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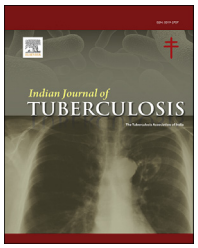

Review article

Challenges of diabetes in elderly TB patients

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ARTICLE INFO

Article history:
Received 2 August 2022
Received in revised form
29 August 2022
Accepted 25 October 2022
Available online 28 October 2022

Keywords:
Diabetes mellitus
Tuberculosis
Multi-resistant tuberculosis (MDR-TB)
Mycobacterium tuberculosis
Ageing population
Prevalence

ABSTRACT

Diabetes mellitus (DM) and tuberculosis (TB) are worldwide health burdens post-COVID-19. TB is the second-leading cause of death by a single infectious microbe. There is much evidence around the world about the responsibility of TB-DM co-morbidity. Both TB and DM prevalence is high in low- and middle-income countries. Especially the elderly with diabetes are more prone to TB infection due to compromised immune systems. Diabetic patients are three times as likely to develop tuberculosis as non-diabetic patients. DM interferes with the status of TB and leads to undesirable outcomes in the treatment of TB. This may later lead to the development of multidrug-resistant tuberculosis (MDR-TB). The coexistence of TB and DM leads to a high mortality rate and therefore becomes an enormous challenge for the medical field. This viewpoint includes the most current information about TB and DM, disease complications, treatment strategies, challenges to be faced in disease management and the importance of TB-DM bidirectional screening in older adults, which helps in early detection and better treatment programme.

Despite rapid medical development, diabetes mellitus (DM) and tuberculosis (TB) remain a global burden affecting millions yearly. Tuberculosis is one of the leading infectious diseases caused by *Mycobacterium tuberculosis* which is very common in diabetic patients. When a susceptible person inhales the droplets containing tuberculosis bacilli, the host's immune response limits the spread of TB infection, which results in a localised disease without any symptoms (asymptomatic). In diabetic patients, tuberculosis usually remains asymptomatic, most likely leading to drug-resistant tuberculosis.[1] Recent reports have identified tuberculosis as the 13th leading cause of death and the 2nd leading infectious disease after COVID-19. Two-thirds of the world's TB cases are reported in eight large countries, followed by India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa. An estimated 10 million people were infected with tuberculosis globally in 2020.[2] DM is a chronic metabolic disorder characterised by high blood glucose, one of the fastest-growing health conditions in the 21st century. In 2021 an estimated 537 million adults (20–79 years) had diabetes; one in two (240 million) adults with diabetes are not diagnosed.[3] The World Health Organization (WHO) has recognised DM as a worldwide epidemic that primarily affects low- and middle-income counties, where 80 per cent of all

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https://doi.org/10.1016/j.ijtb.2022.10.017

related deaths occur.[4] A collaborative framework led by WHO and the International Union Against Tuberculosis and Lung Disease (Union) aims to deal with the prevention and control of TB and DM.[5]

DM is considered a well-known risk factor for TB. Not only DM, but there are also some other risk factors associated with TB, which include ageing, smoking, alcohol consumption, chronic kidney disease (CKD), being underweight, malnutrition, chronic lung disease, and immunosuppressants.[1] However, the high prevalence of TB and multidrug-resistant TB (MDR-TB) are associated with DM, which has become a severe medical problem.[6] DM is more common among the elderly, and diabetic patients are three times more likely to develop TB. The prevalence of MDR-TB co-morbidity is the highest in the elderly.[7] "The majority of DM among TB patients ranged from 1.9% to 45% with a prevalence of 16% (Median with interquartile range - IQR 9.0%–25.3%). Whereas the worldwide prevalence of tuberculosis among patients with diabetes is low the median , the prevalence of TB cases in patients with DM was 4.1% (IQR 1.8%–6.2%) which usually ranged from 0.38% to 14%".[8] In another study, the prevalence of DM in TB patients was 42.6%, 92 of whom were diabetic among the 216 TB patients tested.[9]

