Original Article

IJCIH
Converging Healthcare & Technology

INTERNATIONAL JOURNAL OF CONVERGENCE IN HEALTHCARE

Published by
IJCIH & Pratyaksh Medicare LLP

www.ijcih.com
doi.org/10.55487/ijcih.v2i2.33

Tuberculosis & Diabetes – The Latest Developments

Siva Krishna Naik[1], Manoj Selvaraj[2], Khyatee[3]

[1]MD Consultant VBR Multispecality Hospital, Gandhari Mandal, Kamareddy District, Telangana, [2]MBBS, Thanjavur, [3]Director Pratyaksh Medical Care

Abstract

Early detection can help improve care and treatment outcomes of both diseases. All people with TB should be systematically screened for diabetes. Systematic screening for TB in people with diabetes should be considered in settings with high TB prevalence.

WHO-recommended treatments should be rigorously implemented for people with TB/diabetes. It is important that proper care for diabetes is provided to minimize the risk of TB.

Diabetes prevention on population level also helps prevent TB.

A joint response is needed to ensure coordinated clinical management and address common health system bottlenecks and social determinants

The aim of this review paper is to provide an overview and elimination strategies, and to describe the basics of present and future challenges in TB diagnosis, treatment and prevention under a clinical perspective.

Keywords: *tuberculosis; diabetes; immunity; epidemiology; global burden ; collaboration ; clinical; public health.*

Introduction

The global increase in type 2 diabetes mellitus (DM) is a recognized re-emerging risk and challenge to tuberculosis (TB) control .

Individuals with DM have three times the risk of developing TB and there are now more individuals with TB-DM co-morbidity than TB-HIV co-infection.

Corresponding Author:
Dr. Siva Krishna Naik
Md Consultant Vbr Multispecality Hospital, Gandhari Mandal, Kamareddy District, Telangana
Email Id: dr.sivanaik2019@gmail.com

In the 1980s the publications on joint TB-DM began to re-emerge in parallel with the DM 'pandemic': The global prevalence of DM among adults has increased by 20% in less than 30 years and DM is predicted to reach 642 million worldwide by 2040 with most (80%) of the patients living in low and middle-income countries where TB is also endemic.

Tuberculosis (TB) is still a first-class public health priority, representing the leading cause of death at global level. According to the World Health Organization (WHO), as many as 9.6 million new incident cases and 1.5 million deaths are estimated to have occurred in 2014, with Africa and Asia carrying the greatest burden. Of note, nearly half of the global TB cases are reported in only three countries (India, Indonesia and China)[1].

Epidemiology of TB-DM: The provision of integrated and patient-centred care for people with tuberculosis (TB) and comorbidities, including for those with diabetes mellitus, is embedded within Pillar 1 of the End TB Strategy. In 2018, at the first United Nations (UN) high-level meeting on TB, Member States committed to developing community-based health services with integrated care for TB patients with related health conditions; for example, HIV, undernutrition, mental illness, and noncommunicable diseases (NCDs), including diabetes mellitus .

The prevalence of diabetes influences TB incidence and TB mortality. It is associated with a twofold to threefold risk of TB disease, a twofold risk of death during TB treatment, a fourfold risk of TB relapse after treatment completion and a twofold risk of multidrug-resistant TB (MDR-TB) .In 2020, an estimated 369 000 (UI: 262 000-494 000) new cases of TB were attributable to diabetes .

In 2019, just over 15% of people with TB were estimated to have diabetes globally, compared with 9.3% among the general adult population (aged 20-79 years) .

This equates to about 1.5 million people with TB and diabetes who required coordinated care and follow-up to optimize the management of both conditions.

Global burden of diabetes: The Global Health Observatory provides national estimates of the prevalence of diabetes in adults . The median prevalence of diabetes in the 30 high TB burden countries according to latest available data was 8% (Interquartile range [IQR]: 6-9%), and was 10% or more in Gabon (10%), Mongolia (12%), Pakistan (12%), Papua New Guinea (15%) and South Africa (11%) . The International Diabetes Federation estimates that the number of people with diabetes will increase by about 50% globally between 2019 and 2045, with a median increase in the high TB burden countries of 99% (IQR: 69-151%) .

