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SYSTEMATIC REVIEW: TYPE II DIABETES MELLITUS AND OTHER PREDISPOSING FACTORS FOR *MYCOBACTERIUM TUBERCULOSIS* INFECTION

Isabella Arce
Medical Student, Faculty of Health, Universidad Libre, Cali Section

María Alejandra Romero
Medical Student, Faculty of Health, Universidad Libre, Cali Section
Corresponding author

Armando Lucumi-Moreno
Full Professor, Medical Program, Faculty of Health, Universidad Libre, Cali

Abstract: Type II diabetes mellitus (DMII) is one of the most prevalent chronic diseases worldwide. Beyond its metabolic implications, this condition significantly increases the risk of developing tuberculosis (TB), one of the infectious diseases with the highest global mortality. This study aims to explore the relationship between DMII and susceptibility to Mycobacterium tuberculosis infection, considering sociodemographic factors and other associated determinants such as malnutrition, smoking, and immunosuppression. A systematic review of 50 articles highlights that patients with DMII have a 2 to 3 times higher risk of developing active TB, with higher rates observed in men and low-income populations. These findings underscore the importance of adopting a comprehensive public health approach to mitigate this syndemic interaction.

INTRODUCTION

Type II diabetes mellitus (DMII) is a metabolic disorder characterized by insulin resistance and chronically elevated blood glucose levels[1]. As a syndrome, DMII is associated with an increased risk of developing various chronic and infectious diseases, particularly tuberculosis (TB)[2,3,4]. According to the World Health Organization (WHO), DMII affects approximately 10% of the global adult population and is a significant predisposing factor for infectious diseases. Metabolic alterations induced by DMII impair immune responses, weakening both innate and adaptive immunity, thereby increasing susceptibility to *Mycobacterium tuberculosis* infections[5,6]. Furthermore, chronic hyperglycemia affects neutrophil and macrophage function, compromising phagocytosis and promoting a chronic inflammatory state[7]. This interaction is particularly relevant in regions with high poverty rates, where factors such as overcrowding, malnutrition, and limited healthcare access exacerbate the problem[8].

Tuberculosis is a bacterial disease caused by *Mycobacterium tuberculosis*, predominantly affecting the lungs, although it can disseminate hematogenous and via the lymphatic system, leading to extrapulmonary manifestations, primarily in the central nervous system, pleura, and bones[1,2,3]. It is estimated that approximately 70% of the global population has been exposed to this bacillus at some point in life. However, the likelihood of developing active TB depends on multiple factors, particularly the patient's immune response[3]. In this context, DMII plays a crucial role in the progression of latent TB infection to active disease. A compromised immune system in diabetic patients facilitates the progression of TB, leading to irreversible damage and increased mortality[5,6].

TB is one of the leading infectious causes of mortality worldwide, surpassing HIV/AIDS but preceded by COVID-19[4]. In 2023, an estimated 4,400 deaths and 30,000 new infections occurred daily[3]. The COVID-19 pandemic further exacerbated TB-related mortality due to the reallocation of healthcare resources[3,4]. Although TB is preventable and curable, its treatment requires prolonged antibiotic regimens. The most affected populations are in developing countries experiencing extreme poverty. Given that DMII is one of the most prevalent chronic diseases, studying the relationship between DMII and TB is of critical importance to public health. DMII is currently recognized as a major risk factor for TB, being associated with more complicated TB cases, higher relapse rates, and increased mortality[1,3,5,6,7].

The WHO has emphasized the significance of the TB-DMII relationship, highlighting that diabetic individuals have a 2 to 3 times higher risk of developing TB[2,7,8]. In light of this, the objective of this study was to conduct a literature review on the role of DMII and sociodemographic factors as predisposing elements for *Mycobacterium tuberculosis* infection.

METHODOLOGY

This study employed a systematic review approach based on PRISMA guidelines, utilizing databases such as PubMed, EBSCO, and ScienceDirect. Keywords included "type 2 diabetes mellitus," "active tuberculosis," "risk factors," and "HIV," with filters applied for articles published between 2010 and 2024. Observational, prospective, and retrospective studies examining the relationship between DMII and active TB were included[5]. Narrative reviews, editorials, and animal studies were excluded. Quality analysis was conducted using bibliographic management tools such as Zotero, with variables categorized into sociodemographic, clinical, and immunological dimensions. This approach enabled the identification of relevant patterns in existing literature, ensuring the validity of findings.

SOCIODEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

To explore the potential relationship between sociodemographic aspects and their impact on DMII and active TB development, articles were analyzed to determine:

- Gender predisposition to TB
- Age groups at higher risk
- Ethnic differences in TB susceptibility (e.g., Afro-descendants, Indigenous, Caucasians)
- Socioeconomic status as a determinant in TB progression

RISK FACTORS FACILITATING TB DEVELOPMENT IN DMII PATIENTS

The prevalence of various risk factors for TB was estimated, including:

- HIV and immunosuppression
- Malnutrition
- Smoking
- Alcoholism
- Obesity
- High-risk populations (healthcare workers, incarcerated individuals)

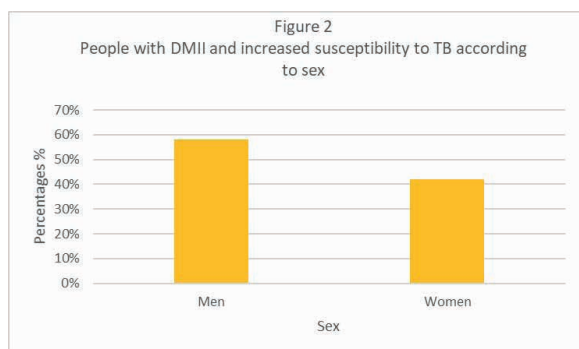## RESULTS

SOCIODEMOGRAPHIC FACTORS
Age and Susceptibility to TB in DMII Patients

The highest TB prevalence among DMII patients was observed in the 48-56 age group (25%), followed by 37-47 years (20%). Younger (15-25 years) and older (58+ years) populations exhibited lower prevalence rates (5% and 15%, respectively). This suggests that TB susceptibility in DMII patients peaks in middle-aged individuals. Figure 1.

Proportions of people with DMII and greater susceptibility to TB by age
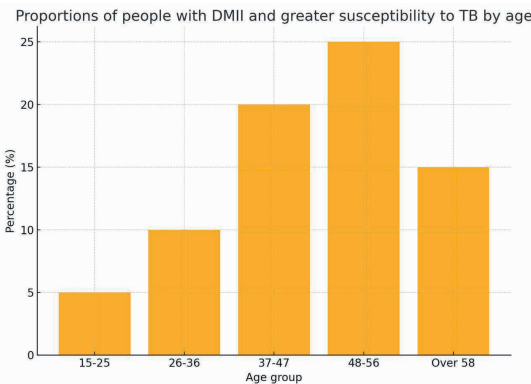
3.1.2 Gender and TB Susceptibility in DMII Patients

Males exhibited a higher probability of contracting TB in the presence of DMII, with a prevalence of approximately 60%, compared to 50% in females. According to *Facteurs de risque et diagnostic de la tuberculose*[9], male TB prevalence is associated with low socioeconomic status and high-risk behaviors. Figure 2.

Figure 2
People with DMII and increased susceptibility to TB according to sex

Figure 5
Risk factors that predispose to the development of TB

Socioeconomic Status and TB Susceptibility in DMII Patients

Individuals from lower socioeconomic strata had significantly higher TB prevalence (54%) compared to those in higher socioeconomic groups (44%). Pérez-Navarro et al.[10] highlighted the correlation between low socioeconomic status, malnutrition, illiteracy, rural living, and overcrowding, which exacerbates DMII and TB risk. Figure 3.

Figure 3
People with DMII and greater susceptibility to TB according to socioeconomic stratum
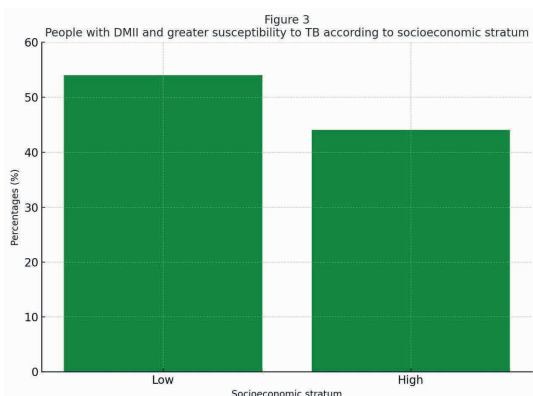
DMII AS A RISK FACTOR FOR TB

All 44 reviewed studies confirmed a direct association between DMII and TB.

Other Risk Factors for TB

Smoking and drug addiction were the most prevalent risk factors (over 40%), followed by alcoholism (35%), HIV (25%), and obesity (20%). Factors such as hypertension and cardiovascular diseases had lower prevalence (<10%). Figure 4.
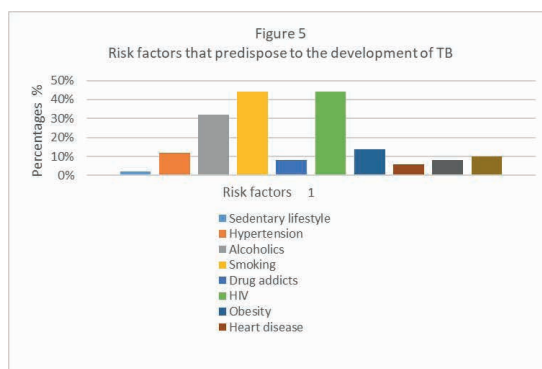
DISCUSSION

Our findings confirm that type 2 diabetes mellitus (DM2) is a significant risk factor for the development of tuberculosis (TB). This is primarily due to the adverse immunological effects that hyperglycemia exerts on immune system cells, including lymphocytes, neutrophils, and macrophages, as explained by Fougère Martínez et al., 2021[11]. Recent research has reinforced this evidence, indicating that individuals with diabetes are 1.5 to 2.4 times more likely to develop tuberculosis compared to those without diabetes[12].

