'Diabetes and tuberculosis' – a co-epidemic of public health importance in the developing world

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With the rising epidemic of diabetes mellitus (DM) and tuberculosis (TB) already being a major infectious disease of the world, when put together, this co-epidemic constitutes a threat to global public health. The situation is critical in countries like India which are facing the dual burden of non-communicable diseases and communicable diseases. This not only affects the national productivity, but also the national exchequer. Henceforth, a crucial health strategy is required to control this co-epidemic. This article reviews the epidemiology of DM and TB, TB and its characteristics, the effect of DM on TB treatment outcomes, screening methods and diagnosis, economic impact on the health sector and guidelines which could prevent this burden.

Keywords: Diabetes, developing countries, epidemiology, tuberculosis.

Introduction

INDIA has a high burden of both tuberculosis (TB) and diabetes mellitus (DM). The global TB report 2015 has shown that India contributes to 23% of all TB cases in the world, which adds up to 2.2 million cases[1]. There is sufficient evidence to support an association between DM and TB. The growing epidemic of DM challenges the global TB control, especially in low and middle income countries with increasing number of people with DM and prevalent TB. About 95% of patients with TB live in the low and middle income countries and 70% of patients with DM also live in such countries, especially in southeast Asia. The escalating prevalence of DM in developing countries is due to rapid economic transition occurring in them.

In 2015, there were 472 million people between 20 and 79 years of age, who suffered from DM. About 5 million deaths were attributed to DM in the same year, among which India has approximately 69.2 million people between 20 and 79 years of age with DM, according to the International Diabetes Federation (IDF) report[2]. The estimates projected for the year 2040 regarding the number of people affected by DM in India will be 123.5 million (ref. 2). In the year 2014, about 9.6 million people were infected with TB and about 1.5 million individuals died from the disease. Among these, approximately 95% of deaths occurred in low and middle income countries. Thus, TB ranks the most infectious disease killer in the world[3]. India along with Sub-Saharan Africa, accounts for the largest burden of TB[4]. Statistics suggested by World Bank estimates the incidence of TB in India as 167/100,000, for the year 2014. However, there is a recent decline in the number of incidence cases, from 180/100,000 for the year 2011. These data pertain to both new and relapse cases, including all forms of TB[5]. Stevenson *et al.*[6] showed 1.5–7.8 odds of developing TB for the individuals affected by DM in about nine studies. Additionally, they observed that the risk of developing TB was higher among young patients. According to the authors[6], nearly 15% of TB burden in India in the year 2000 was attributed to DM, whereas HIV accounted for 3.4% of TB cases. The prevalence of DM among pulmonary TB was 18.4% and it increased to 23.5% among those with infectious forms of TB[6].

Jeon *et al.*[7] have done a systematic review of 13 studies related to TB and DM. They reported an odds ratio ranging from 1.16 to 7.83 from case-control studies and relative risk of 3.11 (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 association of DM and TB in the populations from Central America, Europe and Asia compared to North America.

In 2011, understanding the severity of the co-epidemics of TB and DM, with the absence of national guidelines on joint management and to control the co-epidemics, the World Health Organization (WHO) along with International Union Against Tuberculosis and Lung Disease (The Union) launched a collaborative framework for care and control of TB and DM. The aim of the framework was to guide national programmes, clinicians and other individuals associated with prevention and control of DM and TB. This framework is only provisional and revisions are to be made in order to fill the gaps between the knowledge of DM and TB co-epidemics. However, despite the guidelines having been released, several challenges are

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being faced by countries like India and China, which record the highest load of TB and DM.

There are numerous studies from different regions of the world supporting the association of DM and TB. DM patients with TB have worse treatment outcomes, case fatality and treatment failure. There is some evidence to suggest that TB in diabetic patients may have different clinical manifestation. DM increases the risk of poor treatment outcomes in TB patients. Strict glycaemic control may achieve better treatment outcomes. Patients with DM, particularly those with poor control should be screened for active TB in higher TB burden countries similar to people who are susceptible to TB, such as HIV-infected individuals and prisoners. Screening for active TB among diabetics could improve case detection. Similarly, screening for DM among TB patients is highly recommended.

