INTRODUCTION

With high rates of diabetes and tuberculosis (TB), India faces challenges in controlling both diseases. In India, in 2011, there were 61.3 million people living with diabetes, and 963,000 deaths from the disease. India also has 1.98 million people developing TB and almost 300,000 people dying of it each year.

According to Professor Dr Anthony Harries of the International Union against Tuberculosis and Lung Diseases (The Union), diabetes upsets the immune system in different ways and if the immune system is down, the risk of contracting TB as well as other infections increases. So in patients with diabetes, we need to think about TB and screen them, and in patients with TB, we need to think about diabetes. If we do not seriously think about the link between TB and diabetes, it may begin to derail some of the good advances made in TB control, especially in countries like China and India. The increasing incidence of diabetes, especially in low- and middle-income countries, is threatening to have a negative impact on TB control, and vice versa.

Patients with diabetes are at greater risk of contracting TB, and diabetes can worsen the course of TB. TB can worsen glycemic control in patients with diabetes. To address these diseases, strategies are needed to manage patients with both diseases and cross-screen patients with each disease.

BURDEN OF TUBERCULOSIS IN INDIA

India accounts for one-fifth of the incidence of TB cases and ranks one among the 22 high burden countries, which are contributing to 80% of global TB burden. Nearly 40% of Indian population has been infected with tuberculosis bacilli. According to World Health Organization (WHO-2009) report, the death rate due to TB was 23 per one lakh population in India. The primary goal of STOP TB is to reduce the global burden of TB (deaths and prevalence) by 50% in 2015, compared to 1990 levels. Few countries are well on track with the achievement of the above target. India is one among the high-burden countries which needs special focus to achieve the target.

DIABETES EPIDEMIC—RISK FACTOR FOR TUBERCULOSIS

Several work plans are being implemented to address the recognized barriers such as human immunodeficiency virus (HIV) co-infection and multidrug-resistant TB in accomplishing the task of halving the prevalence and mortality due to this dreadful TB disease. One of the factors facilitating or accelerating the phenomenon of conversion of latent to active form, as well as reactivation of old TB disease is the increasing number of people with diabetes. India ranks second next to China in the number of people affected by diabetes. There are around 62 million people living with diabetes and the estimated prevalence of diabetes in India was 10.4% in 2011 (Whiting 2011).

According to Stevenson et al. nearly 15% of TB burden in India in the year 2000 was attributed to diabetes whereas HIV accounted for 3.4% of TB cases. The estimated number of people with diabetes at that time in India was only 22 million. This study group also reported that the prevalence of diabetes among pulmonary TB was 18.4% and it increased to 23.5% among those with infectious forms of TB (Stevenson et al. 2007).

There are several study reports from different parts of the world showing higher prevalence of diabetes among TB patients than that of the general population. Pakistan reported 10 times higher prevalence of diabetes in TB patients compared to their normal counterparts (Jabbar et al. 2006).

A case-control study conducted among newly diagnosed pulmonary TB patients attending a hospital in Bangalore, for 2 years, with age and sex matched subjects, showed diabetes as one of the risk factors for the incidence of pulmonary TB and they reported an odds ratio of 2.44 (Shetty et al. 2006).

Christie et al. has done a systematic review of 13 studies related to TB and diabetes. The authors reported an odds ratio ranging from 1.16 to 7.83 from case control studies and relative risk of 3.11 [confidence interval (CI) 2.27–4.26] from cohort studies thereby indicating that diabetic subjects are three times at higher risk of acquiring TB. They also found higher associations of diabetes mellitus (DM) and TB in the populations from Central America, European Asia compared to North Americans.

As a result of the growing body of evidence, an expert meeting was organized by International Union against TB and Lung Disease, Paris, France in November 2009. The main objectives of the meeting were to determine whether there was enough evidence to make policy recommendations about joint diagnosis and management of both diseases, to address the research gaps and develop a research agenda around these gaps. Few key research questions were identified and categorized in the order of high, medium and low priorities (Anthony D Harries et al. 2010).

Now the incidence of TB is declining very slowly globally, at less than 1% annually. Speeding up the decline in incidence will require both scaling up of diagnostic and curative services (hopefully with the help of new tools that are now in the pipeline) and additional
preventative actions, including addressing diabetes and other risk factors that increase the individual’s susceptibility for TB. On the other hand, an increasing prevalence of diabetes may counteract the positive effects of improved curative services for TB.

