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Tuberculosis: A Risk Factor Approach

Leonardo F. Jurado and Diana M. Palacios

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Abstract

One in three people in the world is infected with *Mycobacterium tuberculosis*, and 10% of infected individuals will develop the disease at any time in their lifetime. Today, despite the advances in diagnosis and treatment, tuberculosis (TB) remains as one of the biggest challenges in global public health, and low and middle-income countries are the most affected. The risk for developing the disease depends on endogenous, exogenous, and environmental factors. Among the most relevant conditions that could precipitate TB development are those that affect the host-immune response. HIV infection increase about 20 times the risk of TB, and other more common conditions, such as diabetes mellitus, malnutrition, and smoking, also contribute in a big way to the TB pandemic. Global TB control programs in order to achieve the disease control objectives must integrate strategies that have a direct impact on risk factors, not only at an individual level but also on a public health policy level. Here, we review some of the most important risk factors for the development of TB, as one of the most relevant ways for TB control.

Keywords: tuberculosis, risk factor, epidemiology, prevention, control

1. Introduction

Tuberculosis (TB) is a bacterial infectious disease caused by *Mycobacterium tuberculosis* complex organisms, it is an airborne-transmitted condition pathologically characterized by a necrotizing granulomatous response (**Figure 1**) that involves the lungs in 80% of cases, however any organ can be affected [1]. This disease probably emerged about 70,000 years ago, along with the modern-human being's migration from Africa [2]. An estimated of 1 billion people have died of TB in the last two centuries, and now represents one of the biggest public health problems worldwide [3].

Figure 1. This illustration represents a tuberculous granuloma at its most basic way. It is a compact, dynamic and organized aggregate of epithelioid macrophages, and these cells usually fuse into multinucleated giant cells or differentiate into foam cells characterized by lipid accumulation. *M. tuberculosis* is usually present in the central necrotic area in which dead and dying cells are present. Many other cell types are also infiltrating the granuloma (neutrophils, dendritic cells, B and T lymphocytes, natural killer cells and fibroblasts) (original illustration by Jurado LF).

One third of world population is latently infected with *M. tuberculosis*, but only 10% of infected people will develop active disease during their live, half during the first 2 years after infection, and the remainder at any moment of their lifetime [4]. In most infected individuals, the progression is contained by the immune system. In 2013, an estimated 9 million new TB cases were reported globally, equivalent to 126 cases per 100,000 population, with more than 60% of the ill people living in 22 countries (considered as high-burden countries). However, according to WHO estimations during the same year around 3.3 million cases were missed (not reported or undiagnosed), accounting for a detection rate of only around 64%. The global HIV-coinfection proportion was 13% (1.1 million people), and HIV-associated TB deaths accounted for 25% of the total number of TB deaths [5].

The pathogenic mechanisms that determine active-TB progression are a multiple-stage game before and after the infection event, where the host-immune response integrity is one of the most relevant performers [6]. The infected individual may either rapidly progress to disease (primary progressive disease), may develop a particular status called latent TB infection, or may be able to kill the organism [7]. The occurrence of one of these scenarios depends on the determinants of host-immune response and the infection-stage in each individual. Most of the immune determinants that drive this pandemic constitute risk factors, which could be modified in order to impact positively on global TB control.

Among the relevant risk factors for TB, HIV infection is the most important, however, at the population level, diabetes mellitus (DM), malnutrition, tobacco smoking, and even immuno-suppressive drugs, which are present in a larger section of the population than HIV infection, can represent a bigger impact on TB epidemiology [8, 9]. This chapter aims to summarize some of the most relevant risk factors for TB, focusing on general interventions for disease control.

2. Human immunodeficiency virus and TB coinfection

HIV coinfection is the most important immunosuppressive condition for developing active TB [10]. HIV infection substantially increases the possibility of TB reactivation from latent infection [11], and in the same way contributes to rapid TB progression after infection with *M. tuberculosis* [12, 13]. According to WHO estimations, people living with HIV (PLWHIV) latently TB-infected, have a 26-fold-higher risk of disease progression than those with no HIV [14]. Thus, HIV and TB coinfection configure a lethal synergy, where HIV markedly increases susceptibility for TB and exacerbates the severity of the disease, while TB accelerates HIV replication and its associated morbidity and mortality outcomes [10, 15].

In 2012, 34.5 million people were living with HIV worldwide [16]. This epidemic affects every country in the world, but the disease burden is highest in developing countries, among which the sub-Saharan Africa region is the most affected, where 69% of worldwide infected people live [16]. Due to the advances on therapy and prevention strategies, deaths related to HIV have decreased substantially over the past years, but reductions in TB-related deaths have not kept pace, a sample of this, in 2014 TB overpasses HIV as the leading cause of global infectious-related mortality [10].

