Literature review and small observational studies • Pregnancy, hyperglycemia, and TB • Diabetic renal disease and TB • HIV on ART, TB, and hyperglycemia • Diabetes, CLD/CKD, and TB	Medium

ART anti-retroviral therapy; *CKD* chronic kidney disease; *CLD* chronic liver disease; *DM* diabetes mellitus; *DOTS* directly observed treatment, short course; *FBG* fasting blood glucose; *HbA1c* glycated hemoglobin; *HIV* human immunodeficiency virus; *MDR-TB* multidrug-resistant tuberculosis; *OAD* oral anti-diabetic drugs; *OGTT* oral glucose tolerance test; *RCT* randomized controlled trial; *TB* tuberculosis

Acknowledgements The authors thank Priya Ganpathy, ISMPP CMPP™, for medical writing assistance and Sangita Patil, PhD, ISMPP CMPP™ (both SIRO Clinpharm Pvt. Ltd., India), for additional editorial support.

Funding The preparation of this clinical practice recommendation was supported by Mankind Pharma Ltd., India.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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