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Tuberculosis and Diabetes Mellitus: A Double Whammy for the Developing Nations

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Abstract

With one-third of the estimated global population having tuberculosis and 10 million new cases added yearly, tuberculosis remains a persistent global public health problem requiring urgent attention. India has the highest tuberculosis burden (2.1 million new cases and 280,000 deaths annually) with the second largest diabetic population of the world. Nearly 40-50% adult population in India have tuberculosis infection; primary infection reactivates to clinical disease in 5-10% individuals, rest remaining latent. Conversion from latent to active disease is mainly due to underlying immunodeficiency states, diabetes being a pre-eminent cause.

Tuberculosis and diabetes interact with each other at multiple levels. Diabetes triples the risk of tuberculosis. An estimated 15% of adult TB worldwide is attributed to diabetes. India and China together account for >40% of all diabetes associated tuberculosis cases; diabetes accounts for 14.8% of overall pulmonary and 20.2% smear-positive tuberculosis. Diabetic tuberculosis patients on anti-tubercular treatment (ATT) remain contagious longer than non-diabetics on ATT. Tuberculosis itself can lead to impaired glucose tolerance and overt diabetes. Moreover, certain anti-tubercular drugs interact with oral anti-diabetics, making diabetes control difficult.

Development of universal, cost effective bi-directional screening methods for tuberculosis in diabetics and vice-versa could improve outcome of both diseases. However, universal screening for diabetes alone is not feasible in developing nations; additional screening for tuberculosis or bi-directional screening would be an extra burden. Certain measures, based on context of local health systems and availability of resources can be adopted: (i) tuberculosis surveillance among diabetics in regions with medium to high tuberculosis burden; (ii) assessing cost-effectiveness of universal tuberculosis screening in all diabetics; (iii) establishing dedicated referral system for diabetics with suspected tuberculosis to specialized centers; (iv) screening tuberculosis patients for diabetes at the start of ATT; (v) research in developing more effective treatment strategies for concurrent tuberculosis and diabetes.

Keywords: Tuberculosis, Diabetes mellitus, Co-epidemic, Developing nations, Bi-directional screening

Introduction

Tuberculosis (TB) is a global health problem of major magnitude. In 2012, 8.6 million people developed TB and 1.3 million died from the disease [1]. About one in three persons worldwide, an estimated two billion people, live with latent TB infection [1]. In most cases this infection remains dormant and asymptomatic throughout the person's life. However, the risk of progression of this latent infection to active TB increases significantly with compromise in the immune system of the person. Diabetes is one of the common diseases which lead to this compromise in the individual's immune status and hence leading to flare up of latent TB into active form. Diabetes increases the risk of developing active TB and is associated with worse overall TB treatment outcomes. Globally, an estimated 15% of tuberculosis cases are attributable to diabetes [2]. The prevalence of diabetes has increased rapidly during the past few decades, from 35 million in 1985 to nearly 387 million in 2014 worldwide, and is projected to rise to 592 million in 2035, an increase by 53% during the next 20 years [3]. With diabetes on the rise globally coupled with the enormous burden of latent TB infection as well as active TB disease in developing countries, TB and diabetes is a looming co-epidemic [4]. Furthermore, in countries where diabetes is escalating and TB rates are already high, diabetes will increasingly impede efforts to control TB. Therefore, diabetes will make an increasingly important contribution to the TB epidemic, more so in developing nations, making these countries face a double whammy of TB-diabetes co-epidemic.

