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Review Article

Microbiology Section

A Bidirectional Immunological Relationship between Diabetes Mellitus and Tuberculosis: A Narrative Review

PAVITHRA SELVAN[1], NALINI JAYANTHI NAGESH[2], LEELA KAKITHAKARA VAJRAVELU[3], C SYED AKRAM[4], B KARNIHA[5]

ABSTRACT

Tuberculosis (TB) is one of the most common contagious diseases worldwide. Over the past few decades, researchers have made significant efforts to prevent TB. Recent predictions indicate that the prevalence of Diabetes Mellitus (DM) will reach 552 million by 2023 due to ongoing epidemiological changes in several countries across the globe. India is expected to have 62-80 million people with diabetes by 2030, making it the "Diabetes Capital" of the world. Present review discusses the urgent need to understand the mechanisms and implications of DM on the immune systems of TB patients. The correlation between TB and DM has been shown to be bidirectional. Numerous studies have revealed a higher prevalence of diabetes in TB patients, as their immune systems are compromised. TB patients with DM experience progressive deficits in both innate and adaptive immune cell activity, reducing their ability to suppress *Mycobacterium tuberculosis (M. tuberculosis)* and increasing their risk of developing TB. Increased inflammation and elevated levels of inflammatory cytokines in circulation are characteristics of TB with DM co-morbidity, which indicate the active involvement of the angiogenesis-inflammation nexus. Therefore, to alleviate the burden of both disorders, it would be beneficial to make informed therapy choices by gaining a better understanding of TB immunology in the context of DM.

Keywords: Adaptive immunity, Cytokines, Innate immunity, *Mycobacterium tuberculosis*

INTRODUCTION

One of the most prevalent infectious diseases worldwide is TB. In recent decades, researchers have made great strides in TB prevention. The current initiatives to stop the spread of TB appear to have clearly decreased incidence, and these challenges are nearing an end [1]. According to World Health Organisation (WHO) data from July 2023, 10.6 million new active TB cases are anticipated to be recorded annually globally [2]. As per WHO, there were 108 million people with diabetes in the world in 1980 compared to 422 million in 2014 [3]. From this, it was predicted that by 2019, there would be around 463 million people impacted. It was also estimated that by 2030, there would be 578 million people affected, and by 2045, there would be 700 million people affected, respectively [4]. According to WHO, DM may be a factor in 15% of all TB cases worldwide [5]. By 2025, India would be the "Diabetes Capital" of the world, with an estimated 69.9 million people having the disease [6].

DM is still seen as a possible threat that needs to be managed and treated for TB, despite the fact that its prevalence is rising. To lessen the dual burden, the WHO has nonetheless recommended several important intervention strategies, including the establishment of collaborative control programs, the identification and treatment of DM in TB patients, as well as the detection and management of TB in DM patients [7]. Therefore, it is crucial to comprehend the extent and immunological processes by considering the link between TB and diabetes, notably in countries with low and middle incomes. The prevalence of diabetes and TB in different countries indicates an increased preponderance of about 29% in India, 26.5% in Korea, 25% in Mexico-Texas, and 15.8% in Ethiopia [8].

Despite the fact that the relationship between TB and DM has been known for many years, a striking global rise in DM prompted the International Union Against TB and Lung Disease as well as the WHO to issue global recommendations by 2011, mandating that all TB patients be screened for DM [9]. Furthermore, TB screening programs using DM have already started in India. However, it has been discovered that a lack of knowledge about the technology and the most effective ways for screening in TB centers was impeding global responses to this epidemic [10].

Although the relationship between TB and DM, as well as their cooperative effect in producing illnesses in humans, has recently been a top focus for basic and clinical studies, it remains a widely known fact. Pulmonary Tuberculosis (PTB) and DM, along with a combination of both ailments, are the two most prevalent conditions that co-exist in various regions of the world, posing a serious risk to global medical treatment [11]. As DM manifests as a causal factor for becoming an active TB patient, several clinical and epidemiological investigations have come into sharper focus. Furthermore, the correlation between diabetes and TB among those with the condition has had a negative effect on how the disease manifests and how treatments work. However, the available information is currently insufficient for making informed decisions, as it has negative effects on the health of people with diabetes globally [12]. Thus, the present review discusses the robust need for understanding the mechanisms and implications of DM affecting TB patients' immune systems.

