Pulmonary tuberculosis and diabetes mellitus: Epidemiology, pathogenesis and therapeutic management (Review)

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Abstract. The dual burden of pulmonary tuberculosis (PTB) and diabetes mellitus (DM) is a major global public health concern. There is increasing evidence to indicate an association between PTB and DM. DM is associated with immune dysfunction and altered immune components. Hyperglycemia weakens the innate immune response by affecting the function of macrophages, dendritic cells, neutrophils, and natural killer cells, and also disrupts the adaptive immune response, thus promoting the susceptibility of PTB in patients with DM. Antituberculosis drugs often cause the impairment of liver and kidney function in patients with PTB, and the infection with Mycobacterium tuberculosis weaken pancreatic endocrine function by causing islet cell amyloidosis, which disrupts glucose metabolism and thus increases the risk of developing DM in patients with PTB. The present review discusses the association between PTB and DM from the perspective of epidemiology, pathogenesis, and treatment management. The present review aims to provide information for the rational formulation of treatment strategies for patients with PTB-DM.

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1. Introduction

Diabetes mellitus (DM) is a metabolic disease with hyperglycemia, which is attributed to the defect of insulin secretion or the impairment of its biological function (1). DM poses a severe threat to human health, and often results in injuries to a number of target organs, such as retinopathy, nephropathy, and peripheral neuropathy (2). As with other organs, the lungs are also a target organ of DM; the lung function of patients with DM has been reported to be markedly decreased, and pulmonary complications have been attested in patients with DM (3,4). Tuberculosis is an ancient disease caused by infection with Mycobacterium tuberculosis (5). As a major public health concern, pulmonary tuberculosis (PTB) and DM pose a huge social burden in China (6). It has been reported that PTB-DM-associated comorbidity is high, and that the global prevalence rate of PTB-DM comorbidity is estimated to be 13.73% (7). Although the research progresses of epidemiology, pathogenesis, and treatment management for PTB-DM comorbidity have been summarized, the association between PTB and DM has not been completely described. Therefore, based on recent studies, the aim of the present review was to discuss the epidemiology, pathogenesis, and therapeutic management of patients with PTB-DM.

2. Epidemiology

DM leads to an increased risk of developing PTB; an early finding has suggested a link between PTB and DM, and an increased prevalence of DM has been observed in patients with PTB (8). The prevalence of PTB-DM comorbidity is high among the Chinese elderly population (9). A study from Korea found that the prevalence of PTB was significantly higher in patients with DM than in the general population (10); similar results were also demonstrated in Bangladesh (11). In Mexico, the prevalence of DM was shown to have a significant influence on PTB morbidity, and the incidence of PTB was increased by 82.64% in patients with DM, while the incidence of PTB was decreased by 26.77% in patients without DM (12). A recent study suggested a positive association between DM morbidity and PTB in families with tuberculosis (13). Stevenson et al (14) found that DM was a significant risk factor for the incidence of PTB, and that the proportion of incident smear-positive tuberculosis was 20.2% due to DM. The prevalence of DM was 18% in patients with PTB, while the prevalence of DM was 8% in patients with suspected PTB (15). In a prospective study, Wang *et al* (16) demonstrated that PTB also increased the risk of developing DM, and that the prevalence of DM in patients with PTB was higher than that in patients without PTB. The prevalence of PTB and DM comorbidity has been summarized in various studies (Table I). These studies suggest a noteworthy association between PTB and DM as regards epidemiology.

3. Pathogenesis

DM increases the risk of PTB by disrupting innate and adaptive immunity responses. In turn, PTB weakens islet cell function by causing islet amyloidosis, and anti-tuberculosis drugs impair blood glucose homeostasis by affecting liver and kidney functions in patients with PTB, which increases the risk of developing DM in patients with PTB. The mechanisms of the interaction between PTB and DM are presented in Figs. 1 and 2.

