

Type 2 Diabetes Mellitus as a Risk Factor for Tuberculosis

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Aim

To perform a review to summarize evidence for the impact of diabetes on tuberculosis outcomes.

Key Points

1. Diabetes mellitus (DM)-tuberculosis is associated with poor glycemic control in DM patients.
2. DM is the most common risk factor associated with tuberculosis (TB); TB is also the third cause of death due to non-communicable disease (NCD).
3. Screening for DM and if required, subsequent glycemic control may improve the outcome of TB treatment. Diabetes increases the risk of treatment failure and death combined, death and relapse in patients with TB.
4. DM has been associated with increased rates of TB, which may be partially explained by a blunted T cell-mediated immune response. Infection caused by mycobacteria that usually have the glycolipid lipoarabinomannan (LAM), soluble TB factor, and lipopeptid, are recognized by receptors on host cells.

Abbreviations: DM: Diabetes Mellitus; MTB: *Mycobacterium tuberculosis*; LTBI: Latent Tuberculosis Infection; PMNs: Polymorphonuclear Cells; IFN- γ : Interferon Gamma; Th1: Lymphocyte Th1; IL.- Interleukin

Introduction

Diabetes mellitus (DM) TB co-infection is associated with poor glycemic control in DM patients. Reactive hyperglycemia often accompanies chronic infections due to the associated pro-inflammatory state and release of counter-regulatory stress hormones such as epinephrine, cortisol and glucagon, all insulin antagonists.

Tuberculosis (TB) remains a major source of morbidity and mortality throughout the world; one-third of the world's population is estimated to be infected with *Mycobacterium tuberculosis* (MTB), whereby approximately nine million people develop the disease each year, and almost two million die annually as a result [1]. Epidemiological analyses have elucidated an association between DM and the development of TB [2,3].

Diabetes Mellitus

Diabetes mellitus (DM) is the most frequent chronic endocrine disorder; it is a non-transmissible pathological entity, characterized by disorders of the entire metabolism but particularly, of carbohydrate metabolism.

It is difficult to establish its prevalence in the general population, but it has been estimated at 1-6% depending on the diagnostic criteria used. Approximately 90% of cases are patients with non-insulin-dependent type 2 diabetes [4].

The impaired metabolism of glucose, lipids, and proteins in diabetes

leads to abnormalities in the macro- and micro-vascular circulation that are in turn, associated with the five classic complications of the disease, i.e. retinopathy, neuropathy, nephropathy, cardiovascular complications, and delayed wound-healing [5].

Classification

There are two main types of diabetes, insulin-dependent (type 1) diabetes and non-insulin-dependent (type 2) diabetes. Despite their designations, this classification does not solely depend on the need for exogenous insulin since it can sometimes also be required by type 2 diabetes patients.

Etiology and Pathogenesis

The following two mechanisms have been proposed to explain the classic complications of diabetes [4]. 1) Polyol pathway. According to this theory, glucose is converted into sorbitol by the action of aldose reductase, which is implicated as the toxin at the root of almost all complications. 2) Production of advanced glycosylation end-products (AGE).

This second theory proposes that glucose binds to proteins, lipids, and nucleic acids, giving rise to AGEs that alter their functions. Thus, the binding of glucose to hemoglobin, collagen, or albumin leads to complications dependent on the organ in which the AGEs are deposited (e.g., kidney, nervous system, vascular system or retina, among others).

The Impact of Diabetes on TB

The WHO has identified DM as a global epidemic, mostly affecting low and middle income countries where 80% of all deaths due to DM occur and about 10% of global TB cases are linked to diabetes [6]. Simultaneously, TB continues to be a major cause of death worldwide despite the fact that the epidemic appears to be on the verge of declining [7]. The global burden of disease due to DM and TB is immense. In 2010, there were an estimated 285 million people living with DM. In 2011, the International Diabetes Federation (IDF) estimated that about 366 million people worldwide had DM, a number which is expected

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to grow to at least 439 million by the year 2030, with approximately 4 million deaths (International Diabetes Federation 2009). Eighty percent (80%) of these people live in low and middle income countries where tuberculosis (TB) is highly prevalent [8]. In 2007, there were an estimated 14.4 million people living with TB, 9.2 million new cases and 1.7 million deaths (WHO 2009) [9].