Epidemiology

DM and TB are well recognized for their huge global burden. India accounts for one-fifth of incidence of TB cases and ranks first among the 22 high-burden countries. At the same time, the prevalence of DM is also escalating in India. Several reports from different parts of the world showed high prevalence of DM among TB patients than that of general population.

Several Indian studies have reported high prevalence of DM among TB patients. Raghuraman *et al.*[8] conducted a facility-based cross-sectional study and noticed the prevalence of diabetes to be 29% among TB patients. The high prevalence of diabetes among patients with TB has also been shown from the states of Tamil Nadu and Kerala. Viswanathan *et al.*[9] in their cross-sectional study in TB units in South India, reported the prevalence of diabetes and pre-DM among TB patients to be 25.3% and 24.5% respectively, almost 50% of TB patients had some form of hyperglycaemia. Balakrishnan *et al.*[10] using glycosylated haemoglobin (HbA1c) as a diagnostic tool, reported DM prevalence of 44% among TB patients[10].

DM was found as the most frequent risk factor for pulmonary TB in another retrospective study from India[11]. Pakistan reported ten times higher prevalence of DM in TB patients compared to normal population[12]. In Zambia, another country with a very high TB burden (462/100,000 population), it was found that TB comorbidity was significantly associated with DM (OR = 6.5, 95% CI 1.7–25.3)[13,14]. Conversingly, in countries with a low TB burden such as Australia (5.8/100,000), TB risk in diabetic patients was increased only moderately (adjusted relative risk RR = 1.48, 95% CI 1.04–2.10)[15]. In a cohort study from Hong Kong, patients with well-controlled DM had lower risk for TB[16]. This finding suggested that hyperglycaemia itself rather than DM diagnosis per se may play a role in the development of the active TB. In the United Kingdom with low TB prevalence, TB rates due to DM varied greatly among ethnic minorities[17].

A modelling study analysed the potential effect of DM on TB epidemiology in 13 countries with high TB burden. The study estimated the TB burden that can be reduced by alternative scenarios of DM prevention. Lowering the prevalence of DM by an absolute level of 6.6–13.8% could accelerate the decline of TB incidence by an absolute level of 11.5–25.2% and TB mortality by 8.7–19.4%. If interventions reduce DM incidence by 35% by 2025, 7.8 million TB cases and 1.5 million TB deaths could be averted by 2035 (ref. 18). There is little doubt that it is DM predisposing to TB rather than TB infection leading to DM. Also, DM is still more frequently diagnosed earlier than TB[8,19]. Nonetheless, screening for any glucose intolerance in TB patients has to be underscored.

Pathogenesis of DM and TB association

The pathogenesis of the association between DM and TB is quite complex. There is evidence that DM increases the risk of development of respiratory infection[20]. DM impairs both innate and adaptive immune responses to mycobacterium TB. TB-specific IFN-γ-producing T-cells migrate later both to lymph nodes and lung. The cytokines associated with the innate and adaptive immune response were reported to be up-regulated in diabetic TB patients, especially in those with poor metabolic control[21–23]. Several studies reported that patients with TB who have DM present with a higher bacillary load in sputum, delayed myobacterial clearance and higher rates of multi-drug resistance (MDR) infection. The association between DM and TB presents important clinical challenges in terms of stress-induced hyperglycaemia; rifampicin used in anti-tuberculosis treatment may itself have hyperglycaemic effects. The interaction between rifampicin and some of the sulphonylurea group of oral hypoglycaemic agents may also have this effect. There is a need for evidence-based approach for understanding the susceptibility mechanism to tackle the dual burden of DM and TB. Among various mechanisms, vitamin D deficiency was also considered to be associated with TB (OR = 2.9, 95% CI; 1.3–6.5)[24].

