Policy Forum

Mutual Impact of Diabetes Mellitus and Tuberculosis in China

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China has a double burden of diabetes mellitus and tuberculosis, and many studies have been carried out on the mutual impact of these two diseases. This paper systematically reviewed studies conducted in China covering the mutual impact of epidemics of diabetes and tuberculosis, the impact of diabetes on multi-drug resistant tuberculosis and on the tuberculosis clinical manifestation and treatment outcome, the yields of bi-directional screening, and economic evaluation for tuberculosis screening among diabetes patients.

Key words: Impact; Tuberculosis; Diabetes mellitus; China

China has a double burden of diabetes mellitus (DM) and tuberculosis (TB). A national survey conducted in 2010 found that the prevalence of DM was 11.6% (95% confidence interval (CI): 11.3%-11.8%) in Chinese adults, and 113.9 million adults were estimated to have DM in China[1]. China has made substantial progress in TB control in the past two decades, and more than halved the TB prevalence, with a decreased prevalence of smear-positive TB from 170/100,000 to 59/100,000[2]. However, there is still a significant number of TB cases in China because of its large population size, and it is estimated that there were 0.918 million incident TB cases in 2015[3]. The evidence for a positive association between DM and TB has been found in many studies regardless of the study design and population, and the two diseases may complicate each other to different extents. Data from the tuberculosis patient information management system also showed that a high percentage of TB patients with DM was observed in some areas in China, and annually increased in several cities[4,5]. Epidemics and the growing evidence of the link between TB and DM remain a grave global public health concern for researchers and policy-makers in China.

The purpose of the current study was to systematically review the literature on the association between DM and TB conducted in China and to understand the future needs and policy implication for public health. We searched for studies published from 2,000 with the key words ‘tuberculosis/tuberculin’, ‘diabetes/diabetic’, and ‘China/Chinese’. Case reports, nursing research, studies with inconclusive results or inaccessible full text were excluded from this current study.

**Mutual Relationship between TB and DM in Epidemics**

DM and TB have mutual risk factors. A higher prevalence of TB among DM patients and vice versa was consistently observed in many previous studies worldwide[6].

**Impact of DM on TB** Among the Chinese, DM patients have a higher incidence of TB. In a cohort study conducted in Taiwan, China, compared to those in randomly selected matched non-diabetic controls, both female and male patients with DM had a significantly higher risk of incidence of TB, with the cumulative incidence of TB being 1.92 cases per 1,000 person-years for females and 3.25 cases per 1,000 person-years for males within a 5 year follow-up duration[7]. This result was very close to the incidence obtained in another cohort study conducted in Hong Kong, China which yielded 214 cases per 100,000 person-years for culture-confirmed TB and 270 cases per 100,000 person-years for pulmonary TB[8]. DM patients also had a higher prevalence of TB. In a population-based pilot study for TB screening among DM patients conducted in Shandong province, the prevalence of TB was 342.72/100,000[9], while the prevalence of TB among DM patients in Taiwan, China was 3.89 per thousand population[10]. In addition, DM patients

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have a more severe manifestation of TB infection on chest radiograph\textsuperscript{11}. In a tuberculin skin test conducted in Shandong province, a higher prevalence rate of patients with a positive tuberculin test result (mean induration $\geq 5$ mm) was found among hospitalized diabetes patients than that among other patients without diabetes\textsuperscript{12}.

The impact of DM on TB was identified in many studies, and DM was associated with a three-fold increased risk of incident TB using a meta-analysis in a systematic review\textsuperscript{13}. Studies in China also noted similar findings. A population-based study conducted in Taiwan, China found an adjusted hazard ratio (HR) of 1.31 (95% CI: 1.23-1.39) for type 2 DM with TB compared with non-diabetic controls\textsuperscript{9}. This risk increased among the elderly. Another cohort study conducted in Hong Kong, China showed that type 2 DM was associated with a modest increase in the risk of culture-confirmed and pulmonary TB (with or without extrapulmonary involvement) in subjects aged 65 years and more, with adjusted HRs of 1.91 (95% CI: 1.45-2.52) and 1.89 (95% CI: 1.48-2.42), respectively\textsuperscript{8}. The risk of developing TB also increased with increasing severity of DM, and $>3$-fold risk was observed among those with $\geq 2$ DM-related complications [odds ratios (OR), 3.45; 95% CI: 1.59-7.50], compared to that among persons without DM\textsuperscript{14}.