The risk of progression from exposure to the TB bacilli to the development of active disease is a two-stage process governed by both exogenous and endogenous risk factors. Exogenous factors play a key role in accentuating the progression from exposure to infection among which the bacillary load in the sputum and the proximity of an individual to an infectious TB case are key factors. Similarly endogenous factors lead in progression from infection to active TB disease. The key risk factors are: 1) Factors related to the index case; 2) Factors related to the individual; 3) Socioeconomic and behavioural factors; 4) Demographic (ethnic) factors and 5) Health System Issues [10].

A study was performed in Ethiopia in smear positive pulmonary TB among diabetic patients, 52% were males and 48% were females [11]. It has been reported that patients with TB and diabetes are older, more likely to have haemoptysis, pulmonary cavitations, be smear positive at diagnosis, and remain positive at the end of the first or second month of treatment [12]. Diabetes is one of the most serious health challenges facing Native Americans, resulting in significant morbidity and mortality rates. In fact, Native Americans have the highest prevalence of T2D in the world, and rates are increasing at almost epidemic proportions. Although the TB rate among Native Americans is declining, it continues to disproportionately affect this population in the number of cases and severity of disease. The American Lung Association reported that in 1998, the incidence rate of tuberculosis among Native Americans was 12.6 cases per 100,000 persons, which is more than five times the rate for non-Hispanic whites (2.3) [13].

It has provided novel evidence of status and relationship between appetite-related hormones, inflammatory cytokines and body mass index (BMI) in TB patients with or without T2DM. Possible abnormalities in leptin and ghrelin regulation may be associated with the development of poor nutrition (low BMI) during the inflammatory response in TB patients with or without T2DM. TB patients with T2DM may have more complex and different pathogenesis compared to TB patients only [14]. Individuals in lower income countries, where the majority of the world's TB burden is located, are more likely to report symptoms of active TB disease if they also reported a prior diagnosis of T2DM. At the population level, between the 1990s and early 2000s, TB prevalence and incidence were more likely to increase in countries in which diabetes prevalence increased, conditioning on base year, per-capita gross domestic product (GDP) [15]. It has been suggested that patients with DM and severe vitamin D deficiency are more susceptible to develop tubercular infection than those having normal or low vitamin D status [16]. On the other hand, the increased prevalence of T2DM in countries endemic for TB poses a serious complication in the clinical management of this major infectious disease. Moreover, patients with coincident TB-T2DM exhibited increased plasma levels of tissue inhibitor of metalloproteinase-4 (TIMP-4) and elevated peripheral blood neutrophil counts which when considered together with heme oxygenase-1 (HO-1) resulted in increased power to discriminate diabetic from non-diabetic individuals with active TB [17].

Currently, both TB and DM are of great public health importance globally and especially in Sub-Saharan Africa (SSA) due to the converging epidemics of both communicable and non-communicable diseases. With a TB prevalence rate of 193/100,000 in 2010, Uganda

is one of the TB high burden countries in SSA [18]. Recent evidence advocates bi-directional screening and care of TB and DM patients, since both entities adversely affect one another and there is currently no plausible evidence supporting the strong association between DM and TB [19]. Diabetic patients have impaired cell-mediated immunity, renal failure, micronutrient deficiency and pulmonary microangiopathy, all of which increase their propensity to develop TB.

Some of the knowledge gaps and research requirements on the association between these two diseases have recently been identified [9,20]. Since 1995, a population-based prospective study of pulmonary TB in Southern Mexico where almost one-third of TB patients have been previously diagnosed with DM is being conducted [2]. The increasing co-occurrence of TB and DM is a clear case in point, especially in countries with rapidly emerging economies such as India and China, and that has resulted in the confluence of two pandemics—one communicable and another non-communicable [21].

The convergence of these two epidemics may lead to an increased incidence of TB, especially in low and middle-income countries with increasing numbers of people with DM and associated TB. DM almost triples the risk of developing TB [22] in areas such as the border population of South Texas and Mexico known for its high prevalence of DM, and where self-reported DM is the most common risk factor associated with TB development [23].

