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Immune Response to Tuberculosis among Diabetes Patients-A Natural Disaster in Human Defense Mechanism

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Abstract

Focus on the potential connections between DM and TB is growing as the Diabetic Mellitus (DM) pandemic spreads in nations where TB is also widespread. Diabetes is a complicated condition that includes multiple types of dyslipidemia in addition to hyperglycemia. However, it is unclear how much these underlying metabolic variables contribute to a higher vulnerability to TB. Despite the widespread prevalence of the DM-TB relationship, it is startling how little is known about the underlying biology that supports this association, which is a serious public health problem. In this review, we provide an overview of recent research on the mechanism of innate and adaptive immune responses to Mycobacterium tuberculosis (Mtb) in DM patients. The role of these altered responses to TB susceptibility or to the more unfavourable clinical outcomes of TB patients with DM is yet unknown, but recent data suggest that underperforming innate immunity is followed by a hyper-reactive cellular response to Mtb.

Introduction

There are significant medical and societal repercussions from the diabetes epidemic that currently affects 425 million people worldwide and is projected to reach 629 million by 2045 [1]. Type 2 diabetes mellitus, referred to as “diabetes” in this study, is prevalent in low- and middle-income nations as well in regions where tuberculosis (TB) is still widespread. The association between DM and TB was first described by centuries ago by Avincenna, a persian philosopher, and the co-morbidity was a frequent topic in the medical literature from the first half of the 20th century. Diabetes is frequently misdiagnosed and frequently made worse by cardiovascular issues, eye, foot, and kidney issues. Diabetes has frequently manifested itself in various contexts following a significant infection, which raises the risk of numerous infections and associated complications [2]. Diabetes patients frequently get infections, and certain of these illnesses-known as “signal infections”-are so closely related to diabetes that, at least in high-income nations, those without diabetes hardly ever attack them. Since diabetes may be raising TB risk at a number of distinct periods along the disease’s progression due to the complexity of TB’s natural history [3]. Latent TB infection (LTBI) is thought to affect about 25% of people worldwide, and many of them already have diabetes or are at risk of developing it. Over the course of their lives, approximately 5% of infected people will develop active Tuberculosis (TB), with half of those cases occurring within the first two years of infection. Pre-diabetes, also known as intermediate hyperglycemia or non-diabetes dysglycemia, is on the rise worldwide, especially in regions where tuberculosis is widespread. Whatever mechanisms are involved, several systematic reviews have now summarised evidence from observational studies showing that the risks of TB disease are significantly elevated in people with diabetes, about 2-3 times higher [4].

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Methodology

We examined the PubMed database using the following search terms to conduct this review of the available literature. Mycobacterium tuberculosis, immunity, and type of immunity, diabetes to describe tuberculosis. The word "tuberculosis" was then associated with specific key words for each topic (such as innate immunity,adoptive immunity, epithelial cell," "macrophage," "neutrophil," "dendritic cell," "natural killer," "humoral," "antibody," and "granuloma") in order to access relevant specific literature. There was no organised method used in the search or selecting process. Articles had to be in the English language, be fully downloadable, and be relevant; otherwise, they were excluded.

Tuberculosis and diabetes

Diabetes is a chronic (long-lasting) illness that interferes with the body's ability to convert food into energy. A severe health risk, particularly for those with diabetes, is tuberculosis (TB). Latent TB infection and TB illness are two diseases connected to TB. Due to the body's ability to fight off the bacteria and prevent their growth, people with latent TB infection do not get sick. The body can't stop the bacteria from proliferating, which causes TB patients to be ill and have active TB. Diabetes increases the risk of developing TB disease and getting sick from TB in those who are also TB afflicted [5]. Diabetes has reportedly been related to pretty poor TB treatment outcomes among patients with both TB and DM. However, a systematic analysis to both clarify and quantify the association between DM and TB outcomes, including persistence of positive sputum culture, failure, death, and relapse, has not been carried out. An association between DM and TB outcomes would indicate that diabetes could increase the number of people infected by a source case and the number of patients needing anti-TB retreatment regimens, which is significant given the rising global burden of TB patients with DM [6]. The global rise in diabetes is a significant obstacle in the fight against TB. A person with diabetes has a suppressed immune system, which makes them more susceptible to diseases like TB. According to recent estimates, patients with diabetes may account for up to 15% of TB cases.

The combined management of diabetes and TB is challenging. Managing a patient's glucose levels becomes more challenging during TB treatment, and diabetic TB patients are more likely to die to the illness than nondiabetic individuals.