Diabetes- A Potential Tuberculosis (TB) Risk Factor

In developing countries where TB is more prevalent, the incidence of DM is increasing. Consequently, locations with the fewest healthcare resources are most likely to witness the confluence of these two epidemics [13]. Diabetes serves as a separate risk factor for all lower respiratory tract infections. Clinical investigations have yielded contradictory findings. However, patients with concomitant TB and DM may also exhibit atypical radiological abnormalities, as well as a high frequency of haemoptysis and fever [14]. Several studies have indicated that people with diabetes who have TB develop lung cavities more or less frequently compared to those without diabetes who also have TB [15-17]. TB infection is more likely to occur among individuals with Type 1 DM (T1DM), despite the fact that Type 2 DM (T2DM) is more common. Additional risk factors for TB in people with T1DM include low body weight, youth, and inadequate glycaemic management [18].

Tuberculosis (TB)- The Risk Factor for Diabetes Mellitus (DM)

It has been discovered that there is a bidirectional association between TB and DM. Numerous studies have shown that TB patients have higher rates of diabetes due to their weaker immune systems [19-21]. Impaired glucose tolerance is one of the primary causes of DM development in TB patients. In most of these cases, the risk of contracting TB persists even after effective TB treatment, although the altered glucose tolerance level returns to normal. Hyperglycaemia may be the initial symptom of pancreatic TB, as pancreatitis often results from TB [22]. Pancreatic hypofunction emerges as the most crucial factor in this process, despite the possibility that some of the TB-related hyperglycaemic conditions may be caused by intense stress related to the infection itself. Hyperglycaemia associated with TB necessitates diabetic patients to regulate their blood sugar levels, ensuring that the insulin dosage is adjusted accordingly [23].

Aetiological Association

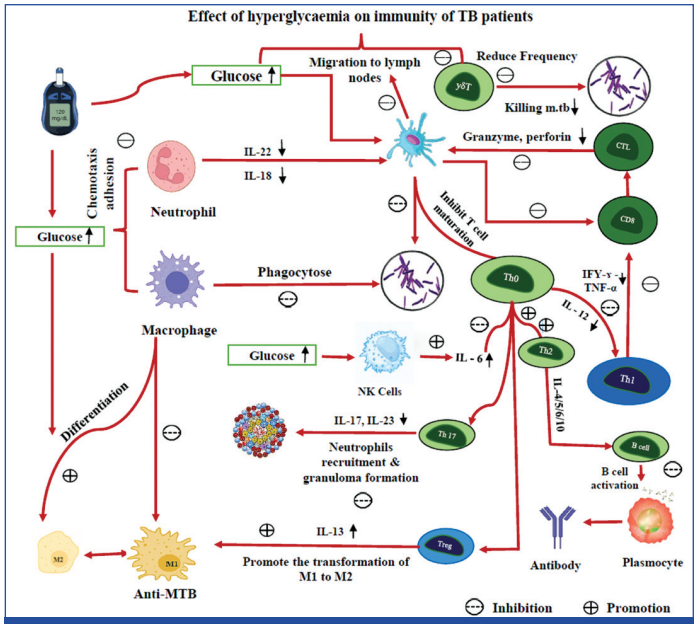
Cellular immunity is known to decline in people with diabetes. Diabetics have a lower neutrophil count and fewer T-cells. Individuals who have both diabetes and TB concurrently exhibit lower production levels of T-helper 1 (Th1) cytokine response, TNF-alpha production, IL-6, and IL-1β compared to those without diabetes [24]. *Mycobacterium tuberculosis* bacilli need to be controlled and inhibited with the help of Th1 cytokines. This reduction in the function and number of T lymphocytes has been considered a key mechanism behind the increased susceptibility of diabetes patients to TB [25]. Moreover, diabetes patients also experience impaired phagocytic, chemotactic, and Reactive Oxygen Species (ROS) generation in macrophages, which inhibits macrophage activity. The interaction of these dysfunctional processes makes diabetes patients more prone to developing TB [26]. It is important to note that the symptoms of these two conditions can resemble each other. Lethargy, exhaustion, fever, weight loss, and loss of appetite are a few symptoms that are common to both. People with diabetes may sometimes complain to their doctors about worsened blood sugar regulation, only to discover that they have TB [27].