Collaborative action to address TB and diabetes: Since 2011, in recognition of the link between TB and diabetes, the World Health Organization (WHO) has recommended collaborative care for people with TB and diabetes in the Collaborative framework for care and control of TB and diabetes[2] . The framework of recommendations is organized around three objectives: establish mechanisms for collaboration, detect and manage TB in patients with diabetes, and detect and manage diabetes in patients with TB .

Key components of the framework include surveillance of the joint burden of TB and diabetes, and monitoring and evaluation of collaborative TB and diabetes activities. WHO does not currently request countries to report routine data about the joint burden of TB and diabetes or the implementation of TB and diabetes collaborative activities. However, efforts are ongoing to assess the uptake of WHO policy and the joint burden of TB and diabetes.

History

On March 24, 1882, Dr. Robert Koch announced the discovery of *Mycobacterium tuberculosis*, the bacteria that causes tuberculosis (TB). During this time, TB killed one out of every seven people living in the United States and Europe.

Dr. Koch's discovery was the most important step taken toward the control and elimination of this deadly disease. A century later, March 24 was designated World TB Day: a day to educate the public about the impact of TB around the world.

Johann Schonlein coined the term "tuberculosis" in the 1834, though it is estimated that *Mycobacterium tuberculosis* may have been around as long as 3 million years!

TB is not just a disease found in humans: TB is a disease that infects animals as well as humans. Archeologists have found TB in the bones of ancient bison in Wyoming. These bison lived over 17,000 years ago.

TB has been part of the human experience for a long time: TB in humans can be traced back to 9,000 years ago in Atlit Yam, a city now under the Mediterranean Sea, off the coast of Israel. Archeologists found TB in the remains of a mother and child buried together. The earliest written mentions of TB were in India (3,300 years ago) and China (2,300 years ago).

Do vampires cause TB?: Before the discovery of the bacteria that causes TB, the disease was thought to be hereditary.

In the early 1800s, there were "vampire panics" throughout New England. When a TB outbreak occurred in a town, it was suspected that the first family member to die of TB came back as a vampire to infect the rest of the family. To stop the vampires, townspeople would dig up the suspected vampire grave and perform a ritual.

Finding TB is the first step towards ending TB: The TB skin test for TB infection measures a person's immune response. The test is performed by injecting a small amount of fluid (called tuberculin) into the skin on the lower part of the arm. A health care worker "reads" the test 48-72 hours later.

The TB skin test is still used today and has remained virtually unchanged for almost eighty years. The test and PPD are still listed on the World Health Organization's essential medicines list. A more recent advancement in TB testing has been TB blood tests, or interferon-gamma release assays (IGRAs).

Albert Calmette and Jean-Marie Camille Guerin developed the Bacille Calmette-Guérin (BCG) vaccine in 1921. Prior to developing the BCG vaccine, Calmette developed the first antivenom to treat snake venom.

Today, four drugs are used to treat TB disease: isoniazid (1951), pyrazinamide (1952), ethambutol (1961), and rifampin (1966). This 4-drug cocktail is still the most common treatment for drug-susceptible TB.

Isolating people and proper nutrition was the best TB medicine before antibiotics: TB sanatoriums were places that provided treatment for TB patients and took the patients out of their home, which reduced the chance to spread TB to their families. Patients were treated for TB with fresh air, good food and sometimes surgery. America built many sanatoriums to care for persons with TB. In 1904, there were 115 sanatoriums with the capacity for 8,000 patients expanding to 839 sanatoriums with the capacity for 136,000 patients in 1953[3].

Dedicated people, agencies, and organizations continue the fight to end TB.

COLLABORATIVE FRAMEWORK FOR CARE AND CONTROL OF TB AND DIABETES.

The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (the Union) have developed a collaborative framework to guide national programmes, clinicians and others engaged in care of patients and prevention and control of diabetes and TB on how to establish a coordinated response to both diseases, at organizational and clinical levels. It responds to a growing concern about what collaborative activities should be implemented and under what circumstances. The framework is complementary to and in synergy with the established core activities of prevention and care programmes for both diseases.

Areas for Collaborative Action

A. Establish Mechanisms for Collaboration

B. Detect and Manage TB in Patients with Diabetes

C. Detect and Manage Diabetes in Patients with TB

For more information www.who.int/tb © World Health Organization 2016

JOINT RESPONSE TO TB AND DIABETES IN THE ERA OF THE

SUSTAINABLE DEVELOPMENT GOALS

The WHO Non Communicable Diseases Global Action Plan 2013–2020 aims to reduce the impact of diabetes.