Limited studies identified the risk factors for TB among DM patients in China. Being male (OR: 5.057, 95% CI: 1.562-16.377), having a body mass index (BMI) $< 18.5$ (OR: 16.189, 95% CI: 2.588-101.260), and having anxiety (OR: 5.214, 95% CI: 1.772-15.339) were found to be significant risk factors for TB after adjusting for confounding factors\textsuperscript{9}. However, healthy habits (OR: 0.333, 95% CI: 0.218-0.508), high socioeconomic level (OR: 0.508, 95% CI: 0.346-0.745), hypertension (OR: 0.517, 95% CI: 0.350-0.764), good housing condition (OR: 0.599, 95% CI: 0.413-0.868), and beneficial change of diet after the diagnosis of DM (OR: 0.630, 95% CI: 0.447-0.889) were shown to be associated with a decreased risk for TB\textsuperscript{15}. In addition, data in the tuberculosis patient information management system showed an increasing trend of DM-TB concurrent rate with age\textsuperscript{16}.

**Impact of TB on DM** Several studies verified the impact of TB on DM. In a descriptive study conducted in peripheral health facilities in Kerala, 32.4% of TB patients were diabetic, and 7% of DM patients were newly diagnosed\textsuperscript{17}. In another cohort study in Georgia, the prevalence of DM (HbA1c $\geq 6.5\%$) and pre-DM (HbA1c $\geq 5.7\%$-$6.4\%$) was 11.6% and 16.4%, respectively among 318 newly diagnosed patients with TB\textsuperscript{18}. A retrospective cohort study conducted in Malaysia showed that DM was more likely to be present in Chinese, with an OR of 1.401 (95% CI: 1.079-1.818)\textsuperscript{19}.

A higher prevalence of DM among TB patients was also found in China. A prevalence rate of 12.4% in TB patients with DM was identified by a screening pilot survey in mainland China in 2011-2012\textsuperscript{20}. In two studies conducted in Taiwan, China, an average DM prevalence rate of 27.9% in newly diagnosed TB patients\textsuperscript{21} and 31.2% in newly culture positive pulmonary TB patients\textsuperscript{22} were obtained, which were more than four times the prevalence of DM among the general population. Hospital-based retrospective studies have determined the DM prevalence in urban areas in mainland China. By using medical records, a DM prevalence rate of 19.9% and 12% was observed in Shanghai\textsuperscript{23} and Guangzhou\textsuperscript{24}, respectively. The DM prevalence among TB patients decreased in rural areas. In a prospective community-based survey carried out in Shandong province, the prevalence of DM among TB patients aged 18 years old and above was significantly higher than that among non-TB controls (6.3% vs. 4.7%, $P < 0.05$). The DM risk was higher in TB patients than that in the non-TB group (adjusted OR: 3.17, 95% CI: 1.14-8.84) after adjusting for confounding factors\textsuperscript{25}.

Older age was significantly associated with DM, and several new independent factors have been ascertained to be associated with DM, including heart failure (OR: 1.27, 95% CI: 1.09-1.48), ischemic heart disease (OR: 1.23, 95% CI: 1.09-1.39), cerebrovascular disease (OR: 1.30, 95% CI: 1.15-1.48), hypertension (OR: 2.32, 95% CI: 2.05-2.62), dyslipidemia (OR: 3.26, 95% CI: 2.88-3.68), chronic kidney disease (OR: 1.60, 95% CI: 1.33-1.92) and liver disease (OR: 1.68, 95% CI: 1.51-1.86)\textsuperscript{21}. In addition, DM prevalence increased with age, and compared with TB patients aged under 30 years, adjusted ORs were 5.35 (95% CI: 2.47-11.57), 9.46 (95% CI: 4.61-19.43) and 13.20 (95% CI: 6.71-25.96) for those aged 30, 40, and 50 years and above, respectively. Also, TB patients with normal BMI had the lowest DM prevalence (5.8%), in comparison with 7.4% for TB patients with BMI $< 18.5$ and 7.7% for those with BMI $\geq 24.0$\textsuperscript{25}.