Among 9.6 million new TB cases reported worldwide in 2014, 12% (1.2 million) were also HIV positive, and of the 1.5 million who died from TB, 33% (4,00,000) were HIV coinfected, thus TB constitutes main mortality cause in PLWHIV [14]. Evidently, the TB incidence and TB-related mortality are strengthened by HIV burden and represent a real public health challenge in areas where HIV and poverty coexist [10].

It is clear that antiretroviral therapy (ART) reduces rapidly and substantially TB incidence in PLWHIV, and this is true both in high and low endemic TB areas [17–19]. Nevertheless, even in people under ART, the risk of TB remains high compared with the general population. For HIV-negative people with latent TB infection (LTBI), the lifetime risk of developing TB rounds 5–10% [20, 21], but in the case of PLWHIV the annual risk of reactivation is 3–16% [22], with the higher risk of TB disease almost immediately after HIV infection, even with normal CD4 cell levels [10].

The immunologic control of TB is an intricate phenomenon that involves multiple pathways, cellular lines, and host-pathogen interactions [6]. In PLWHIV, macrophages present a phenotype with altered activity of molecules like iNOS and TNFα, which is reflected as incapacity for *M. tuberculosis* killing [23]. The histopathologic features in PLWHIV who develop TB, correlate and depend on the level of immunosuppression, individuals with apparently normal immune response present typical granulomas (**Figure 1**), these well-structured aggregates may break down, giving way to cavitary disease and bacilli expectoration, but as the immunodeficiency advance, granulomas are poorly formed or even absent, so the cavitary form is less frequent, with sputum smears likely negative [24].

In like manner that HIV infection increases the TB risk and its related complications, TB also affects HIV infection outcomes. In a study conducted by Lawn et al. [25], HIV patients on

ART who develop TB, presented more alterations on CD4 counts than individuals who never developed TB. Studies have shown that TB associates with rapid progression to AIDS and higher death risk [26, 27] and TB also appears to induce viral replication and viral diversity via up regulating the host-immune response [15, 28].

As we previously exposed, PLWHIV have the higher risk of progression from latent to active TB disease, this possibility can be reduced using two fundamental strategies: adequate ART and prophylactic LTBI treatment [19, 29], studies support the use of both strategies even in patients with high CD4 counts [33]. Thus, it is highly recommended to provide ART to all HIV-infected people irrespective of CD4 count [17].

Considering the risk, all PLWHIV should be screened using TST for LTBI at the time of HIV diagnosis [30]. Once a patient has a positive result for LTBI, active disease must be ruled out, and preventive therapy offered. Among the preventive therapy options, two of the most accepted are: daily isoniazid 5 mg/kg (maximum 300 mg) for 9 months plus pyridoxine supplementation or once a week rifapentine plus isoniazid (900/900 mg) for 3 months (12 total doses) [31, 32]. These regimens can be used with nucleoside reverse transcriptase inhibitors and efavirenz [33], rifapentine cannot be administered together with protease inhibitors, but it could be offered with raltegravir [34].

3. Diabetes mellitus and TB comorbidity

The worldwide rising in type II diabetes mellitus prevalence constitutes one of the biggest challenges for TB control [35]; in fact, nowadays there are more individuals living with DM-TB comorbidity that HIV-TB coinfection [36]. This association has been recognized historically [37]; however, it became less evident in the 1950s, in part due to the development of insulin therapy for a DM and antibiotics for TB [35]. Since 1980 as the DM pandemic (prevalence increasing >20% in three decades) was more evident, many papers on the DM-TB association began to reemerge [35].

As a result of a sedentary lifestyle, changes in diet, population aging, and urbanization, the global DM prevalence by 2000 was 171 million people, and is predicted that this number reaches 642 million in 2040, considering that 80% of DM population live in low- and middle-income countries, where the TB situation is worst [38].

Biological evidence supports that DM induces a direct impairment on innate and adaptive immune responses, increasing TB susceptibility [8]. However, the DM case differs from other causes of immunological impairment like HIV infection or malnutrition, because DM response is more dysfunctional rather than dismissing, characterized by excessive and/or delayed responses against *M. tuberculosis* [39]. Investigations in humans and animals have shown altered production of cytokines as INF-γ and IL-17 that affects the T-cell immune response [40] and reduced chemotaxis of neutrophils [41].