Historical Background

Anecdotal evidence about the deadly interplay between TB and diabetes has existed since time immemorial. Avicenna, the Greek philosopher recorded around 1000 A.D. that TB, then known as "pthisis" caused complications among people having diabetes, and diabetes was responsible for increasing the risk of developing "pthisis" [5]. The Indian saint Yugimahamuni described the symptoms caused by TB and diabetes as a syndrome he called "meganoikal" [6]. Newer data demonstrating the important link between TB and diabetes have re-emerged within the last decade. In 2007 and 2008 two systematic reviews [7,8] conducted by the Medical Research Council (WHO) and Harvard University respectively has clearly shown that diabetes makes a person two to three times more likely to develop TB and that the interaction between the two diseases constitutes a worldwide health threat. On account of such growing evidence, in 2011, the

International Union against Tuberculosis and Lung Disease, Paris, France, and the World Health Organization released The Collaborative Framework for Care and Control of Tuberculosis and Diabetes, which provides evidence-based guidance for policymakers and health program implementers to begin addressing the growing epidemic of diabetes and TB [9].

Epidemiological Evidence of Association between Tuberculosis and Diabetes

TB, which is caused by Mycobacterium tuberculosis, continues as a latent infection in up to one-third of the global population. People with latent TB, on an average, have a 5-10% of lifetime risk of progressing to active TB. This conversion from latent to active disease is mainly due to underlying immunodeficiency states, diabetes being a pre-eminent cause [1]. The treatment of TB normally requires the use of multiple anti-tubercular drugs for at least 6 months or even longer. This is further complicated by the development of multi-drug resistant TB, accounting for approximately 500,000 cases globally, which requires treatment with expensive and potentially toxic, second-line anti-tubercular drugs for much longer durations. Evidence shows that diabetes can increase TB risk. Studies from Africa and Asia have shown that as much as 40 - 50% of the adult population have TB [1]. India and China together account for greater than 40% of the diabetes associated TB cases [10]. India has the highest burden of TB in the world. It is estimated that about 40% of the Indian population is infected with TB with 2.1 million new cases and 280,000 deaths annually [1]. Studies suggest that diabetes accounts for 14.8% of overall pulmonary tuberculosis and 20.2% of smear-positive (infectious) TB [11].

The TB – Diabetes Interaction

TB and diabetes interact with each other on a number of levels, with each disease exacerbating the other. Diabetes triples a person's risk of developing tuberculosis [12]. The likelihood that a person with TB will die, or will have a relapse after being successfully treated for TB is also significantly higher among people with diabetes [13]. Studies have further shown that among patients who are being treated for TB, those having diabetes remain contagious for a longer duration than non-diabetics [14]. TB can lead to impaired glucose tolerance, which is a risk factor for developing overt diabetes [15]. Diabetes increases the general risk of infection, but the precise cellular or molecular mechanisms that cause diabetes to predispose a person to develop TB is not known. Data from meta-analysis have shown that the combined outcome of tuberculosis treatment failure and death was significantly higher in patients with diabetes than in those without diabetes and they were more likely to remain sputum smear positive at 2-3 months after starting treatment for tuberculosis [13].

Furthermore, treatment with anti-tubercular drugs, especially rifampicin, can make it more difficult to control diabetes because of interaction between anti-tubercular and anti-diabetic medications. There are also growing concerns that oral anti-diabetic medicines can decrease the effectiveness of anti-tubercular drugs. Controlling blood glucose levels has been shown to reduce the risk of developing TB in diabetics, but it is not yet clear what should be the optimum glucose control necessary to reduce this risk of TB development [16].

Clinical Presentation of Tuberculosis in Patients with Diabetes

Evidence with respect to the clinical presentation of TB in individuals with diabetes is inconsistent. Nevertheless, patients with TB with concurrent diabetes have a slight male preponderance, are usually older, and have a higher BMI than the general TB population without diabetes [2]. Two systematic reviews [17,18] have shown that there is no strong evidence of differences in radiographic presentation of TB in patients with or without diabetes. However, a recent study has shown that patients with TB with concurrent diabetes had more lung cavities and parenchymal lesions than TB patients without diabetes; among TB patients with concurrent diabetes these radiographic abnormalities were found to be more common in those with poorer glycaemic control [19].

Challenges in Diagnosis and Treatment

The management of TB and diabetes is challenging, especially so in low-income settings with medium to high burden of disease. In this regard development of a bi-directional screening system is the primary need of the hour for optimal management of this looming epidemic.