The new **Sustainable Development Goals** also place the spotlight on ending TB as well as reducing premature mortality from NCDs – including diabetes – by one third. Ending TB and Diabetes will require a joint response to ensure that all people with TB and those with diabetes have access to much-needed care on both fronts.

India has been engaged in Tuberculosis (TB control activities for more than 50 years). Yet TB continues to be India's severest health crisis.

This NSP for 2017– 25 for TB elimination in India (NSP) embraces these opportunities to leverage its full potential and proposes transformational changes to TB care service delivery.

The NSP 2017-2025 builds on the success and learnings of the last NSP and encapsulates the bold and innovative steps required to eliminate TB in India by 2030.

It is crafted in line with other health sector strategies and global efforts, such as the draft National Health Policy 2015, World Health Organization's (WHO) End TB Strategy, and the Sustainable Development Goals (SDGs) of the United Nations (UN).

The NSP for TB elimination 2017 -2025: The NSP for TB elimination 2017–25 is a framework to guide the activities of all stakeholders including the national and state governments, development partners, civil society organizations, international agencies, research institutions,

private sector, and many others whose work is relevant to TB elimination in India.

The NSP 2017-2025 which builds on the success and learnings of the last NSP, and articulates the bold and innovative steps required to move towards TB elimination, is a 3 year costed plan and a 8 year strategy document.

Screening: In March 2021, WHO released the WHO consolidated guidelines on tuberculosis. Module 2: Screening – systematic screening for tuberculosis disease

(1). These guidelines include 17 new and updated recommendations for the screening of TB disease. Populations identified as priorities for TB screening include contacts of TB patients, people living with HIV, people exposed to silica, prisoners and other key populations.

The following screening tools are recommended: symptom screening, chest radiography, computer-aided detection (CAD) software, molecular WHO-approved rapid diagnostic tests and testing for C-reactive protein. This is the first time that CAD has been recommended for use in interpreting chest radiography for TB[4].

The new guidelines are accompanied by the WHO operational handbook on tuberculosis.

TB DIAGNOSTICS-PAST, PRESENT AND FUTER

In July 2021, WHO released the WHO consolidated guidelines on tuberculosis. Module 3: Diagnosis – rapid diagnostics for tuberculosis detection 2021 update .

Three new classes of nucleic acid amplification test (NAAT) are now endorsed by WHO:

Moderate complexity automated NAATs, which are recommended for the initial detection of TB and resistance to rifampicin and isoniazid, providing more options for early diagnosis of TB and rifampicin-resistant TB but also addressing an important gap in the rapid diagnosis of isoniazid-resistant and rifampicin-susceptible TB; low complexity automated NAATs, which are recommended for the detection of resistance to isoniazid and second-line anti-TB agents, helping to improve access to testing of resistance to fluoroquinolones at peripheral level; and

High complexity reverse hybridization-based NAATs, which are recommended for the detection of pyrazinamide resistance and are the first molecular tests for resistance to this drug.

In June 2021, WHO released a catalogue of Mycobacterium tuberculosis mutations as a reference standard for the interpretation of mutations conferring resistance to all first-line and a variety of second-line TB drugs .

WHO operational handbook on tuberculosis. Module 3: Diagnosis – rapid diagnostics for tuberculosis detection 2021 update. Geneva: World Health Organization; 2021

TB should be suspected when at least one of four suggestive symptoms is reported (long-lasting fever, cough of 2-week duration or more, night sweats and weight loss). Epidemiological aspects, such as history of contact with a pulmonary TB case and/or exposure to other risk factors for TB acquisition or reactivation, also need to be carefully evaluated.

Direct microscopic examination is a fast and inexpensive method to identify acid-fast bacilli through the use of Ziehl–Neelsen staining; however, it is limited by poor sensitivity and the inability to discriminate between mycobacterial species, which can be a relevant issue especially among children and immunocompromised individuals[12].

Fluorescence or light-emitting diode microscopy may be an alternative to traditional microscopy with a moderate improvement in sensitivity (+10%) but also slightly higher costs and the need for well-trained technicians .