According to multiple studies, at an individual level, people with DM have three times more risk of developing TB, and two-fold increase in adverse TB therapy outcomes [8]. A systematic review of 13 studies reported that DM increases three times the risk of developing TB,

(relative risk 3.11; 95% IC 2.27 – 4.26) [42], notwithstanding, this epidemiological aspect is the best characterized in the DM-TB association, a wide variation between studies is observed, with risk ratios around 0.99 and 7.83 [39], which evidences the difficulty of studying DM-TB relation, in part due the heterogeneity in the prevalence and other sociodemographic and cultural features of DM and TB in each part of the world. Besides, in the case of DM, the presence of other host characteristics as smoking, malnutrition, micro- and macrovascular compromise, can synergize and increase the TB risk [43].

The relevance of the DM-TB comorbidity is higher in low and middle-income countries, where both diseases are more prevalent. In fact, as reported by the WHO, of the 10 countries with more DM patients worldwide, six are also classified as high burden countries for TB (China, India, Brazil, Bangladesh, Indonesia, and Russia) [44]. During the last years, studies have marked differences in DM's frequency among patients with TB, from 36% in Mexico to 40 and 56% in the Pacific Islands and India, respectively [45–48].

Talking about the impact of DM in TB control, at the population level, the general attributable risk is 10–20%, and also a variation between different populations is observed, even in the same country, for example, in the United Kingdom, the general population risk rounds 10%, but rises 20% for Asian males [49], in countries like Mexico, where DM is endemic the general attributable risk is about 20% [50], and in the EU – Mexico border, 51% of the TB patients who are 35–60 years-old also have DM [45]. And even though the DM confers a notably lower risk compared with HIV, in certain populations where the HIV prevalence is low, the contribution of DM is more important than HIV infection [51].

Recently, an elegant study by Pan et al. [52], using models of dynamic TB transmission, esti-mated the potential effects of DM on TB epidemiology in 13 high burden countries, found that interrupting the rise in DM incidence, could prevent 6 million cases and 1.1 million deaths due TB in 2 decades. These findings show how beneficial for TB control would be an integral intervention on DM occurrence.

It is known that DM modifies the clinical presentation, disease-course and TB prognosis, and represents a risk factor for treatment-failure [35]. DM-TB patients (versus TB patients without DM) are more prone to develop sputum smear-positive TB, pulmonary TB (versus extrapul-monary), cavitary (versus noncavitary) at the moment of diagnosis, and in DM-TB patients the sputum smear conversion takes more time [53]. *Mycobacterium tuberculosis* infection induces a strong cell-mediated immune response that triggers a granulomatous response, which, according to recent investigations is a double-edged sword for the host [54], because although this phenomenon initially limits bacilli replication, the growing and rupture of these structures into the airways, facilitates not only the cavitary form of the disease but also, its sputum smear-positive presentation [44]. These findings, allows to postulate that DM-TB patients would be more infectious that TB-only patients.

Evidence from observational studies, have shown that DM comorbidity is related to adverse TB outcomes, as delays in sputum conversion, increased risk for treatment failures, relapse, death, and even reinfection [55]. Baker et al. [56] in a meta-analysis of recent DM-TB associa-tion studies found that the odds of dying of TB, or any other reason, was 2-fold higher [RR, 1.89; 95% CI, 1.52–2.36], and this risk rise to 4.95, when data was adjusted for age and potential

confounders, the same study also calculated a 4-fold risk of relapse for DM-TB individuals versus TB-only patients.

Considering this, the World Health Organization has argued that DM is a reemerging and an important risk factor for TB, which needs programmatically routed efforts to positively impact on TB control [57].

4. Malnutrition and TB

For centuries, the association between malnutrition and TB has been recognized. Nutritional supplementation with protein-rich foods for sick people was reported since the ancient Greece [58]. A classic report from Denmark reports high TB rates during the First World War, once food supplies were restored, TB rates were drastically reduced, while persisting high in neighboring countries where shortages persisted [59].

During the pre-chemotherapy era, the only treatment offered to TB patients consisted in a nutritional plan, resting, and sun therapy. The pharmacological advances of the past century, with the development of streptomycin and isoniazid, replaced nutritional therapy as the focus of anti-TB treatment, however, considering the high rates of TB in areas where malnutrition is endemic, in the last decades, an interest in this association has reemerged [60].

