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HYPERGLYCEMIA: A RISK FACTOR FOR TUBERCULOSIS

Harish Kumar,* Poonam Thakur, Monika Chauhan and Vivek Sharma
Govt. College of Pharmacy, Rohru, Distt Shimla-171207, Himachal Pradesh, India
***Corresponding Author: Harish Kumar**
Email: harish.verma1611@gmail.com

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ABSTRACT

Tuberculosis (TB) is a chronic and serious infection which affects endocrine function of pancreas, adrenal, thyroid and pituitary, warranting exogenous insulin and other hormone replacements. TB can be asymptomatic or latent for whole life unless a concurrent pathologic condition like hyperglycemia is not present. TB is thought to exacerbate and worsen the outcome for diabetes mellitus (DM) and vice versa is also true. TB is so aptly described as a complication of DM as people with diabetes are more susceptible to infections due to their immuno-compromised status with reactivation of older foci of TB rather than through fresh contact. They often exhibit lower lobe involvement more commonly than in non-diabetics. Various studies have shown that 5-30% of patients with TB have DM as well. T cells, Interferon's, interleukins are various mediators and autophagy, chemotaxis and antigen presentation are the various complicated pathways that precisely interlinks diabetes and tuberculosis. The present work advocates screening for diabetes while individualizing drug therapy in patient with tuberculosis.

Keywords: Chemotaxis, Diabetes, Inteleukins, Tuberculosis

INTRODUCTION

As per the reports, around 1.5 million deaths due to TB and 7.8 million TB infections could be prevented if diabetes could be reduced by 35% globally.[1] One-third of the world's population have TB infection and about 9.4 million new cases of TB are diagnosed every year.[2] The burden of TB is highest in Asia and Africa, with India and China together accounting for almost 40% of the world's TB cases. With the rising prevalence of Diabetes mellitus (DM) in countries where TB is endemic, there has been renewed interest in the question of whether DM increases the risk of active TB and thus add to the worldwide burden of disease.[3] Although the current preventive efforts against the spread of TB have lowered its incidence, the problem is far from over. Therefore the focus of research has now shifted to the previously untargeted risk factors involved in the spread of TB. Poorly controlled diabetes can lead to multiple complications, including vascular disease, neuropathy and increased susceptibility to infections. Diabetes might also lead to increased susceptibility to disease caused by tuberculosis via multiple mechanisms that include factors

directly related to hyperglycaemia and cellular insulinopenia, as well as indirect effects on macrophage and lymphocyte function, leading to diminished ability to contain the organism.[4]

DM is a chronic condition that occurs when the pancreatic beta cells unable to produce enough insulin or body cannot effectively utilize insulin, resulting in high levels of glucose in the blood stream (hyperglycaemia) causing tissue damage over the period of time. Despite availability of several effective regimens and laudable progress, the disease continues to be a major public health threat. There are three common forms of DM that account for the majority of cases: Type 1, Type 2 and Type 3 (AD related). In 2013, it was estimated that 382 million people worldwide had DM, with 90% or more having Type 2 diseases. About 80% of these people live in low- and middle-income countries and if the trends of the past 10–15 years continue with 10 million new cases occurring every year, an estimated 592 million people will have DM by 2035[5]. DM impairs the immunity of individual and therefore is an independent risk factor for infections such as TB[6-7].

TB infection occurs when a susceptible person inhales droplets containing Mycobacterium tuberculosis bacteria, which travel through the respiratory tract to the alveoli. In most patients, host's immune response limits the propagation of TB infection, resulting in an asymptomatic, non-transmissible localized infection that may remain in the body for many years, if not forever. One in three people in the world has latent tuberculosis.[8] Exposure to the bacterium, Mycobacterium tuberculosis leads to the active form of TB in 5-10% of infected individuals and the development of active TB is often the result of a known TB risk factor, either intrinsic to the individual or acquired as a communicable or non-communicable disease. An association between diabetes and TB has long been recognized, but only recently was diabetes confirmed to increase the risk of developing active TB disease. The convergence of a growing diabetes epidemic on regions with endemic TB has positioned diabetes as an emerging global threat to TB control.

The overall risk of TB in persons with DM is three times higher than in the general population.[9] Both type 1 and type 2 DM increase the risk of TB, but as type 2 disease accounts for 90% or more of the global cases of DM, the public health burden of co-morbid disease from type 2 DM dominates the interaction[5] yet, type 1 DM carries a stronger risk of contracting TB. Other risk factors for developing TB in people with type 1 DM include a low body weight, young age, and poor glycemic control.

