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Viewpoint

Defining the research agenda to reduce the joint burden of disease from Diabetes mellitus and Tuberculosis

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Summary The steadily growing epidemic of diabetes mellitus poses a threat for global tuberculosis (TB) control. Previous studies have identified an important association between diabetes mellitus and TB. However, these studies have limitations: very few were carried out in low-income countries, with none in Africa, raising uncertainty about the strength of the diabetes mellitus–TB association in these settings, and many critical questions remain unanswered. An expert meeting was held in November 2009 to discuss where there was sufficient evidence to make firm recommendations about joint management of both diseases, to address research gaps and to develop a research agenda. Ten key research questions were identified, of which 4 were selected as high priority: (i) whether, when and how to screen for TB in patients with diabetes mellitus and *vice versa*; (ii) the impact of diabetes mellitus and non-diabetes mellitus hyperglycaemia on TB treatment outcomes and deaths, and the development of strategies to improve outcomes; (iii) implementation and evaluation of the tuberculosis 'DOTS' model for diabetes mellitus management; and (iv) the development and evaluation of better point-of-care diagnostic and monitoring tests, including measurements of blood glucose and glycated haemoglobin A_{1c} (HbA_{1c}) for patients with diabetes mellitus. Implementation of this research agenda will benefit the control of both diseases.

keywords research, diabetes mellitus, tuberculosis, screening, treatment outcomes

Background

The global burden of disease from diabetes mellitus and tuberculosis (TB) is immense. In 2010, there will be an estimated 285 million people living with diabetes mellitus with approximately 4 million deaths (International Diabetes Federation 2009). In 2007, there were an estimated 14.4 million people living with TB, 9.2 million new cases

and 1.7 million deaths (WHO 2009). While it is widely known that 95% of patients with TB live in the low- and middle-income countries, 70% of patients with diabetes mellitus also live in these same countries, especially in South-east Asia and the Western Pacific.

Among several risk factors for TB, which include HIV/AIDS, silicosis, malnutrition, alcoholism and smoking, diabetes mellitus has received recent recognition. A systematic review of the literature in 2008 identified 13 age-adjusted, quantitative, observational studies in North America, UK, Russia, Mexico, Korea, Taiwan and India, finding a relative risk of TB in patients with diabetes mellitus of 3.1 in cohort studies and odds ratios that ranged from 1.16 to 7.83 in case–control studies (Jeon & Murray 2008). These findings were similar to those reported in a previous systematic review (Stevenson *et al.* 2007a), were supported by data included in an epidemiological model indicating that, in India, diabetes mellitus might account for nearly 15% of pulmonary tuberculosis (PTB) cases (Stevenson *et al.* 2007b), and have been further endorsed by a review in 2009 that provided a synopsis of the evidence of the role of diabetes mellitus in influencing the clinical presentation and response to treatment for TB (Dooley & Chaisson 2009).

The important association between diabetes mellitus and TB is not in doubt. However, the previous studies published between 1965 and 2009 have limitations. Many are health facility-based case–control studies using medical chart diagnoses of diabetes mellitus and may be subject to confounding. Most studies are from industrialized countries. The evidence base from low-income countries is weak, with none at all from Africa, raising uncertainty about the strength of the diabetes mellitus association in these settings. There are also many critical unanswered questions: Should patients with diabetes mellitus be screened for TB in diabetes mellitus clinics and *vice versa*, and how and when? What is the effect of diabetes mellitus on the presentation of TB and subsequent TB treatment outcomes? What is the natural history of multidrug-resistant TB (MDR-TB) in patients with diabetes mellitus, and what steps are needed for prevention and management? Should TB preventive therapy be considered in patients with diabetes mellitus? Would life-style changes be helpful in preventing both diseases?

Systematic review and expert meeting

As a result of these uncertainties and questions, a systematic review of the literature was commissioned from the Harvard School of Public Health, USA, in May 2009. The review addressed key questions such as screening for TB and diabetes mellitus in routine clinics, TB chemoprophylaxis and the impact of diabetes mellitus on clinical and programmatic management of TB. The systematic review was completed by the end of August, and the findings presented and discussed at an expert meeting in November 2009 at the International Union Against Tuberculosis and Lung Disease, Paris, France. 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, address research gaps and develop a research agenda around these gaps. This article summarizes the research agenda that emerged at the meeting, which we believe if carried out will assist in reducing the joint burden of disease from diabetes mellitus and TB.

Research agenda for Diabetes and Tuberculosis

The key research questions are shown in Table 1, divided into high, medium and low priority. We identified four high-priority research questions: whether and how to screen for TB in patients with diabetes mellitus and *vice versa*; the impact of diabetes mellitus or non-diabetes mellitus hyperglycaemia on TB treatment outcomes and deaths, and the development and testing of strategies to improve outcomes; implementation and evaluation of the tuberculosis 'DOTS' model for diabetes mellitus management; and development and evaluation of better point-of-care (POC) diagnostic tests for patients with diabetes mellitus.