Clinical presentation

The co-existence of TB and DM in patients may modify TB symptoms, radiological findings, treatment, final outcomes and prognosis. One study conducted in Indonesia reported a higher symptom score in DM–TB patients[25]. In another study from Turkey, the only symptom more commonly found in diabetic patients was cough, suggesting that the distribution of symptoms is not seriously affected by DM[19]. Similarly, in a retrospective analysis of TB patients, no difference was found in presenting symptoms between the TB–DM and control TB group. The most common symptoms observed equally in both groups were low-grade fever and productive cough[26]. The bacteriological aspects of TB revealed that diabetic subjects

with TB are more likely to have higher bacillary load. DM is an independent risk factor associated with more acid fast bacilli (AFB) on sputum smear examination[26,27].

With respect to the radiological manifestation of TB, few studies reported that the DM subjects with TB are more likely to have cavitary lesions in lower lung fields[28,29]. One explanation for this atypical presentation may be that in the elderly and DM patients, increased alveolar oxygen pressure in the lower lobes promotes disease development in these areas. A study conducted in Saudi Arabia showed lower lung field lesions as well as cavitary lesions to be significantly more common in DM–TB than in the control group (23% versus 2% and 50% versus 39%)[26]. On the contrary, Bacakoğlu *et al.*[30] reported that involvement of multiple lobes and 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 the control subjects[30]. The differences may be more apparent in DM patients with uncontrolled diabetes[31]. The other factor related to the frequency of cavitary lesions was insulin dependency[30]. These conflicting results may be partly due to varied selection of patients.

DM does not seem to modify the clinical course of TB with respect to sex distribution. It is widely known that there is higher frequency of pulmonary TB in males. DM patients with TB appear to be older than non DM subjects[25]. DM was classified as type-2 (T2DM) in majority of studies in TB–DM[32]. Socio-demographic and clinical characteristics were different in patients with DM–TB compared to those with DM only. DM–TB patients were older, had lower education levels and socio-economic status, a higher frequency of smoking, alcohol use, a longer duration of DM, a greater likelihood of being on oral medication and insulin, and lower BMI and poor glycaemic control[33].

Effect of DM on treatment of TB

DM increases the risk of adverse treatment outcomes in patients with TB[25,32]. A delay in sputum conversion was observed in TB–DM patients[25,27,34–36]. Restrepo *et al.*[36] reported that within 60 days the mycobacterial clearance was delayed by 5 days. Alisjahbana *et al.*[25] conducted a prospective cohort study to predict the negative treatment outcome of diabetes with TB in urban settings of Indonesia. At the end of 6 months of therapy, TB and DM were associated with more positive sputum culture, after adjusting for confounders[25]. Viswanathan *et al.*[34] assessed the sputum conversion rate at the end of the intensive phase of DOTS therapy and about 14.7% of TB–DM patients had positive sputum smear. The relative risk to remain sputum smear positive at the end of the intensive phase was estimated to be 3.9 (95% CI: 1.5–10.6). The average duration in days, required to convert to smear negative in the TB–DM arm was higher (64.5 ± 10.5), compared to non-DM–TB arm (61.5 ± 7.5; $P < 0.001$)[34]. DM was also found to be responsible for higher rates of treatment failure and deaths in individuals affected by TB[37]. In India, when the treatment outcomes were compared between DM–TB and non-DM–TB patients, there was about 4.2% of treatment failure in the former group compared to 0.7% in the latter group of patients[34].

