Tuberculosis and Diabetes Mellitus: Merging Epidemics

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Abstract
The link between tuberculosis (TB) and diabetes mellitus (DM) has occupied the center stage of discussion. Experts have raised concern about the merging epidemics of tuberculosis 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. This review looks at the link between these two merging epidemics. We discuss the epidemiology, clinical features, microbiology and radiology, and management and treatment outcomes of patients with tuberculosis and diabetes mellitus.

Introduction
Tuberculosis (TB) continues to infect an estimated one-third of the world’s population, to cause disease in 8.8 million people per year, and to kill 1.6 million of those afflicted. The global burden of diabetes mellitus (DM) is expected to rise from an estimated 180 million prevalent cases currently to a predicted 366 million by 2030 with the greatest increase projected in the developing world.

Experts have raised concerns about the twin epidemics of DM and TB, especially in low to middle income countries like India and China that are experiencing the fastest increase in DM prevalence and have the highest burden of TB in the world. Several recent studies suggest that DM increases the risk of active TB with an approximately three fold risk of developing active TB been reported. Recent papers have also reflected increasing concern among tuberculosis field workers, that DM may be a major force in converting latent infection into overt disease. Thus the link between DM and TB has occupied the center stage of discussion.

Historical Perspective
Evidence of TB was found in Egyptian mummies dating back to 1550 BC. Hippocrates identified TB, then referred to as “phthisis pulmonaris” or “consumption” or “white plaques”, as a widespread, usually fatal disease, causing high mortality. As early as 1694, Richard Morton’s Phthisiologia, a treatise on consumption, stated that an association between diabetes mellitus and tuberculosis was suggested even in Roman times.

Tuberculosis was recognized as an infectious disease in the late 17th century in Europe. Most of the population of Europe was infected at that time with one in four deaths attributed to TB. Sir William Osler, in his famous textbook, which was recognized as a masterful survey of the entire field of internal medicine in 1892, has a long and exhaustive section on tuberculosis. Tuberculosis was identified as the number one killer of that era. Osler wrote “Tuberculosis is the most universal scourge of the human race.”

He gives a complete description of modes of infection in TB, with emphasis on the inhalation of the bacterium. As far as treatment is concerned Osler wrote “The cure of tuberculosis is a question of nutrition; digestion and assimilation control the situation; make the patient grow fat, and the local disease may be left to take care of itself.”

Diabetes mellitus was uncommon in Osler’s time. The modern distinction between juvenile onset and adult onset diabetes did not exist then and the majority of cases occurred between the third and sixth decades. There was however no mention about any association between tuberculosis and diabetes in his textbook.

Since the early part of the 20th century, clinicians have observed an association between DM and TB, although they were often unable to determine whether DM caused TB or whether TB led to the clinical manifestation of DM. The mid 20th century saw a few reports documenting such a link and speculating on its significance.

More recently, multiple rigorous epidemiological studies investigating the relationship, have demonstrated that DM is indeed positively associated with TB. McCornick and colleagues from the University of Texas school of Public Health, in 2007 explored the association between the two conditions in over 5000 TB patients on the two sides of the Rio Grande River. Using retrospective data they found that the co morbidity of TB-DM exceeded that of TB-HIV. Patients with TB and DM were older, more likely to have hemoptyisis and pulmonary cavitations, be smear positive at diagnosis, and remain positive at the end of the first and second month of treatment. Type 2 DM was the major factor associated with TB in both Mexicans and the Hispanic Americans. These observations raise important scientific and public health questions concerning possible immunological impairment in DM, the importance of DM control in exposed individuals and the control of tuberculosis in communities with an increasing prevalence of DM.

TB remains a major cause of mortality in developing countries and in these countries the diabetes prevalence is increasing rapidly. The rising prevalence of DM in TB-endemic areas may adversely affect TB control. Given the public health implications of a causal link between DM and TB, there is a clear need for a systematic assessment of the association in the medical literature.
**Epidemiology**

**Global Diabetes Epidemic**

The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise by 2030 of 440 million cases occurred in India. Estimates of the urban and rural distribution of the annual risk of tuberculosis infection suggest that, on average, smear-positive tuberculosis incidence in India is 69.2% higher in urban compared with rural areas. Therefore, the increased prevalence of diabetes in urban areas may also play a role.

