



The Challenge of Tuberculosis Diagnosis and Management in the Era of the COVID-19 Pandemic and Diabetes Mellitus

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1. Introduction

According to WHO, the COVID-19 pandemic has deleterious effects on global health, including services provided for those with tuberculosis. Tuberculosis (TB) primarily affects the lungs and has clinical similarities with pulmonary SARS-CoV-2 involvement. During the COVID-19 pandemic, the diagnosis and treatment of tuberculosis are negatively affected and mixed with COVID-19 control strategies. Corticosteroids like dexamethasone are one of the main treatment strategies for patients with severe COVID-19 infection, especially those who need hospitalization or oxygen support. Corticosteroids can cause immunosuppression, in addition to their anti-inflammatory properties. During the COVID-19 infection, host immunity alters with corticosteroid therapy, which induces a significant risk for secondary infections or reactivation of dormant infections like latent tuberculosis. Diabetes is also a highly prevalent disease with a severe course and increased mortality rate in those affected by COVID-19. Many patients with concomitant diabetes and severe COVID-19 need dexamethasone treatment, raising the awareness of concealed tuberculosis.

2. Prevalence of Diabetes in the World and Iran

According to the most recent data published in the IDF Atlas, nearly 537 million (10.5%) people aged 20 to 79 have type 2 diabetes (1). Due to this high prevalence, diabetes is a substantial global health burden that needs special attention from multiple stakeholders. In the MENA region, including IRAN, the prevalence of type 2 diabetes is around 16%, the highest in the IDF regions. (1). In Iran, according to national data, the prevalence of diabetes increased from

7.2% in 2007 to 11.3% in 2011 (2). The recent unpublished data from STEPS showed that the prevalence of type 2 diabetes is 14% in Iran, with a significant rise during the last decade.

3. Incidence and Mortality of Tuberculosis

Based on the WHO report, in 2020, nearly 10 million patients developed tuberculosis, while only 5.8 million were diagnosed, with an 18% decrease since 2019. At the same time, roughly 1.5 million deaths occurred due to tuberculosis (3). The deaths caused by TB increased by 0.2 - 0.4 million because of improper diagnosis and treatment associated with the COVID-19 pandemic (4).

4. What Immunological Mechanisms are Impaired in *Mycobacterium tuberculosis* Infection in Patients with Diabetes Mellitus?

Evidence shows that diabetes is a risk (predisposing) factor for tuberculosis. Although animal studies exploring the mechanisms of immune response in hyperglycemic states against *Mycobacterium tuberculosis* did not show any definitive findings, the following mechanisms have been suggested:

- Impaired innate immune response of alveolar macrophages in hyperglycemic mice with impaired antimicrobial defense against mycobacterium (5).
- Delayed myeloid cell recruitment to the infection site, induced by hyperglycemia that causes impaired antigen presentation and activation of T cells.
- Another presumptive defect is chemotaxis. Delayed delivery of *Mycobacterium* to the lymph nodes and defective antigen-specific T-cells activity also occur.

- The other defect is related to neutrophil functions, including migration, bactericidal, and killing abilities.

- Promotion of bacilli replication due to the defects in cytokines and IFN-gamma production (5).

To summarize, in animal models, the hyperglycemic state may alter phagocyte function, microbial killing, T-cell activity, leukocyte function, and chemotaxis with a delay in antigen presentation, creating an opportunity for bacilli boosting (6).

5. Diabetes and Tuberculosis

In patients with diabetes, some types of infections are more prevalent, especially, urinary and respiratory tract and mucocutaneous infections (7). Diabetes is one of the main risk factors for tuberculosis (8, 9), and multiple studies have revealed that up to 30% of patients with TB present with accompanying diabetes (10).

Besides, the incidence and prevalence of tuberculosis are higher in patients with diabetes (11). For example, the risk of developing tuberculosis was nearly twofold higher in patients with diabetes than in patients without diabetes (12).

