Screening patients with Diabetes Mellitus for Tuberculosis in China

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Abstract

Objective There is a high burden of both diabetes (DM) and tuberculosis (TB) in China, and as DM increases the risk of TB and adversely affects TB treatment outcomes, there is a need for bidirectional screening of the two diseases. How this is best performed is not well determined. In this pilot project in China, we aimed to assess the feasibility and results of screening DM patients for TB within the routine healthcare setting of five DM clinics.

Method Agreement on how to screen, monitor and record was reached in May 2011 at a national stakeholders meeting, and training was carried out for staff in the five clinics in July 2011. Implementation started in September 2011, and we report on 7 months of activities up to 31 March 2012. DM patients were screened for TB at each clinic attendance using a symptom-based enquiry, and those positive to any symptom were referred for TB investigations.

Results In the three quarters, 72% of 3174 patients, 79% of 7196 patients and 68% of 4972 patients were recorded as having been screened for TB, resulting in 7 patients found who were already known to have TB, 92 with a positive TB symptom screen and 48 of these newly diagnosed with TB as a result of referral and investigation. All patients except one were started on anti-TB treatment. TB case notification rates in screened DM patients were several times higher than those of the general population, were highest for the five sites combined in the final quarter (774/100 000) and were highest in one of the five clinics in the final quarter (804/100 000) where there was intensive in-house training, special assignment of staff for screening and colocation of services.

Conclusion This pilot project shows that it is feasible to carry out screening of DM patients for TB resulting in high detection rates of TB. This has major public health and patient-related implications.

Keywords Tuberculosis, diabetes mellitus, screening, China

Introduction

China is a country with 1.3 billion people (or 18.5% of the world’s population) that is undergoing rapid development and urbanisation. As a consequence of this social and economic change, which is associated with increasing physical inactivity, an unhealthy diet and obesity, there has been an escalating epidemic of diabetes mellitus (DM) (Danaei et al. 2011; International Diabetes Federation 2011; Alcorn & Ouyang 2012). An estimated 11% of urban people and 3% of rural people above the age of 15 years have DM. A study in a nationally representative sample of over 46 000 adults found that the prevalence of DM and pre-diabetes was 9.7% and 15.5%, respectively, accounting for 92.4 million adults with DM and 148 million adults with pre-diabetes (Yang et al. 2010). In this
representative sample, the prevalence of DM increased with age, was higher in urban than rural areas, and in over 60% of people, the disease was undiagnosed at the time of the survey. In terms of absolute numbers and given the size of the population, this makes China one of the highest DM burden countries in the world.

DM is a well known risk factor for the development of active TB, doubling or tripling the risk (Stevenson et al. 2007; Jeon & Murray 2008; Dooley & Chaisson 2009; Ruslami et al. 2010). Patients with TB who have DM also appear to have worse treatment outcomes than those who do not have DM, with delays in sputum culture conversion, and an increased risk of both death and recurrent disease after successful completion of treatment (Baker et al. 2011). Although China has an excellent national TB programme, follows the ‘DOTS’ model for TB control and has had much success in the last 20 years in reducing the burden of TB, the disease is still a considerable problem. In 2010, there were an estimated one million incident cases of TB (range 0.9–1.2 million), with 6% of new cases and 26% of retreatment cases thought to be multidrug resistant (MDR-TB = resistance to both isoniazid and rifampicin) (WHO 2011).

Given the high burden of TB and DM in China and the association between the two, DM patients would merit being screened for TB. In 2011, WHO and the International Union Against Tuberculosis and Lung Disease (The Union) launched a new ‘Collaborative Framework for the care and control of Diabetes and Tuberculosis’, with one of the important activities being the routine implementation of bidirectional screening of the two diseases (WHO & IUATLD 2011). However, ways of screening, recording and reporting for the two diseases in routine healthcare settings are not well determined, and these knowledge gaps need to be addressed (Harries et al. 2010a; Jeon et al. 2010).

In China, a standardised procedure of screening DM patients for TB, a monitoring tool and a quarterly system of reporting were developed and agreed upon in the first half of 2011 with the implementation starting in the second half of the year. This article describes the implementation, results and challenges of screening DM patients for TB within routine healthcare settings in China.