**Incidence of Tuberculosis in Diabetic Patients in India**

Recent studies published in BMC public health (2007) suggest that a substantial proportion of incident tuberculosis in India is attributable to diabetes. As much as 14.8% of pulmonary tuberculosis and 20.2% of smear-positive i.e., infectious tuberculosis was directly linked to diabetes. Diabetes is also probably responsible for the urban incidence of smear positive tuberculosis being 15.2% higher than that in rural areas. One underlying risk factor for tuberculosis that may not be equally distributed between those with and without diabetes in India is poverty. Consistent with this, a recent case control study from India of risk factors for TB found a univariate odds ratio of 1.8 for previously diagnosed diabetes, which strengthened to 2.44 when controlling for other risk factors, including low socioeconomic status.

**Prevalence of Diabetes Among Tuberculosis Patients in India**

In India in 2000, there were an estimated 481,573,000 people over the age of 25 years. Among these, 4.3% i.e., around 20,707,639 had diabetes, and 939,064 developed pulmonary tuberculosis, of which 575,900 were smear-positive and hence infectious. The recent studies predict that in India 18.4% (12.5% to 29.9%) of people with pulmonary tuberculosis (both smear-positive and smear-negative) have diabetes and that in the smear-positive group diabetes prevalence is 23.5% (12.1% to 44%).

**Impact of Diabetes on the Progression of Tuberculosis**

In general a person who becomes infected with Mycobacterium tuberculosis has a 10% chance of developing active disease during their life-time; 5% during the first one to two years and another 5% later in life. Recent studies have shown that patients with diabetes are at increased risk for the progression of the disease.

**Do Patients with Tuberculosis Have a Higher Prevalence of Diabetes Mellitus?**

There is not enough evidence to give a definitive answer, but some trends are emerging. Studies conducted after the introduction of the glucose tolerance test in 1950s, have shown high prevalence of impaired glucose tolerance test in patients with tuberculosis with rates ranging from 2% to 41%. The use of different criteria for diagnosis of diabetes mellitus makes comparisons between the results of the studies almost impossible. There have been reports of high prevalence rates of diabetes in cases of pulmonary tuberculosis (4-20%) and rates are higher for impaired glucose tolerance test (16-29%). Interestingly, after antituberculosis therapy, 50% of these patients had normalization of their glucose tolerance.

Some investigators have reported an association between severity of tuberculosis and abnormal glucose tolerance. However, no association has been found with age, family history of tuberculosis, ethnicity or duration of treatment.

**Risk Factors for Tuberculosis**

Currently, about one-third of the world’s population is latently infected with tuberculosis. WHO has identified the progression of latent infection into active contagious disease as a pressing challenge. The overall importance of diabetes as a risk factor for tuberculosis is still largely unknown, although a recent analysis in Mexico concluded that, in the population studied, 25% of pulmonary tuberculosis was attributable to diabetes.

Host-related and environmental-related factors have been shown to play a role in the development of tuberculosis, but very few studies were carried out to identify their respective roles in resource-poor countries.

A multicentre case-control study was conducted in Guinea, Guinea Bissau and Gambia in West Africa, from January 1999 to March 2001, wherein 846 newly detected sputum smear positive cases, 702 household controls and 828 community controls were recruited in the three countries. The spectrum observed was as described in Table 1. From India, few studies are available which have shown a higher incidence of tuberculosis in patients with silicosis. In 1949, Sikand and Parma reported TB in 28.6% of patients with silicosis.

**Biological Plausibility**

The prevailing multiplicity of concepts which deal with the causal connection between diabetes and tuberculosis attests to the uncertainty in this respect. The dominant manifestation of
diabetes mellitus, namely hyperglycemia has been assumed to favor the growth, viability and propagation of tubercle bacilli. Furthermore, it was thought that the concomitant increase in dextrose in the tissues resulted in decreased resistance to infection in situ and also in impaired repair capacity. Predilection to infection was also attributed to local tissue acidosis and imbalance of electrolytes.

A number of investigators advanced the view that there was a lowering of protective cytological function which, in turn, brings about increased susceptibility to infection. Increased availability of glycerol, and nitrogenous substances which aid the growth of tubercle bacilli, were considered possible contributory causes.

In contemporary medical thinking the assumption is gaining ground that dysfunction of the pituitary gland may have a role in the increased susceptibility to tuberculosis. A relative and absolute overproduction of adrenocorticotropic hormone and consequent increased supply of corticosteroids to the blood may interfere with the normal defense mechanism of the mesenchymal tissues. As a result, exudative inflammatory response is enhanced while formation of granulation tissue is decreased. Corticosteroids are insulin antagonists. Their overproduction may result in insulin resistant diabetes. This postulate is now being validated.