The poorest performances of microscopic examination for the diagnosis of TB are usually

There is increasing interest in the mycobacterial lipoarabinomannan (LAM) urinary detection method (and its ‘lateral flow’ variant) that may be very useful in diagnosing active TB.

LAM is an antigen located in mycobacterial outer cell wall, and it is thought to be present in individuals with active disease but not in those with LTBI, irrespective of their immunological conditions.

Based on the current evidence, the WHO does not recommend the use of urinary LAM detection in patients with presumptive TB with the exception of HIV-positive

individuals with low CD4+ counts or who are seriously ill, who may benefit from this test in addition to a well-established diagnostic tool[13].

TB Treatment: Anti-TB treatment aims to cure the patient, prevent complications and death, avoid relapses, reduce the transmission potential to susceptible individuals, and limit the emergence and spread of drug-resistant strains. For all these reasons, the therapeutic approach to TB requires the use of multiple drugs. Treatment should include an intensive phase aimed at markedly decreasing the bacterial burden, followed by a 'sterilising' consolidation phase, with an overall duration of at least 6 months. Longer treatments may be required in selected situations, such as in patients with extensive bone involvement or those with cerebral tuberculomas.

The first-line standard regimen that is currently recommended for drug-susceptible TB is based on a 2-month intensive phase with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol; HRZE) followed by a 4-month consolidation phase with two drugs (isoniazid and rifampicin; HR).

Dose adjustment is required for children according to body weight, but the regimen composition remains the same.

Comorbidities do not justify any changes in the therapeutic approach to TB, although potential drug–drug interactions should be carefully evaluated and managed if necessary[8]. Optimal adherence throughout the whole duration of treatment is crucial, as poor compliance is among the major causes of treatment failure, being associated with a high risk of resistance selection.

TB CONTROL FROM THE BEGINNING TO THE END -TB STRATEGY: The global agenda beyond 2015 stands on seventeen Sustainable Development Goals (SDGs), one of which (SDG 3) is specifically addressed to health issues and calls for ending the major global epidemics including that of TB.

The WHO's End-TB Strategy, that was approved by the World Health Assembly in May 2014 and further developed throughout 2015 to come into effect in January 2016, clearly points to the global elimination of TB.

In 2006, the Stop-TB Strategy replaced the former one by strengthening its basic components to reach more ambitious targets within the following decade.

This approach is very well summarised in the three basic pillars of End-TB:

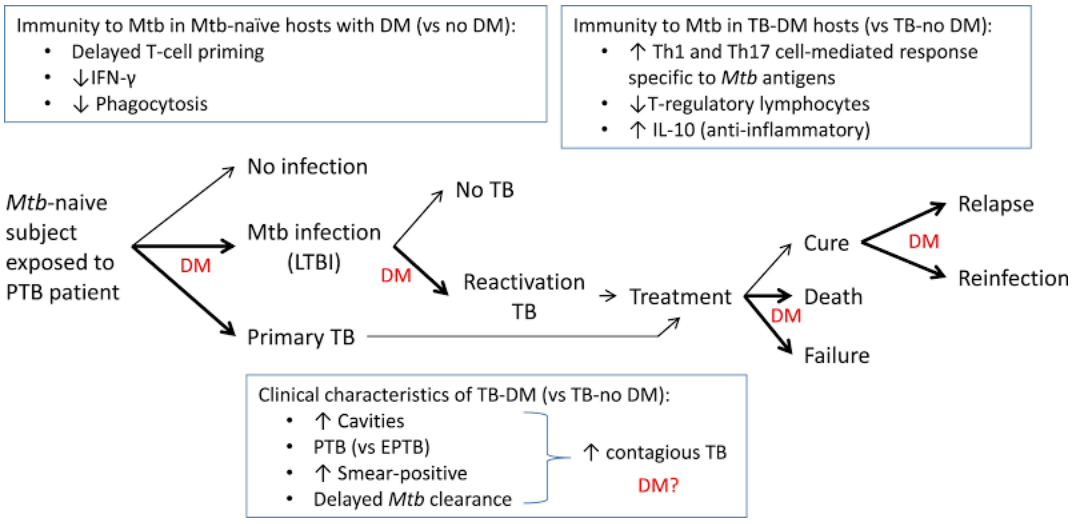
(1) Promote integrated patient-centred care and prevention;

(2) Foster bold policies and supportive systems; and

(3) Encourage intensified research and innovation.