Innate immune dysfunction increases the susceptibility to PTB in patients with DM. Macrophages are primary immune cells in the innate immune response of PTB. An increased susceptibility to PTB occurs due to a delayed innate immune response to the alveolar macrophages in Mycobacterium tuberculosis infection in DM (17). A recent study found that hyperglycemia affected the phagocytosis ability of macrophages by the change of the expression pattern of recognition receptors in PTB (18). In anti-tuberculosis immunity, the phagocytosis ability of alveolar macrophages is significantly decreased when human alveolar macrophages are directly exposed to hyperglycemia (19). In a previous study on mouse with diet-induced diabetes infected with Mycobacterium bovis, the reduced uptake, killing, and production of inflammatory cytokines in alveolar and peritoneal macrophages were observed, compared with macrophages from non-diabetic mice (20). The expression of the macrophage marker, CD14, and its receptors with collagen structure is reduced in the alveolar macrophages of diabetic mice, promoting the susceptibility of diabetic hosts to tuberculosis (21). In a study on diabetic mice with Mycobacterium fortuitum infection, the mycobacterium load was found to be significantly increased in the liver, spleen, and lungs compared with controls, and the uptake of mycolic acid coated beads was significantly reduced in macrophages isolated from diabetic mice, indicating the decreased bacterial internalization, killing, and cytokine responses of macrophages isolated from diabetic mice (22). Evidently, these studies suggest that the macrophage-mediated innate immune response is a key pathological mechanism in PTB-DM comorbidity.

Dendritic cells exist in the lung parenchyma, bronchoalveolar fluid, and nasal mucosa of humans, rats, and mice (23). It has been suggested that infection with *Mycobacterium tuberculosis* can induce dendritic cells to mature and migrate into the draining lymph nodes (24,25). The results from a clinical study revealed that the frequency of plasmacytoid and myeloid dendritic cells in PTB-DM comorbidity was decreased at baseline and at 2 months of anti-tuberculosis treatment compared to PTB without DM, and that a significantly increased frequency was observed in plasmacytoid and myeloid dendritic cells when the antituberculosis treatments were successful completed, suggesting that DM may alter the frequency of innate subset distribution of dendritic cells in PTB-DM comorbidity (26). Kumar *et al* (27) found that coincidence DM resulted in a significant reduction in the frequency of plasmacytoid and myeloid dendritic cells in PTB, and that DM altered the distribution of dendritic cells in patients with active and latent tuberculosis.

Neutrophils are another innate cell type that plays a crucial role in the pathogenesis of PTB. Patients with PTB-DM have an elevated peripheral neutrophil count compared to PTB patients without DM (28). Similarly, the neutrophil count of patients with DM infected with *Mycobacterium tuberculosis* is higher than that in patients without DM, and neutrophils exhibit a reduced phagocytic capacity for *Mycobacterium tuberculosis*, suggesting an impaired immune function of neutrophils for the tuberculosis in patients with DM (29). Eruslanov *et al* (30) reported that the accumulation of neutrophils contributed to the development of tuberculosis, indicating that the neutrophils may function as a 'Trojan horse' for mycobacterium.

Natural killer (NK) cells are effector cells in an innate immunity response, and play an important role in the host defense against mycobacterial infection (31). Zahran et al (32) suggested that the natural killer cell count could be used as a marker to assess disease activity in patients with PTB, and that the peripheral natural killer cell count was a prognostic indicator for patients with active PTB. Of note, the natural killer cells in both peripheral blood and bronchoalveolar lavage have been reported to be significantly increased in patients with PTB-DM compared with PTB patients without DM (33). An increased frequency of tuberculosis antigen-stimulated natural killer cells expressing cytokines has also been observed in PTB-DM (34). Another study demonstrated that natural killer cells promoted the pathological immune response in the infection of Mycobacterium tuberculosis in diabetic mice via NK-CD11c⁺ cell interactions (35).