Prevalence of pulmonary TB in patients with DM, in contrast to the relative infrequency of extrapulmonary forms of TB, may be due to hepatic dysfunction and consequent hypovitaminosis A and D. However, this postulate has not been proven yet. Numerous studies have presented convincing biological evidence in support of the causal relationship between DM and impaired host immunity to TB.

In experimental studies of human plasma cells, high levels of insulin have been shown to promote a decrease in Th1 immunity through a reduction in Th1 cell to Th2 cell ratio and interferon gamma to IL-4 ratio. Additionally, an ex vivo comparison study of production of Th1 cytokines showed that nonspecific interferon gamma levels were significantly reduced in people with diabetes compared to controls without diabetes. Another study indicated a dose-response relationship; levels of interferon gamma were negatively correlated with levels of HbA1c (glycosylated haemoglobin).

Furthermore, neutrophils from people with diabetes had reduced chemotaxis and oxidative killing potential than those of non-diabetic controls, and leukocyte bactericidal activity was reduced in people with diabetes, especially those with poor glucose control. Some believe that another cause of increased susceptibility is due to decreased production of interleukin-1 beta, and tumor necrosis factor by the peripheral blood monocytes in patients with tuberculosis and co-existent diabetes mellitus. Taken together, these studies strongly support the hypothesis that DM directly impairs the innate and adaptive immune responses necessary to counter the proliferation of tuberculosis.

### Clinical Presentation

There are conflicting reports about the influence of associated diabetes on the clinical features, radiological manifestations, sputum conversion rates, drug resistance patterns and treatment outcomes of pulmonary tuberculosis patients. Most previous studies have been limited either by the small number of diabetic patients or a lack of proper statistical analysis. It appears that diabetic patients as a group are more susceptible to having a more aggressive course of tuberculosis disease. There are reports that TB might progress rapidly in diabetic patients. Uncontrolled diabetes mellitus or lapse in its control may cause flare-up or spread of tuberculosis.

Case series by Deshmukh et al with 138 TB-DM patients revealed that 82.6% of the study population was above 45 years of age and there was a male preponderance. 43.4% of TB patients gave history of DM and 56.6% were detected subsequently on the examination of urine, confirmed by blood sugar examination. In this study, the authors observed that, when a known case of diabetes presents with symptoms of general ill-health like fever, weakness, apathy, cough, haemoptysis, and chest pain; investigations may reveal the presence of tuberculosis.

They also noted that in a few cases a rapid deterioration of health took place with persistent fever, loss of weight, and investigations revealed presence of co-existent diabetes and pulmonary tuberculosis. Sometimes in the study population a patient who has been put on anti-tuberculosis treatment failed to respond adequately in a given period of time and further investigations revealed the presence of diabetes. In another study by Tripathi et al, the authors observed 55% of TB-DM group were underweight and this group was mostly more than 40 years of age.

Experienced clinicians observe that patients with both diabetes and tuberculosis usually have a prolonged duration of fever and more significant weight loss with co-existent disease than with diabetes or pulmonary tuberculosis alone. Thus, pulmonary tuberculosis should be considered in patients with diabetes mellitus who have weight loss, fever and general debility that cannot be fully explained by poor diabetic control.

Diabetes may be diagnosed for the first time when blood sugars are initially sent off in the patient with pulmonary TB and found to be high. We would advocate checking fasting and post-prandial sugars in all newly diagnosed TB patients. However, there are recent reports that show no significant difference in the mean duration of symptoms between the TB-DM patients and the TB patients without DM. Low grade fever and productive cough were the most common symptoms and were observed with almost equal frequency in both groups. Taken together these studies suggest that the clinical spectrum of this group of patients with co-existent pulmonary tuberculosis and diabetes mellitus is quite varied.

Radiology of Pulmonary Tuberculosis in Diabetic Patients

Comparative studies of radiology in diabetics with tuberculosis have also yielded contrasting results. In a number of published studies chest radiograph images from these patients have been described as 'atypical', mainly because they frequently involve the lower lung fields, often with cavities.
The largest study done by Perenz-Guzman et al in Mexico, which compared the radiological findings of pulmonary tuberculosis in 192 diabetic patients with a control group of patients with pulmonary tuberculosis alone, revealed that both the groups had a similar evolution time of tuberculosis, around two years.\textsuperscript{37}

In this study they found that the TB-DM patients were older (51.3 ± 0.9 vs. TB group 44.9 ± 1.8 years), and had a decreased frequency of upper (17% vs. 56%), and an increased frequency of lower (19% vs. 7%) and upper and lower (64% vs. 36%) lung field lesions. More TB-DM patients developed cavitations (82% vs. 59%) more often in the lower lung fields (29% vs. 3%). Cavities were more often multiple in the TB-DM patients (25% vs. 2%). Statistical analysis with multiple logistic regression showed that being a diabetic patient was the most important factor determining lower lung field lesions and cavities. Thus this study, along with some earlier studies\textsuperscript{41-43} confirmed that their chest radiograph images significantly depart from the typical presentation.