Risk of diabetes among tuberculosis patients

However, individuals with diabetes may also have higher infection risk due to increased exposure to M. tuberculosis. This might happen as a result of more people using medical facilities or due to immune system changes in people with diabetes, which increase the likelihood of first infection. People with diabetes have a very slight increased risk of M. tuberculosis infection, according to a recent systematic study (RR 1.18, 95 percent CI 1.06 to 1.30 [7]. Numerous investigations have also discovered that diabetes changes how TB presents itself, causing more cavitation, higher severity TB ratings, and more pulmonary TB that is smear or culture positive [8]. Although this assertion is debatable, it appears that persons with diabetes have less extra-pulmonary TB illness. Patients with HIV co-infection, on the other hand, very obviously present with extrapulmonary and disseminated TB at higher rates [9]. This pattern is considerably distinct from those patients. Diabetes may also delay the time it takes for a tuberculosis smear or culture to go negative and somewhat increase the amount of M tuberculosis bacteria present; approximately twice as many patients with TB plus diabetes have positive cultures at months 2-3 as those with simply TB. Although the exact cause of death during treatment in patients with TB and diabetes is not always known, both conditions are linked to an increased risk of cardiovascular problems like myocardial infarction and stroke [Although the exact cause of death during treatment in patients with TB and diabetes is not always known, both conditions are linked to an increased risk of cardiovascular problems like myocardial infarction and stroke [10], which could account for the higher rate of deaths in the initial months of TB treatment in patients with diabetes, which could account for the higher rate of deaths in the initial months of TB treatment in patients with diabetes **(Figure 1)**.

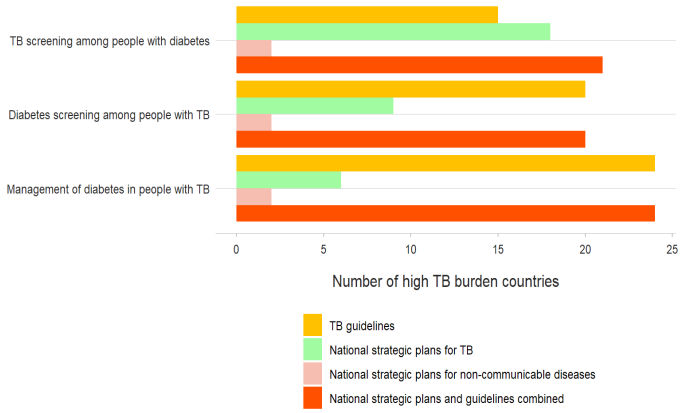


Figure 1: WHO recommendations on TB and diabetes by the 30 high TB burden countries in 2020.

Immuneregulation to Mtb and Diabetes

Through one or more of the metabolic effects of hyperglycemia, DM may affect TB immunity. The constant correlation between blood glucose or HbA1c levels and the results of the immunological response in TB serves as indirect confirmation for this [12].

Innate immune response to Tuberculosis

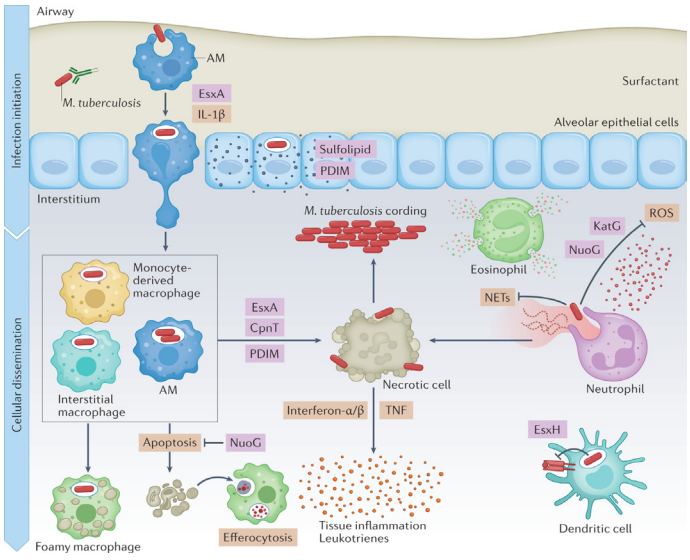
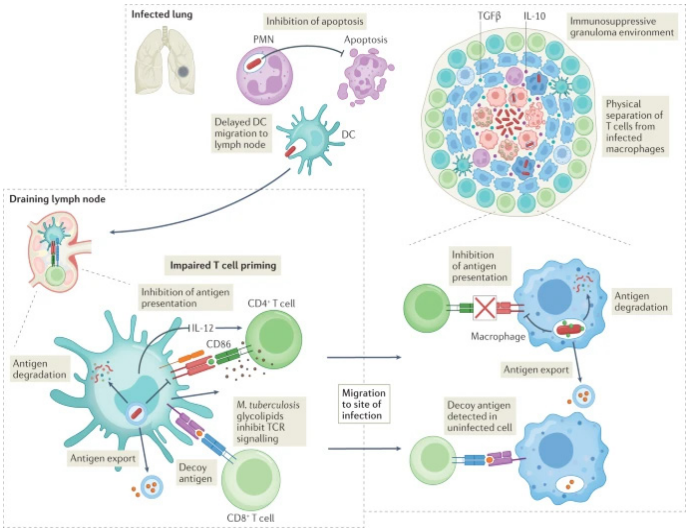


Figure 2: Mechanism of action of immune cells toward tuberculosis infection.