Immunological Characteristics of Tuberculosis (TB) and Diabetes Mellitus (DM) Patients

Persistent hyperglycaemia is a hallmark of diabetes, which includes both T1DM and T2DM caused by escalating insulin resistance or insufficient insulin production [28]. Previous studies have shown that persistent hyperglycaemia in DM affects the immune system in several ways, including: 1) inflammation leading to a decrease in Dendritic Cells (DCs); 2) Proinflammatory substances are produced more often as a result of increased macrophage infiltration, which will cause islet cell malfunction and death; 3) heightened generation of ROS by neutrophils, increasing the risk of organ damage; and 4) Increases in Natural Killer (NK) cells are accompanied with dysfunctional NK cells that express a lot of Glucose Transporter Type 4 (GLUT4) [29-31]. Additionally, apart from impacting the humoral immune system, high blood glucose levels in diabetes patients also lead to functional abnormalities in CD4+ and CD8+ T lymphocytes due to non enzymatic glycosylation and a number of protein covalent compounds. These impair their ability to eliminate infections and make them more to apoptosis-prone [Table/Fig-1] [30].

Traits of the Immune System in Tuberculosis (TB) and Diabetes Mellitus (DM)

Diabetes can hinder the host's adaptive and innate immunity, making it more challenging to eradicate *M. tuberculosis* and increasing the risk of developing TB. Firstly, elevated blood sugar levels can make macrophages more M2 polarised, which reduces their ability to phagocytose by raising the quantity of *M. tuberculosis* that is present in-vivo [32]. Secondly, hyperglycaemia increases the absolute neutrophil count but decreases their phagocytic ability. Thirdly, the increased presence of NK cells, which release TNFα, IL-2, and IL-17F, further exacerbates the illness or results in larger bacterial loads [33]. Fourthly, DM decreases the secretion of DCs, thereby reducing CD4+ T-cell activation and compromising adaptive immunity. Hyperglycaemia inhibits the production of cytokines like TNF and Interferons (IFN-γ) by Th1 T-cells, diminishing the effectiveness of the Th1 immune response in eliminating and eradicating *M. tuberculosis* [34]. Additionally, a decrease in IFN-α may impede the activation of CD8+ T lymphocytes by Th1-type cells, leading to reduced production of bactericidal molecules such as IFN-γ, granzyme, and lysozyme. Consequently, the cytotoxic T-cells' ability to kill the bacilli is compromised. The impaired ability of TB patients with DM to control *M. tuberculosis* increases their susceptibility to acquiring TB, as both innate and adaptive immune cell functions progressively decline [35].



[Table/Fig-1]: Hyperglycaemic effects on the immunity of tuberculosis patients.

Innate Immunity of Tuberculosis (TB) with Diabetes Mellitus (DM)

There is limited information available regarding the circumstances leading to the initial interaction between *M. tuberculosis* and the innate immunity of hosts with DM. To address this, an in-vitro experiment has been initiated to examine how *M. tuberculosis* interacts with human blood monocytes obtained from *M. tuberculosis*-naive patients with and without diabetes [36].

Differences in innate immunity between individuals with and without diabetes significantly influence the susceptibility and pathogenesis of TB. Modifications in DM's metabolism have been shown to negatively impact macrophages, neutrophils, NK cells, DCs, and other components of the innate immune system. Therefore, malfunctioning of the immune system in DM patients can significantly affect the host's susceptibility to exogenous TB infections and the likelihood of recurrence [37].

