Screening and intervention of diabetes mellitus in patients with pulmonary tuberculosis in poverty zones in China: Rationale and study design

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ABSTRACT

Background: The merging epidemics of pulmonary tuberculosis (PTB) and diabetes mellitus (DM) have been raised concerns by many experts but no large scale screening and intervention have been launched yet, especially in low-income areas. The current study aims to understand the prevalence of DM in active PTB patients and evaluate the outcomes of diet and living habit intervention in poverty zones in China.

Methods/design: A cross-sectional investigation and intervention study will be carried out. At least 7000 active PTB patients will be recruited, together with 7000 nonTB persons from the same community. The project will be divided into two stages. The first stage is to train TB workers on DM screening and regular treatment. Screening and related investigation will be carried out afterwards. The second stage is focussed on intervention. A comprehensive strategy will be utilized to conduct health promotion among the patients, the health providers and the lay public.

Discussion: To our knowledge, this is the first and largest study which focuses on the prevalence of DM in PTB in China. We hypothesize that the current prevalence of DM in PTB in China will be understood and the results of our study will provide important evidence for preventing and controlling DM and PTB.

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1. Introduction

The linkage between pulmonary tuberculosis (PTB) and diabetes mellitus (DM) and the merging epidemics of PTB and DM have been raised concerns by many experts [1], especially in populations with low socio-economic status and high incidence rates for both diseases. In the developed world, the prevalence of PTB has fallen to low level and the association is seen less and less frequently. But in low to middle income countries, such as in China, where there are experiencing incredible increase in DM prevalence [2] and the highest burden of TB in the world [3], both diseases are major

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Abbreviations: PTB, pulmonary tuberculosis; DM, diabetes mellitus; HIV, human immunodeficiency virus.
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public health problems and the link between the two diseases should be paid special concern.

Despite the availability of effective therapy, PTB continues to infect an estimated one-third of the world’s population, to cause disease in 8.8 million people per year, and to kill 1.6 million of those afflicted. China accounts for nearly 17% of the world’s TB burden, with estimated 1.5 million new cases and approximately 270,000 deaths each year. In addition, China has noted a significant increase in the incidence of multidrug-resistant PTB [4].

Simultaneously, following the change of diet pattern and lifestyle, China is experiencing the fastest increase in DM prevalence. It was recently reported that the age standardised prevalence of diabetes was 9.7% (10.6% in men and 8.8% in women) and prevalence of prediabetes was 15.5% (16.1% in men and 14.9% in women) [2]. Moreover, Xu et al. discovered that the prevalence of DM was higher in residents of northern compared to southern China [5] and the rates of awareness, treatment and control of DM are relatively low. Improving the awareness, treatment, and control is urgently needed for the intervention of DM in the Chinese population.

Since the early 20th century, clinicians have observed an association between DM and PTB. Decreased activation of alveolar macrophages has been demonstrated in humans with DM [6]. Furthermore, neutrophils from people with diabetes had reduced chemotaxis and oxidative killing potential than those of non diabetic controls, and leukocyte bactericidal activity was reduced in people with diabetes, especially those with poor glucose control. Similarly, DM animals possess lower level of Th1-related cytokines (IL-12 and IFN-γ) than controls, which plays a crucial role in controlling PTB infection, and their alveolar macrophages are not fully activated by infection with M. tuberculosis [7]. On the other hand, it has been shown that glucose intolerance, and even manifest DM, occurs in the context of PTB infection. Perez et al. conducted a case–control analysis based on cross-sectional data from the Texas hospital discharge database. They found that PTB patients in both border and non border regions of Texas were more likely to have DM, determining an OR of 1.82 (95% CI: 1.57–2.12) and 1.51 (1.36–1.67), respectively [8]. Basoglu et al. found that PTB disease induces temporary hyperglycemia, which resolves with treatment [9]. And it was found that T2DM is the most common co-morbidity among the studied PTB patients. Also, it was shown that PTB patients together with DM were more likely to present with pulmonary rather than extra-pulmonary disease. Furthermore, Tsukaguchi et al. [10] discovered a dose–response relationship: levels of IFN-γ were negatively correlated with levels of HbA1c (a measure of serum glucose levels over time in humans).

