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THE GLOBAL OUTBURST OF DIABETES AND TUBERCULOSIS: DOUBLE TROUBLE

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ABSTRACT

The risk of developing tuberculosis (TB) is long associated with diabetes. DM is becoming more and more prevalent all over the world. The linked burden of TB and diabetes has received considerable attention. Diabetes can double to triple the risk of contracting tuberculosis. In addition, TB may promote hyperglycemia and decrease glycaemic control in diabetics. Moreover, it raises the chances of failure of TB therapy, symptom exacerbation, and even premature death. Concern for epidemics interacting with TB and diabetes in low-income countries including India, China, Indonesia, Pakistan, and South Africa has been highlighted by healthcare experts. In 2021, 10.6 million people were confirmed diagnosed with TB while 1.6 million lives have been lost due to TB. It is also the second most common infectious killer in the globe, behind COVID-19, and the 13th greatest cause of death globally. Extensive healthcare improvement and unification might well be required to maintain these elevated risks in patients' care after the completion of their TB treatment.

Keywords: Diabetes, Tuberculosis, glycaemic control

INTRODUCTION

Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis and it generally affects the lungs. It is transmitted from one person to another. TB bacteria can be spread into the atmosphere when patients have pulmonary TB which can be transmitted from one infected patient to another (e.g., by coughing, sneezing, or spitting) **[1]**. It is estimated that more than 10.6 billion people (6 million cases of male,

3.4 million cases of female, and 1.2 million cases of children) have M. tuberculosis. The incidence of TB peaked globally in 2003 and is now slowly declining World Health Organization (WHO) estimates that in 2021, 10.6 million persons had TB diagnoses and 1.6 million TB-related death encountered in 2021. The incidence of TB is declining at a pace of about 2% year worldwide, and between 2015 and 2020, this decline totalled 11%. **[2]**. Diabetes is a complex metabolic chronic condition caused by either altered insulin levels or the ineffective bodily response to insulin. T2DM also known as non-insulin-dependent or diabetes of adulthood, results from the body's inefficient use of insulin. T2DM affects almost 95% of all patients with the disease. The main reason behind this is due to being overweight and physically inactive **[3]**. According to the most recent data available, the 30 high TB-burden nations had a median prevalence of diabetes of 8% (interquartile range [IQR]: 6–9%), with ten percent or higher prevalence rates in Gabon (10%), Mongolia (12%), Pakistan (12%), Papua New Guinea (15%), and South Africa (11 %) **[4]**. Recent researches and studies show that DM can also raise the incidence of latent and active Tb by 1.18 and 3.11 times, respectively. Furthermore, Treatment outcomes for TB are significantly impacted by DM; in particular, it is linked to the delayed conversion of sputum cultures, an increase in the risk of failure of the therapy, an elevated risk of death, and TB relapse **[5]**. Diabetes can also lead to challenges with bacterial recognition, phagocytes, and cellular activation that result in the affected synthesis of cytokines and chemokines are the basis of immune mechanisms behind the higher vulnerability of DM patients to TB **[6]**. Furthermore, it appears that the degree of this risk is correlated with the severity of DM. Poor glycaemic management has been recognized as a risk factor for TB, and insulin dependency has been shown as a measure of the severity of the disease and indicates an increased risk of TB **[7]**. In this review, we analyze the information and the link association between DM and TB and also give an overview of the effect of DM and TB epidemiology amongst the population.

EFFECTS OF DIABETES ON TB

Diabetes poses a risk for TB and other respiratory diseases. At the population level, diabetes is still a greater threat to TB infections, even though TB is more frequently associated with other immunosuppressive illnesses like HIV infection **[8]**. The risk of acquiring TB is higher among those with uncontrolled diabetes compared to people who have adequate glycaemic control, indicating that diabetes may be a significant factor in the emergence of TB **[9]**. DM can raise the incidence of latent and active Tb by 1.18 and

3.11 times. Through a variety of mechanisms, diabetes may potentially enhance susceptibility to M. tuberculosis illness. The mechanisms involve direct impacts on insulin production in cells and hyperglycemia, as well as unintended consequences on the function of macrophage and lymphocyte activity **[10]**. Diabetes may further prolong the time to smear or culture negative and slightly raise the bacterial burden of M tuberculosis. When compared to patients with just TB, people with diabetes and TB have nearly twice as many positive cultures at months 2-3. The results of TB treatment are now worsened by diabetes, according to numerous research and reviews, with the probability of mortality during TB treatment increasing by double **[11]**.