Among DM patients, a decreased rate of *M. tuberculosis* phagocytosis, altered expression of genes involved in *M. tuberculosis* antigen presentation, and increased production of anti-mycobacterial peptides have been observed, resulting in changes in innate immunity. Additionally, defects may exist in cell trafficking within peripheral blood monocytes. Despite DM potentially causing immunological abnormalities first and then predisposing individuals to TB, patients with both TB and DM may share similar acquired or genetic vulnerabilities that make them more susceptible to both diseases [38].

Adaptive Immunity among Tuberculosis (TB) Patients with Diabetes Mellitus (DM)

Several studies have compared TB patients with DM to TB patients without DM, and it has been found that adaptive immunity to *M. tuberculosis* plays a more crucial role than DM. TB patients with DM tend to have lower levels of naturally occurring T-regulatory cells (CD4+, CD25+, and CD127-) and elevated levels of cytokines such as Th1 (IL-2, IFN-γ) and Th17 (IL-17A, but not IL-22) [39]. Both anti-inflammatory and proinflammatory cytokine levels have been shown to be higher in TB patients with DM compared to TB patients without diabetes, attributable to higher levels of Interleukin-10 (IL-10) [40]. Additionally, Sun L et al., discovered that TB patients with diabetes may exhibit an unusual Th2 response in the lung lobes, characterised by lower levels of IFN-γ but higher levels of IL-10 in bronchoalveolar lavage [41].

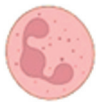
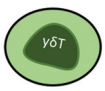
The majority of studies on the adaptive immune system suggest that TB patients with DM exhibit an overactive cell-mediated response against *M. tuberculosis* antigens. However, further research is needed to explore this hyper-response and its connection with DM, including its role in immunopathology and increased susceptibility to TB [42-44]. Data from TB patients without DM indirectly support the notion that individuals with diabetes have compromised immunity, rendering them more susceptible to TB. One of these investigations also found that individuals with TB and DM had significantly lower ratios of IFN-γ to IL-10 [Table/Fig-2] [28,31-33,37,41,43].

Immunological Effects of Diabetes over Tuberculosis (TB)- Severity and Treatment Outcomes

Diabetes patients experience a faster progression of *M. tuberculosis* infection compared to non diabetic controls, as well as shorter lifespans, higher rates of pulmonary and extrapulmonary infections, and heavier bacterial loads. Several studies have also noted the detrimental impact of DM on the effective management and prognosis of TB [44-46]. However, there is no conclusive evidence regarding the impact of DM on the efficacy of TB treatments, and the findings are mixed. It is worth noting that DM can alter the pharmacokinetics of certain anti-TB medications. Understanding the detrimental impact of DM on TB therapy is important because the effectiveness of most anti-TB drugs depends on their plasma concentration [47]. The altered plasma levels in diabetics may be due to variations in drug absorption, distribution, metabolism, and/or excretion. Lower plasma levels of anti-TB drugs are associated with drug resistance, which can make the treatment of TB in diabetics more challenging [48].

Furthermore, individuals with TB and DM have higher mortality rates due to the disease's progression, miliary TB, and increased bacterial burdens. Laboratory studies on animals have shown that inducing hyperglycaemia increases the frequency of *M. tuberculosis* shedding from the airways, even in the absence of cavitations. This increase in *M. tuberculosis* shedding may be attributed to changes in the diabetic airway microenvironment and an increase in pulmonary bacterial burden. The persistent hyperglycaemia, coupled with oxidative stress, leads to a proinflammatory response that exacerbates inflammation and increases the risk of TB infection in diabetics [49].