The reasons for the increased risk of TB in DM are not clear but dysfunctional and exaggerated T-cell and cytokine responses are important mediators in concurrent emergence of two epidemics. The biological and immunological mechanisms contributing to them are the subject of intensive basic science research. Whatever the molecular mechanisms, there is also growing evidence that patients with uncontrolled hyperglycaemia are at higher risk for TB than those with controlled blood glucose levels suggesting that hyperglycaemia is an important determinant in this interaction.[10-12]

Immunity, DM and TB: An interplay of T cells and Interleukins

In 2013 investigators from the World Diabetes Foundation revealed that DM increases the risk for active TB by 2 to 3 fold, with the highest risk being in the individuals with the poorer glucose control. Diabetic patients are not only more susceptible to infection but when infections do occur they are more severe, as the diabetic is a comprised host. In UK, tuberculosis is quoted first

among common infections in diabetes, although the last UK publication on increased frequency of tuberculosis in diabetics appeared in 1948.

People affected by DM are at higher risk of acquiring other co morbidities due to the immune depressed state that the illness present on the face of metabolic derangements of DM that can predispose the individual for associated illness. It is well known that individuals with good control of their DM are less likely to acquire infections, including TB.

DM is a clinical syndrome and apart from the classical micro and macrovascular complications of the disease, DM has been associated with reduced T cell and neutrophil functional activity as well as humoral immunity disorders [13,14] which in turn compromises the protective role that cellular immune response plays against TB. Consequently, DM patients show increased susceptibility to infections, notably TB, compared to individuals without DM.[15]

IFN-γ, the main T-helper-1 (Th1) cytokine and the main mediator of protective immunity against TB is adversely affected especially in high-glucose conditions. Consequently, T cell growth, function and proliferation is affected, further compromising effective mononuclear phagocytes and NK cell mediated response to tuberculosis.[8] The Th1 cytokine interferon (IFN)-γ is considered a principal mediator of protective immunity against TB.[16,17] In diabetic patients, pulmonary TB progress rapidly as there is decline in T cell proliferation and reduced synthesis of interferon gamma (IFN-γ),[18] which compromises body's protective defenses against TB. In turn, by compounding the decrease in IFN – γ, DM predisposes the aging patient to infections where cell-mediated immunity plays a pivotal role, such as tuberculosis.[8]

Further, with age the thymus naturally atrophies and the ability of stem cells to undergo clonal proliferation declines. This further emphasizes the reduced secretion of IL IFN gamma by the macrophages and NK in aging individuals with DM. The inability to produce adequate numbers of mature T lymphocytes compromises the ability of elderly individuals to respond effectively to infections.[8] Lymphocyte proliferation in response to phytohaemagglutinin has been found to be weak in patients with poorly controlled DM.[19]

Resistance to mycobacterial infections is mediated largely by T helper type 1 (Th1) cells and their cytokines, whilst Th2 cells and their cytokines correlate with disease susceptibility and pathology in TB. Whilst Th1 cytokines induces Th1 activity and block Th2 activity, Th2 cytokines promote Th2 activity while inhibiting Th1 activity. The decrease in Th1: Th2 ratio may be of great importance in age-related immune changes, since Th1 mainly induces maturation and activation of the cytotoxic T lymphocytes which decrease with ageing, while Th2 induces increased B lymphocyte immunoglobulin production which increases with ageing. A recent study showed that diabetic TB patients had lower Th1: Th2 cytokine ratios and a higher Th2 bias. Also, the concentration of IL-4 alone was significantly higher in diabetic TB patients compared to non-diabetic TB patients and healthy subjects. As higher concentration of IL-4 is also found in aged individuals due to dysregulation between Th1 and Th2, this

Synergistic elevation in IL-4 secretion may contribute to increased pathogenesis in diabetic TB patients because IL-4 impairs anti-microbial activity of infected cells and increases availability of iron to intracellular M. tuberculosis.

TB is thought to exacerbate and worsen the outcome for DM and vice versa is also true and TB is therefore aptly described as a complication of DM as people with diabetes are more susceptible to infections and suffer from relatively severe illness due to their immuno-compromised status with reactivation of older foci of TB rather than through fresh contact and often exhibit lower lobe involvement more commonly than in non-diabetics. Various studies have shown that 5-30% of patients with TB have DM as well [6]. It is suggested that DM depresses the immune response (impairing chemotaxis, phagocytosis, and antigen presentation in response to *Mycobacterium tuberculosis* infection and affecting T-cell function and proliferation) facilitating infection and progression to symptomatic disease.[20-22]

Chemotaxis, phagocytosis and antigen presentation

The most important effectors cells for containment of tuberculosis are phagocytes and lymphocytes. Diabetes is known to affect chemo taxis, phagocytosis, activation and antigen presentation by phagocytes in response to tuberculosis. In diabetic patients, chemotaxis of monocytes is impaired, and this defect does not improve with insulin.[23]