According to estimations of the United Nations, by 2015 there were 795 million undernourished, comprising around 13% of the population of low- and middle-income countries, with the highest prevalence in Sub-Saharan Africa and Southern Asia [61]. In the developing countries, protein-calorie malnutrition is the most frequent form of under nutrition; however, specific micronutrient deficiencies are also common [60]. In addition, the advent of climate change, population growth, the HIV pandemic, and economic inequality, have originated a negative impact on food and nutritional insecurity, and malnutrition rates, constituting one of the most challenging public health problems worldwide [43]. The general way to epidemiologically defining malnutrition is the body mass index (BMI), and malnutrition constitutes a well-known risk factor not only for TB development, but also for poor response to antibiotic treatment and TB-related complications [59].

A biologically plausible association between TB and malnutrition clearly exist; animal studies have shown that PCM affects the immune mechanisms for TB control, among the impaired processes are the TNF, iNOS, and interferon γ production; it is also known that this phenomenon can be reversed thought protein supplementation [59, 62]. Active TB and HIV infection induce a 14 and 30% increment in the resting metabolic rate, respectively, which reflects the physiological cost of the immunologic mechanisms that are activated during these diseases [63]. These conditions aggravate even more the patient-immune impairment in the malnutrition setting [64].

Considering this, is essential that all newly diagnosed individuals with TB have a complete nutritional evaluation, and in the cases with a BMI under 18.8 a micro and macronutrients supplementation at least for the first 2 months of treatment, is strongly recommended [65]. Historical evidence supports the beneficial impact of social interventions, such as improving

housing conditions and nutritional interventions on TB epidemiology, therefore a well-planned wide intervention would impact positively on TB control.

5. Anti-TNF treatment and TB

People with immune-mediated inflammatory diseases, such as rheumatoid arthritis, systemic erythematous lupus, ankylosing spondylitis, inflammatory bowel disease, etc., also represent a high-risk group for developing TB, and this risk is even higher when they are treated with tumor necrosis factor α (TNF α) – antagonist [66, 67].

Different cells produce TNF, including macrophages, T cells, fibroblast, and keratinocytes. TNF is a molecule with a wide functional spectrum, plays a key role in immune response to infections, cancer etiology, and the physiopathology of many immune-mediated disorders [67]. It is also known that is important in the immune response against intracellular bacteria, and the physiology and integrity of granulomatous (**Figure 1**) TB-related response during LTBI, therefore its antagonism associates with TB progression [6].

During the past two decades, TNF antagonists have been successfully used for the treatment of inflammatory diseases, when patients do not respond to conventional therapy [67]. In the United States, using national surveillance data, found that TB incidence in AR patients increased from 6.2 per 100,000 people to 144 per 100,000 in who received infliximab and 35 per 100,000 for etanercept-treated individuals [69]. A Spanish study collected data from 71 information centers, with a total of 1540 patients receiving infliximab, estimated a TB incidence in 1893 per 100,000 people, compared with a previous reports incidence of 21 per 100,000 in the general population and 95 per 100,000 in AR patients without TNF treatment [70]. An important proportion of extrapulmonary TB is observed, and several reports have attributed differential risk for each TNF antagonist [68].

Most of the active TB cases in individuals treated with TNF antagonist correspond to reactivation from LTBI, when this occurs, generally happen concomitantly with the initiation of the TNF antagonist, nevertheless, also cases with long treatment periods, have been reported [67]. Therefore, screening for LTBI before any TNF inhibitor treatment initiation is mandatory, here, as in the case of other immunosuppressive conditions, such as HIV infection, both TST and IGRAs assays could be used, nowadays, there is not sufficient evidence to recommend one method over another, and considering this, an expert consensus, suggest using IGRAs or TST in people without history of BCG vaccination [71].

Once a patient has a positive result for LTBI, active disease must be ruled out, and preventive therapy offered. Among the preventive therapy options, two of the most accepted are: daily isoniazid 5 mg/kg (maximum 300 mg) for 9 months plus pyridoxine supplementation or a combined regimen with isoniazid and rifampicin for 3 months [69]. Multiple recommendations on delay periods between LTBI preventive chemotherapy and TNF antagonist have been proposed, ranging from starting both concurrently, to waiting even a month after finishing LTBI prophylaxis [67, 68], these decisions must always consider the patients clinical status.

In the cases when active TB is diagnosed during TNF antagonist treatment, there is no evidence that the length of anti-TB therapy needs to be prolonged, and evidence regarding the time for restarting TNF antagonist therapy is limited [72]; however, some international guidelines recommends starting TNF inhibitor at least when initial anti-TB phase is completed, while others recommend waiting until completing all TB treatment [68].