Understanding the initial events of tuberculosis infection **(Figure 2)** is essential for the development of a vaccine. The infectious dose of *M. tuberculosis* is remarkably low, estimated to be approximately three bacilli, highlighting how effective *M. tuberculosis* is at evasion the innate immune response [13].

According to studies on the adaptive immune system, Mtb antigens cause hyperreactive cell-mediated responses in TB-DM patients. This dissimilarity from non-DM TB patients offers indirect support for the idea that DM patients' compromised immunity contributes to their susceptibility to TB, but this hyper-response is intriguing and needs further investigation to ascertain whether it contributes to the higher susceptibility of DM patients to TB, contributes to immune pathology and their worse clinical outcomes, or contributes to their inability to eradicate Mtb [14].

Adoptive immune response to M.tuberculosis (Figure 3)



In tuberculosis infection, immunodominant antigens may act as decoys, priming T cell populations that fail to recognize the directly infected cells because the antigen they recognize is exported from or not expressed in infected cells **(Figure 4)**.

Influence of diabetes on M.tuberculosis infection

CMI response to M.Tuberculosis infection with or without diabetes

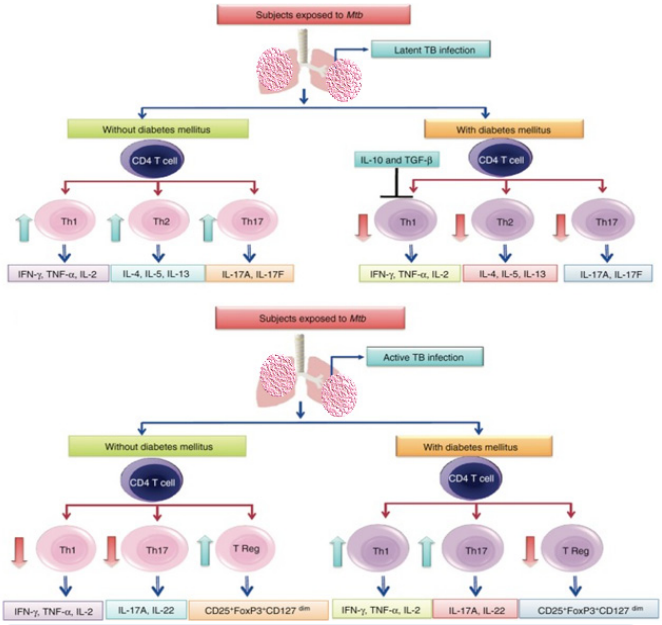


Figure 4: Immune action to tuberculosis patients with or without diabetes.

Impact of diabetes on tuberculosis

The risk of TB can be divided into two categories: the risk of infection, which affects 30% of household contacts, and the risk of TB advancement, which affects 5-10% of individuals with an infection [15]. Recent studies provide data on how innate and adaptive immune responses to Mtb define these outcomes [16]. Lung alveolar macrophages largely phagocytose inhaled Mtb, and the outcome depends on how well the host reaction balances the bacterial methods for evading death.

Diabets Increases TB Disease Severity and the Risk of Adverse Tuberculosis Treatment

Diabetes Patients who acquire active TB usually have worse illness on chest X-rays, a slower conversion of cultures, and higher sputum smear grades [23]. Higher lung mycobacterial loads are indicated by higher smear grades in patients with TB-Diabetes co-morbidity, suggesting that these people are more contagious than TB patients without co-morbidities [17].

TB patients with Diabetes have worse treatment results and increased mortality, which was shown in several retrospective studies [18]. The risk of early mortality during TB treatment was significantly higher for people with diabetes, according to a recent prospective study that followed more than 700 people from West India (aHR, 4.36; 95% CI, 1.62-11.76) [19]. A multicenter prospective cohort study from Brazil found that those with diabetes but not prediabetes have a higher chance of poor outcomes (1.76 and 2.45 times from two different cohorts, respectively) and a higher risk of death (1.93 and 2.16 times). Patients with diabetes usually use medications to decrease their cholesterol and blood sugar. Statins and metformin, two of the most popular abetes medications, have recently drawn interest as potential hosts for host-directed therapy for TB treatment after being assessed in relation to the severity of TB disease and treatment outcomes.

Conclusion

There is solid evidence that people with diabetes are more likely to get a primary Mtb infection, advance from latent to active TB infection, and experience negative TB treatment results. The risk of increased susceptibility to TB in diabeties patients was previously assumed to be primarily influenced by hyperglycemia, but there is now accumulating evidence that other host metabolic variables, such as hypercholesterinemia and high triglycerides, also change this risk. High cholesterol may have a favourable impact on the clinical presentation and outcomes of TB treatment, despite the fact that high triglycerides are linked to unfavourable TB treatment outcomes.

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