A prospective study carried out for 15 years in southern Mexico found a prevalence rate of TB in diabetics as 29.6%. Additionally, it identified that DM with TB was related with severe clinical manifestation based upon presence of pulmonary cavities in chest X-ray (aOR = 1.80), delayed sputum conversion (aOR = 2.9), recurrence rate (aHR = 1.76) and a relapse rate (aHR = 1.83). The risk of failure as a sole outcome of diabetes was found to be 2.93 (95% CI 1.18–7.23)[38]. Analysis of TB patients in Brazil found that TB with DM was associated with higher acid fast bacilli-positive sputum smear samples at the time of diagnosis; this remained higher up to 30 days after anti-tubercular treatment. Although, at the end of 60 and 180 days, no difference in sputum smear samples was found in diabetic TB and non-diabetic TB arms[39]. In contrast, few studies reported that TB treatment outcome among DM subjects was as good as that of non-DM subjects with the current treatment regimen[26,40,41].

The association of poor TB treatment outcome among TB patients with DM could be attributed to high rate of drug resistance, due to impaired cellular immunity and lower plasma levels of anti-tubular drugs, particularly rifampicin[42,43]. Few studies showed an increased risk (2.1–8.8 times) of multi-drug resistant (MDR)-TB among patients with DM[44,45]. Few studies showed no relation between DM and MDR-TB[46,47]. All the above findings indicate the need of standardizing rifampicin dosage for the high-risk group, but there is not sufficient evidence to recommend alternative anti-tuberculosis regimen for DM. The treatment remains the same for TB patients with and without DM. It is important to maintain a better glycaemic control throughout the TB treatment regimen to achieve better TB treatment outcomes.

Screening and diagnosis

A pilot project in India explored the potential for bidirectional screening – patients with DM for TB and patients with TB for DM[48,49]. This was inspired by a study conducted in China[50]. In 2011, a prospective observational study was done in China to monitor the implementation project for screening in five diabetic clinics for TB, strictly based upon the criteria set by China National TB Control Programme (NTP). Results obtained from the study found relatively less individuals identified with TB in absolute terms. However, the TB case notification rate was higher (range 31–111/100,000 population) when compared with the general population (78/100,000). Challenges faced with implementation of this strategy were lack of properly trained staff in diabetic clinics, a constant

pressure upon doctors to screen diabetic patients for TB under routine settings, under-reporting of positive sputum screen and lack of active tracking system that failed to report the adherence for treatment among DM–TB patients. Conclusively, this study proved to be advantageous as it shows that screening active TB in diabetic clinics leads to early detection of TB, prompt treatment and better clinical outcome for anti-TB treatment as well as routine DM care. Additionally, it also sets an example for establishing strong monitoring, recording and reporting of TB–DM cases[50].

Screening in India resulted in the case rate of TB among diabetics to be higher than TB case notification released by Regional National Tuberculosis Control Programme (RNTCP), i.e. 107/100,000 in 2011. Challenges in this study included no additional staff appointed to screen diabetic patients for TB and hence the study faced additional work, reluctance of patients to give sputum specimen, loss of follow-up of patients and lack of electronic database system. Besides several limitations of the study, the strengths were an implementation screening strategy possible without any extra allotment of special support and feasibility of screening diabetic patients for TB in a routine system[48]. Additional study which assessed the practicability of screening TB patients for DM in India showed the prevalence of 13% DM in patients with TB. According to the findings of this study, if scaled up, there could be approximately 286,000 cases of known DM in TB cases and 110,000 cases of newly diagnosed DM[49]. The study showed the feasibility of identifying DM in patients with TB and TB in patients with DM, prompting the Indian authorities and policy makers to recommend such screening as part of their control efforts.

Among the various available screening methods, Oral Glucose Tolerance Test (OGTT) and Glycosylated Haemoglobin (HbA1c) are the standard ones for DM. In determining the most appropriate screening strategy, the impact of DM on clinical manifestation of TB should be considered. A recent study from South India compared the performance of HbA1c and Fasting Plasma Glucose (FPG) of DM screening for diabetes among people with TB, and reported HbA1c to be a better diagnostic tool for the diagnosis of DM among TB patients[51]. The study highlighted the urgency to have a reliable, convenient, accurate screening and diagnostic tool for patients suffering from TB and DM.