Profile of the TB-DM patient: The profile of TB-DM patients versus TB only is strikingly different, with TB-DM patients being older, obese and more likely to be females who are not likely to present behaviors classically associated with TB such as alcohol abuse, consumption of illicit drugs, incarceration or HIV-AIDS.

CLINICAL PRESENTATION OF TB IN TB-DM PATIENTS AND PUBLIC HEALTH IMPLICATIONS



During the course of TB treatment, TB-DM patients take longer to convert from sputum smear-positive to -negative. Some studies also find that DM patients are more likely to present with drug-resistant and multi-drug resistant TB, although this relationship is not seen in all studies .

I expand on each of these:

Pulmonary versus extra-pulmonary TB: Pulmonary TB accounts for 70-80% of the cases, and it is generally accepted that immune compromise facilitates hematogenous dissemination of Mtb, predisposing to extrapulmonary TB. Such is the case of TB patients with HIV-AIDS or those taking TNF blockers.

Cavitary and smear-positive TB: Mtb induces a strong cell-mediated immunity leading to the formation of pulmonary granulomas (tubercles) that are thought to be a double-edged sword for the host .Granulomas initially limit Mtb growth, but in hosts in whom Mtb continues to replicate, these structures undergo central caseation with rupturing and spilling of thousands of viable bacilli into the airways. This "cavitary TB" is associated with sputum smear-positivity .

Drug and multi-drug resistant (MDR) TB: The relationship between drug or MDR TB in DM is unclear, with conflicting findings on the association between higher drug or MDR-TB in TB-DM patients versus TB-no DM .In a meta-analysis of publications up to 2010, the prevalence of drug-resistant or MDR TB among recurrent TB cases was not significantly higher in TB-DM patients.

TB TREATMENT OUTCOMES IN TB-DM PATIENTS: There is growing evidence from observational studies that TB-DM is associated with an increase in adverse TB treatment outcomes, specifically for delays in mycobacterial clearance, treatment failures, death, relapse and re-infection.

Delays in sputum smear clearance and treatment failure: TB-DM versus TB-no DM patients are more likely to remain sputum smear-positive after completion of the intensive phase of treatment, and this outcome is an early predictor of treatment failure (sputum smear or culture positivity at five months or later during treatment), which is also more likely in TB-DM versus TB-no DM .

DEATH: Death was a hallmark of the co-morbidity in the 1950s with studies reporting that patients with DM were likely to die from a diabetic comma or TB .

In a systematic review and meta-analysis of contemporary literature, Baker et al concluded that the risk of death from TB or any other cause in 23 unadjusted studies was nearly 2-fold and this increased to 4.95 (95%) in 4 studies that adjusted for age and potential confounders.

Relapse and re-infection: TB-DM patients also appear to have a higher risk of relapse. The review by Baker et al reported a nearly 4-fold risk of relapse in TB-DM versus TB-no DM .

BIOLOGICAL BASIS FOR THE ASSOCIATION BETWEEN TB AND DM: Immunological impairment has played a major role in TB susceptibility throughout history, and with the DM pandemic, DM is now among the most common causes of compromised immunity that favor TB development in contemporary times, along with HIV/AIDS, malnutrition, aging and smoking .

But DM contrasts from these other underlying conditions in that the immunity against Mtb is not necessarily "compromised" but rather, "dysfunctional", with excessive and/or delayed responses against Mtb.

Innate immunity to Mtb in the TB-naïve DM host—In studies to simulate the first encounter between Mtb and the innate immune response of a TB-naïve host with DM, we find that monocytes from healthy individuals with DM (versus non-DM) have significantly reduced association (binding and phagocytosis) of Mtb.

Adaptive immune responses to Mtb in DM hosts with LTBI and TB: Studies in individuals with LTBI and DM—The scanty literature in individuals with It is possible that lower levels of pro-inflammatory cytokines in DM can favor progression from LTBI to TB in DM, but further studies are required to understand the impact of lower anti-inflammatory cytokines as well.

There are several possible explanations for the contribution of dysfunctional immunity to these adverse treatment outcomes.

(1) The higher Th1 and Th17 response is only present in the peripheral blood of TB-DM patients, while anti-inflammatory responses that facilitate Mtb growth only occur in the lungs.