ETIOLOGICAL RELATIONSHIP OF DM & TB

DM–TB comorbidity elevates the risk among patients because of their bidirectional link. The consequences of DM on people with TB include alterations in latent infection, sensitivity towards infection, reactivation, progression of the disease, contagiousness, smear positivity, and even death in some serious consequences **[9]**. The main mechanism behind this TB-DM interaction is due to imbalanced cellular immunity and different biological parameters in the body. TNF-alpha and TNF-beta, interleukin-1 and interleukin-6 production, as well as the T-helper 1 (TH 1) cytokine levels are altered among diabetic patients as compared to non-diabetic persons. Diabetes individuals are more prone to acquiring TB because the levels of T-lymphocyte are lower. For instance, Mycobacterium tuberculosis is inhibited by TH1 cytokines. Diabetes causes macrophage dysfunction, which impairs phagocytic and chemotactic activity as well as the generation of reactive oxygen species. Patients with diabetes also have poor monocyte chemotaxis, which does not improve with insulin **[8]**. The combination of these malfunctioning mechanisms elevates the risk of developing TB in people with diabetes **[12]**. The comorbidity condition of DM and TB may lead to an increase or worsens the symptoms of each other. Diabetes patients frequently complain to their physicians about their blood glucose control getting worse mostly to eventually discover they have TB **[12]**. Patients with TB increase adrenaline, glucagon, and cortisol simultaneously due to malnutrition and inactivity, which raises blood sugar levels **[13, 14]**. The research is also supporting the evidence that lung resection in pulmonary TB and diabetic patients lowered the DM's severity and after the TB therapy, glucose tolerance improved in diabetic patients **[15]**. When DM is not well-controlled in a patient with PTB which is also known as latent TB (LTB), then the

circulating levels of adiponectin and adipsin, which are both low in PTB, and leptin, visfatin, and PAI-1, which are all elevated in LTB which demonstrates that patients with DM have a noticeable inflammatory condition. Changes in the levels of adipocytokine throughout the body suggest that altered adipose tissue inflammation may be involved in the aetiology of the comorbidities of TB-DM **[16]**.

CLINICAL FEATURES AND FINDINGS

DM exacerbates the symptoms of TB and worsens its clinical appearance. T2DM patients with inadequate glycaemic management experience an even higher exacerbation of the clinical TB disease characteristic **[16]**. Since T2DM is commonly associated with a higher body mass index (BMI) than TB alone, it is not surprising that the majority of research show that people with TB and co-morbid DM had higher BMIs. It has been established that having a higher BMI act as a standalone preventative measure against contracting TB, despite also being a risk factor for treatment failure and mortality while the unadjusted risk ratio for mortality was 1.89 and after age and other confounding factors were taken into account, it increased to 4.95. Additionally, the risk ratio for relapse was found to be 3.89. In their study, they observed that the variation in and width of the impact of co-existing DM on sputum conversion ranges from 0.79 to 3.25 after 2-3 months of the therapy. The authors conclude that death is not caused by drug-resistant TB or severe hyperglycemia, but rather by advancing age and underlying co-morbidity **[20]**.

A systematic review of the impact of diabetes on tuberculosis treatment outcomes demonstrated that having diabetes increases the chance of failing to respond to therapy for TB and death from it. Diabetes patients have a risk ratio of 1.69 (95% CI: 1.36-2.12) for both combined outcomes of failure and death **[17]**.

Similar to another study conducted by Faurholt-Jepsen D et al 2003 which demonstrated that within 3.2 months of TB treatment. In T2DM patients the comorbidity was linked to a five times greater risk of mortality and HIV-coinfected patients with 2 times higher risk of developing infection **[21]**.

The widespread DM-TB co-morbidity also poses several clinical difficulties. It is firstly more difficult to control diabetes when coexisting with a major infection because it worsens catabolism and raises blood sugar.

SCREENING FOR DIABETES IN TB PATIENTS

To effectively manage infections in any patient with an infectious condition, the detection and monitoring of hyperglycemia are crucial **[20]**. Additionally, in the initial

