Rediscovering the Association Between Tuberculosis and Diabetes Mellitus: A Perspective

Zakeya Abdulbaqi Bukhary MD, MIDSA
Department of Internal Medicine, College of Medicine
Taibah University, Al Madinah Al Munawarah
Saudi Arabia

Abstract
Objective
To provide an overview, understanding and future prediction of the prevalent concomitant diabetes mellitus and tuberculosis in Saudi Arabia. The literature between 1990 to 2007 was reviewed and combined with personal views which are supported by scientific evidences.

Results
Diabetes mellitus is a risk factor to develop active tuberculosis with odd ratio (4.7; 95%) confidence interval (2.7-8.1). The odd ratio of patients with active tuberculosis who has type 2 diabetes mellitus ranges from 1.3-7.8 folds. Patients with tuberculosis who have diabetes mellitus present a higher bacillary load in sputum, more frequently positive culture at tow month after anti-tuberculous treatment and high rates of multi-drug resistant mycobacterium. Pulmonary tuberculosis in diabetes mellitus present with atypical radiographic features. Diabetes mellitus may adversely affect the outcome of tuberculosis treatment.

Conclusion and Recommendations
There is a need to alert all physicians about the potential impact of diabetes mellitus on the control of tuberculosis and its treatment. It is important to check fasting blood sugar in new patients with tuberculosis and to screen all patients with diabetes mellitus for latent mycobacterium tuberculosis infection. Patients with combined diabetes mellitus and tuberculosis require close monitoring for the control of both diseases.

Key words: Diabetes mellitus, tuberculosis, epidemiology, Saudi Arabia

Introduction
Diabetes Mellitus (DM) is epidemic worldwide and it is estimated to affect 366 million by 2030 when majority of those affected will be living in low and middle income countries where Mycobacterium Tuberculous infection is endemic. The combination of DM and tuberculosis (TB) was life threatening in the pre-antibiotic era and before the readily available treatment of both diseases. Currently the association
between DM and TB is re-emerging because the epidemiology of both diseases is progressive worldwide and cases of DM are increasing in the developing countries where TB is of high burden. The association of DM with TB was confirmed with Odd Ratio: (OR 4.7; 95 % CI, 2.7-8.1 ) 4. Host defense against mycobacterium tuberculosis (M.TB) infection is largely mediated by cellular immune responses. Type-1 helper (Th1) cells play a central role in the host defense by inducing the production of interferon (IFN-\(\gamma\)) which potentiates the nitric oxide (NO)-dependant killing activity of macrophages 5 . Interleukin(IL)-12 is essential cytokine for the development of Th1 cells from naïve cells 6.

The mechanism for the increased susceptibility of patients with DM to TB is still unclear and remains to be fully understood. In clinical investigations Th1 cells and the production of IFN-\(\gamma\) and IL-12 were demonstrated to be attenuated in TB patients with DM when compared to non-diabetic cases. The reduced Th1 responses correlated well with the progression of the diabetic conditions 7.

The consequence of this combination is substantial but it was largely marginal in the late century probably due to the following explanations:
1) Improved health care facilities including diagnosis and management of both diseases which are on the contrariety overriding the primary preventive care in the developing communities. 2) Diminution of TB control measures to prevent re-activation of latent M.tuberculosis infection in specific group of patients including diabetics. 3) Lack of major epidemiological surveys which determine the prevalence of TB in diabetic patients. 4) Increased awareness about DM as a major risk factor for coronary artery diseases (CAD), cerebrovascular diseases, renal diseases, and neuropathies yet the awareness of the infectious diseases complications as an immunosuppressive condition. In Saudi Arabia, there is neither a national surveillance of cases of active TB among patients with diabetes mellitus nor surveillance of latent TB among this group of patients.

The aim of this perspective is to provide an overview, understanding and future prediction of the prevalent concomitant DM and TB in Saudi Arabia. The English literature between 1990 and 2007 was reviewed and combined with expert opinion and views which are supported by scientific evidences.

Epidemiology

Eight of the ten countries with the highest incidence of DM worldwide are also classified as high burden countries for TB by the World Health Organization (WHO) 8,9. As a result, a growing number of patients with TB will present with DM and almost 10%-30% patients with TB may have DM 4,9. Type 2 DM (NIDDM) increases the risk of developing active TB. The odd ratio (OR) of patients with active TB who has type 2 DM ranges from 1.3-7.8 folds, indicating that DM clearly increases the risk of tuberculosis 10,11. There was a 26- and 7-fold risk of developing TB among IDDM (type 1 DM) IDDM and NIDDM patients respectively 12. Comparing the incidence of pulmonary TB in diabetics and non diabetics the relative risk (RR) of developing pulmonary TB and bacteriologically confirmed cases were 3.47 times and 5.15 times higher 13. The prevalence of TB in diabetic patients was 10 times higher than in non-diabetic patients in Pakistan 14.