Till now, although there are several reports [11,12] about the causal association between PTB and DM in China, the sample sizes were rather small and no large scale epidemiology investigation and intervention have been launched yet. Therefore, we initiate this epidemiology research with large-scale sample size to understand the current prevalence of DM in PTB and to elucidate whether a comprehensive intervention can increase the awareness of the association between PTB and DM in the patients, the health providers and the lay public. Also, we want to improve the nutrition and health status of the patients through this study.

2. Methods/design

2.1. Study design

Cross-sectional investigation and comprehensive intervention will be carried out in this project. Generally, this project is divided into two stages. The first stage is to train PTB workers or local medical staffs on DM screening and regular treatment. Screening and related investigation will be carried out afterwards. The second stage will be focussed on health intervention based on community level. The flowchart of the trial design is summarized in Fig. 1.

This study will be carried out in accordance with requirements documented in the Declaration of Helsinki. Ethics approval has been obtained from medical ethics committee of Qingdao disease prevention and control center. All participants will be fully informed by the investigators and give their written informed consent.

2.2. Training activities

The training will be conducted in a stepwise manner including the top-level training held in the city in concentrated form, the second-level training held in various communities of the city and the third-level training held in township health center of each community. The content of the training includes the goal and objective of this project; knowledge of controlling DM and PTB and the suggested guideline; skills of screening, health education, field work, data collection and the methods of quantity control, etc. The planning of the training was shown in Table 1.

### Table 1 – Planning of the training for the project.

<table>
<thead>
<tr>
<th>Level</th>
<th>Participants</th>
<th>Style of the training</th>
<th>Faculty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top-level</td>
<td>TB workers who will be in charge of the field work of each community; endocrine doctors, etc.</td>
<td>Concentrated training</td>
<td>Three from the project team, one from the bureau of disease control, two PTB experts, two endocrine experts</td>
</tr>
<tr>
<td>Second-level</td>
<td>TB workers from the county TB dispensary; county chest hospital; township health center</td>
<td>Concentrated training</td>
<td>One from the project team, two trainees from the top-level training course</td>
</tr>
<tr>
<td>Third-level</td>
<td>Village nurses</td>
<td>Concentrated training, informal discussion, etc.</td>
<td>Three trainees from the second-level training course</td>
</tr>
</tbody>
</table>
2.3. Screening for diabetes mellitus

2.3.1. Study population and recruitment
The current study will be conducted in two representative areas in China, Shandong province and Gansu province, which locate in the northeast and northwest parts of China, respectively. In China, the economic level differs among different areas. Shandong province is located in the northeast of China, which represents the middle-income area. Gansu province, which is located in the northwest of China, is low-income area where the average income level is lower than the average income level of China.

![Fig. 1 – Flowchart of the design of the whole study.](image-url)
Active pulmonary tuberculosis patients will be recruited to take part in the trial. HIV-positive patients will not be included in this study due to the influence of antiretroviral therapy on insulin resistance [13]. The screening of PTB patients will depend on the existing PTB prevention and control Internet in China. Pulmonary tuberculosis will be diagnosed by chest X-ray followed by sputum analysis for those with a suspicious shadow, X-ray and clinical examinations.

As to the cohort without PTB, cluster random sampling will be used to recruit subject from the same communities.

2.3.2. Sample size
We calculated the number of PTB screening as formula,

\[ N = \frac{t^2 \times PQ}{d^2} \]

where \( P \) is the prevalence of DM in PTB patients, \( Q = 1 - P \), \( d \) is tolerance error. In our study, \( t = 1.96 \approx 2 \), \( \alpha = 0.05 \), \( P = 6.7\% \), \( d = 0.1 \times P \), \( N = 400 \times Q/P = 5570 \) [14].

Considering sampling error, patients’ compliance, none response and withdraw, the number of screening is 7000 PTB patients in our study.

According to the prevalence of PTB in China, 7000 PTB patients we need may be screened from 6.1 million populations, which should be in nearly 19 communities from Gansu and Shandong provinces.

2.3.3. Criterion of DM screening
Subject whose fasting plasma glucose (FPG) is equal to or higher than 126 mg/dl will be screened as DM. And the result will be confirmed with a second test on a different day. The screening for DM will be carried out both in the 7000 PTB patients and the 7000 controls without PTB.