Methods

This was a prospective observational implementation project carried out in five DM clinics within routine health services in China. As a result of support from the World Diabetes Foundation (WDF), a national stakeholders meeting was held in Beijing, China, in May 2011, between The Union, WHO, the World Diabetes Foundation (WDF) and national diabetes, non-communicable disease and TB authorities to review and discuss linkages between DM and TB, the need for bi-directional screening and the WHO-Union Collaborative Framework. Broad guidelines for how the screening should be performed were worked out and agreed upon, and 5 sites for screening DM patients for TB were selected. These were Taian Central Hospital; Dingxi Number 2 Hospital; The Affiliated Hospital of Guiyang Medical College; Jinan Central Hospital; and Shijiazhuang Number 2 Hospital. The hospitals and their geographic location in China are shown in Figure 1.

The hospitals were selected because of their geographic locations (Northwest [Dingxi], Southwest [Guiyang], Central [Shijiazhuang] and East [Jinan and Taian]); the high prevalence of active TB in the surrounding communities; and their degree of urbanisation (provincial capital with good economic status [Jinan], provincial capital with poor economic status [Guiyang and Shijiazhuang], midsize city [Taian] and county [Dingxi]). Details of the hospitals and the DM clinics, the facilities to which suspected TB patients were referred for the investigation and diagnosis, and the local TB case notification rates in each of the sites are shown in Table 1.

In July 2011, a training module was held with healthcare staff from the 5 sites on standardised guidelines for screening and referral of patients, and monitoring and reporting of data. Treatment cards and cohort reporting forms were developed and printed and distributed to the study sites. Staff officers returned to their health facilities and provided in-service training for staff working in the clinics. Implementation of activities started on 1 September 2011. It was agreed that data would be reported in quarterly cohorts: Q3-2011 (September); Q4-2011 (October to December); and Q1-2012 (January to March), and that implementers would convene in May 2012 to discuss results, challenges and ways forward.

Patients included persons aged 14 years and above who had been diagnosed with DM and who were receiving care and treatment in the 5 DM clinics from September 2011 to the end of March 2012.

The screening for active TB followed the guidelines of the China National TB Control Programme (NTP) (China NTP). Screening was expected to be carried out every time the patient visited the DM clinic and was based on asking about five symptoms: cough for longer than 2 weeks; night sweats for 4 weeks or longer; fever for 4 weeks or longer; weight loss over the previous 4 weeks; and any suspicion of active TB to account for extrapulmonary TB (EPTB). If a patient gave an affirmative answer to any of the five questions, this was regarded as a positive symptom screen, and the patient was referred to TB services for investigation in accordance with the Opera-
tional Guidelines stipulated by the China NTP (China NTP). In brief, investigations and diagnosis of TB were made using sputum smear microscopy for acid-fast bacilli and chest radiography. When a diagnosis of active TB was made, the patient was referred to the NTP for the registration and treatment. Whether TB was diagnosed or excluded, patients were expected to be referred back to the DM clinic for continued care of their DM disease.

Monitoring, recording and reporting

A DM treatment card (Figure 2) was developed for recording data about the patient’s DM history and current DM status, and every time the patient came to the clinic whether screening for TB symptoms had been carried out, the results of the screening and the results of investigations if the symptom screen was positive. To trace the DM