Adaptive immunity dysfunction increases the susceptibility to PTB in patients with DM. CD4⁺ and CD8⁺ T-cells are critical for Mycobacterium tuberculosis in the adaptive immune response (36). The subsets of CD4+ T-cells include helper T-cells (Th)1, Th2, Th17, and regulatory T-cells (Tregs) (37). CD4⁺ T-cells are the main antigen-specific cells that are responsible for inhibiting infection with Mycobacterium tuberculosis (38). The CD4 cell proportion has been found to be significantly decreased in PTB-DM compared with household contacts (39). Kumar et al (40) suggested that PTB-DM increased the frequency of Th1 and Th17 cells, and that DM participated in the altered immune response of PTB. It has been well-documented that the susceptibility of Mycobacterium tuberculosis infection is attributed to the defective Th1 cytokine response, while the defective non-specific immune response may increase the susceptibility of Mycobacterium tuberculosis in patients with DM (41). Compared with patients with PTB or DM, peripheral blood mononuclear cells exhibit a biased Th1 response to Mycobacterium tuberculosis stimulation in patients with PTB-DM (42). It has been shown that in patients with PTB-DM, the imbalance between Treg and effector T-cells is associated with an impaired immune function at pathological sites (43). Increased Th1 and Th17

Authors, year of publication	Study design	Study population	Main results	(Refs.)
Mugusi <i>et al</i> , 1990 Cross-sectional		506 Patients with PTB, and 693 individuals of an urban community	A crude DM prevalence rate was 4.0% in patients with PTB; prevalence rate of DM was 0.9% in individuals of an urban community	(8)
Wu et al, 2022	Cross-sectional	784 Patients with PTB	8.12% Patients with PTB-DM	(9)
Lee et al, 2017	Cross-sectional	1,044 Patients with active PTB, and 14,655 contemporaneous general individuals	044 Patients with ctive PTB, and 14,655The prevalence of DM was 24.2% in patients with PTB and 11.6% in contemporaneous general individuals	
Rahim <i>et al</i> , 2012	Prospective	17,344 Patients with DM	The prevalence of patients with PTB was 213.3/100,000 in patients with DM; an estimated incidence of PTB was 101/100,000 patients in Bangladesh	(11)
Delgado-Sánchez <i>et al</i> , 2015	Cross-sectional	181,378 Patients with PTB	19.29% Patients were diagnosed with DM, during the study period, the incidence rate of PTB with DM increased by 82.64% while PTB without DM decreased by 26.77%	(12)
Guo et al, 2022	Cross-sectional	801 Patients with PTB, and 972 household contacts	The prevalence of DM in culture (+) PTB patients 9.2% was higher than the culture (-) PTB patients 7.8% and the non-PTB 3.4% subjects	(13)
Stevenson et al, 2007	Cross-sectional	139,000 Patients with PTB	DM accounted for 14.8% in patients with PTB; the proportion of incident smear-positive tuberculosis was 20.2% due to DM	(14)
Mave <i>et al</i> , 2017	Cross-sectional	890 Patients with PTB, and 552 patients with suspected PTB	The prevalence of DM was 18% in patients with PTB; DM was 8% in patients with suspected PTB	(15)
Wang <i>et al</i> , 2013	Prospective study	6,382 Patients with PTB, and 6,674 non-PTB patients	The prevalence of DM in patients with PTB 6.3% was significantly higher than non-TB patients 4.7%	(16)

	Table I. Prevalence of	pulmonary	tuberculos	is and	diabetes	s mellitus	comorbidity	v in different	studies.
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cytokines exhibit an association with latent tuberculosis (LTB)-pre-diabetes (PDM) and DM comorbidities (44). Following mycobacterial antigen stimulation, the frequency of $\gamma\delta$ T-cells expressing Th1 and Th17 is significantly reduced in LTB with DM and/or PDM individuals compared to LTB without DM individuals (45).

