

## Type 2 Diabetes Mellitus and Tuberculosis, the next syndemic

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Recent years have witnessed the development and progression of a new syndemic, which includes two diametrically opposed diseases: on the one hand, we have the participation of an infectious disease, Tuberculosis (TB), and on the other, a chronic degenerative disease, Type 2 Diabetes mellitus (T2DM). Both diseases are combined to generate serious epidemiological scenarios in the short and medium term that require immediate and well-organized attention by the health authorities if the objectives of the "End TB" strategy for 2030 want to be achieved (1).

TB is an infectious disease caused by *Mycobacterium tuberculosis*, a bacterium that predominantly affects the lungs; however, it can also spread to other organs and tissues. According to the WHO, in 2021, more than 10 million new cases and 1.6 million deaths from TB were reported globally, with most of these deaths occurring in Asia (1). Additionally, it was estimated that 3% of new and 18% of treated cases would evolve into aggravated forms of resistance, such as multidrug-resistant TB (MDR-TB), of which 8.5% will develop extensively resistant TB (XDR-TB) (2); these are unprecedented figures considering our historical evolution with this disease.

On the other hand, Diabetes mellitus is characterized by a disorder in the production and action of insulin, triggering

a state of hyperglycemia, if this disease is not adequately treated generates immunosuppression, systemic inflammation, and eventually serious damage to various organs. Type 2 diabetes mellitus (T2DM) is the most common form of the disease and accounts for 90% of diagnosed cases (3). According to the International Diabetes Federation (IDF), 425 million people were estimated to have T2DM worldwide in 2017, with North America and the Caribbean being the regions with the highest prevalence in the Americas (50 million) (4). These figures exemplify the growth of T2DM, which would be explained mainly by the population's modification in dietary habits and lifestyle.

In the context of the comorbidity, those individuals living with T2DM increase up to threefold the risk of contracting TB (RR=3.1, 95%CI 2.27-4.26) (5), and also promoting the activation of a previously acquired latent TB infection. The macrophages are the main line of defense of the innate immune system against TB through phagocytosis, which generates reactive oxygen and nitrogen species and the release of inflammatory cytokines, promoting the death of the bacteria (6). However, in hosts with T2DM, hyperglycemia decreases the function of macrophages, causing defects in phagocytosis and chemotaxis, suppression of cytokines production such as Interleukin (IL)-10 and IL-12 and IFN- $\gamma$  by myeloid cells, and tumor necrosis factor-alpha (TNF- $\alpha$ ) by T cells (7).

In addition, the occurrence of the TB-T2DM binomial increases the risk of anti-TB treatment failure (RR=1.69, 95%CI 1.36 - 2.12), promotes relapse (RR=3.89, 95%CI 2.43 - 6.23) and death during treatment (RR=1.89, 95%CI 1.52 - 2.36) (5). Furthermore, patients with the TB-DMT2 binomial present a delay in the negativization of the follow-up smear microscopy, which induces a longer period of active infection and promotes TB transmission (7); this should imply a closer follow-up by health personnel and modification of traditional treatment protocol for these patients. In addition, the presence of the binomial increase the probability of developing drug-resistant TB (8,9) due to the reduction of the plasma concentration of anti-TB drugs (10), which can generate a positive selection of strains with resistance until they become the dominant population.

According to WHO, in 2019, 360,000 new TB cases (95%CI 120,000 - 740,000) accounted for T2DM, while approximately 15% of people with TB also had T2DM. This approximates 1.5 million people with TB and T2DM who require special care conditions and follow-up to optimize comorbidity management (11).

Considering the growing scenario of this syndemic, since 2011 (12), the WHO issued the first recommendations to develop a combined working group to consider the

particularities of both diseases and promote actions that help in the control and reduction of TB, with special emphasis on avoiding the emergence of drug-resistant forms. The recommendations focused on three main actions: i) establishing collaborative mechanisms between operational TB and T2DM programs, ii) detecting and managing TB in patients with T2DM, and iii) detecting and monitoring T2DM in TB patients.

Unfortunately, countries are not required to report information on the implementation of these actions or their actions against TB; because of this, in 2020, the WHO investigated the implementation of recommendations and monitoring of progress in TB-T2DM care in countries with high TB incidence (13). The review examined the scope of national policies and guidelines and paid special attention to national TB strategic plans (treatment guidelines and programmatic guidelines for managing drug-resistant TB, among others). From this review, it was estimated the number of countries that adopted the recommendations on screening and co-management of TB and T2DM in the respective national health programs. The findings showed that implementation was variable. In this regard, 22 countries collectively reported 47,041 new TB cases that underwent T2DM diagnosis, representing a median testing coverage rate of 55% (IQR: 13–92%).

In conclusion, it is recognized that the "End TB Strategy" objectives cannot be reached without intensifying research and innovation, especially in countries with high TB incidence, and now the influence of T2DM must be considered. Even if the actual priorities are centered on vaccines, improving diagnostic methods, and new anti-TB drugs and treatments (1). In this context, the commitment to address the global burden of TB-T2DM must not be ignored. The integrated approach to attend the binomial represents an opportunity to join efforts in diagnosing and caring for these two important pathologies, thereby optimizing the results of anti-TB treatment (8). Follow-up and detailed evaluation of joint strategies to address both diseases are essential to promote their implementation and to assess their impact; in this context, countries are required to establish collaborative activities between TB and T2DM programs and to monitor their success as part of surveillance activities, operational research, and cost-effectiveness analysis, but without forgetting the very particular characteristics of TB in patients with T2DM, and the need for closer surveillance and even personalized treatment, this is fundamental, if we really want to successfully address the issues established for the End TB strategy and the sustainable development goals (SDG-WHO).

#### Author contribution Statement

All authors reviewed the writing and approved the final version of the manuscript. All authors agreed to be responsible for all aspects of the work to ensure the accuracy and integrity of the published manuscript.

#### Ethics statement

The authors declare that the published work reflects an investigation and analysis carried out truthfully and completely.

#### Conflict of interest

The authors declare no conflict of interest.

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