2.3.4. Collecting the related information
In the process of screening, the information of local economy, environmental situation, food resource, dietary pattern and health-related behaviors including cigarette smoking and alcohol drinking will be collected by using questionnaire. The main content of the questionnaire is shown in Table 2.

2.4. Intervention
The intervention will be based on community level. A comprehensive strategy, which incorporates intervention measures simultaneously to individual patient, the health providers, their family members and the lay public, will be utilized to maximize the effectiveness. Coordinating with the local CDCs, chest hospitals, community PTB dispensaries, township health centers and village clinics, appropriate health information will be delivered not only to the patients but also to health professionals and the lay public of the causal linkage between PTB and DM and the suggested guideline of prevention and treatment. At the end of this stage, we will obtain the rate of awareness, the effect of acceptability and applicability of intervention knowledge in high risky population and access the effect of the intervention. Also, the change of dietary pattern and nutritional status of the subject will be valued. The specific activities of intervention include:

2.4.1. Face-to-face health education
To individual patient, face-to-face health education will be carried out, which will be implemented by PTB workers in

<table>
<thead>
<tr>
<th>Categories</th>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>General information</td>
<td>Age, residence, occupation, education level, family economic situation, height, body weight, blood pressure, history of diseases</td>
</tr>
<tr>
<td>Basic knowledge in nutrition and PTB, DM, etc.</td>
<td>- Food guide pyramid knowledge</td>
</tr>
<tr>
<td>- Nutrient-food association knowledge</td>
<td></td>
</tr>
<tr>
<td>- PTB, DM related knowledge</td>
<td></td>
</tr>
<tr>
<td>Food frequency questionnaire (FFQ)</td>
<td>- Frequency and amount of cereals intake</td>
</tr>
<tr>
<td>- Frequency and amount of vegetables intake</td>
<td></td>
</tr>
<tr>
<td>- Frequency and amount of fruits intake</td>
<td></td>
</tr>
<tr>
<td>- Frequency and amount of meat intake</td>
<td></td>
</tr>
<tr>
<td>- Frequency and amount of eggs intake</td>
<td></td>
</tr>
<tr>
<td>- Frequency and amount of milk and its products intake</td>
<td></td>
</tr>
<tr>
<td>- Frequency and amount of soybean and its products intake</td>
<td></td>
</tr>
<tr>
<td>- Frequency and amount of dietary oil intake</td>
<td></td>
</tr>
<tr>
<td>- Frequency and amount of other substance intake (alcohol, tea, etc.)</td>
<td></td>
</tr>
<tr>
<td>24-h diet recall</td>
<td>- Food constituents and amount of breakfast</td>
</tr>
<tr>
<td>- Food constituents and amount of lunch</td>
<td></td>
</tr>
<tr>
<td>- Food constituents and amount of dinner</td>
<td></td>
</tr>
<tr>
<td>- Food constituents and amount of snacks</td>
<td></td>
</tr>
<tr>
<td>Health-related behaviors and physical activities</td>
<td>- Cigarette smoking</td>
</tr>
<tr>
<td>- Salty food intake</td>
<td></td>
</tr>
<tr>
<td>- Ventilation</td>
<td></td>
</tr>
<tr>
<td>- Basking in the sun</td>
<td></td>
</tr>
<tr>
<td>- Outdoor activities</td>
<td></td>
</tr>
</tbody>
</table>
Also, during the investigation, different methods of quality control including inter-lab comparison of glucose measurement will be carried out.

2.7. Statistical analysis

Descriptive statistics will be calculated and checked for balance in PTB and nonTB groups in demographic, physical and other related measurements at baseline. Comparisons between the groups of DM prevalence, etc. will be performed by Chi-square (categorical variables), t test (continuous variables, normal distribution) or Kruskal–Wallis H test (ranked data). All statistical analyses will be performed by using SPSS 12.0 statistical software package (SPSS Inc, Chicago, IL, USA).

3. Discussion

The causal association of PTB and DM has long been suggested [15], and Jeon and Murray [16] reported recently that the association was indeed genuine that DM was associated with an increased risk of PTB regardless of study design and population. But the author acknowledged that there were limitations to their approach: the estimate of the total prevalence of diabetes in England is based on old and relatively small population based studies.