Among patients afflicted with both TB and DM, diabetes is reported to be associated with poor TB treatment outcomes [3,24]; however, a systematic analysis to clarify and quantify the association between DM and TB outcomes, including persistence of sputum culture positivity, treatment failure, death and relapse, has not been performed [20]. This systematic review of the impact of DM on TB treatment outcomes has determined that DM increases the risk of the combined outcome of treatment failure and death, death, and relapse. The risk of death has been reported to be 6.5–6.7 times higher in TB patients with DM. The question of TB preventive therapy may only be answered with a randomized controlled trial, an expensive and difficult to conduct proposal. A study from Kerala, India showed that non-drug resistant TB patients with DM were more likely to fail first-line TB treatment when compared with patients without DM [25]. Screening and attention to better DM control might be a more cost-effective way of preventing TB and reducing other DM complications [26]. Routine screening of TB patients for DM using HbA1c yielded a large number of DM cases and offered earlier management opportunities that could improve TB and DM outcomes. However, the most cost-effective ways of screening DM need to be established by further operational research [27].

Major efforts should be directed at preventing tuberculosis in patients who are at risk for diabetes (Table 1).

Diabetes as a Risk Factor for TB

Studies from different parts of the world has shown that 5-30%

Genetic susceptibility
Family history of diabetes mellitus
Previous gestational diabetes
Dyslipidemia
Infertility, hirsutism
Obesity
Smoking
Environmental factors

Table 1: Risk factors for diabetes.

of patients with TB have concomitant DM [2,28,29] and available evidence indicates that DM is a risk factor for the development of TB. Data from the 1930s reported that patients with DM had a three to four-fold increased risk of developing TB [30,31].

TB is the third cause of death among subjects with non-communicable diseases (NCD), and among the NCD, DM is one of the most important [32,33]. The relationship between diabetes and TB has already been the subject of many investigations but the association between these two diseases is not fully understood [24,26,34].

HIV is by far the strongest risk factor for TB at an individual level, but DM may be the most important at the population level. For example in India, a recent study estimated that DM accounts for 14.8% of pulmonary TB cases, while HIV infection accounts for 3.4% of cases [22]. Diabetes triples the risk of TB by predisposing to both primary and reactivation TB [24]. A prospective cohort study showed that patients with DM and TB have more severe clinical manifestations, delayed sputum conversion and a higher probability of treatment failure, recurrence and relapse. Using molecular tools, subsequent TB episodes among patients with DM have been shown to be due to bacteria with the same genotype or to reinfection with bacteria with a different genotype. DM has also been proven to exacerbate the clinical course of TB. Given the absence of international guidelines on the joint management and control of TB and DM, national programs need to establish a coordinated response to these two diseases at both the organizational and clinical levels [35]. In this same population, about 30% of TB cases can also be attributed to diabetes [36]. Among Tanzanian patients, a study found that the majority of TB patients with diabetes were young and lean [37].

The presence of DM alone does not justify screening or treatment of latent TB infection (LTBI). However, when combined with other risk factors for TB, the presence of DM may be sufficient to justify screening and treatment of LTBI, even in a low TB incidence setting [38].

The gene *HK2* encodes hexokinase 2, a critical mediator of aerobic glycolysis. Aerobic glycolysis is the unique energy source for macrophages. The gene *CD28* encodes T-cell *CD28* surface antigen. The Th1 response plays a key role in activating macrophages in immune responses against TB. Genes *HK2* and *CD28* appear to be the potential culprits in the diabetes-associated increased susceptibility to TB [39].

On the other hand, distribution of IL-10 gene polymorphisms appears to have an ethnic distribution, because its frequency varies depending on the population studied, in addition to its known association with the major histocompatibility complex (MHC). Our working group, recently described that the IL-10 (-592 A/A and -592 C/C) polymorphism were found in a greater proportion in a group of patients with T2D and TB than in healthy subjects [40].

Effect of DM on the Clinical Presentation of TB

The question of whether DM affects the clinical presentation of TB has been previously addressed but there is no evidence that DM is preferentially associated neither with the so-called “primary TB” nor with “reactivation tuberculosis” [2].

Diabetic TB patients are usually 10-20 years older than those without DM, since type 2 DM (T2DM) usually develops in an older population. In addition, compared to non-DM patients, TB patients with DM usually have a higher body weight before initiating treatment and even more so after treatment [41]. Rifampicin hampers glycemic control, calling for the use of higher doses of sulfonylureas and

thiazolidinediones (TZDs). These may not be effective and other hypoglycemic drugs should be considered [42].