In Saudi Arabia, the overall prevalence of DM obtained by a major national survey over 5 years period in Saudi subjects in the age group 30-70 years between 1995 and 2000 was 23.7% 15. DM prevalence was consistently increasing with advanced age 15-19. Studies showed that diabetes is epidemic in the country with exceedingly high rates concentrated in urban areas with significant different geographical distribution. The highest prevalence of DM was observed in the northern region of 27.9% followed by the eastern region of 26.4% then from western region 24.7% and from the central region of 23.7% whereas the southern region had the lowest prevalence of 18.2% 15-19. Although the western region is mainly an urban community, there were foci of high
prevalence of latent *M. tuberculosis* infection as evident by a positive Tuberculin Skin Test (TST) reaction in 20% ⁴⁻°. This problem may be caused by the fact that the province receives every year over a million pilgrims. Based on our knowledge about the life time risk of developing active TB from latent TB infection in normal individuals which is reaching up to 20% ²¹, we are facing potential dual risk of TB re-activation in this country which is not only the growing nature of population with advanced age but also the concomitant underlying DM in the growing young individuals. These strong epidemiological associations provide important alert for physicians about the potential impact of DM on the control, eradication and treatment of TB.

**Clinical presentation of combined TB and DM**

Both diseases may impact adversely on each other with a resultant poor glycemic control of DM and poor response to anti-TB treatment. DM may not be discovered at time of TB diagnosis. Half of the diabetic patients were unaware about DM at the time of the national survey in Saudis ¹⁵. One-third of non-diabetic men with TB had abnormal glucose screening tests ²². Active TB may worsen blood sugar control with increase risk to develop sepsis in diabetic patients ²¹. Recently, in a major prospective clinical trial, patients with DM and TB found to have more symptoms than non-diabetic patients ²³. The correlation between the prevalence of TB and the duration of diabetes is variable ¹⁵, ²⁴. The mean age was 55.4 years (SD +/- 13.5) in majority of patients with concomitant disease ²⁴. Pulmonary TB in DM frequently present with atypical radiographic features compared to upper lobe cavitations in non-diabetic patients ²³. The lower lung field was most frequently involved followed by the upper and middle lobe. Bilateral involvement, an associated pleural effusion, and cavitations were seen in about 50% ³³%, 30% respectively ¹⁵. Radiological findings included fibrosis, consolidation, homo- and heterogenous opacities ²⁴. There are data indicating that patients with DM who have TB present a higher bacillary load in sputum. Sputum microscopic examination results are more frequently positive among diabetic patients and associated with positive culture for *M. tuberculosis* tow months after starting the anti-TB treatment ²³⁻²⁵⁻²⁷. Higher rates of Multi-drug resistant (MDR) *M. tuberculosis* may be associated with treatment failure in patients with DM and TB concomitant disease.

In certain population MDR is more frequent among patients with TB and DM, yet the mechanism is unknown ²⁸. Rifampicin pharmacokinetics indicated that plasma levels of the drug were 2 folds lower in patients with TB who have DM than in patients with TB who do not have DM. The difference may be the underlying cause to acquire drug resistance and may explain the lower mycobacterium response to anti-TB treatment in diabetic patients. However, non-compliance or non-adherence to treatment may lead to treatment failure ²⁷⁻³⁰.

**Role of prevention of TB reactivation in the diabetics**

Physicians treating DM have only a little concern on TB. Probably because there are no longitudinal epidemiological studies about TB in diabetics and non-diabetics in Saudi Arabia and no cross sectional studies about the prevalence of TB in this high risk group of patients. There were only few observational studies about pulmonary, miliary and extrapulmonary TB in which DM was the most common underlying disease associated ³¹⁻³². Early effective interventions in high risk groups will reduce the burden of cavitating disease and associated transmission of the disease in the community ³³. Adequate chemoprophylaxis substantially reduces the risk of TB reactivation by 70% and is economically cost-effective ³⁴. The prevention of active TB through the treatment of latent TB infection is a major element for TB control and elimination strategies. Targeted treatment for persons...
who are at high risk for reactivation TB will be needed to achieve this goal and could help to eliminate the tuberculous disease. In making decisions about the need to treat latent TB in a person with a positive TST, risks other than that of reactivation should not be considered since these risks cannot be decreased by the treatment of latent TB. Chemoprophylaxis is recommended and considered to prevent the development of TB from diabetics in whom chest X-ray examination shows healing of TB (no signs of active TB) in the absence of previous history of TB treatment. Isoniazid prophylaxis should preferably be set. As diabetics are considered high risk group of developing pulmonary TB as compromised hosts, physicians need to perform periodic health exam including CXR and when the patient has symptomatology to proceed with sputum for AFB and had a tight blood sugar monitoring and control of hyperglycemia in these patients. As shown by various experimental studies, the control of hyperglycemia improves the impaired Th1 related cytokine synthesis with improvement of the impaired host protection against the infection.

Future Prediction

The epidemiology of DM and TB is progressing and the impact of this convergence is serious in the control of TB. There are many questions to be answered: what is the magnitude and impact of the combination of DM with TB locally, regionally and internationally? should every patient with DM be screened for latent TB infection and if the results are positive what is the level of evidence to receive INH prophylaxis to prevent development of active diseases? Is there a need to modify the anti-TB treatment in patients with TB and DM? However, on the basis of the current available knowledge and evidence it would be a wise approach to check fasting blood sugar in new patients with TB whom will be monitored closely with special attention for potential treatment failure.

In the author’s opinion, there is a national requirement to start a community-based epidemiological health survey of TB, in diabetic patients to determine the prevalence of TB among Saudis with DM. Public health education and awareness programs should be encouraged. Such programs must include the importance of screening all TB patients for DM and screening all DM patients for TB using the new WHO criteria to diagnose both diseases.

References