### Table 1 Details of the 5 hospitals involved in the implementation of TB screening in patients with diabetes

<table>
<thead>
<tr>
<th></th>
<th>Taian Central Hospital</th>
<th>Dingxi Number 2 Hospital</th>
<th>Guiyang Medical College Hospital</th>
<th>Jinan Central Hospital</th>
<th>Shijiazhuang Number 2 Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Hospital Beds</td>
<td>2100</td>
<td>503</td>
<td>2000</td>
<td>1200</td>
<td>670</td>
</tr>
<tr>
<td>Number of daily out-patient visits</td>
<td>2000</td>
<td>650</td>
<td>3500</td>
<td>2500</td>
<td>750</td>
</tr>
<tr>
<td>Number of daily DM patient visits</td>
<td>40</td>
<td>123</td>
<td>200</td>
<td>60</td>
<td>110</td>
</tr>
<tr>
<td>Number of doctors at the DM clinic</td>
<td>20</td>
<td>33</td>
<td>20</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Number of nurses at the DM clinic</td>
<td>32</td>
<td>72</td>
<td>24</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Main source of Patients</td>
<td>Urban and Rural</td>
<td>Urban and Rural</td>
<td>Urban and Rural</td>
<td>Urban</td>
<td>Urban</td>
</tr>
<tr>
<td>To where are TB suspects referred</td>
<td>TB and Chest TumorCenter, Taian</td>
<td>Anding District CDC TB Clinic</td>
<td>TB clinic at the same hospital</td>
<td>Shandong Chest Hospital</td>
<td>Shijiazhuang Number 5 Hospital</td>
</tr>
<tr>
<td>Distance of TB clinic from DM clinic (km)</td>
<td>2</td>
<td>1.0</td>
<td>0</td>
<td>0.5</td>
<td>6.0</td>
</tr>
<tr>
<td>TB case notification rate/100 000 general population</td>
<td>55</td>
<td>73</td>
<td>111</td>
<td>31</td>
<td>63</td>
</tr>
</tbody>
</table>
patients and avoid duplicate recording, a green patient identification card was developed, which was stickered onto the patient record.

Standardised quarterly report forms were developed and used for the recording of data. These were compiled by health clinic staff 30 days after the end of the quarter to allow for the collection of data from TB Clinics. These reports were kept at the facilities and also sent to the Union China Office and TB clinical centre of the China Centre for Disease Control (CDC) for collation. Supervision and site visits were carried out by staff of the Union China Office and the TB clinical centre of the China CDC during the first period of the study.

Individual patient data were received and cross-checked by staff of the Union China Office and the TB clinical centre of the China CDC during the first period of the study.

Individual patient data were received and cross-checked by staff of the Union China Office and the TB clinical centre of the China CDC, then double entered to an EXCEL file and analysed. Comparisons between groups were made using the chi-squared test, and odds ratios (OR) were calculated where appropriate with 95% confidence intervals (CI). The level of significance was set at 5%.

National authorities in China stated that this was a pilot project aiming to test the feasibility of the TB screening approach amongst DM patients with a view to learning lessons for national scale up. As such, formal ethics approval in China was deemed not to be necessary. However, permission to use, report and publish the collected data was obtained from the Union Ethics Advisory Group, Paris, France.

Results

Results for TB screening in all five sites combined for quarter 3-2011, quarter 4-2011, quarter 1-2012 are shown in Table 2. Between 68% and 79% of patients with DM were recorded as having been screened for TB in each of the quarters. Altogether, from the 15 342 patient-screening episodes during the study period, 7 patients were identified as known to have TB and were receiving anti-TB treatment, 92 (0.6% of those screened) had a positive TB screen, 88 were referred for TB investigations and 48 (55% of those investigated) were newly diagnosed with TB. All except one of these patients was started on anti-TB treatment, one patient being lost to follow up after diagnosis. A total of 55 DM patients (known and new) were identified with TB: 40 with new and 15 with recurrent TB, and 28 with smear-positive pulmonary TB, 24 with smear-negative pulmonary TB and 3 with EPTB. The TB case notification rate was significantly higher for quarter 1-2012 (774 per 100 000 DM screened) than for quarter 4-2011 (352 per 100 000 DM screened) – OR 2.2 (95%CI 1.9–2.5, P < 0.001).

The process of screening and referral in Guiyang Medical College was different from the other four health facilities: after training, the hospital staff developed a uniform patient flow chart that was understood by all clinical and nursing staff in the clinic; clear roles and responsibilities were given to DM clinic staff; special assigned staff were always available for screening patients for TB symptoms before they saw clinic doctors, and these staff recorded results of TB screening...
symptom screening in the treatment cards; the DM and TB clinics were situated close to each other on the same floor within the same facility. Results of TB screening in Guiyang Medical College and in the other four sites combined for each of the quarters are shown in Table 3. Apart from quarter-3 2011 (just the month of September), when screening was first started, Guiyang Medical College had higher TB case notification rates per 100 000 DM patients screened than the other four sites together (P < 0.001). For each site, these were consistently higher than TB case notification rates observed in the general population in the catchment areas served by the 5 facilities (Table 1).