In the face of this unprecedented health challenge, it is troubling that the potential public health and clinical importance of this relationship seems to be largely ignored and no significant initiative has been undertaken to jointly address this double burden. This neglect may have disastrous consequences.

RECENT INDIAN STUDY ON DIABETES MELLITUS PREVALENCE AMONG TUBERCULOSIS PATIENTS

In view of all these supporting facts, a study was conducted on screening TB patients for diabetes in India by MV Hospital for Diabetes along with World Diabetes Foundation. After obtaining a proper approval from central and state TB authorities, diabetes screening was conducted among TB patients registered in selected 5 TB units viz. 2 urban TB units—Jaibheem Nagar, Medavakkam, 1 semi-urban—Nandivaram and 2 rural—Budur and Beerakuppam of Chennai, Kanchipuram and Thiruvallur districts in Tamil Nadu for directly observed treatment, short-course (DOTS) treatment in the first quarter of 2011. More than 800 TB patients were screened for diabetes using 2 hours oral glucose tolerance test (OGTT) under this program. A pretested questionnaire was administered to collect sociodemographic, anthropometric details and other relevant details regarding TB and diabetes.

The key findings of the study were that 25.3% of TB patients had diabetes and another 24.5% had prediabetes. Out of 25.3%, 9% were newly detected and 16% were already diagnosed with diabetes. Moreover, the study revealed that men with TB are more likely to have diabetes than women. This gender difference was not observed among prediabetic subjects. Nearly half of the subjects, who had TB and diabetes, had infectious form of pulmonary TB. This particular finding and the growing number of people with diabetes in the community, denote the possibility of potential impact on TB control and TB treatment outcome as well (V Viswanathan et al. 2012). A retrospective study conducted in Texas also showed similar findings of more sputum smear positive cases in subjects with diabetes and TB compared to nondiabetic subjects (Restrepo et al. 2007).

Increasing age, body mass index (BMI), positive family history of diabetes, sedentary occupation and presence of pulmonary TB were the factors significantly associated with diabetes among TB patients. Age, central obesity, low income and smoking were the risk factors associated with prediabetes among TB patients (V Viswanathan et al. 2012). The available evidence also supports the findings of the current study such as TB patients with DM are usually older and more likely to have higher body weight. The outcome of the study suggests the need for screening each TB patient for diabetes.

In this study, it was also reported that among those previously diagnosed with diabetes, 34% had good control of diabetes, i.e. hemoglobin A1c (HbA1c) less than 7%, whereas another 33% had HbA1c more than 10%. The median duration of diabetes was 2.3 years ranging from 0.5–24 years? Regarding the compliance to treatment for diabetes, 92.4% reported regular compliance to diabetic treatment and about 39% were undergoing treatment in government health centers and 41% were undertaking treatment in private clinics. The complications and comorbid conditions reported among subjects with diabetes were hypertension (9.1%), cardiovascular disorders (6.8%), foot ulcers (2.3%) and one case with retinopathy (0.7%).

PATHOPHYSIOLOGY BEHIND DIABETES MELLITUS-TUBERCULOSIS ASSOCIATION

The diabetes patients have evidence of impaired cell-mediated immunity, micronutrient deficiency, pulmonary microangiopathy and renal insufficiency, all of which predispose to pulmonary tuberculosis (PTB). Innate and type 1 cytokine responses are higher in TB patients with associated diabetes than in nondiabetes control subjects.

Several studies indicate that patients with TB who have diabetes present with a higher bacillary load in sputum, delayed mycobacterial clearance and higher rates of multidrug-resistant (MDR) infection. Reviews of clinical studies show that diabetes patients with TB often present with lower lung infiltrates [similar to the radiographic pattern seen in patients with HIV/AIDS (acquired immunodeficiency syndrome)] and more cavitary lesions and may have worse treatment outcomes in terms of smear and culture conversion, case fatality and treatment failure. Recurrence or reactivation of previously treated TB with the onset of diabetes has been reported. Some risk factors may predispose to both diabetes and TB, e.g. tobacco smoking and alcoholism.