stage patients with TB should be checked for persistent symptoms of DM such as polyuria, polydipsia, polyphagia bodily wasting, hazy eyesight, weakness, sluggishness, and inadequate wound healing **[15]**. WHO and other national agencies have issued guidelines, for screening newly enrolled TB patients for diabetes and has been included in DOTS (Directly Observed Therapy Short course) for the management of TB **[22]**. According to international recommendations, screening might be accomplished with a straightforward blood glucose or glycated hemoglobin test **[23]**. The specific types of tests performed to evaluate for DM in patients with TB rely on the accessibility of medical facilities in the area, the cost of the testing, and the patient's willingness to undergo extra or follow-up exams **[20]**. Based on glucose criteria, such as the FPG (fasting plasma glucose) or the 75-g OGTT (oral glucose tolerance test), diabetes has been diagnosed. OGTT (oral glucose tolerance test) of 2 hours and 75 grams is the gold standard for diagnosing pre-diabetes, diabetes, IGT (impaired glucose tolerance), and frank DM **[24, 25]**. HbA1C, a measure of normal blood glucose levels over a two- to three-month period is nowadays widely used as a standard biomarker of chronic glycemia **[25]**. Two tests are necessary for diabetes diagnosis one is FBG of 126 mg/dL or an RBS (Random Blood Sugar) of 200 mg/dl while Impaired fasting glucose is classified as FBG levels between 110 and 125 mg/dL, while impaired glucose tolerance is classified as post-glucose values between 141 and 199 mg/dL **[18]** and the levels for HbA1c $\geq$ 6.5% confirms that patient is diagnosed with DM. Hence, it is recommended that all DM diagnoses be made at an early stage and confirmed by repeat tests during subsequent follow-ups. Furthermore, if we evaluate the results from the recent studies conducted in this comorbidity condition, we can conclude that HbA1c performed a better diagnostic tool if we compare it with FBG **[16]**. There are many difficulties involved in screening for diabetes in tuberculosis patients, including when to screen and what test to employ to ensure better services are provided to the patients to comply with these various precautionary measures are already being taken in nations with a substantial infection burden and increasing prevalence of DM and India being the fourth-largest country in the world, it has 25% of the global TB burden **[9, 26]**. Incorporating this national TB control program in Kerala State, India has already started screening TB patients for DM, and assessing the impact of this on the results of TB treatment under routine campaigns **[27]**.

SCREENING FOR TB IN DIABETES PATIENTS

TB is still a serious issue for worldwide public health. Among infectious diseases, TB is the second-leading cause of death worldwide killing close to two million people annually. An effective tuberculosis control program depends on early disease detection and quick treatment implementation Delay in diagnosis may result in deterioration of the illness, an increased risk of death, and increased tuberculosis transmission in the population **[28]**. Detection and Diagnosis of TB amongst DM patients can be evaluated via various methods like a clinical assessment of the patient for signs and symptoms of productive cough for more than 2 weeks, Chest X-Rays, Sputum Culture, and various other methods. For patients with past TB, their details about the organs involved, the history, the mode of diagnosis, and the course of treatment were noted. Old chest radiographs from patients with pulmonary tuberculosis (PTB) were evaluated to better comprehend the illness and the effects of treatment. Three sputum examinations were carried out on patients with suspected active PTB, including a chest x-ray, AFB smear, and X-pert MTB/Rif and MGIT culture. Ziehl-Neelsen staining was used to analyze sputum for AFB smear, and X-pert MTB/Rif & MGIT tests were conducted by the reference standard. (TST) Mantoux tuberculin skin test was used for screening patients with latent TB. To diagnose TST, tuberculin 2TUsolution was used (PPD RT 23). TST was regarded as positive if the indurations were ≥ 10 millimeters, confirmatory result shows the patient having latent TB **[29]**. It is thought that better DM care will help reduce the incidence of TB, particularly in areas where this illness is prevalent **[30]**.

Table 1: Important considerations when screening patients

Screening TB patients for DM	• **In various developing and middle-income nations, screening can detect a large number of individuals with poorly managed or untreated diabetes mellitus.** • **In various developing and middle-income nations, TB clinics do not routinely offer blood glucose or HbA1c testing, while other diagnosing methods were less accurate.** • **Patients who have just received a diagnosis of hyperglycemia ought to get retested later on in the course of treatment.**
Screening DM patients for TB	• **Testing difficulties in DM clinics (such as the lack of sputum sample and culture, and chest X-ray availability).** • **Low yield; unlikely to be economical unless TB incidence is quite high.**
Screening DM patients for LTBI	• **There is currently no direct evidence evaluating the costs, risks, or advantages of diagnosing and managing LTBI in patients with DM.** • **Expected difficulties with scaling up and maintaining quality standards, especially the exclusion of TB infection in an active condition.**

DM= diabetes, LTBI= latent tuberculosis infection

Table 1 lists important concerns about screening for diabetes and TB together.

Some suggestions have been included in the most recent diabetes and tuberculosis guidelines **[11]**.