One approach for TB detection would be to systematically screen for active tuberculosis in people with diabetes. Systematic screening for TB in people with diabetes could improve early detection in settings with a high TB burden. The number needed to be screened to detect one previously undetected case of TB in countries with a high TB burden like India ranges from 17 to 776, depending on background TB epidemiology and the sensitivity of the screening algorithm [12]. To screen people with diabetes for TB, diabetes has to be diagnosed first, and therefore TB screening is subject to improved access to diabetes diagnostic services. Increase access to health services is the key to improve the early diagnosis of both diseases, and this should be integrated across health conditions and health sectors [20]. Studies from various settings have shown that screening on the basis of symptoms and chest radiography for TB is operationally feasible in diabetes clinics in countries with a high tuberculosis burden, like India and China [2]. Most of the studies that have been carried out such screening for TB are either based on radiography or sputum microscopy. We failed to find any study that used alternative tests in individuals with diabetes to detect TB, such as computer-aided radiography reading or Xpert MTB/RIF assay which are being increasingly utilized in countries with a high burden of tuberculosis [21]. At a minimum, people with diabetes should be screened for chronic cough, night sweats and fever at the time when they are first diagnosed to have diabetes and, if possible, this screening for TB should be carried out during regular check-ups for their diabetes. People found to have symptoms of TB should be investigated according to the existing national TB guidelines of the country.

As a step further, universal screening for TB in all persons in whom diabetes is diagnosed, regardless of their symptoms of TB, should be explored as part of the research agenda to improve the diagnosis of TB among people with diabetes and to determine whether screening is in fact cost-effective. If it is found to be so, it can be implemented in the national health policies of TB in countries where the disease is endemic. However such mass screening policies can be technically and economically challenging. The type of screening and diagnostic tests should also be adapted to the context of local health systems and the availability of resources.

Latent tuberculosis infection can be detected with the tuberculin skin test or interferon gamma release assay, both of which screen for immunological memory [22]. Few studies have addressed the issue whether individuals with diabetes and latent tuberculosis infection are at an increased risk of progression to active tuberculosis [23]. Screening for latent tuberculosis infection in individuals with diabetes, in particular those with highly deranged glycaemic control, could help to identify a high-risk population that could be offered preventive therapy. Though screening for latent TB has yet not been recommended by WHO, it may be a topic of debate in the years to come.

Another issue of controversy is the use of TB chemoprophylaxis in high endemic countries. The effectiveness of chemoprophylaxis has been well established for close contacts of people with active tuberculosis such as household members. TB contacts with additional risk factors such as diabetes probably benefit more from treatment than those without such risk factors. However, there has been a paucity of randomised controlled trials to specifically assess the effectiveness of TB chemoprophylaxis in people with diabetes. A couple of observational studies from the 1950s and 1960s have reported a lower risk of tuberculosis in people with diabetes who were taking chemoprophylaxis than in those who were not [24,25]. However both the studies had methodological flaws; neither study specified the indication for chemoprophylaxis, nor used controls for confounders. Further research is hence needed to elucidate the possible use of chemoprophylaxis regimens for future use.

Surveillance of TB should be conducted among diabetes patients in settings with medium to high burdens of TB. Surveillance of diabetes should be conducted among TB patients in all countries. A referral system should be established so that patients suspected of having TB are promptly referred to TB diagnostic and treatment centres. They should also be evaluated according to national guidelines of the national TB control program. Healthcare facilities, including diabetes clinics, should have an infection control plan in line with the established WHO guidelines for TB infection control.