On the other hand, TB and diabetes are often associated with malnutrition. TB patients frequently suffer from deficiencies in nutrients, such as vitamins A and D, which are fundamental to the integrity of the immune response, especially the host's immune response against *Mycobacterium*. Furthermore, vitamins play an important role in glucose metabolism. Vitamin D also regulates β cell function in pancreatic islets, insulin activity and the levels of systemic inflammation [43].

Likewise, the significant clinical predictor associated with DM in tuberculosis patients is an elevated mean serum alanine aminotransferase concentration [44].

The TB Directly Observed Treatment, Short-course (DOTS) Model for DM Management

The concept of using components of the TB ‘DOTS Model’ for managing DM has been previously proposed [45]; diabetes clinics in urban areas in high-burden countries need to pilot and evaluate this approach through operational research, and particularly, assess whether quarterly cohort reporting of incident cases, cumulative outcomes, complications and survival analysis can lead to better management and care, more rational drug predictions and uninterrupted drug supplies [46].

Immune Response Implications in Tuberculosis

Mycobacteria usually possess the glycolipid lipoarabinomannan (LAM), soluble TB factor, and lipopeptides recognized by host cell receptors [47]. These components are known as pathogen-associated molecular patterns (PAMPs) and the immune cell receptors with which they interact are known as pattern recognition receptors (PRR).

Host response to MTB

MTB is a very successful human pathogen that can persist and survive in the host in spite of an intense immune response. It has been currently shown that many host-derived immune factors are involved in the mounting of a protective immune response against MTB. Components such as T lymphocytes (TL) that are fundamentally responsible for cellular immune responses (via Th1 lymphocyte activation), cytokines (such as interferon- γ (IFN γ)), interleukin-12 (IL-12), Tumor Necrosis Factor α (TNF- α), IL-6, IL-2, etc.), antigen-presenting cells (macrophages and dendritic cells), signaling proteins (co-stimulatory molecules, transcription factors), all play a pivotal role in the regulation and activation of TL against the *Mycobacterium* and all display key potential elements that may modulate the host's immune response. The functions of each component of immune response activation against *mycobacteria* have not been completely elucidated, although it appears that it may be different in acute vs. chronic infection. It is thus crucial to understand the interaction between this pathogen and the host's immune response in order to successfully contribute to the design of new and effective vaccines or control the microorganism's infectivity.

The importance of the innate immune response has currently peaked in terms of infectious disease; tuberculosis is no exception. We have yet to understand why some individuals that have been exposed to MTB do not develop the infection [48].

Immune response against MTB

From a synthesized immunological point of view, the initial MTB

infection in the host compromises his innate immunity, first at the alveolar macrophage level, the cell responsible for MTB phagocytosis after its recognition via its mannose receptors and complement; once other processes have been activated and other phagocytic cells such as dendritic cells, have been engaged, processed MTB fragments are presented to a great number of host cell receptors such as Toll-like receptors (TLR) and specifically, TLR2/1/6/9 [49]. The host's innate immune recognition of MTB leads to cellular activation and the production of pro-inflammatory chemokines and cytokines that in turn, recruit inflammatory cells such as T and NK lymphocytes and neutrophils to the infection site in order to coordinate the adaptive immune response. Once MTB phagocytosis is initiated by alveolar macrophages, a non-specific local inflammatory response develops and most of its mediators such as IL-1 β , IL-12, TNF- α , IL-15, IL-18 etc. are produced by macrophages or dendritic cells; however, IFN- γ is secreted by NK and T lymphocytes [48]. This phase demonstrates the delicate balance between all immune response factors, one in which a preponderance of IL-12 in the inflammatory milieu would favor a Th1 response over a Th0 (secreting IL-2, TNF- β , IFN- γ , among others), a characteristic cellular immune response; on the other hand, if IL-4 predominates, the development of a Th2 response would be favored (secreting IL-4, IL-5, IL-6, IL-10, among other cytokines) and lead to an antibody-producing immune response. However, the protective host immune response in tuberculosis is Th1 since the production of IFN- γ by CD4⁺ and CD8⁺ T cells is critical to disease control [50] (Figure 1).

Although a strong humoral immune response is present in tuberculosis, the role of B lymphocytes is not well-defined since individuals with B lymphocyte activation abnormalities are not more susceptible to TB [51].