Other authors have been unable to find differences in the chest x-ray patterns of pulmonary tuberculosis in diabetics and non-diabetic patients.\textsuperscript{44} Thus a range of X-ray patterns and locations may be encountered in the TB-DM patient. Lower lobe involvement with cavitation is a pattern which, when encountered, should raise the possibility of co-existing diabetes in the patient with pulmonary TB.

**Time to Sputum Conversion**

The relative risk of developing sputum positive pulmonary TB is up to five times higher in diabetics.\textsuperscript{45} Sputum smear and culture conversion are important indicators for the infectivity of the patient and effectiveness of treatment.

In a recent study from Turkey, the bacteriological profile of 737 patients hospitalized from 2000 to 2005 with pulmonary TB was looked into.\textsuperscript{45} Three hundred six (193 men and 113 women) human immunodeficiency virus (HIV) negative patients newly diagnosed with pulmonary TB were evaluated. Factors associated with both sputum smear and culture conversion time were investigated. It was found that patients with DM, cavitary disease and radiologically extensive disease had longer sputum smear and culture conversion time than the other groups.

In the logistic regression analysis, the presence of DM and extensive disease were determined as independent risk factors influencing both sputum smear and culture conversion time in pulmonary TB. Thus they concluded that sputum smear and culture examinations should be considered together to assess the poor prognosis.

Another study looked at the influence of diabetes on the manifestations of pulmonary TB patients.\textsuperscript{46} Records of 692 consecutive smear-positive pulmonary TB patients admitted to a referral hospital in Riyadh, Saudi Arabia, were reviewed retrospectively. The characteristics of 187 patients with DM (TB-DM group) were compared to 505 patients without DM (TB group). In the TB-DM group, 65.2% of the patients had numerous (>1 bacillus per oil immersion field) acid fast bacilli (AFB) on the sputum smear examination compared to 54.1% in the control group.

They concluded that TB-DM patients have a higher pre-treatment bacillary load and DM was an independent risk factor associated with numerous AFB on sputum smear examination. They explained that the immune suppression induced by DM could be responsible for the high bacillary load in TB patients with DM.

The same authors also analyzed sputum conversion rates among new cases. At the end of 2 months of treatment, sputum conversion rates were slightly lower in diabetic patients compared to non-diabetics. In patients who remained sputum positive at the end of 2 months of treatment, the intensive phase was extended by one month. At the end of 3 months of treatment, the sputum conversion rates among TB-DM patients improved. The logistic regression analysis, even when adjusted for age and sex, also showed that DM was an independent significant factor associated with a lower rate of sputum conversion at the end of 2 months of the intensive phase treatment.

This observation also signifies that the routine treatment strategy of prolonging the intensive phase of treatment by 1 month in patients who remain sputum positive at the end of 2 months, as suggested by the WHO guidelines, may also be valid for diabetic patients. Published data on this subject are lacking.

**Treatment Outcome**

There is paucity of data regarding the outcome of treatment among TB patients with associated diabetes. Some reports suggest adverse effects of diabetes on the treatment outcome of TB patients with an increased rate of failures, deaths, defaults and relapses.\textsuperscript{15} Mortality rates in these patients are reported to be several times higher than in non-diabetic pulmonary TB patients.\textsuperscript{23}

Recent studies, on the contrary, showed that the association of diabetes did not alter the response of pulmonary TB to treatment.\textsuperscript{46} Favorable outcomes (cured/treatment completed), failures, deaths, defaults, relapse rates were comparable in both groups i.e. pulmonary TB patients with or without DM. Reports have also pointed out that, in well-controlled diabetes the course of pulmonary tuberculosis is not different from that in patients without diabetes.