**Impact of DM on Multi-drug Resistant TB**

Although it was reported that type 2 DM was
significantly associated with multi-drug resistant tuberculosis (MDR-TB) in other populations\textsuperscript{[26]}, inconsistent results were obtained from limited studies conducted in China. In a hospital-based retrospective analysis conducted in Shanghai, the frequency of MDR-TB among DM-TB patients was higher than that among TB patients (17.7% vs. 8.4%, $P < 0.01$)\textsuperscript{[27]}. However, in a cross-sectional and retrospective study that reviewed records of culture positive TB patients, no significant difference in MDR-TB prevalence was found among TB patients with and without DM\textsuperscript{[28]}. Studies conducted in Taiwan, China showed a significant association of DM with isoniazid (INH) resistance ($OR = 6.76, 95\% CI: 1.53-29.98$), but not with MDR-TB ($OR = 1.52, 95\% CI: 0.59-3.95$) in Eastern Taiwan, China\textsuperscript{[29]} and DM-TB patients had potentially higher probabilities of developing MDR-TB than did TB-only patients\textsuperscript{[30]}. Another study found a significant association between blood glucose and anti-TB drug resistance and made the conclusion that DM-TB patients with poor glucose control and higher blood glucose levels were prone to getting a higher resistance rate and extent of resistance\textsuperscript{[30]}. Since most of these studies were hospital-based record reviews and did not use population data, the evidence was not strong enough to be generalized directly beyond hospitals.

China is experiencing a rapid increase in the prevalence of DM, and incidence of TB patients with high rates of MDR-TB. Although there was limited evidence on the association of DM and MDR-TB in China, DM may soon join the many factors driving the rise of MDR-TB. More prospective studies are needed to further identify the association of DM and MDR-TB and explore the possible basis for the increased susceptibility to infection with resistant strains for DM.

**Impact of DM on Clinical Manifestation and Treatment of TB**

DM and glycemic control could influence both the chest radiograph findings and sputum acid-fast bacilli (AFB) test results. Five hospital-based studies conducted in China consistently showed that TB patients with DM had worse clinical presentations. DM-TB patients were more likely to have an abnormal opacity over the lower lung field ($OR = 1.37, 95\% CI: 1.04-1.81$)\textsuperscript{[31]}, more likely to have pulmonary cavities (for Shanghai: $OR = 3.02, 95\% CI: 1.31-6.98$; for Taiwan, China: $OR = 2.27, 95\% CI: 1.74-2.96$)\textsuperscript{[23,31]}, and had a higher probability of cavitary nodules (19.2% vs. 8.8%, $P = 0.028$)\textsuperscript{[32]}. Glycemic control significantly influenced the radiographic manifestation of TB, and the relative risk for lower lung field opacity and any cavity rose with increasing glycemic levels\textsuperscript{[31]}. In addition, DM-TB patients had higher mycobacterial loads and prevalence of sputum AFB positivity (88% vs. 59%, $P < 0.01$)\textsuperscript{[11]}, and the OR of sputum smear positivity for DM-TB patients was 2.90 (95% CI: 1.12-7.51)\textsuperscript{[23]}. The status of glycemic control also influenced the risk of having positive smear results. The risk for smear positivity increased with elevated levels of HbA1c, and the adjusted ORs were 1.62 (95% CI: 1.07-2.44) and 3.55 (95% CI: 2.40-5.25) for diabetic patients with HbA1c 7%-9% and HbA1c > 9%, respectively\textsuperscript{[33]}.