To our knowledge, this study is the first and largest epidemiologic investigation and intervention project which focuses on the prevalence of DM in PTB and the effectiveness of diet and lifestyle intervention in China. This evidence-based study is designed on the basis of the latest literature research on the related domain. The major limitation of this study is that cross-sectional investigation will be used to understand the prevalence of DM in PTB patients instead of follow-up.

Fig. 2 – Institutional framework and the relevant responsibility.
study. Further research on cohort study will also be very interesting. Also, how PTB risk and clinical manifestation varies by type, duration, and severity of DM, which will provide a more thorough understanding of the association between PTB and DM will also been investigated in further studies.

We hypothesize that through this study the prevalence of DM in PTB patients in China will be understood, and the intervention will increase the awareness of the causal association between PTB and DM in TB workers, the patients, and the lay public and the nutrition and health status of the patients may be improved due to a balanced diet and reasonable lifestyle. This will benefit the patients and the prevention and control of the diseases. And appropriate protocols for managing patients with both PTB and DM will be developed by the end of the study. If so, the results of our study will provide especially important evidence for the prevention and control of the complex diseases.

**Acknowledgements**

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**Appendix A. The suggested guideline of controlling diabetes mellitus and pulmonary tuberculosis (by the project team)**

1. Guarantee the basic treatments of diabetes and pulmonary tuberculosis.

   The short illustration: Take effective measures to treat and control diabetes and pulmonary tuberculosis, to ensure that patients have access to basic medical services.

2. Get a balanced diet to ensure adequate supply of micronutrients.

   The short illustration: Take various kinds of food to meet the full nutritional needs and to prevent micronutrient deficiencies, especially deficiencies of vitamin A, vitamin C, iron and so on. In addition, sufficient micronutrients can effectively improve the body's immune system.

3. Patient who has an overweight or obese (BMI > 25) should control the total energy intake and maintain a healthy weight.

   The short illustration: Diabetic patients often have overweight or obese. So they should make individualized plans to control the total energy intake and the quantity and kinds of foods. Their body weight should be controlled as BMI < 24.

4. Those who are thin (BMI < 18.5) should promote their energy intake and increase the intakes of protein.

   The short illustration: PTB patients often are thin. As with diabetes at the same time, they should increase the intakes of protein, and reduce the intake of carbohydrates, so as to ensure energy supply and to control blood glucose levels.

5. Make outdoor activities to increase the illumination time.

   The short illustration: Lighting may increase the body’s vitamin D level, and enhance the immunity. Activities can also improve the insulin resistance. The recommended duration of sunshine is no less than 2 h a day.

6. Quit smoking and drinking. Eat less spicy, salty, smoked, grilled foods and so on. Drink enough amount of water.

   The short illustration: Smoking and drinking have impact on the treatment of pulmonary tuberculosis treatment as well as diabetes. Spicy, salty, smoked, grilled foods may stimulate the body and affect drug efficacy and physical rehabilitation. Patients with pulmonary tuberculosis, diabetes should pay drink adequate amount of water to promote the metabolism and excretion of body wastes. The recommended amount of water daily is not less than 1200 ml.

7. Have enough sleep to prevent fatigue.

   The short illustration: Take a regular schedule and do not stay up. Adequate sleep is conducive to disease rehabilitation and maintenance of the body's immune function. The recommended time sleep a day is no less than 6–8 h. Because overtire is not conducive to PTB treatment and rehabilitation, patients should avoid heavy manual labor, excessive physical exercise, and heavy domestic work, and so on.

8. Keep a good mood.

   The short illustration: Patients should adopt an optimistic attitude toward the disease and actively cooperate with treatment and care arrangements. Keep a good mood, be confident in the fight against the disease.

9. Form good health habits.

   The short illustration: Ventilate and disinfect the house regularly. Disinfect and wash clothing regularly and bathe regularly. Deal with the sputum and secretions of patients should harmlessly right away. Do not eat any poisonous and harmful or decomposed food. Meat and leftovers should be reheated in order to prevent food poisoning.

**References**