TREATMENT AND MANAGEMENT

There is currently no recognized best practice for treating diabetes and TB together. Diabetes patients are more likely to experience relapse, mortality, and treatment failure for tuberculosis **[31]**. For patients with DM and TB, starting TB therapy comes first, but DM management requires consideration as well **[11]**. A patient-centered WHO technique called DOTS is used to treat patients with active TB **[20]**. Qualified volunteers and health professionals watch over patients as they take the recommended amount of anti-TB medications for the full course prescribed to them (treatment lasts six to eight months). The most often prescribed anti-TB medications include isoniazid, rifampicin, pyrazinamide, streptomycin, and ethambutol **[34]**. Drug-susceptible TB is often treated with two medications (rifampicin and isoniazid) for 6 months course, along with two additional drugs (ethambutol and pyrazinamide), administered during the first two months of therapy after that 4 months of continued treatment with (isoniazid, rifampicin, and ethambutol) and for those patients who relapsed the therapy the intensive therapy is given with five drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin) for 3 months and then 4 months of continuous phase with (isoniazid, rifampicin, ethambutol) **[20, 31]**. TB-DM comorbidity aids the development of MDR-TB, which makes the anti-TB treatment worse, which could lead to an increase in the financial burden of therapy, promote the spread of MDR-TB, and potentially increase the rate of development of highly drug-resistant TB(XDR-TB) **[35]**. Longer duration of therapy and larger doses of TB therapy also might help with treatment outcomes **[36]**. Due to the increased risk of side effects, drug toxicity, and drug-drug interactions, anti-TB treatment may need to be followed more closely than in those with TB alone in individuals with DM and TB combined **[36]**.

Diabetes management involves lifestyle counseling (nutrition, weight loss, exercise, giving up smoking, and abstaining from excessive drinking) and medication to reduce blood sugar levels. Treatment should be given for extreme hyperglycemia, which can be symptomatic and may have an impact on TB results **[36]**. In the treatment of patients with TB-DM, medication adherence is a major problem. The patient's drug consumption may be interrupted for a variety of reasons. One of them has side effects from taking TB and DM medications together, the most typical of which are itchiness, dizziness, and vomiting **[37]**, and even there are more serious ADRs can be

caused due to a combination of medications without proper advice. The pharmacist can also play a major role in preventing ADRs and side effects by giving proper drug knowledge and pharmaceutical care to the patients which can minimize the chances of errors. Proper medication adherence also plays an important role in the management of glycemic levels. Diabetes patients with TB should be closely monitored with regular follow-ups. Patients with pulmonary tuberculosis and diabetes should take this strong approach to control their blood sugar with OHAs and insulin. As a result of their interactions with OHAs, isoniazid, and rifampicin have been reported to worsen glycemic control. Insulin is used as a choice of treatment in DM with TB comorbidity and its anabolic impact in addition, it also lowers the pill burden, enhances appetite, and stimulates weight gain. Although insulin administration increases the risk of hypoglycemia episodes, it is more effective than OHAs at attaining glycemic levels in control. To achieve better control of glucose levels in the body, particularly in cases of severe TB, some have suggested using insulin therapy to change or supplement with OHAs when diabetic individuals have been diagnosed with TB **[18, 38]**. The best way to treat diabetes in people with TB is yet unknown, however, the best course of action may involve avoiding sulphonyl urea derivatives and managing diabetes with dietary modification, lifestyle changes, metformin, and insulin because these two treatments have limited drug interactions with anti- TB drugs **[39]**. People with DM and those who have TB and DM co-infection should have their blood sugar levels constantly checked. Patients with DM may benefit from improved TB outcomes, better glycemic control, and reduced morbidity by adapting TB therapy procedures **[40]**.

CONCLUSION:

Diabetes has been associated to significantly impact therapeutic outcomes of TB and thereby increases the risk of treatment relapse and mortality **[5]**. Diabetes also affects the immune mechanism by interfering with the cytokine and chemokine synthesis making it highly vulnerable for the patients to contact TB **[6]**. In addition to this, poor glycaemic control in diabetic patients contribute as a risk factor **[7]**. However, only uncontrolled diabetes contributes to the emergence of TB, sufficiently maintained blood glucose values does not serve any risk of acquiring TB **[9]**. According to national and international agencies including WHO issued guidelines, TB patients should regularly be screened for DM and the same has been adopted in the DOTS for TB **[22, 23]**. TB along with DM may further progress into MDR-TB which adds up to medication non-adherence and poor treatment outcomes **[35]**. The concomitant therapy involving

anti tubercular drugs along with OHAs contribute to various drug interactions and side effects which should be routinely monitored and followed up in the patients **[38]**. Currently there are no standard guidance on the management of patients with DM-TB co-morbidity. However, in a diabetic patient with TB, treatment of TB infection should be prioritized maintaining the glycaemic control. In view of the increasing burden of DM-TB patients, the task of creation and implementation of recognized practice for treating diabetes and TB together, collating the best evidences available should be prioritized.

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