On the other hand, DM exerted an impact on the outcome of TB treatment. A systematic review of 33 studies reported an increased risk of failure and death combined, death, and relapse in TB patients\textsuperscript{[34]}, and comparable results were obtained from different studies conducted in China. TB patients with DM had a higher proportion of TB patients with positive smear at 2 months (21.7% vs. 5.6%, relative risk ($RR$): 3.85, 95% CI: 2.24-6.63)\textsuperscript{[24]}, longer delayed clearance of mycobacteria (2.5 ± 3.0 months vs. 1.6 ± 1.4 months, $P < 0.01$)\textsuperscript{[11]}, higher proportion of patients lost-to-follow-up (5.2% vs. 1.7%, $RR$: 3.23, 95% CI: 1.08-9.63), and higher treatment failure rates (10.3%-17%)\textsuperscript{[11,24]}. DM-related comorbidities could increase the further risk for unfavorable outcome, and the risk of one-year mortality for TB patients with DM-related comorbidities was found to be 2.80 (95% CI: 1.89-4.16)\textsuperscript{[33]}. In addition, DM was independently associated with the recurrence of TB. The risk for TB relapse were from 1.51 (95% CI: 1.02-2.13)\textsuperscript{[35]} to 1.96 (95% CI: 1.22-3.15)\textsuperscript{[36]} and the 2-year relapse rates were 2.20%-20.0%\textsuperscript{[17,37]} and 5-year relapse rate was 10.0%\textsuperscript{[23]}. The relapse rate could be reduced by treatment supervision or prolonged treatment. Compared to the 6-month anti-TB treatment course, a 9-month course of treatment was associated with a lower recurrence rate ($HR$: 0.76, 95% CI: 0.59-0.97). However, this benefit disappeared under directly observed treatment, short course (DOTS)\textsuperscript{[37]}.

**Bi-directional Screening Conducted in China**

The high yield for the bi-directional screening of TB patients for DM and DM patients for TB had been evaluated in a systematic review including 30 studies\textsuperscript{[6]} and the feasibility of implementing bi-directional screening within the routine health care setting was also assessed in a prospective
observational study in India. In China, bi-directional screening pilots were also carried out in clinics and the community.

**TB Screening Among DM Patients** A pilot TB screening among DM patients was conducted in five clinics, and every DM patient who was suspected to show symptoms of active TB underwent screening at each clinic visit, followed by referral for TB investigation for those with TB symptoms. A higher TB detection rate was obtained in this pilot, and TB case notification rates in screened DM patients were several times higher than those of the general population. Another pilot using the same screening procedure was conducted in 10 community health centers. Although the wide difference of case notification found in the clinic-based pilot was narrowed, the TB case notification in DM patients was 2.8 times higher than that in the general population in this community-based pilot. A community hospital-based TB screening study conducted in Taiwan, China focused on DM patients aged over 65 years old and supported active screening to detect TB in elderly DM patients. Independent risk factors, including body weight loss (OR: 6.635, 95% CI: 2.096-21.007), liver cirrhosis (OR: 10.307, 95% CI: 2.108-50.395) and a history of smoking (OR: 3.981, 95% CI: 1.246-12.718), were found to give a clue for active case finding among subjects.

**DM Screening Among TB Patients** Only one pilot study for DM screening among TB patients was conducted in six health facilities within a routine healthcare setting. Asking whether TB patients had DM and providing blood glucose test for those not known to have DM resulted in 12.4% of patients being identified with DM, and 2.9% and 7.8% of screened TB patients were identified to have DM and impaired fasting glucose, respectively. This pilot obtained a high yield of patients with known and newly diagnosed DM and showed a feasibility to screen DM patients among TB in routine settings.