In a study of patients with tuberculosis, alveolar macrophages were less activated and had decreased hydrogen peroxide production in those with diabetes. In their role as antigen-presenting cells for the initiation of lymphocyte activation, phagocytes bind and then internalise antigen for processing and presentation via their Fc receptors; once activated, they produce interleukin 2, enhancing T- cell proliferation. Insulin deficiency can cause impaired internalisation of Fc-receptor-bound material.[24,25]

The primary cell type infected by tuberculosis is the mature myeloid cell collectively referred to as the macrophage and alveolar macrophage is the first cell to be infected by this primarily pulmonary pathogen. While alveolar macrophages may be the first cell to be infected, the rate of infection is quickly exceeded by the rate of neutrophil and dendritic cell infection. As the inflammatory response progresses, macrophages that are recruited from the periphery to pulmonary sites of inflammation also become infected. One correlate for protection in animal models is the rate by which dendritic cells become infected because the establishment of adaptive immunity is dependent on presentation of antigens by dendritic cells in the lung-draining lymph nodes.[26-28]

M. tuberculosis is promiscuous in receptor binding on macrophages to encourage phagocytosis. M. tuberculosis has been shown to bind multiple receptors to gain access to myeloid cells where bacterial-mediated inhibition of phagolysosomal fusion effectively harbors the pathogen initially within the phagosome. These receptors include complement receptors such as CR1 and CR3, transmembrane C-type lectins including the mannose receptor, and scavenger receptors including SR-A and CD36. In contrast, these receptors play less of a role in infecting dendritic cells in vitro, which is mediated predominately by DC-SIGN, a C-type lectin that recognizes mannose molecules. Host innate pulmonary defense mechanisms such as surfactant D, which has an affinity for lipoarabinomannan of M. tuberculosis may enhance protection by promoting phagolysosomal fusion, while other surfactant proteins may enhance uptake of the bacterium.[29-32]

Within the host cell the bacterium may exist in multiple intracellular compartments. The recently recognized role of autophagy adds an additional factor to consider in the intracellular fate of the bacterium, beyond the long-accepted process of preventing phagosomal maturation. The type

VII secretion system, ESX-1, of M. tuberculosis facilitates phagosomal degradation and escape, allowing the organism to replicate in the cytosol. It is thought that this ESX-1 system allows for the initial recognition of the pathogen by gaining access to cytsolic pattern recognition receptors including NOD2, which occurs only if the ESX-1 system is intact. Organisms residing in the cytosol may become ubiquinated and sequestered further in an autophagosome, which facilitates antigen presentation, as has been shown in M. marinum infected macrophages.

However, M. tuberculosis is able to inhibit autophagy, leading to suppressed innate immune defenses. Therefore, M. tuberculosis follows a complex intracellular survival pattern that reduces host recognition of the organism and limits an effective immune response.[33,34]

The innate response to M. tuberculosis infection leads to synthesis of IL-12, which promotes a Th1-skewed T cell response. The production of IL-12 is critical for dendrite cell migration to the trachea bronchial lymph nodes. However, TLR signaling is linked to efficient induction of effector T cells and therefore may be involved in balancing the protection of the host. The production of TNFα during the innate response to infection, similar to IFNγ during the adaptive response, is an indispensable cytokine. TNFα is a macrophage activation signal that synergizes with IFNγ. The induction of apoptosis by TNFα is recognized in vitro, and the importance of inducing this cell death mechanism in vivo is becoming increasingly recognized. Recently, it has been demonstrated in the zebra fish model of M. marinum infection, that optimal TNFα levels are required because TNFα in reduced or excess concentration promotes necrosis, an unfavorable mechanism of cell death, and inflammation.

Mice deficient in TNFα have been shown to develop a severe inflammatory response that does not necessarily correlate with high bacterial load, indicating that this cytokine has regulatory function as well. CD4 T cells are absolutely necessary for an effective response to M. tuberculosis infection, and more specifically a Th1-skewed response. This is most obvious in mouse models lacking IFNγ, which rapidly succumb to progressive TB, but also in human populations where a lack of CD4 T cells due to HIV infection is the major risk factor for the development of TB. The beneficial effects of adoptively transferring T cells to deficient hosts demonstrated the requirement of T cells in a successful response.[33,34]

CONCLUSION

Diabetes Mellitus and Tuberculosis are two chronic pathologies having major impact on the population. DM is a chronic, noncommunicable disease, characterized by hyperglycemia, caused by insulin-resistance and inadequate insulin secretion or both while TB is caused by Mycobacterium tuberculosis, an airborne bacteria. DM implies a three times greater risk of developing TB and their association can be considered one of the most important challenges regarding TB control. Physicians managing people with diabetes should be aware of the risk of active TB and should include screening for diabetes as part of their investigation. If a person has concurrent diabetes and TB, their physician could consider a more individualized TB treatment strategy. Both health professionals and the people receiving treatment should be aware of possible drug- drug interactions, as well as the importance of the careful management of diabetes.

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