This is evident on the basis that dendritic cells obtained from healthy individuals produce IFN- γ in response to stimulation with BCG via a TLR2-dependent mechanism [52].

To date, the previously described initial response determines either MTB local growth or infection containment. It is also evident

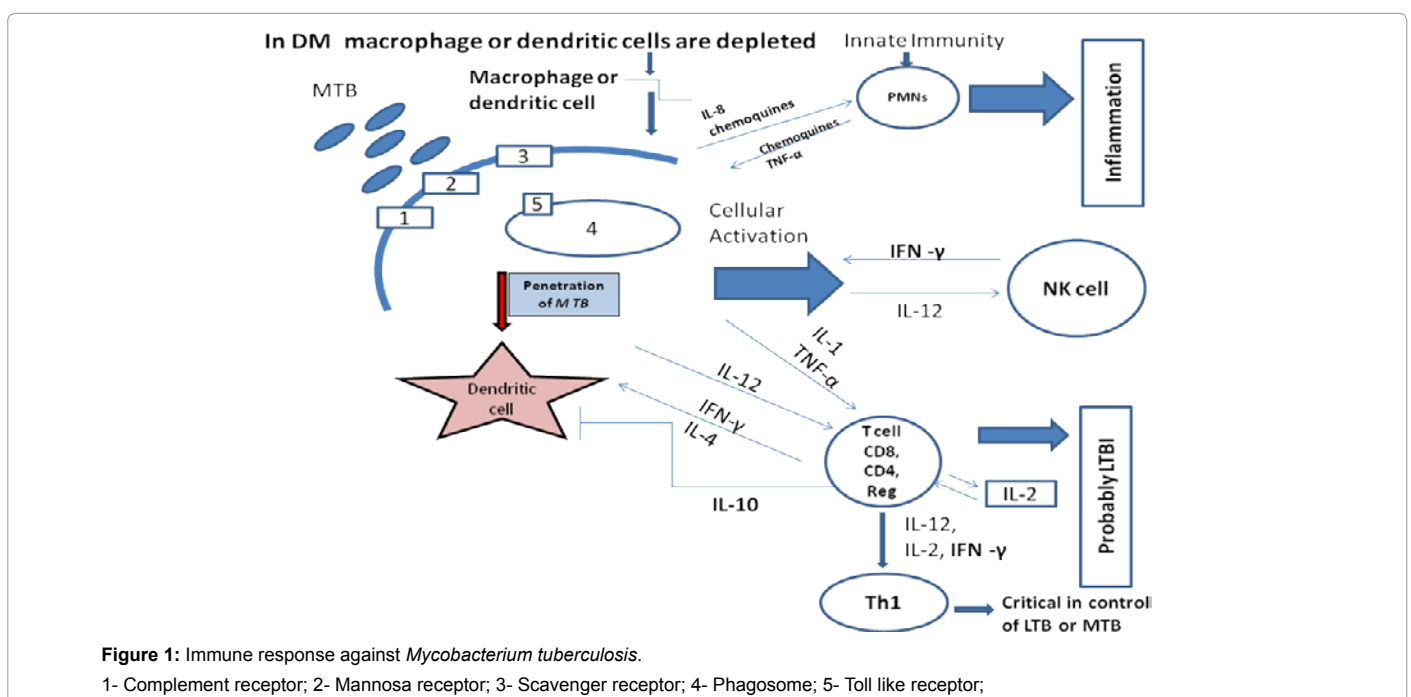
that phagocytic cells play a critical role in the initiation of the local inflammatory response as well as cell-mediated immunity.

Patients with severe, combined immunodeficiencies develop disseminated or fatal BCG infections and patients on immunosuppressive therapy compromising T lymphocyte function are at greater risk of developing mycobacterial disease; as previously described, this is reflected in diabetes, a disease in which patients easily develop infectious processes that may become severe and that underscores the relevance of the host's immune response in the maintenance of an infection-free milieu.

Host immune response in TB

In order to conclude this brief outline of the host's immune response to MTB infection, a primarily inflammatory response that activates cellular immunity, we must mention that Th1 and Th17 populations are reciprocally regulated; that is, the Th1 population acts as an anti-inflammatory brake, limiting the damage caused by Th17 cells [53]. Moreover, the stimuli inducing the generation of Th17 and T regulator cells are mutually exclusive. TGF- β acts as a critical regulator of Th17 cell-mediated tissue damage in collaboration with IL-6 as well as an activator of T_{reg} cells in the absence of IL-6 [53].