IMMUNOLOGICAL ALTERATIONS IN DM2 PATIENTS AND THEIR RELATIONSHIP WITH TUBERCULOSIS

Diabetes is associated with dysfunctions in both innate and adaptive immune responses, facilitating Mycobacterium tuberculosis infection. Specifically, neutrophils in diabetic patients have been observed to exhibit increased cytokine and enzyme production, inducing a chronic inflammatory state, as evidenced by Murillo et al.[13]. Additionally, Aguilar-Salinas et al. demonstrated that hyperglycemia in DMII leads to increased protein glycosylation, thereby inhibiting the production of key cytokines such as IL-10, IL-12, IFN-γ, and TNF-α, which are essential for chemotaxis and phagocytosis.

Another important finding is the impairment of the complement system in DM2 patients. According to Fougère Martínez et al.[11], hyperglycemia inhibits the activity of the C3 component of the complement system, reducing opsonization and phagocytosis capacity against M. tuberculosis. This immune system deterioration favors bacillus proliferation within macrophages, as the ESAT-6 antigen blocks phagosome-lysosome fusion, preventing the apoptosis of infected macrophages, as demonstrated by Pérez-Navarro et al.[10].

Recent studies have highlighted that the coexistence of DM2 and TB can complicate clinical management, as diabetes influences the clinical presentation of tuberculosis and affects treatment response. It has been observed that diabetic patients with tuberculosis tend to develop more severe forms of the disease and experience more complications during treatment[14,15]. These findings reinforce the importance of strict glycemic control in diabetic patients to reduce the risk of developing tuberculosis and to improve treatment outcomes, as recommended by the Pan American Health Organization (PAHO)[16].

PREDISPOSING FACTORS IN THE DM2-TB RELATIONSHIP

Age

Age is a determining factor in susceptibility to infections, as aging leads to immunosenescence, which affects adaptive immunity and reduces the body's ability to combat infections such as tuberculosis, as described in the WHO report in 2022[17]. However, in contrast to our findings, Fougère Martínez et al. (2021)[11] identified that the highest risk group for TB-DM2 co-infection consists of individuals under 40 years of age, with a relative risk of 10.8, which decreases with age.

Gender

Our results indicate that male patients exhibit a higher prevalence of tuberculosis in the presence of diabetes (58%). However, the research by Fougère Martínez et al. (2021)[11] suggests that women have a higher risk of developing both diseases. Additionally, the WHO reported in 2022 that, out of the 10.6 million tuberculosis cases, 5.8 million occurred in men, while 3.5 million affected women (WHO, 2022)[17]. Additional studies, such as those by Herrera et al. (2013)[18] and the Chilean Ministry of Health's National Health Survey (ENS 2009-2010)[19], also support the greater prevalence of active tuberculosis in women with diabetes.

Socioeconomic Level

Low socioeconomic status is another significant factor in the prevalence of DM2 and TB. Our study found that individuals with lower income levels are at higher risk of contracting both diseases due to inadequate healthcare access and precarious living conditions, consistent with the findings of Aguilar-Salinas et al. (2019)[20]. Similarly, Pérez-Navarro et al. (2018)[10], in a study conducted in Veracruz, Mexico, found that 49% of TB-DM2 patients belonged to a low socioeconomic level.

Other Risk Factors

Beyond diabetes, other factors such as HIV, alcoholism, and smoking can increase susceptibility to tuberculosis. Smoking affects immunity and compromises pulmonary structure, increasing the risk of *M. tuberculosis* infection (WHO, 2022)[17]. According to WHO, 10% of tuberculosis-related deaths are attributed to tobacco use. Likewise, HIV is a strong immunosuppressor that significantly raises the probability of developing active tuberculosis.

Alcohol consumption also weakens the immune response, as highlighted in the thesis by Arias Padilla (2020)[21], who found that harmful habits such as alcoholism increase TB prevalence by 38%. Furthermore, deficiencies in vitamins A and D can triple the risk of contracting the infection.

CONCLUSION

Our findings reinforce the idea that type 2 diabetes mellitus (DM2) is a significant risk factor for tuberculosis due to its effects on both innate and adaptive immunity. Additionally, other factors such as age, gender, socio-economic status, and lifestyle habits can further increase susceptibility to infection.

Recent evidence highlights the need for integrated strategies for the surveillance and management of DM2 and TB, as diabetes not only increases tuberculosis incidence but also worsens its clinical course and reduces treatment effectiveness. Therefore, international organizations such as the Pan American Health Organization emphasize the importance of proper glycemic control to reduce infection risk and improve therapeutic outcomes (PAHO, 2025)[16].

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