Screening

Patients with diabetes mellitus, particularly those with suboptimal control, should be screened for active TB in areas of high TB prevalence. Prospective observational cohort studies should be conducted in diabetes mellitus clinics with a focus on adults and stratified by quality of diabetes mellitus control. Key questions, similar to those being asked about intensified TB case finding in people living with HIV (Havlir *et al.* 2008; Kranzer *et al.* 2010), include: (i) what type of screening algorithm will be most effective, i.e. should all patients with diabetes mellitus be investigated by standard TB laboratory investigations or should these investigations be targeted to those with symptoms suggesting active TB or with poor control of diabetes mellitus as defined by symptoms or measurements of blood glucose or glycated haemoglobin A_{1c} (HbA_{1c}); (ii) how often should screening be conducted; and (iii) what are the most appropriate screening tools (sputum smear examination and chest radiography for pulmonary disease, ultrasound for extra-pulmonary abdominal lymphadenopathy) and how do these compare to the gold standard of sputum

Table 1 Key research questions and methodology for improving the prevention, management and care of diabetes mellitus and tuberculosis (TB, tuberculosis; HIV, human immunodeficiency virus)

Key research questions	Priority	Study design and methodology
Screening for Disease: Screening patients with diabetes mellitus for active TB Screening patients with TB for diabetes mellitus	High	Prospective observational cohort studies of patients with diabetes mellitus routinely attending diabetes clinics and screened for TB, and patients with TB starting anti-TB treatment and screened for diabetes mellitus
TB treatment outcomes in patients with diabetes mellitus and with non-diabetes hyperglycaemia, including a more detailed assessment of death during anti-TB treatment, and the development and testing of strategies to improve outcomes for both diseases	High	Prospective observational cohort studies using standardized TB regimens and standardized treatment outcomes and focusing on defined primary outcomes Prospective observational cohort studies to determine when death occurs in relation to start of TB treatment, the aetiology and whether case fatality is reduced by better control of diabetes mellitus or hyperglycaemia or modification to TB drug regimens, duration of therapy and TB drug doses
Implementing and evaluating the 'DOTS' model for standardized case management of diabetes mellitus	High	Operational research that includes quarterly cohort reporting of new cases, treatment outcomes of cumulative cases including frequency of co-morbidities such as TB, and survival analysis
Development and evaluation of better point-of-care diagnostic and monitoring tests for diabetes mellitus	High	Developmental work to produce a reliable low cost finger stick test for measuring blood glucose and glycated haemoglobin A_{1c} (HbA_{1c}) in rural areas, which then needs to be tested for efficacy and feasibility in the field
Rates of hospitalization and additional medical costs associated with diagnosis and management of dual disease	Medium	Cross-sectional and case–control studies
Use of the community to improve diagnosis, management and care of patients with diabetes and TB	Medium	Operational research
Household contact tracing of adult patients with smear-positive Pulmonary TB	Medium	Prospective observational studies to determine the yield of screening household contacts of index patients with pulmonary TB for TB infection, active TB, HIV and diabetes mellitus and assess whether diabetes mellitus influences the risk of TB infection
Radiographic findings in diabetes mellitus patients with tuberculosis	Medium	Systematic review of the literature, and prospective cross-sectional studies if further evidence is required, to determine the common radiographic patterns that are associated with diabetes mellitus
Modelling the effect of the diabetes mellitus epidemic on the TB epidemic	Medium	Mathematical modelling studies, ideally informed by higher quality studies of the association between diabetes mellitus and TB, particularly from low-income settings
TB preventive therapy in patients with diabetes mellitus	Low	Randomized controlled trial assessing efficacy and safety of isoniazid preventive therapy in reducing risk of active TB in patients with diabetes mellitus

culture for *Mycobacterium tuberculosis*. In determining the most appropriate strategy, the impact of diabetes mellitus on clinical manifestations of TB should be considered. The value of formal clinic education in diabetes clinics with TB posters, leaflets or group talks about the links between diabetes mellitus and TB needs to be explored in terms of improving health care staff and patient awareness and for future guidelines and training materials. Urban and other settings known to have high TB and diabetes mellitus incidence would be the most appropriate places to conduct such studies, for example Dar es Salaam in Tanzania, Blantyre in Malawi, Chennai in India and Beijing in China all being possibilities.