The stress due to a chronic infectious disease, such as TB, that causes considerable catabolism may increase insulin resistance and increase the demand for insulin secretion. When the increased demand cannot be met (due to a pre-existing low β-cell mass), as is often the case in poor TB patients with associated malnutrition, the potential underlying risk of diabetes may be unmasked.

Regardless of the direction of the association, the common diabetes-TB comorbidity presents clinical challenges: first, as a result of stress-induced hyperglycemia; second, because rifampicin [one of the key drugs in any antituberculosis treatment (ATT) regimen] may in itself have hyperglycemic effects; and third because of the interaction between rifampicin and several of the sulfonylurea group of oral hypoglycemic agents, including glimepiride, glipizide and glimepiride, which are metabolized by cytochrome P450 2C9 (CYP2C9), a liver enzyme induced by rifampicin.

Vallerskog et al. conducted an animal study which demonstrated that there was a delay in innate and adaptive immune responses against M. tuberculosis infection in diabetic mice compared to the normal mice. Diabetic mice also had significantly lower production of interferon-c (IFN-c) and interleukin-12 (IL-12) and fewer Mycobacterium tuberculosis antigens early secreted antigenic target 6 (ESAT-6)-responsive T cells immediately after the course of TB infection. This indicates a diminished adaptive immunity, which is essential for the control of TB infection (Martens et al. 2007).

REVERSE RELATIONSHIP—TUBERCULOSIS AS A RISK FACTOR FOR DIABETES MELLITUS AND ITS COMPLICATIONS

Some studies reported the reverse relationship, i.e. TB being associated with incidence of diabetes, possibly due to increased insulin resistance provoked by the intake of ATT drug—rifampicin.

The inflammatory changes associated with chronic infectious conditions may also be responsible for this association. In addition to the above, TB and its treatment may also worsen the glycemic control in a subject with diabetes, it may also facilitate the progression of complications related to diabetes especially neuropathy (Brostrom 2010).

TREATMENT OUTCOMES OF TUBERCULOSIS AMONG DIABETIC SUBJECTS

A delay in sputum conversion was observed in TB patients with diabetes (Singla et al. 2006; Restrepo et al. 2008, Dooley et al. 2009). A comparatively higher proportion of subjects with TB and DM had treatment failures, deaths compared with those without diabetes in Indonesian population (Alisjahbana et al. 2007). Though the authors had reported significant association of drug resistant TB with diabetes, there were few studies reporting that multidrug-resistant
TB was common among patients with TB and DM among certain populations in China (Zhang Quing et al.), United States and Mexico border (Basher et al. and SP Fisher-Hoch et al.), but it was not clear whether it was due to primary or acquired resistance.

In contrast, there were few studies reporting that TB treatment outcome among DM subjects was as good as when compared with non-DM subjects with the current treatment regimen (Singla et al. 2006, Rani B et al. 2007).

The association of poor TB treatment outcome among TB patients with diabetes could be attributed to the low serum level of rifampicin among diabetic subjects. Nijland et al. reported that exposure to rifampicin was 53% lower in TB-DM subjects compared to TB patients without DM. The low level of serum rifampicin was well-correlated with the increased body weight, plasma glucose concentration and presence of diabetes in this study. These findings indicate the need of standardizing rifampicin dosage for this high-risk group, although the study was done with limited study subjects (Nijland et al. 2006).

The association of severity of blood glucose level and TB treatment outcome among diabetic subjects with TB is not clear. The importance of maintaining a better glycemic control throughout the TB treatment regimen to assist in achieving better TB treatment outcomes is generally advised but it is yet to be cleared through longitudinal studies.

**MORTALITY RATE DUE TO TUBERCULOSIS—COMPARISON BETWEEN DIABETIC AND NONDIABETIC SUBJECTS**

Several studies indicate that diabetes is associated with increased death rate in patient with TB (Oursler et al. 2002, Dooley et al. 2009, Wang et al. 2009). These studies showed that the risk of death was six times higher in TB patients with DM. The study conducted in Taiwan showed that presence of type 2 DM, age more than or equal to 65 years and extensive radiographic disease were independently associated with poor TB treatment outcome (Wang et al. 2009). A recent review report by Baker et al. from studies adjusted for all confounding factors, reported a relative risk of 4.95% of TB patients with DM dying during TB treatment (Baker et al. 2011).