Some studies have also shown that the prevalence of TB doubles in patients with diabetes, especially those with poor diabetes control and HbA1c greater than 7% (13). Those with concomitant diabetes and tuberculosis usually have a severe course, with more cavitation, increased hospital admission, more antituberculosis drug side effects, and a higher probability of relapse after treatment (14). Moreover, multiple-drug-resistant tuberculosis risk seems to double in patients with diabetes (15, 16). Furthermore, the coincidence of TB and DM increases mortality risk (15).

In patients with diabetes and tuberculosis, the glycemic control may be poor (17), while good glycemic control could improve immune system function and ultimately better treatment response (18). One recent study found that the INH-resistance or multiple drug resistance occurs more commonly in those with HbA1c greater than 7% (19). In a systematic review of 13 observational studies, the risk of active tuberculosis increased in patients with diabetes mellitus (11). Besides, diabetes increases the risk of cavitary TB and even mortality (13, 20-23). On the contrary, the risk of stress-associated hyperglycemia and insulin resistance increases in those with tuberculosis (24, 25). The risk of infections increases in patients with diabetes due to micro and macrovascular complications, impaired immunity including neutrophil dysfunction, and defects in humoral immunity (26).

6. COVID-19 and Tuberculosis

A study of 46 Chinese patients with COVID-19 showed that both active and latent tuberculosis induced more severe and progressive COVID-19 infections. Moreover, tuberculosis was more common in COVID-19 pneumonia (27). Another cohort of 49 cases also showed concomitant active tuberculosis, its sequelae, and COVID-19, with a 12% fatality rate in patients with co-existed infections (28). Also, pneumonia induced by COVID-19 can increase the progression of tuberculosis in those with latent infection. The immunological environment of the lung induced by COVID-19 infection (e.g., high level of chemokines) can exacerbate tuberculosis immunopathogenesis in patients with latent tuberculosis and induce its progression (29).

Tuberculosis and COVID-19 are linked as syndemic with other comorbid conditions like diabetes, obesity, hypertension, and cardiovascular diseases. These comorbid conditions predispose patients with both TB and COVID-19 to more severe diseases.

7. Corticosteroid Therapy and Tuberculosis

Many north American societies, including the American and Canadian Thoracic Society, Canadian Lung Association, and CDC in the USA, describe that patients with tuberculosis who receive more than 15 mg daily of corticosteroids for two to four weeks are prone to developing active tuberculosis (30, 31). The beneficial effects of corticosteroids in those with tuberculosis are variable and depend on the organ involved in TB, but overall, it reduces mortality.

8. Corticosteroid Treatment for TB Patients with Comorbidities

Population-based studies that used any type of corticosteroids for treatment of COPD and asthma showed a positive association between corticosteroid therapy and active TB due to the immunosuppressive effects of CSTs (32-36).

In a case report of severe COVID-19, the progression of symptomatic tuberculosis occurred in a patient with no comorbidity that used tocilizumab and corticosteroids. The immunosuppression induced by COVID-19 and/or CST treatment was suggested to reactivate latent TB (2).

In a guideline proposed by the Massachusetts General Hospital for COVID-19, it was recommended to screen and document TB before administering more than 20 mg/day prednisone or equivalent dose of dexamethasone. It should be emphasized that when corticosteroids are prescribed for more than two weeks, the risk of reactivation of TB increases.

9. Conclusion

In the COVID-19 pandemic, diabetes is significant comorbidity that increases patients' mortality. Many studies have suggested that tuberculosis flare-ups may occur due to synergistic effects of diabetes, corticosteroid treatment, and pulmonary involvement by COVID-19. Expert consensus solutions and implementation for case findings seem to be very salient. Appropriate control of hyperglycemia and diabetes is of utmost importance. Because there is no global policy for treating latent tuberculosis in those with diabetes, we need more longitudinal clinical and epidemiological studies among those with COVID-19, diabetes, and tuberculosis to answer this vital question.

Footnotes

Authors' Contribution: Mardani proposed and designed the study concept and reviewed the manuscript. Esteghamati drafted the manuscript.

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