### Discussion

This is the first report from China about routine implementation of screening DM patients for TB. Although small numbers of TB patients were identified in absolute terms, the TB case notification rates per screened population were consistently higher than those found in the general population of the catchment areas of the five facilities (range 31–111/100 000 population – Table 1) and compared with the national figure of 78/100 000 in the general population (WHO 2011). The TB case notifications for all five sites combined and for the individual sites in general improved by the third quarter, possibly reflecting improved clinic performance and better familiarity with screening procedures over time. There was also one hospital with generally higher TB notification rates compared with the other four, which was associated with the following screening features: well-conducted training, clear roles and responsibilities, special staff assigned to screening and recording of data, easy referral to TB services facilitated by proximity to the DM clinic, all important

### Table 2  Screening of Diabetes Patients for Tuberculosis during each quarter for all five sites combined

<table>
<thead>
<tr>
<th>patients with diabetes who were screened and diagnosed with tuberculosis</th>
<th>Q3-2011</th>
<th>Q4-2011</th>
<th>Q1-2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of DM patients seen in the clinic in each quarter</td>
<td>3174</td>
<td>7196</td>
<td>4972</td>
</tr>
<tr>
<td>Number (%) of DM patients screened at least once for TB symptoms in each quarter</td>
<td>2300 (72%)</td>
<td>5669 (79%)</td>
<td>3361 (68%)</td>
</tr>
<tr>
<td>Number of DM patients already diagnosed with TB from elsewhere</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Number of DM patients with a positive TB symptom screen</td>
<td>27</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td>Number of DM patients referred for TB investigations</td>
<td>25</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>Number newly diagnosed with TB after referral for investigations</td>
<td>9</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Total number identified and registered with TB (known and new)</td>
<td>9</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Smear-positive PTB</td>
<td>3</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Smear-negative PTB</td>
<td>5</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>EPTB</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>New TB</td>
<td>5</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Previously treated TB</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Number placed on TB Treatment</td>
<td>9</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>TB case notification rate per 100 000 screened DM patients each quarter</td>
<td>391</td>
<td>352</td>
<td>774</td>
</tr>
</tbody>
</table>

Q, quarter; DM, diabetes mellitus; TB, tuberculosis; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis.

### Table 3  Screening of Diabetes Patients for Tuberculosis each quarter in Guiyang Medical College and the other four health facilities

<table>
<thead>
<tr>
<th>patients with diabetes who were screened and diagnosed with tuberculosis</th>
<th>Guiyang Medical College</th>
<th>Dingxi, Jinan, Sijiazhu, Taian Hospitals*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of DM patients seen in each quarter</td>
<td>899 1426 714</td>
<td>2275 5770 4258</td>
</tr>
<tr>
<td>Number of DM patients screened at least once for TB symptoms in each quarter</td>
<td>899 1426 714</td>
<td>1401 4243 2647</td>
</tr>
<tr>
<td>Number of DM patients diagnosed and registered with TB</td>
<td>3 9 11</td>
<td>6 11 15</td>
</tr>
<tr>
<td>TB case registration rate per 100 000 DM patients screened per quarter</td>
<td>334 631 804</td>
<td>428 259 567</td>
</tr>
<tr>
<td>TB case registration rate per 100 000 general population</td>
<td>Guiyang (111)</td>
<td>Dingxi (73); Jinan (31); Shijiazhuang (63); Taian (55)</td>
</tr>
</tbody>
</table>

*Results of the four hospitals are combined.*
lessons to take on board when considering feasibility and effectiveness of national scale up.

There were various challenges identified in the screening of DM patients for TB. First, in the hospitals where no special staff had been assigned to DM clinics, the doctors felt under too much pressure to routinely screen patients, and in many cases, screening was not performed at all or not comprehensively performed. This also reflects a lack of understanding of the importance of screening for an infectious disease amongst a group of patients who are at higher risk of active disease in the event of infection than the general population (Stevenson et al. 2007; Jeon & Murray 2008; Dooley & Chaisson 2009; Ruslami et al. 2010).