**PRESENTATION OF TUBERCULOSIS AND X-RAY FINDINGS IN DIABETIC SUBJECTS**

The presentation of TB in diabetic subjects may not be always different as they may also manifest themselves with the common symptoms in diabetic subjects as in any other individual without DM. The diabetic subjects with TB are more likely to have higher bacillary load.

There are two different opinions regarding the radiological images of TB patients with DM. Few studies reported that the DM subjects with TB are more likely to have cavitary lesions in lower lung fields. In contrast to the above findings, Bacakoglu et al. reported that involvement of multiple lobes and the presentation of multiple cavities were more common among diabetic patients and the disease in the lower lung was rarely common in diabetic patients than in controls, except for patients aged over 40 years in their study.

**ANTICIPATED PRACTICAL CHALLENGES**

The main challenge is to identify the high-risk group due to the iceberg phenomenon associated with diabetes. Considering the magnitude of undiagnosed diabetes in our population due to long asymptomatic period, a feasible strategy to screen the TB patients for diabetes must be initiated to address the dual burden. Regular diabetes screening in the patients diagnosed with TB and routine screening for symptoms for TB among DM patients attending various private and government organization will help in this issue. Bidirectional screening has been piloted in few TB and diabetic centers across India.

Among the various available screening methods, OGTT and HbA1c are the gold standard methods of screening for diabetes. Collaborative Framework for Care and Control of Tuberculosis and Diabetes recommends simple postprandial, random or fasting blood glucose estimations for mass screening followed by a confirmative test with gold standard methods in settings with limited resources.

Next, we have the challenges in screening for TB among DM patients. The intradermal tuberculin injection and the results read after 48–72 hours is found to be convenient but not specific in adults. Sputum examination is laborious and time-consuming but cost-effective. Interferon-gamma release (IGR) solves all the above issues. But the question is regarding the use of this more expensive tool in countries with limited resources and another concern is the lack of availability of specific laboratory facilities and equipment to perform this test.

The other major issue is the lack of any standard guideline for the management of diabetes in TB patients. The drug interaction between insulin and first line TB drugs is not reported so far except for the inducing effect of rifampicin on certain enzymes particularly CYP2C9 which is associated with the metabolism of sulfonylureas (Ruslami et al. 2010). A study conducted among elderly population in Canada showed that the use of gatifloxacin was associated with increased risk of hypoglycemia and hyperglycemia (Park-Wylie et al. 2006).

Diabetologists opine that the management of diabetes in patients with coexisting TB infection is individualized and recommend the use of insulin in the intensive phase of TB treatment, and gradually prescribe oral hypoglycemic agents depending upon the blood glucose control of the individuals in the continuation phase of TB treatment. The use of metformin in patients with liver disorders is not advisable. A study done in China reported a 50% increase in risk of hepatotoxicity among patients with TB and DM (Xiao et al. 2004). Moreover, diabetic subjects with complications such as neuropathy and nephropathy should be closely monitored when they are on ATT. Subjects with prediabetes need frequent monitoring of blood glucose, as they are prone to have full blown diabetes, when they are on standard TB regimen.

**CONCLUSION**

The diabetic epidemic challenges the global TB control, particularly because most of the countries with higher TB burden bear the higher burden of diabetes too. There are several unanswered questions, such as the association of TB treatment outcome and the glycemic control, whether regularly advised DOTS is adequate for patients with both the conditions, and whether chemoprophylaxis should be made mandatory for the diabetic subjects with latent TB infection. All these have to be addressed by conducting well-designed prospective studies. Integration of national level TB and diabetes programs is also essential to tackle the situation in India. As stated by Professor Anthony Harries et al. as in TB-HIV, we must adapt similar methods to prevent, screen and manage the two diseases DM and TB together and it is also vital to ensure the availability of medicines for proper management of the two diseases (Harries et al.).

The advantage of TB treatment adherence through existing DOTS can be utilized for the compliance to diabetic drugs and lifestyle modifications also, which will have benefit in the long run for the management of diabetes among those affected with both diseases.

The link between TB and DM has been established; what is needed now is good-quality implementation research to screen for, care for, prevent and monitor this dual burden of disease.
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