**Economic Evaluation for TB Screening among DM** Very few studies focused on the economic evaluation of the association between TB and DM. Only one unpublished study made an economic evaluation of the association between TB and DM. Data from two different pilot studies for active TB screening among DM patients, that is, a community-based and clinic-based pilot, were used. For the community-based screening pilot, all registered DM patients were provided with symptom screening and chest X-ray examination, followed by sputum screening. For the clinic-based pilot, TB symptom-based screening was provided to every DM patient at each clinic attendance, followed by referral for TB investigation for those with TB symptoms. All data for cost and number of TB cases identified were collected or obtained from published research, and a decision tree-Markov model was established to make the analysis. It was concluded that community-based TB screening among DM patients was better than clinic-based screening, as more TB patients were identified (26 TB patients identified in community-based screening and 13 TB patients in clinic-based screening), more cases were prevented (if we used community-based TB screening, 31 TB development could be prevented among 10,000 DM patients. However, if we used clinic-based screening, 10 TB development could be prevented among 10,000 DM patients), there was a greater decline in TB incidence (26.2/100,000 decline vs. 8.5/100,000 decline in TB incidence), more life years were saved (167 vs. 65 years), and the number of quality-adjusted life years was higher (152 years vs. 61 years) among 10,000 simulated DM patients.

**Public Health Implication**

In China, the current national TB control strategy is a passive case finding approach, followed by standardized treatment and management for all TB patients identified, and no special strategies for TB control among DM patients. The strong evidence for the association between DM and TB and the high burden of these two diseases highlight the need for more effective control strategies in China.

Firstly, population-based data on these two diseases is absent; population studies on the association between these two diseases should, therefore, be strengthened. Although there are many studies conducted in Taiwan and Hong Kong, China studies in mainland China are limited. On the one hand, epidemiological studies at the population level will provide baseline data for the incidence and prevalence of these two diseases and the influence of risk factors (especially for the specific risk factors of DM for TB patients and those of TB for DM patients), and further test the association between DM and MDR-TB to help us further understand the mutual influence of these two diseases. Also, intervention studies will provide evidence to identify
the priority of target populations and screening strategies for active case finding, and a model of treatment and management for DM-TB patients, especially in economically undeveloped and resource-limited areas.

Secondly, although some pilots for bi-directional screening between TB and DM had been conducted in some areas, this strategy should be expanded and included in routine care. The National Basic Public Health Service Project provides an opportunity to realize this. A quarterly follow-up for DM and TB patients management have been proposed by this project, by which community-based active TB case finding among DM patients could be implemented routinely. When community doctors visit DM patients every quarter, they can perform a TB symptom screening face to face, and transfer DM patients with TB symptoms to designated TB hospitals to receive further TB investigation. Meanwhile, TB patients could receive knowledge for TB and DM, encouraging them to visit the DM clinic when they have symptoms as soon as possible.

Thirdly, TB case management should be further strengthened. For all DM-TB patients, directly observed therapy supervised by a doctor or nurse should be more strictly adhered to according to the National Tuberculosis Program in China. The influence of DM on TB treatment outcome raises the importance of controlling the blood glucose level of TB patients during their treatment course. We suggest that blood glucose surveillance should be added to the TB follow-up surveillance package to provide more information for TB treatment.

Finally, infection control in the DM clinic is very important. A typical survey in DM clinics showed that the infection control measures to prevent TB transmission in DM clinics are inadequate. Just as TB facilities, DM hospitals, and clinics should establish an infection control plan for TB, and maintain good ventilation. When doctors find DM patients with TB symptoms, they should use a respiratory mask immediately, and distribute surgical masks to DM patients. All regulations and equipment for TB infection control should be established and provided in DM hospitals and clinics, to prevent TB transmission in these settings.

**Author’s Contributions**

Conceived and designed the manuscript: CHENG Jun, CHEN Ming Ting; Searched and read papers: CHENG Jun; Wrote the manuscript: CHENG Jun; Revised manuscript critically: ZHANG Hui, ZHAO Yan Lin, WANG Li Xia, CHEN Ming Ting; Made final approval of manuscript to be published: ZHAO Yan Lin, WANG Li Xia.

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