However, DM patients who acquire TB infections deteriorate rapidly before developing *M. tuberculosis* adaptive immunity. This is attributed to high levels of IL-4 and anti-inflammatory cytokines, which suppress the expression of IFN-γ and contribute to the inability to control bacterial growth. Cohort studies have shown that individuals with

Immune cells	Aetiology	TB-DM Mechanism	Cytokines produced	References
 Macrophages	TB eradication via cytokine production, autophagy, reactive oxygen, nitrogen species, and antigen presentation	• Reduce Th1 immune response and antigen presentation, and alter macrophage activation state. • Alveolar macrophages are reduced by impaired sentinel function, which delays bacterial reproduction and triggers adaptive immunity. • Fall in Macrophage 1 polarisation and raise in macrophage 2 polarisation.	Macrophage 1: IL-1, IL-12, TNF-α, type I IFN-γ Macrophage 2: IL-10	[32]
 Neutrophils	Rapid recruitment at the site of infection that assists macrophages in engulfing *M. tuberculosis*	• Reduced neutrophil levels and cytokines secreted by them. • The adaptive immune response is hindered by neutrophil influx suppression. • Neutrophil microenvironment changes result in decreased adhesion capacity.	IL-22, IL-8	[37]
 Natural Killer cells	The development of immunomodulatory cytokines to eliminate diseased cells from the body	IL-6 secretion is increased by NK cells, while CD4+ T-cell production is decreased.	CD16, CD56	[28]
 Dendritic Cells (DC)	• T cells by antigen presentation naïve T lymphocyte activation triggers adaptive immunity • An intermediary among innate and adaptive immunity	• Diabetes promotes the release of DC cells. • DC subsets secreting cytokines altered, while DC1's frequency reduced and DC2's frequency barely changed at all.	Dendritic Cells 1: IFN-γ, IL-12, and IL-18 Dendritic Cells 2: IL-4 and IL-10.	[41]
 CD4+ T cells	IFN-γ and TNF-α mediated cytokine secretion prevent *M. tuberculosis* proliferation	• Cytokine release by CD4+ T-cells dropped. • Decline in ratio of Th1/Th2 ratio as well as Th1 reduction (IFN-γ secretion) • Promote Treg opposes Th1, Th2, and Th17, stimulates secretion of Treg, and encourages macrophage M2 polarisation. • Cytokine secretion by Th17 was significantly reduced.	Th1 cells: TNF-α, IFN-γ, IL-2, and IL-12, Th2: IL-4 and IL-10	[43]
 CD8 + T cells	Destroying *M. tuberculosis*-infected cells by secreting cytokines or other cytotoxic agents	• CD8+ T-cells and the associated subgroups secreted fewer cytokines. • Cytotoxic substance secretion gradually reduced with the transition from LTBI to TB, whereas cytokine secretion will be high.	Perforin, CD107a, Granzyme B, IL-4, IL-5, IL-13, IL- 17A and IL-17F	[33]
 γδT cell	Cytokine production, chemokines and cytotoxic effector molecules to combat *M. tuberculosis* infection.	• T cells and their subgroups' reduced cytokine secretion. • A decline in the cytotoxic agents secretion.	Granzyme B , Th1, Th17, and perforin	[31]

[Table/Fig-2]: Impact of diabetes on adaptive and innate immune cells among TB patients [28,31-33,37,41,43].

diabetes have a higher risk of mortality during TB treatment compared to those without the disease [48-50]. The increased bacterial load at diagnosis is believed to contribute to the likelihood of TB treatment failure and delayed TB clearance in DM patients. These factors may be explained by delayed immune response kinetics in DM patients and alterations in the pharmacokinetics of anti-TB medications (drug absorption, distribution, metabolism, and excretion) in TB patients with DM [51].

Management of Diabetes

Aggressive management of DM is necessary in TB patients. Achieving optimal glycaemic control is crucial as it improves patient outcomes. It is recommended to initiate insulin therapy immediately, using a basal bolus schedule or premixed insulin. The American Association of Clinical Endocrinologists advises the use of modern insulins or insulin analogues as they work more predictably and result in less hypoglycaemia [52]. The use of traditional human insulins is discouraged. Initially, insulin requirements are high but tend to decrease after a few weeks once glucotoxicity is corrected and the infection is controlled. However, insulin needs may increase again as appetite returns to normal and calorie intake rises. Sick patients should be checked for ketonuria. Those with ketonuria may not require hospitalisation, and the use of rapid-acting analogues such as part insulin can be beneficial for critically ill patients. Oral hypoglycaemic medications can be used once the TB infection has subsided, but they should not be taken during severe TB [53].