Systematic screening of patients with DM for TB by enquiring about TB symptoms such as chronic cough, night sweats and weight loss will be a cost-effective strategy in most countries with higher burden of TB. The number of diabetics needed to screen to find one extra case of TB is directly related to the local TB prevalence. For example, in the setting with TB prevalence less than 25 per 100,000 persons, at least 1000 diabetic persons have to be screened to find one extra case of TB. When the prevalence is greater, the number needed to screen to find one additional case of TB ranges from 4 to 442. Therefore, the yield of screening increases with the prevalence of TB in the region[52].

Further research is needed to determine the optimal time and best methods for diagnosing DM in patients with TB, focusing on adults stratified by the type of TB. The most appropriate ways of DM screening should be explored[53].

Training of healthcare staff

The alarming figures on the prevalence of DM and TB has highlighted the need to create awareness on screening for DM in TB patients and for TB in DM patients. Healthcare staff should understand the link between DM and TB. Education in DM clinics on symptoms of TB, screening and diagnosis may improve care and preventive therapy in patients with DM. Similarly, it is also essential to assess the knowledge, attitude and practice of TB health workers towards DM. A training programme specifically directed at TB healthcare providers on DM screening, diagnosis and management empowered them with knowledge, improved their attitude and practice[54].

Viswanathan *et al.*[54] aimed to increase the knowledge and skill of 300 paramedics and 350 health workers for screening and detection of DM, as well as help doctors for treating TB patients for the prevention, diagnosis and management of DM. The study proved the importance of training for better understanding of TB–DM epidemics among health professionals and paramedics. Furthermore, it demonstrated increased awareness of DM among TB patients, and thus better compliance of patients towards screening and positive attitude towards DM care. Urban settings and other countries known to have higher TB and DM incidence would be the most appropriate places to conduct such training programmes.

Economic burden

DM and TB have existed for many years and even now the global disease burden is huge. The burden of DM is increasing exponentially in countries where TB is endemic. The intersecting double burden is hence ominous, particularly as several studies and systematic reviews have indicated that DM increases the risk of TB and results in poor treatment outcomes. Economic burden of TB and DM has a significant impact on society, which includes the direct costs of healthcare and indirect costs of disability, lost productivity and death. No well-designed assessments have been made out on the economic impact of TB–DM, though assessments have been made on the economic impact of each disease individually.

In 2007, the World Bank conducted a study on TB and found that the economic burden of the disease between 2006 and 2015 for the world's 22 'high burden countries' would have ranged between US$ 1.18 billion and US$ 3.33 billion for each country[55]. An estimated 75% of

people who develop TB are between the ages of 15 and 54 years, which tend to be their most economically productive years[56]. In developing countries such as India, there is no insurance coverage to treat DM; the out-of-pocket costs towards treatment are significant, commonly leading households to sell their possessions, which has significant impact[57]. It is projected that by the year 2030, the direct costs of DM will increases to US$ 486 billion globally; high-income countries are projected to face 25.4% of the cost, with middle-income countries facing 72.1% and low-income countries facing 2.5% (ref. 58). Previous studies have revealed that the cost spend towards TB and its treatment is overwhelming, especially for poor people. An average of 20–30% of the annual income and nearly 70% of the per capita income was incurred towards TB treatment[59–63]. The India study highlighted that the average cost towards treatment of TB was much higher than the annual income of patients in the groups with lowest socio-economic status compared to those in groups of higher socio-economic status (68% versus 32% of annual per capita income in the case of Myanmar)[64,65]. In these studies, most of the cost of TB treatment was incurred before start of the treatment. It covered both direct costs, including medicines, laboratory tests, consultation fees, transport and indirect costs due to loss of income. Much of the cost was incurred in the private sector. Other studies highlighted that the direct cost for TB treatment was substantially higher when people accessed care in the for-profit private sector[66,67]. TB patients incurred more indirect cost than direct cost, which indicated their economic burden even though anti-TB drugs were provided free of charge through DOTS programme. Thus, it is recommended to develop a strategy for financial protection of low-income groups against the economic impact of disease. Adverse social consequences of TB, such as rejection by family and friends, divorce, expulsion from school and loss of employment have been reported in many studies, and seem to be particularly severe for women[68–70]. The enormity of cost burden for treatment and mounting evidence of a TB–DM co-epidemic underscore the urgent need for a robust economic assessment that accounts for the pernicious interaction of TB and DM.