(2) There is a higher production of pro-inflammatory cytokines like IFN-γ in the lungs of humans (as observed in mice), but it is not effective for downstream activation of macrophages or cytotoxic T-cells that ultimately kill Mtb.

(3) The hyper-reaction to Mtb antigens may be deleterious and contribute to lung tissue damage with more severe TB and the higher frequency of death in TB-DM patients.

DM AND LTBI: Risk of LTBI in patients with DM—The literature often refers to DM as a risk factor for reactivation of LTBI to TB, but the relative risk of primary versus reactivation TB has never been systematically studied in DM.

In a population-based study in TB patients from Southern Mexico, the proportion of Mtb strains with genotypes that were clustered (similar genotypes suggesting recent infection) versus non-clustered (different Mtb genotypes suggesting re-activation TB) did not differ between TB-DM and TB-no DM patients (Mtb genotype clusters in 24% and non-clustered in 76% in both study groups).

Immunoassays for diagnosis of LTBI (or TB): is there immune compromise in DM patients?

The in-vivo tuberculin skin test (TST) and ex-vivo Interferon-gamma release assays (IGRAs, namely QuantiFERON-TB Gold assays by Qiagen and T.Spot-TB by Oxford Immunotec) are used in the clinical setting to diagnose LTBI in individuals with high risk of TB progression (targeted testing), or to support the diagnosis of TB.

What are radiological findings of TB?: Common findings include **segmental or lobar airspace consolidation, ipsilateral hilar and mediastinal lymphadenopathy, and/or pleural effusion**. Atelectasis may occur in primary pulmonary tuberculosis, often as a consequence of tuberculous airway involvement.

What are the basic pathological changes of tuberculosis?: Arthur Dannenberg described the pathology of tuberculosis in detail . There are five stages: **onset, symbiosis, early stages of caseous necrosis, interplay of cell-mediated immunity and tissue damaging delayed-type hypersensitivity, and liquefaction and cavity formation**.

Chest X-ray: Tuberculosis creates cavities visible in x-rays like this one in the patient›s right upper lobe.

A posterior-anterior (PA) chest X-ray is the standard view used; other views (lateral or lordotic) or CT scans may be necessary.

In active pulmonary TB, infiltrates or consolidations and/or cavities are often seen in the upper lungs with or without mediastinal or hilar lymphadenopathy

However, lesions may appear anywhere in the lungs. In HIV and other immunosuppressed persons, any abnormality may indicate TB or the chest X-ray may even appear entirely normal.

Conclusion

The converging pandemic of DM in low- and middle-income countries where TB is endemic has been identified as one of the factors that will hinder the global TB target of 90% reduction in TB incidence by 2035 .

Ethical Clearance: Taken

Source of Funding: Self

Conflict of Interest: Nil

References

1. World Health Organization. *Global Tuberculosis Report* (World Health Organization, 2015).
2. Ploubidis, G. B. et al. Social determinants of tuberculosis in Europe: a prospective ecological study, (2012).
3. Nadjane Batista Lacerda, S. et al. Individual and social vulnerabilities upon acquiring tuberculosis: a literature systematic review. (2014).
4. Walker, N. F., Meintjes, G. & Wilkinson, R. J. HIV-1 and the immune response to TB. 57–80 (2013).
5. Ford, N. et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. (2015).
6. American Lung Association. The History of Christmas Seals. 2018.
7. International Diabetes Federation. IDF Diabetes Atlas. 7th edn. Brussels, Belgium: 2015.

8. Liu Q, Li W, Xue M, Chen Y, Du X, Wang C et al. Diabetes mellitus and the risk of multidrug resistant tuberculosis: a meta-analysis. Scientific Reports. 2017
9. Noubiap JJ, Nansseu JR, Nyaga UF, Nkeck JR, Endomba FT, Kaze AD et al. Global prevalence of diabetes in active tuberculosis: a systematic review and meta-analysis of data from 2.3 million patients with tuberculosis. Lancet Glob Health 2019;
10. IDF Diabetes Atlas, 9th edn. Brussels: International Diabetes Federation (IDF); 2019 .
11. Collaborative framework for care and control of tuberculosis and diabetes. Geneva: World Health Organization; 2011
12. WHO operational handbook on tuberculosis. Module 2: Screening – systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021
13. WHO operational handbook on tuberculosis. Module 2: Screening – systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021