One medication that has a significant impact on DM management in TB is rifampicin, which is a strong inducer of hepatic enzymes. Rifampicin accelerates the metabolism of various oral hypoglycaemic medications, particularly sulphonylureas and biguanides, leading to decreased plasma levels of these drugs. Therefore, using these medications in diabetic patients may result in hyperglycaemia. Rifampicin can also mimic the signs and symptoms of diabetes and enhance intestinal glucose absorption, even in individuals without diabetes [54]. Unlike rifampicin, which may increase the plasma levels of these drugs, isoniazid decreases the metabolism of oral hypoglycaemic agents. Sulphonylureas are their primary interaction, whose effect it opposes and makes worse for diabetics using this medication's glycaemic control. Additionally, it hinders the action and release of insulin, causing hyperglycaemia even in those without diabetes [55]. Therefore, insulin doses should be adjusted when adding or removing these drugs from a patient's prescription. Dipeptidyl protease inhibitors (gliptins), a relatively new class of hypoglycaemic medications, have the potential to reduce immunocompetence due to their mode of action. This may potentially worsen the outcomes of TB patients [56]. Researchers now have a new perspective and an opportunity to better understand the aetiology of the illness because of the increasing involvement of DM in TB. They hope that teams from basic science and epidemiological research will eventually work together to produce a strategy for classifying millions of people with DM into groups depending on their risk of contracting *M. tuberculosis* or developing TB. Accordingly, those who would benefit the most from Latent TB infection treatment would be advised to do so, while others with the worst prognoses would receive TB treatment tailored to meet their unique needs. Numerous studies have been conducted to show that hyperglycaemia impairs the host's defense systems by promoting the onset and spread of TB and producing a significantly worse prognosis for therapy [57-59]. Expanding the role of DM in TB offers a fresh viewpoint and an opportunity for researchers to learn more about the aetiology of the disease. It is crucial that to conduct in-depth research into the pathogenic processes of TB with DM to fully understand how hyperglycaemia affects the host's immune system and provide effective therapy. Hence, to reduce the combined burden of both disorders, it would be helpful to make sensible therapy choices by gaining an improved comprehension of TB immunology with DM.

CONCLUSION(S)

The co-occurrence of TB and DM poses a significant concern for individuals as it substantially complicates the treatment process and adversely affects the overall outcome of the disease. Considering the significant influence of the concurrent presence of TB and DM on the treatment and control of diseases, it is imperative to implement public health measures that prioritise early diagnosis and effective management of both TB and DM. Modifying TB treatment protocols for individuals with DM could result in improved glycaemic control, more favourable outcomes, and decreased morbidity. Therefore, this will contribute to the realisation of the End-TB Strategy and the attainment of Sustainable Development Goals for the elimination of TB.

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PARTICULARS OF CONTRIBUTORS:

1. Research Scholar, Department of Microbiology, SRM Medical College Hospital and Research Centre, Faculty of Medicine, SRMIST, Chengalpattu, Tamil Nadu, India.
2. Professor and Head, Department of Respiratory Medicine, SRM Medical College Hospital and Research Centre, Faculty of Medicine, SRMIST, Chengalpattu, Tamil Nadu, India.
3. Professor and Head, Department of Microbiology, SRM Medical College Hospital and Research Centre, Faculty of Medicine, SRMIST, Chengalpattu, Tamil Nadu, India.
4. Postgraduate, Department of Respiratory Medicine, SRM Medical College Hospital and Research Centre, Faculty of Medicine, SRMIST, Chengalpattu, Tamil Nadu, India.
5. Senior Resident, Department of Respiratory Medicine, SRM Medical College Hospital and Research Centre, Faculty of Medicine, SRMIST, Chengalpattu, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Ms. Pavithra Selvan,
Research Scholar, Department of Microbiology, SRM Medical College Hospital and Research Centre, Faculty of Medicine and Health Sciences, SRM Institute of Science and Technology, SRM Nagar, Kattankulathur, Chengalpattu-603203, Tamil Nadu, India.
E-mail: jeevepavi123@gmail.com

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