During the immune response against MTB, different lymphocyte populations are activated including Th1, Th2, Th17, Th22, T_{reg} and multifunctional T cells among others; these are the result of virgin T cell differentiation mediated by the induction of cytokines that activate transcription factors at the gene level. Considering the cytokines required to differentiate the various Th sub-populations, it has been suggested that during a stationary stage, TGF- β may favor the generation of inducible T_{reg} lymphocytes that suppress inflammation and prevent the development of autoimmune phenomena. However after infection, IL-6 is produced by the innate immune system and inhibits the generation of T_{reg} Lymphocytes and in conjunction with TGF- β , induces the differentiation of Th17 cells while IFN- γ induces the differentiation of Th1 cells. Therefore, Th1 and to a lesser extent Th17



responses, are required reflecting the key role of IL-12, IFN- γ y TNF- α , IL-17 and IL-23 in the induction and maintenance of a protective immune response against TB [54]; it has been shown that Th1 and Th17 activity increases in tuberculous multifocal lymphadenitis suggesting that more than likely, the Th1 and Th17 cell responses in tuberculosis correlate more with disease severity than with the degree of protective immunity [55].

Different host response levels to TB

More than likely and based on what was previously described we know that a minority of individuals infected with MTB will develop clinical disease. In general terms, 90% of them will maintain the bacillus in a lifelong latent state because of their immune system responses. Five percent (5%) will develop primary progressive pulmonary tuberculosis and another 5% will develop the disease late in life, a condition known as reactivation or post-primary human pulmonary tuberculosis (PTB) [56].

T2DM and MTB Infection

T2DM is an important risk factor for the development of active PTB although the immune mechanisms fostering it remain to be further explored. The influence of sub-optimally controlled diabetes specifically on Th1 and Th17 cells, has not been thoroughly examined although some data reveal that TB in T2DM patients is characterized by an increase in the numbers of Th1 and Th17 cells, reflecting an abnormality in the immune response to TB; this in turn, leads to partial induction of the Th1 and Th17 sub-sets that may perhaps mediate cellular responses that further immune-mediated pathology in MTB infection [57].

Although the biologic basis explaining the increased susceptibility to TB in diabetic patients remains to be elucidated, perhaps chronic hyperglycemia leads to an immunocompromised state that facilitates the progression of tuberculosis to an active phase. An *in vitro* system has been developed that can detect differences in the immune response to TB in diabetic patients and that has allowed the determination that the most sensitive predictor among all detectable differences, is chronic hyperglycemia that leads to altered immune responses to MTB [58].

An imbalance in this delicate immune system regulation network including that of cells and mediators, alters the body's homeostasis and even the innate immune system may contribute to the development of T2DM per se [59].

Further studies are necessary in order to fully understand the effect of chronic hyperglycemia on the immune response as well as the increased susceptibility of diabetic patients to TB, an inflammatory immune process involving the innate immune response and associated to T2DM.

Conclusions

Patients with T2DM are at an increased risk of developing TB. The disease itself compromises the prevention and treatment of infections in diabetic patients. Therefore, studies on the management of TB in patients with DM are warranted.

Diabetes is associated with an increased risk of the combined outcomes of treatment failure and death during TB treatment as well as relapse. Considering the increasing disease burden of DM, particularly in areas with highly prevalent TB, TB control programs will need to expand their efforts and focus on treating and monitoring patients with DM and TB disease.

DM has been associated with increased rates of TB, which may be partially explained by a decreased T cell-mediated immune response. Impaired neutrophil function has also been documented in diabetes, although this topic is currently being debated.

It is very important to note that in diabetes the number of macrophages is lower than for people without diabetes, whereby the activation of the cellular immune response is defective and hence the control of infection that is essentially the Th1 cells. In the figure shown recognition of MTB by specific receptors and TLRs activated signaling pathways that lead to cell activation and cytokine production. The activated macrophages or dendritic cells secrete cytokines and chemokines that activate macrophages, T cells, NK cells and neutrophils, producing inflammation. The T cells and NK cells producing IFN- γ with other cytokines that induces activation of macrophages contributing to control of MTB or LTBI.

Author Contributions

Both authors made substantial contributions to this paper.

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