6. Smoking, alcoholism and TB

Globally, there are more than 1.5 billion smokers, the majority live in low- and middle-income countries, where, in addition, the per capita tobacco consumption is increasing continuously [73]. The prolonged exposure to tobacco smoke may directly affect the respiratory and systemic immune function, which can impair alveolar macrophage function by decreasing its TNF production [74]. Therefore, it is considered that smoking has an impact upon the susceptibility to TB development.

There is growing evidence that correlates smoking with TB disease; a cross-sectional study in Shanghai compared heavy smokers with nonsmokers and found that the odds of smokers were 2.2 times higher than nonsmokers [75]. The risk also seemed to be influenced by the amount smoked, and a study from the United States found that the greatest risk was for people who smoked for more than 30 years [76].

At a population level, exposure to tobacco smoke has a relevant impact on TB epidemiology; a Chinese modeling-study suggested that a complete cessation of smoking in that country would reduce the estimated TB incidence between 14 and 52% [77]. Considering this situation, smoking cessation as a public health strategy is a global priority.

Alcohol is one of the most abused substances in the world. By 2005 among people aged 15 years and older, the annual *per capita* consumption was 6 l [78] with the highest rates in high-income countries. Alcohol abuse is an important cause of immunological impairment, often associated with smoking and malnutrition, increasing its impact on public health [8].

There is considerable evidence to support the association between alcohol abuse and TB, even if it is independent of smoking [79]. Studies have shown that excessive alcohol consumption increases the risk of active TB development and other respiratory infections, a meta-analysis estimated a combined risk of 2.9 for active TB developing [25]. Studies have also shown higher rates of MDR-TB, TB relapse, and treatment failure in alcohol abusers [8].

7. Genetic susceptibility

Historically, infectious disease research has considered TB as a purely infectious condition. During the last decades, increasing evidence suggest that TB reflects the human genetic vulnerability [80]. Nevertheless, the precise significance and behavior of the genetic factors involved remains widely unknown, in part due to the complex game of infection, latency, and disease, which characterizes TB.

Recent findings have exposed two major principles: there is a main locus that controls most of the TB-resistance phenotypes, and there is evidence that severe forms of childhood TB are directly related with single-gene inborn errors (Mendelian Inheritance), meanwhile genetic association studies of adulthood-TB has shown limited success and reproducibility [81]. Clinical and epidemiological studies conducted since the past century has provided evidence that each step during infection and disease is strongly influenced by host genetic factors [82].

Familial studies aimed to investigate the human susceptibility to *M. tuberculosis* infection, have used TST and IGRAs responses as quantitative traits of resistance. Its results suggest that the initial infection-related events mostly depend on the IFNγ and TNF1 and its related cellular functions [83]. In regard to severe primary TB forms, during the last two decades, germ line mutations in seven autosomal and in two X-linked genes have been discovered in particular patients, further analysis have shown that these mutations result in an impairment of IFNγ- and IL12-related immunity [80, 84, 85].

Many questions of this field remain unanswered, the identification of the genetic variants underling the stages and forms of TB is critical for understanding TB pathogenesis. These findings could represent a formidable opportunity in the definition of prevention strategies, optimization of vaccines, the development of novel treatments and therefore TB control.

8. Final considerations

After this short review, it makes evident that a risk factor approach for TB control would have a huge impact on disease burden worldwide. Identification of LTBI along with prophylactic therapy and active disease surveillance constitute the most important tools for reducing the risk of TB and achieve favorable outcomes, especially in the high-risk groups previously described.

Over the last decades, the understanding of TB epidemiology behavior in the country, and at global level, has changed from an "exposure to bacteria" vision to a phenomenon where the host susceptibility plays a crucial role. Even although, HIV coinfection is the most potent risk factor, globally the most frequent conditions impacting on people immune function include malnutrition, Diabetes, smoking, and immunosuppressive drugs, and while at the individual level, these factors cause an apparently mild immunological impairment, its cumulative importance in a community needs much more attention. So, it is imperative for clinicians, researchers and policy makers, a better consideration, and understanding of these conditions as drivers of TB epidemiology, developing in this way more integrative strategies that could have a bigger impact on TB control.

Conflict of interest

The authors have no conflict of interest to declare.

Author details

Leonardo F. Jurado[1,3]* and Diana M. Palacios[1,2,3]

*Address all correspondence to: lfjuradoz@unal.edu.co

1 Pathology and Laboratories Department, Fundación Santa Fe de Bogotá University Hospital, Bogotá D.C., Colombia

2 School of Medicine, Los Andes University, Bogotá D.C., Colombia

3 Pathology Department, School of Medicine, National University of Colombia, Bogotá D.C., Colombia

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