For patients with TB, previous studies suggest that it is more reliable to screen for diabetes mellitus later in the course of anti-TB treatment rather than at the start (Dooley & Chaisson 2009), because TB as a chronic infectious disease may elevate blood glucose levels because of cytokine stimulation resulting in false positive diabetes mellitus diagnoses if investigations are performed too early. However, delayed screening may be a missed opportunity for subsequently modifying treatment, and many TB programmes, especially in Africa, have decentralized services to peripheral facilities where it is difficult to get laboratory investigations performed (Edginton 1990; Drabo *et al.* 2006). Research is required to determine the

optimal time and best methods for diagnosing diabetes mellitus in patients with TB, focusing on adults stratified by type of disease (smear-positive PTB, smear-negative PTB and extra-pulmonary TB). The most appropriate ways of screening should be explored [urine, random or fasting blood glucose and/or glycated haemoglobin A_{1c} (HbA_{1c})].

TB treatment outcomes

Patients identified by the two screening strategies discussed earlier need to be entered into prospective studies assessing the impact of diabetes mellitus or non-diabetes mellitus hyperglycaemia on TB treatment outcomes, using standardized TB regimens and outcomes, in which other confounding factors (age, smoking status, alcohol, body mass index and HIV) are taken into account. The level of hyperglycaemia and quality of diabetes control, measured, for example by HbA_{1c}, are important factors to consider. Primary treatment outcomes should include (i) liver function tests; (ii) pharmacokinetic levels of rifampicin and oral diabetes medications; (iii) TB treatment outcomes; (iv) recurrence of TB 1 year after completion of TB treatment as determined by sputum culture; and (v) culture and drug-sensitivity testing, at the start of treatment and at the time of failure or TB recurrence to assess linkages and associations with drug-resistant TB.

Death is reported to be more frequent in patients with diabetes mellitus on anti-TB treatment (Dooley & Chaisson 2009), but research is required to address unanswered questions such as when death occurs in relation to start of anti-TB treatment, the aetiology, and whether better diabetes mellitus control or modified TB drug regimens, duration of anti-TB therapy and TB drug doses reduce case fatality.

The TB DOTS model for managing diabetes mellitus

The concept of using components of the Tuberculosis 'DOTS Model' for managing diabetes mellitus has already been proposed (Harries *et al.* 2008), and diabetes clinics in urban areas in high-burden countries need to pilot and evaluate this approach through operational research, and particularly to assess whether quarterly cohort reporting of incident cases, cumulative outcomes, complications and survival analysis can lead to better management and care, more rational drug forecasting and uninterrupted drug supplies (Harries *et al.* 2009).

Better POC diagnostic and monitoring tests

In the same way that the rapid POC HIV test revolutionized counselling and HIV testing replacing cumbersome and slow HIV-ELISA methodology (De Cock & Odhiambo 2006), better POC tests need to be developed for diabetes mellitus management. These tests could include measurements of blood glucose and HbA_{1c}, the latter helping to differentiate diabetes mellitus from stress-related hyperglycaemia, and they should be assessed for both diagnosis and monitoring of the disease. If such tests are to be used widely in resource-poor settings, they should be simple to use; rely on finger-prick blood sampling; be independent of instrumentation or electronics; be robust and able to withstand elevated ambient temperatures without cold-chain shipment or storage; have a long shelf-life; and be inexpensive (e.g. costing less than USD$2 per test). These would have the potential to be used in peripheral clinics and remote health centres in Africa and Asia and would improve access to diabetes mellitus diagnosis and care.

Other research questions are listed in Table 1. Among these, we consider TB preventive therapy to have low priority. Two studies conducted before the 1970s indicated that active TB in patients with diabetes mellitus could be reduced through TB chemoprophylaxis (Pfaffenberg & Jahler 1958; Lesnichii & Karpina 1969). Both studies were flawed, and therefore, the true benefit of chemoprophylaxis remains unknown. The question can only be properly addressed through a randomized controlled trial (RCT). However, given the expense of conducting RCTs, the low uptake of isoniazid preventive therapy in people living with HIV despite proven efficacy from a number of well-conducted RCTs (World Health Organization 2009) and other issues such as feasibility of implementation, this research is not given high priority because we feel it is unlikely to be carried forward to policy and practice. Better diabetes mellitus control might be safer and more cost-effective in preventing TB and reducing other diabetes mellitus complications.

Conclusion

The epidemic of non-communicable diseases, especially diabetes mellitus, is steadily growing. Diabetes mellitus in particular threatens TB control efforts and the achievement of the 2015 TB targets (WHO 2006). In the same way, HIV threatens TB control and has lead to the development of an HIV-TB research agenda (Smart 2009); the threat of diabetes mellitus requires a research agenda focussed on providing tools for national and international agencies charged with the control of both these diseases. Many critical questions regarding the association between diabetes mellitus and TB remain unanswered because of either poorly conducted studies or no studies at all. These major concerns led to the assembly of an expert group who systematically reviewed

existing data and developed a research agenda providing a clear basis for future action.

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