There is a positive association between DM and MDR-TB, where DM accelerates the rate of MDR-TB.[10] TB in diabetic patients in India reveals that men are more likely to have TB than women; therefore, men are more likely to develop co-morbidities.[11] The incidence of MDR-TB in patients with DM was higher in those who did not, with an increase of 1.6–3.8 times in MDR-TB. The prevalence of MDR-TB among older adults has increased from 14.3% to 18.2%.[12] 10.4 million people were reportedly infected with tuberculosis in 2015. Five hundred eighty thousand suffered from MDR-TB, while only 125,000 were detected and reported. One hundred and eleven thousand people received treatment for MDR-TB in 2014; while there was no effective treatment, 190,000 MDR-TB patients died.[6]

Cell-mediated immunity plays a significant role in the host defence against *M. tuberculosis*, where Th1 cells producing INF-gamma and CD4-T cells are activated during TB infection. Cellular-mediated impaired immunity increases the risk of tuberculosis being reactivated. Ageing and DM are the two critical factors in reducing IFN-γ, increasing TB susceptibility. Diabetes in elderly persons may further alter Protein-Energy Malnutrition (PEM), which results in the impairment of T cells, increasing the risk of developing active TB.[13] TB-DM coexistence complicates treatment strategy. Treatment of (MDR-TB) is even more difficult. MDR-TB occurs when *M. tuberculosis* is resistant to two essential TB medications, rifampin and Isoniazid.[14] In some cases, MDR-TB may develop into XRD TB when the bacterial strain is resistant to rifampin, Isoniazid, fluoroquinolone, and at least one additional Group A drug, bedaquiline or linezolid.[15]

DM and TB interact, and one worsens the condition of the other in patients with DM-TB; it delays treatment, which can also affect the cure rate.[7] DM also increases the risk of treatment failure. Treatment of TB in the elderly is risky; 65-year-olds have a higher mortality rate (almost tripled) than those under 65.[16] The cure rate for susceptible drug TB is 96%, and the cure rate for MDR-TB is 54%, so it is considered a deadly disease.[17] The incidence of DM was higher among patients with MDR-TB (47.2%) than patients those without MDR-TB (28.1%).[14] According to WHO 2022 guidelines, the new TB regimens include: 1) BPaLM 6-month regimen (bedaquiline, pretomanid and linezolid and moxifloxacin. 2) BPaL 6-month regimen without moxifloxacin in pre-XDR-TB patients. 3) 6–9 months/9–12 months modified short regimen comprises three Group A drugs".[15] A high risk of developing tuberculosis and reactivating old tuberculosis is commonly observed in patients with diabetes. Uncontrolled, undiagnosed or belatedly diagnosed diabetes worsens the status of TB and negatively affects treatment outcomes. Screening for active TB disease in patients with DM and screening for DM in patients with TB contribute to early detection for better treatment.[18]

TB screening in patients with DM is recommended in areas with a prevalence rate of 100 per 100,000 population. The gold standard for diagnosing TB-DM patients is FBG (Fasting Blood Glucose) and HbA1c. Patients with FBG $\geq$7 mmol/l ($\geq$126 mg/dl) or HbA1c $\geq$ 6.5% ($\geq$48 mmol/l) are considered diabetic.[19] Drug resistance is the major problem in TB-DM treatment, which is more commonly seen in TB-DM patients than non-DM-TB patients. In patients with TB-DM, there is a high risk of isoniazid resistance[20] and rifampin resistance[21] than in non-DM-TB patients. The rates of drug-resistant TB (DR-TB), polydrug-resistant TB (PDR-TB), isoniazid (INH)+streptomycin resistant (SM) TB, were found to be 21.83% and 16.96%, 6.10% and 3.80%, 4.93% and 3.13%, in TB-DM and non-TB-DM cases respectively.[22] At the same time, Isoniazid interrupts the control of blood glucose levels by interacting with metformin[23].

New treatment guidelines provided by the Revised National Tuberculosis Control Programme (RNTPC), national programmes in India and WHO, proper screening and novel diagnostics should be seriously considered to reduce adverse treatment events in TB and DM, especially in elderly populations, reduce the global health burden. In the case of DM management in India, traditional/alternative medicine prescription is followed. Too many options with questionable quality products are also responsible for confused DM management. This leads to the complex management of TB and related co-morbidities in elderly diabetes.

Conflicts of interest

The authors have none to declare.

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