Recent advances

In terms of recent advances to halt the co-epidemic of DM and TB, in 2014 the World Health Assembly approved the new WHO stop TB strategy, by addressing the importance of DM, a risk factor for TB. In the same year, the World Diabetes Foundation (WDF) and The Union made recommendations for practical action around policy, programme implementation, financial and technical assistance, health service delivery, and advocacy to control the dual burden of DM and TB. In 2015, The Union and WDF co-hosted a Global Summit in Bali, Indonesia. This was done to launch the sustainable development goals (SDGs), initiated from January 2016 to guide the development agenda for control of TB and DM epidemic up to 2030 (ref. 71). The Bali Declaration featured some interesting points regarding the co-epidemics of TB and DM. First, it has declared the dual burden of DM and TB as greatest global health challenge of the present time. Furthermore, it stressed that co-epidemics of DM and TB is hampering control of TB. Therefore, an immediate action should be taken to avoid death related with dual burden of DM and TB. Lastly, the Declaration aimed at enhancing the health as well as offering financial protection and quality of life to people are affected by the co-epidemics. Thus Bali Declaration stresses upon the following: to accelerate the implementation of collaborating framework for control of TB and DM and promote the policy of bidirectional screening; support and increase the capacity building for prevention, diagnosis and treatment of both DM and TB; to provide continuous and uninterrupted treatment of DM and TB with affordable cost; to foster the research development in the field of diabetes and TB co-epidemic; and lastly, to advocate a swift, decisive action against TB and DM dual burden in affected states, national and international forums[71]. SDGs aim to end TB-related deaths, transmission and catastrophic costs by 2030. A multisectorial action to accelerate socio-economic development and to develop new vaccines and novel diagnostics and medicines are the key advances needed to end TB transmission. Minimizing the costs associated with TB requires the expansion of health insurance coverage, comprehensive coverage of TB services and limited indirect costs by vulnerable and poor populations[72].

A very recent interim report from South India studying the effect of diabetes on tuberculosis severity (EDOTS) revealed a strikingly high prevalence of DM and pre-DM in adults with pulmonary TB. Glycaemic control heterogeneity was also noted, which has implications for the TB–DM interaction and interpretation of the diagnosis in TB studies[73].

Conclusion

An emerging body of evidence has shown that where rates of TB–DM have been carefully measured showed significant and higher rates than the researchers previously believed. The association between DM and TB is a major challenge for global TB control. The rising prevalence of DM might counteract gains in TB control by adding to the disease burden in low- and middle-income countries. Furthermore, a greater focus is needed on the epidemiology of the association between DM and TB. There is strong evidence of an adverse influence of DM on TB manifestation and treatment. We need to know whether optimal metabolic control reduces TB risk and improves the outcomes. Given the economic losses caused by TB and DM, and the cost of drug-sensitive and

drug-resistant TB, control of these epidemics is crucial. Moving from polycentric governance to a proper streamlined and coordinated effort as this convergent burden unfolds is perhaps the greatest challenge in meeting the co-epidemics of TB and DM due to their multifactorial pathogenesis nature. The current DM epidemic in developing countries like India has potentially serious implications for TB control. An integration of national-level TB and DM programmes will serve as a major solution to tackle the situation in our country. It must become a priority to initiate focused and coordinated action, including new research in parts of the world where DM is epidemic and TB endemic to properly inform public health and clinical practice. All the issues related to DM–TB must be addressed by conducting well-designed prospective studies.

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