The optimum treatment strategy for concurrent TB and diabetes is not clearly defined. In general, patients with TB and diabetes are not treated differently than patients with TB alone. However, this approach might need to be reconsidered in view of higher rates of treatment failure in cases of TB with concurrent diabetes. Increase in the rates of TB treatment failure in patients with diabetes is unlikely to be due to high rates of M. tuberculosis drug resistance or low treatment compliance [26]. Alternative causes of treatment failure that can be speculated could be more extensive TB disease, an altered immune response in people with concurrent diabetes or reduced concentrations of anti-tubercular drugs in patients with diabetes [2]. Diabetes could indeed affect the pharmacokinetics of anti-tubercular drugs and hence doses of these drugs should be adjusted according to a patient's weight, although this strategy might be difficult when fixed drug combinations are used. Another option to improve TB treatment outcomes in patients with diabetes might be to extend treatment duration, a possibility that is advocated in some guidelines but has yet to be methodically studied. However, toxic effects of first-line anti-tubercular drugs, especially peripheral neuropathy with isoniazid and ocular toxic effects with ethambutol, should be considered as these could be more common in patients with co-existing diabetes [27]. To achieve good glycaemic control, an aggressive approach for diabetes management in patients with TB has been suggested [6]. With respect to the choice of anti-diabetic medications, possible drug-drug interactions should be taken into account, especially for rifampicin, which is the most important anti-tubercular drug.

Diabetes and TB - The Way Ahead

Studies carried out in India and China has paved the path for avenues in future research. The India Tuberculosis-Diabetes Study Group [28] assessed the screening of TB patients for diabetes in eight hospitals and more than 60 clinics across India. The study found that the screening process was feasible and worked well. Thirteen percent of the more than 8,000 TB patients screened had diabetes. If similar rates of diabetes exist among TB patients nationwide, the result of this screening process could be extrapolated to identify 286,000 persons with concurrent TB and diabetes across the country. This is an important and promising observation, because diabetes is believed to be undiagnosed in over half of individuals living with the disease. This pilot study has shown that it is feasible to conduct bidirectional screening for diabetes and TB in India, but more research is needed to determine the most effective way of doing it. If carried out effectively, given the high rate of both diseases in India, bidirectional screening should lead to earlier detection of both TB and diabetes, and earlier and better treatment of both diseases.

Similarly, based on the 2011 "Collaborative Framework for the care and control of Diabetes and Tuberculosis" [29], the healthcare system in China also piloted routine bi-directional screening of TB and diabetes. The pilot project was carried out in five diabetes clinics throughout China. The outcome of the project suggests that screening diabetic patients for TB results in increased and earlier detection of TB, better and earlier treatment of TB, improved outcomes for TB treatment and diabetes care, as well as a reduced risk of TB transmission. This pattern of screening, which included routine data recording and analysis, may also improve data collection on diabetes and serve as a model for other non-communicable diseases.

Conclusion

Diabetes is rising rapidly worldwide and is increasing the spread of TB in the developing countries. Successful TB control programs are being undermined by the increasing rates of diabetes in many developing countries. It is within our power to respond to the looming TB-diabetes co-epidemic and forestall its most harmful consequences. However, appropriate measures need to be taken effectively and promptly at multiple levels of the health care delivery system. Integration of health services could result in better TB prevention, an early diagnosis and treatment for diabetes, and improved care for concomitant disease. The call for the hour is to generate the necessary evidence for improvements in patient services and policies with respect to the combined epidemic of TB and diabetes.

References

1. WHO. Global tuberculosis report (2013) Geneva: World Health Organization, 2013.
2. Riza AL, Pearson F, Ugarte-Gil C, Alisjahbana B, van de VijverS, et al. (2014) Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. The lancet Diabetes & endocrinology 2: 740-753.
3. IDF Atlas 2014.
4. Harries AD, Lin Y, Satyanarayana S, Lönnroth K, Li L, et al. (2011) The looming epidemic of diabetes-associated tuberculosis: learning lessons

from HIV-associated tuberculosis. The International Journal of Tuberculosis and Lung Disease. 15: 1436-1445.

