Review Article

Tuberculosis and Diabetes - The Converging Epidemic

Navneet Wadhwa, MD (Pharmacology), *Mumbai, India*

Introduction

Tuberculosis (TB) is the number one bacterial killer worldwide and the current increase in type 2 diabetes mellitus (DM) patients, particularly in countries where TB is also endemic, has led to the re-emerging importance of DM as a risk factor for TB. The dual burden of TB and diabetes has attracted much attention in the past decade as diabetes prevalence has increased dramatically in countries already afflicted with a high burden of TB.

The confluence of these two major diseases presents a serious threat to global public health; at the same time it also presents an opportunity to learn more about the key elements of human immunity to TB that may be relevant to the general population. Some effects of diabetes on innate and adaptive immunity that are potentially relevant to TB defense have been identified, but have yet to be verified in humans and are unlikely to fully explain the interaction of these two disease states. DM increases the risk of TB by two to three times and adversely affects TB treatment outcomes. The increasing epidemic of DM is due to decreased physical activity, unhealthy diet, and obesity.

Despite the clarity for the association between DM and TB, the interrelationship of DM as a predisposition factor for TB is incompletely understood hence it has been termed as a paradox, which has driven interest at the molecular level to decipher this paradox. Therefore, this peculiar association has also been referred as a double trouble.

From: Medical Services, Alkem Laboratories Ltd., Mumbai, India (N.W.)

Corresponding Author: Navneet Wadhwa, MD (Pharmacology)
Deputy General Manager, Medical Services, Alkem Laboratories Ltd., Mumbai, India.

Email: navneet.wadhwa@alkem.com

TB might induce glucose intolerance and worsen glycemic control in people with diabetes.

Diabetes and Immunity in Tuberculosis

Diabetic patients are often at a higher risk for developing several types of infections and infection does alter the handling of glucose by tissues. Pulmonary infections in diabetics are characterized by alteration in host defense, in entire body and in the lung locally as well as in the function of respiratory epithelium and ciliary motility. Impairment of host defense plays an important role for changing the clinical, radiological and bacteriological presentation in diabetic patients. It is also reported by the various studies that hyperglycemia favors the growth of TB bacilli. So the severity of TB appears more critical with the degree of hyperglycemia and host defense activity. This overlap between the diabetic and TB epidemics could adversely affect global TB control efforts. Also, observational studies have shown poor treatment outcome in TB related to hyperglycemia.

Diabetes mellitus is characterized by hyperglycemia. Interestingly, glucose has been shown to stimulate NADPH oxidase, the key enzyme involved with respiratory burst in monocytes and macrophages. This glucose-induced genesis of reactive oxygen species via respiratory burst is contrary to the survival strategy of Mycobacterium TB as an intracellular pathogen in phagocytic cells.

Diabetes is associated with a higher age and body weight among patients with TB, but probably not with a specific clinical presentation of TB. Rifampicin hampers glycemic control by increasing the metabolism of most oral antidiabetic drugs, while diabetes patients may have lower concentrations of anti-TB drugs. Therefore, this might be one factor contributing to higher TB treatment failure rates. The pharmacokinetic issues related to the co-management of diabetes and TB makes it even more challenging to address this deadly duo.

Epidemiological Trends and Patterns - The Deadly Duo Disease Burden

It is estimated that 12.6% of new TB cases in the 10 countries with the highest TB burden will be attributable to DM in 2030, a relative increase of 25.5% compared to 2010. China has nearly the highest incidence of both DM and TB worldwide

In recent decades, TB incidence has declined in high-income countries, but incidence remains high in countries that have high rates of infection with HIV, high prevalence of malnutrition and crowded living conditions, or poor TB control infrastructure. In parallel, DM prevalence is rising globally with increasing prevalence of obesity. There is growing evidence that DM is an important risk factor for TB and not only affect disease presentation but also the treatment response. Clearly, the association of TB and DM demonstrates the convergence and merger of two epidemics.

Experts have raised concern about the merging epidemics of TB and diabetes particularly in the low to medium income countries like India and China that have the highest burden of TB in the world, and are experiencing the fastest increase in the prevalence of DM. There is good evidence that DM makes a substantial contribution to TB incidence. The huge prevalence of DM in India, may be contributing to the increasing prevalence of TB.

A systematic review and a meta-analysis of 13 observational studies (n = 1,786,212 participants) with 17,698 TB cases, suggests that DM increases the risk of active TB. Random effects meta-analysis of cohort studies showed that DM was associated with an increased risk of TB (relative risk = 3.11, 95% CI 2.27-4.26). Case-control studies were heterogeneous and odds ratios ranged from 1.16 to 7.83. Subgroup analyses showed that effect estimates were higher in non-North American studies. Importantly, DM was associated with an increased risk of TB regardless of study design and population.

Screening for Tuberculosis and Diabetes Mellitus

Active screening has been suggested to lead to the detection of more TB and DM with variable success and yield. Screening and preventive therapy would have role in combating this deadly duo. A systematic analysis has documented that screening for TB in persons with DM demonstrated that TB prevalence in this population is high, ranging from 1.7% to 36%, and increasing with rising TB prevalence in the underlying population as well as with DM severity. Screening patients with TB for DM also resulted in high prevalence of DM ranging from 1.9% to 35%.

It has been suggested that the screening and care should be integrated. This is imperative since, the large dual burden of disease may make management of both conditions more difficult. High-quality implementation research is needed to assess the value and ways of screening for DM in patients with TB and vice versa, and to set up standardized systems of monitoring and evaluation based on the directly observed treatment, short-course (DOTS) model used for TB control.

Conclusions

There is an urgent need to implement strategies for TB prevention among the millions of DM patients exposed to Mycobacterium tuberculosis worldwide, but knowledge is limited on how and when DM alters the natural history of this infection.

Issues that merit further investigation - such as geographic host and pathogen differences in the diabetes/TB interaction, the role of hyperglycemia induced epigenetic reprogramming in immune dysfunction, and the impact of diabetes on lung injury and fibrosis caused by TB

The WHO recommends screening for diabetes among all patients with TB and optimized glycemic control aiming at improving TB outcome. However, no intervention studies support this notion. Patients with TB are often vulnerable with high degree of comorbidity, and, therefore, at high risk of adverse effects of intensive glucose control. Controlled intervention studies of the effect of glucose lowering treatment on TB outcomes are clearly warranted to justify screening for- and tight control of diabetes. Call for more research is required to examine whether the diagnosis and treatment of diabetes in TB patients may improve TB outcomes and patient survival.

The implications of the global increase of diabetes for TB control and patient care are going to be widespread. It has been suggested that prospective studies are needed to improve prevention, early detection and treatment of concomitant diabetes and TB, especially in developing

countries. The rising prevalence of DM in TB-endemic areas may adversely affect TB control. People with DM may be important targets for interventions such as active case finding and treatment of latent TB and efforts to diagnose, detect, and treat DM may have a beneficial impact on TB control. There is strong evidence for an association between TB and DM, which has potential public health implications

Suggested Reading

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