Effector CD8⁺ T-cells are cytotoxic cells that produce interferon (IFN)- γ (37). Reportedly, hyperglycemia reduces the counts of CD8⁺ T-lymphocytes in patients with PTB-DM (46). DM modulates the function of CD8⁺ T-cells during LTB infection (47), and it decreases the activity of CD8⁺ T-cells by increasing the differentiation of Th2 and Th17 cells in the regulation of anti-tuberculosis immunity (48). Notably, the frequency of CD4⁺ and CD8⁺ T-cells has been shown to be associated with blood glucose and glycated hemoglobin levels in patients with PTB-DM (49). DM alters the immune responses to tuberculosis, resulting in the induction of CD4 and CD8, which contributes to increased immune pathology in *Mycobacterium tuberculosis* infection (50). The reduced frequency in Th1/Tc1 and Th17/Tc17 cells has been confirmed in LTB-PDM, determining that PDM is also associated with altered immune responses with impaired CD4⁺ and CD8⁺ T-cell functions in LTB (51). CD4 transcription is decreased, while CD8 transcription is increased in patients with PTB-DM, and sputum interleukin (IL)-10 transcription levels are negatively associated with fasting blood glucose and hemoglobin A1c levels in patients with PTB-DM (52). Moreover, the frequency of CD8⁺ T-cells expressing IFN- γ , IL-2, and IL-17F cytokines has been found to be increased following stimulation with mycobacterium antigen in PTB-DM (34).

The IFN- γ response of peripheral blood mononuclear cells is decreased in PTB-DM (53). In diabetic mice infected with *Mycobacterium tuberculosis*, Yamashiro *et al* (54) found the production of IFN- γ was significantly lower than that in



Figure 1. Schematic diagram of the mechanisms through which diabetes

mellitus increases the risk of developing pulmonary tuberculosis.

non-diabetic mice, and that the decreased number of Th1-related cytokines leaded to an impaired host defense against infection with *Mycobacterium tuberculosis*. In a study performed by Meenakshi *et al* (55), the production of IFN- γ was markedly decreased following *Mycobacterium tuberculosis* stimulation in patients with PTB-DM. Moreover, Stalenhoef *et al* (41) observed decreased levels of non-specific IFN- γ in patients with DM without PTB. However, Gan *et al* (56) suggested that no significant difference was observed in the T-cell IFN- γ responses to *Mycobacterium tuberculosis*-specific antigens between PTB-DM and PTB-non-DM. Thus, further investigations are required to confirm the IFN- γ response in PTB-DM.

PTB increases the susceptibility to DM. In a previous study, the pancreatic endocrine function was investigated in 51 patients with primary active PTB before and after glucagon stimulation, the results revealed that relative insulin deficiency resulted in persistent hyperglycemia in these patients, and that the delayed concentration peaks of immunoreactive insulin and C peptide were observed in these patients (57). Compared with patients with PTB or DM alone, infection with Mycobacterium tuberculosis evidently sustains hyperglycemia in patients with DM (58). The prevention of Mycobacterium tuberculosis infection effective reduces weight loss, hyperglycemia, and insulin resistance during DM progression, manifesting that these parameters of glucose metabolism may be affected by Mycobacterium tuberculosis (59). Liver and kidney function



Figure 2. Schematic diagram of the mechanisms through which pulmonary tuberculosis increases the risk of developing diabetes mellitus.

play indispensable role in maintaining glucose metabolism homeostasis (60,61). Patients with PTB may be subjected to glucose metabolism dysfunction due to the impairment of liver and kidney function during anti-tuberculosis therapy. It has been reported that isoniazid can cause liver damage in anti-tuberculosis treatment (62). Isoniazid, rifampicin, and pyrazinamide cause hepatotoxicity at a probability ranging from 1 to 57% (63). Rifampicin re-administration may lead to an acute kidney injury (64). In addition, the specific amyloidosis of the pancreas is demonstrated in patients with tuberculous infection, while intense islet cell amyloidosis is also commonly observed in DM (65). Of note, islet cell amyloidosis, as a by-product of systemic tubercular infection, is dissolved by rifampicin; thus, it is suggested that infection with Mycobacterium tuberculosis may increase the risk of developing DM by causing the islet cell amyloidosis in patients with PTB (65). However, further studies are warranted to elucidate the mechanisms through which PTB increases the risk of developing DM.