5. Dooley KE, Chaisson RE (2009) Tuberculosis and diabetes mellitus: convergence of two epidemics. The Lancet Infectious Diseases 9: 737-746.
6. Niazi AK, Kalra S (2012) Diabetes and tuberculosis: a review of the role of optimal glycemic control. J Diabetes Metab Disord 11: 28.
7. Stevenson CR, Critchley JA, Forouhi NG, Roglic G, Williams BG, et al. (2007) Diabetes and the risk of tuberculosis: a neglected threat to public health? Chronic Illness 3: 228-245.
8. Jeon CY, Murray MB. (2008) Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 5: e152.
9. Kapur A, Harries AD (2013) The double burden of diabetes and tuberculosis-Public health implications. Diabetes research and clinical practice 101: 10-19.
10. Tahrani AA, Cobelli C, Renard E, Kovatchev B, Rigby MR, et al. (2014) Diabetes and tuberculosis—a wake-up call. The Lancet 2: 677-764.
11. Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, et al. (2007) Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. BMC public health 7: 234.
12. Lönnroth K, Roglic G, Harries AD (2014) Improving tuberculosis prevention and care through addressing the global diabetes epidemic: from evidence to policy and practice. The Lancet Diabetes & Endocrinology 2: 730-739.
13. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, et al. (2011) The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC medicine 9: 81.
14. Viswanathan V, Vigneswari A, Selvan K, Satyavani K, Rajeswari R, et al. (2014) Effect of diabetes on treatment outcome of smear-positive pulmonary tuberculosis—a report from South India. Journal of Diabetes and its Complications 28: 162-165.
15. Guptan A, Shah A (2000) Tuberculosis and diabetes: an appraisal. Indian Journal of Tuberculosis 47: 2-8.
16. Restrepo BI, Schlesinger LS (2013) Host-pathogen interactions in tuberculosis patients with type 2 diabetes mellitus Tuberculosis (Edinb) 93: S10-S14.
17. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W (2009) Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg 80: 634-639.
18. Ruslami R, Aarnoutse RE, Alisjahbana B, van der Ven AJ, van Crevel R (2010) Implications of the global increase of diabetes for tuberculosis control and patient care. Trop Med Int Health 15: 1289-1299.
19. Chiang CY, Lee JJ, Chien ST, Enarson DA, Chang YC, et al. (2014) Glycemic control and radiographic manifestations of tuberculosis in diabetic patients. PloS one 9: e93397.
20. Lönnroth K, Glaziou P, Weil D, Floyd K, Uplekar MR, et al. (2014) Beyond UHC: monitoring health and social protection coverage in the context of tuberculosis care and prevention. PLoS Med 11: e1001693.
21. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, et al. (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev, 1.
22. Pai M, Zwerling A, Menzies D (2008) Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med 149: 177-184.
23. Vega Torres RA, Conde JG, Díaz M (1996) Prevalence of tuberculin reactivity and risk factors for the development of active tuberculosis upon admission to a nursing home. P R Health Sci 15: 275-277.
24. Pfaffenberg R, Jahler H (1958) Isoniazid and recurrence of tuberculosis in diabetics. Z Tuberk 111: 167-173. (In German)
25. Lesnichii AV, Karpina LZ (1969) Experience with the chemoprophylaxis of pulmonary tuberculosis in diabetes mellitus patients. Probl Tuberk 47: 1-3.
26. Ruslami R, Aarnoutse RE, Alisjahbana B, van der Ven AJ, van Crevel R (2010) Implications of the global increase of diabetes for tuberculosis control and patient care. Trop Med Int Health 15: 1289-1299.
27. Hall RG, Leff RD, Gumbo T (2009) Insights from the Society of Infectious Diseases Pharmacists. Treatment of active pulmonary tuberculosis in adults: current standards and recent advances. Pharmacotherapy 29: 1468-1481.
28. Kumar A, Jain DC, Gupta D, Satyanarayana S, Zachariah R, et al. (2013) Screening of patients with tuberculosis for diabetes mellitus in India. Screening. Trop Med Int Health 18: 636-45.
29. Lin Y, Li L, Mi F, Du J, Dong Y, et al. (2012) Screening patients with diabetes mellitus for tuberculosis in China. Tropical Medicine & International Health. Trop Med Int Health 17: 1302-1308.