In summary, these results indicate that as far as tuberculosis is concerned, the survival rate and socio-economic rehabilitation of adequately treated patients with diabetes and pulmonary TB are the same as that of TB patients without diabetes.\textsuperscript{46}

**Multidrug Resistance (MDR) & Extensive Drug Resistance (XDR)**

Conventionally, it is believed that diabetics have a higher incidence of anti-tuberculosis drug resistance.\textsuperscript{47} A case-control study by Condos et al from New York University School of Medicine, reviewed retrospectively over ten years, the records of patients with a discharge diagnosis of tuberculosis and diabetes mellitus.\textsuperscript{47} Fifty three identified patients had verified tuberculosis infection and diabetes. One hundred five control cases were selected from non-diabetic patients with a discharge diagnosis of tuberculosis during the same time period. Thirty six percent of the patients with diabetes and TB had MDR-TB, compared to only 10% in the control group. Adjusting for homelessness, HIV status, and directly observed therapy (DOT), the relative risk of MDR-TB was calculated to be 8.6 in the diabetic group compared to the control group. Thus, Condos et al concluded that there was a significant association between diabetes and MDR-TB. A greater suspicion for MDR-TB should be entertained in diabetic patients.

Although this study was limited by its small number of subjects and by retrospective data collection, it is evident that the pattern of tuberculosis in diabetic patients differed from the non-diabetic patients. The diabetic patients were 8.6 times as likely to have infection with a multidrug resistant strain of tuberculosis. The authors postulated that the hyperglycemic state may interfere with achieving adequate tissue levels of medications or might
interfere with alveolar macrophage or CD4+ cell function. They also postulated that occasional diabetic patients might have some degree of impaired gastrointestinal drug absorption even in the absence of clinically obvious gastroparesis. This has important clinical and treatment implications.

Another recent study found no significant difference in the incidence of MDR-TB in their diabetic-TB population. Thus, the relation between diabetes and MDR-TB remains unproven. More studies on the influence of diabetes on the incidence of resistance to antitubercular drugs are needed. They would have particular relevance in a country like India with the highest pool of MDR-TB patients in the world coupled with the largest projected diabetic population.

Pointers on Treatment
Management of Tuberculosis

Conversion from a sputum smear positive state to smear negative state can be accomplished in most instances by medical means, mainly by chemotherapy. Controversies exist regarding various issues in the management of pulmonary tuberculosis in the diabetic patients.

Should new cases with pulmonary TB who are also diabetic, be treated for 6 months as per the standardized WHO regimen, or should their treatment be extended to a total of 9 months, as these patients might have an increased relapse rates? This is an issue with important repercussions that demands clarification. At present initial treatment would include the standard four drug regimen with isoniazid along with pyridoxine, rifampicin, ethambutol and pyrazinamide but in the diabetic with extensive cavitary disease should an additional drug (possibly a quinolone like moxifloxacin) be added to the initial regime to rapidly reduce sputum AFB load? This is also presently an important but unanswered question.

Management of Diabetes Mellitus

Tuberculosis worsens glycemic control and makes the control of diabetes difficult. Maintenance of blood sugar level at normal or near normal level, is one of the most fundamental aspects in patient care. Whether this aggressive control of hyperglycemia should be done only with oral hypoglycemic agents or whether the use of insulin is mandatory in patients with pulmonary tuberculosis and diabetes is still an area of uncertainty. Insulin is clearly the preferred agent of choice in Diabetes with TB (of any type) due to its anabolic action apart from it lowering the pill burden, improving appetite, and promoting weight gain. Especially in the intensive phase of anti-TB chemotherapy Insulin has clear curt advantages though one may shift to oral antidiabetic agents during the maintenance phase of anti-TB chemotherapy. Insulin has clear curt advantages though one may shift to oral antidiabetic agents during the maintenance phase of anti-TB chemotherapy. Insulin is still preferred. Its is logical though yet to be validated that the outcomes of TB therapy and relapses / recurrences are cleared altered by better glycemic control with Insulin. So optimal glycemic control aided by Insulin has clearly improved outcomes in patients wuth DM and TB.

Conclusions

Recent data from India has stirred up a horns nest by revealing that diabetes makes a substantial contribution to tuberculosis incidence. The current diabetes epidemic may thus lead to a resurgence of tuberculosis in endemic regions like India. This has potentially serious implications for tuberculosis control, and it must become a priority to use this knowledge to initiate focused and coordinated action like active case finding, treatment of latent tuberculosis and new research in parts of the world where diabetes is epidemic and TB endemic to properly inform public health and clinical practice. Conversely efforts to diagnose, detect and treat DM may have a beneficial impact on TB control. There is growing evidence of one disease fueling the other. There are numerous issues of basic, applied and operational research waiting for solutions. This is a wake up call for all clinicians and researchers to gear-up to meet the challenge of patients afflicted by tuberculosis and diabetes. It is time that the “unhealthy partnership” of tuberculosis and diabetes receives the attention it deserves.

References