4. Therapeutic management of patients with PTB-DM

Glucose control and PTB outcomes. DM is associated with the prognosis in patients with PTB, and DM has an adverse effect on the outcomes of PTB treatments (66). In patients newly diagnosed with PTB with DM or PDM, DM and hyperglycemia have been found to be associated with an increased bacterial burden of Mycobacterium tuberculosis and the risk of PTB transmission (15), and a poor blood glucose control has been demonstrated to increase the risk of PTB in patients with DM (67,68). Gil-Santana et al (69) suggested that DM was associated with the severity of PTB. An association between blood glucose levels and the computed tomography severity score has been found in patients with PTB-DM (70). Recently, a prospective cohort study indicated that patients with PTB with DM had a poorer prognosis than those without DM (71). A poor blood glucose control has been shown to be associated with the outcomes of PTB treatments, while improved hyperglycemia can reduce the effects of DM in patients with PTB (72). A meta-analysis suggested that DM was associated with an increased risk of a poor treatment response in patients with PTB, and that DM might increase the risk of PTB

resistance (73). PTB patients with DM are more likely to have a failed response to anti-tuberculosis therapy than those without DM (12). In addition, DM is a risk factor for the positive rate of tuberculosis culture after receiving anti-tuberculosis treatment, anti-tuberculosis treatment failure, and mortality in patients with PTB (74). Evidently, blood glucose control is associated with the outcomes of anti-tuberculosis treatment in patients with PTB-DM.

DM and anti-tuberculosis treatment. Anti-tuberculosis medications are divided into first- and second-line drugs; first-line anti-tuberculosis drugs include rifampicin, isoniazid, pyrazine, ethambutol, and streptomycin; these have a high efficiency and acceptable toxicity; second-line anti-tuberculosis drugs, such as fluoroquinolones, aminoglycosides, are used for multidrug resistance (75-77). Mycobacterium tuberculosis has the ability to manipulate innate and adaptive immune responses, which is known as the tuberculous escape mechanism; thus, Mycobacterium tuberculosis can avoid the intracellular killing and macrophage phagocytosis by the escape mechanism; however, hyperglycemia aggravates its escape mechanism, leading to an increased risk of anti-tuberculosis treatment failure in patients with PTB-DM (78). Poor blood glucose control increases the risk of pyrazinamide treatment failure, and DM also appears to influence the pharmacokinetic-pharmacodynamic association between isoniazid and rifampicin (79). Babalik et al (80) demonstrated that the plasma concentrations of isoniazid and rifampicin were reduced by $\sim 50\%$ in patients with PTB-DM; their data indicate that hyperglycemia significantly reduces the efficiency of anti-tuberculosis drugs.

DM significantly increases the risk of resistance to anti-tuberculosis medications (81). The use of hypoglycemic drugs significantly increases the effectiveness of anti-tuberculosis treatment in patients with PTB-DM. For instance, metformin can be used as an effective auxiliary anti-tuberculosis drug in patients with PTB-DM, as it can improve sputum culture transformation following 2 months of therapy (82); secondly, metformin use has been reported to be significantly associated with reduced mortality during antituberculosis treatment in patients with PTB-DM (83). Therefore, clinically, additional attention needs to be paid to the treatment and management of patients with PTB-DM; a satisfactory blood glucose control increases the efficacy of anti-tuberculosis treatment in these patients.

5. Conclusions and future perspectives

The present review provided an update on PTB-DM from the perspectives of epidemiology, pathogenesis, and treatment; however, there are still a number of issues that need to be further addressed in the future. First, the majority of epidemiological studies are based on a cross-sectional design; thus, further prospective cohort studies with large sample sizes are required to clarify a causality between PTB and DM. Second, islet cell dysfunction plays a key role in the pathogenesis of DM; current studies mainly focus on the effects of hyperglycemia on the susceptibility to *Mycobacterium tuberculosis*; however, few studies have explored the mechanisms through which *Mycobacterium tuberculosis* infection affects islet cell function in patients with PTB-DM.

In conclusion, the present review provides insight for future studies on the link between PTB and DM, particularly as regards the mechanisms of their interaction. A better understanding of the mechanisms of the association between DM and PTB may help to formulate effective treatment strategies with which to reduce the double burden of PTB-DM.

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YFP conceived and designed the study. YFP performed the literature search and wrote the manuscript. YFP has read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The author declares that he has no competing interests.

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