Second, even when symptom screening was performed, almost all sites admitted to under-reporting of a positive symptom screen, and if there was no suspicion of TB despite prolonged cough, fever and weight loss, this was recorded as a negative screen. This would explain the low proportion with a positive symptom screen (<1%) and the very high yield of active TB amongst those with a positive symptom screen (>50%), with doctors just selecting those likely to have active TB. Chest radiography is commonly used in China, and although not part of the screening algorithm, it is possible that some patients were investigated with chest X-ray before or in parallel with symptom screening, thus increasing the screening precision. Many DM patients also did not understand the meaning of the term night sweats, and this enquiry was invariably scored as negative.

Third, some patients with a positive symptom screen who were referred to the TB clinics for further investigation did not go, and without an active tracing system, it was not possible to ensure attendance.

Fourth, of the patients diagnosed with TB, only about 5% had extrapulmonary disease. While this proportion appears to be low, just under 7% of all nationally reported TB cases in China in 2010 had EPTB (World Health Organization 2011), so this finding fits with the wider picture.

Fifth, there was a problem in most sites with knowing the number of DM patients ever registered. The monitoring system could capture the number of DM patients attending the clinic each quarter, and in many cases, these may have been the same patients who attended the clinic in the previous quarter. However, because there was no formal registration of patients as occurs in TB or HIV/AIDS programmes (Libamba et al. 2005), the cumulative number of patients ever registered, and which increased each quarter as new patients were added to the pool, was not known. Hence, it was not possible in this study to obtain the denominator for DM patients; thus, we used DM patients screened per quarter to calculate the case notification rates per screened patients. The lack of systemic recording, reporting and follow-up of people with DM in most developing countries is a serious health system gap not only for DM care delivery, but also for almost all other non-communicable diseases (Harries et al. 2008).

The strengths of this study are that we implemented screening within the routine system, and there was no special budget set aside for the implementation of this activity. Thus, decisions to continue or to expand depend entirely on the benefits perceived for patients and public health. We think that given their higher risk for TB and the fact that patients with diagnosed DM are anyway much more likely to attend health facilities, the marginal costs for an opportunistic symptomatic TB screen performed properly are likely to be small and to prove cost-effective in countries with a high double burden of disease.

Limitations include some of the problems discussed above and not knowing how comprehensively symptom screening was performed. Comparisons of TB case notification rates in screened DM patients with those from the general population are also not strictly valid as the notification rates in DM patients are de facto from active case finding, while the general population rates are derived from the usual NTP procedures of passive case finding. Measuring the true prevalence rate of TB amongst DM patients requires more formal research than can be accomplished through the routine screening process described here, and both formal and operational research using mycobacterial culture or new diagnostic techniques such as Xpert MTB/RIF would be needed (Boehme et al. 2010). We need a better understanding of the costs incurred by patients by being referred to other services. Finally, further research to better socio-demographically characterise patients with DM at higher risk of TB to further improve yields of positive symptom screening is required.

While this study shows that it is feasible to screen DM patients for TB, better performance requires more attention to detail, a consideration of additional staff to assist with the workload and possibly electronic medical record systems to assist with cohort recording (Douglas et al. 2010; Allain et al. 2011). As is the case with HIV-associated TB (Harries et al. 2010b; Lawn & Wood 2012), colocation of DM and TB clinics is essential if efficient and timely referral is to occur, and this may be difficult to achieve within an already established hospital structure. A final caveat is that globally about half of all patients with DM are undiagnosed (International Diabetes Federation 2011), and recent data from China confirm these findings at the country level (Yang et al. 2010). The screening approaches we discuss in this study cannot obviously address this issue, but routine screening of TB patients for DM is one way of helping to reduce the undiagnosed proportion of people with DM.
Conclusion

Screening for active TB in DM clinics should lead to increased and earlier detection of TB, earlier and better treatment of TB (which might have gone unrecognised) and improved clinical outcomes on anti-TB treatment and for routine DM care. Moreover, identifying TB patients early in DM clinics will help to reduce the risk of nosocomial TB transmission in these settings. Finally, the introduction of active TB screening into DM care potentially allows the use of the well-established ‘DOTS’ system for monitoring, recording and reporting on case numbers and their outcomes (Allain et al. 2011). This may result in improved data on DM and help those involved in policy-making work out the best methods for collecting data on other non-communicable diseases such as hypertension and cardiac disease. This should be of benefit not only for China and also for the global community.

Acknowledgements

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