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Short Communication

Tuberculosis Complicated by Diabetes Mellitus at Shanghai Pulmonary Hospital, China

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SUMMARY: An association between diabetes mellitus (DM) and tuberculosis (TB) has been implied for a long time. We previously reported that KDP type 1 diabetic rats and GK type 2 diabetic rats are highly susceptible to *Mycobacterium tuberculosis* infection. As a next step, we conducted a retrospective analysis of 2,141 patients with pulmonary TB newly diagnosed during the period from 2008 to 2009 to evaluate the influence of DM on the drug response rate and the long-term relapse rate of TB. There were 203 DM patients with TB (type 1 DM, 7 [3.4%]; type 2 DM, 196 [96.6%]). The TB relapse rate (2 years after discharge) was higher in DM patients than in non-diabetic patients (20% versus 5.3%). The frequency of multidrug-resistant-TB among DM patients with TB was higher than that among TB patients (17.7% versus 8.4%, $P < 0.01$). These results suggest that the period of TB treatment should be prolonged, and that in the meantime the blood glucose level should be maintained within a reference value range.

Diabetes mellitus (DM) is a high-risk factor for tuberculosis (TB). An association between diabetes and TB has been implied for centuries. In the late 17th century, Morton recognized a link between diabetes and TB (1). Since then, a body of clinicoepidemiological data has been accumulated (2-7). However, there is no definitive evidence of an association between DM and TB. Patients with DM have been noted to have impaired granulocyte chemotaxis, phagocytosis, bactericidal activity and superoxide production (8,9). In order to obtain conclusive evidence of the link between DM and TB, we have employed two kinds of rat diabetes models, the Komeda diabetes-prone (KDP) type 1 rat model and the Goto-Kakizaki (GK) type 2 rat model, and have reported that both type 1 and type 2 diabetic rats are highly susceptible to *Mycobacterial tuberculosis* (10,11). Although there are a few reports on the association between TB and DM in Asia (7,12,13), no such report has come from China. Therefore, we focused on TB patients with DM in Shanghai, China. A total of 2,141 TB patients were hospitalized between April 2008 and March 2009, of whom 1,464 (68.4%) were smear- and culture-positive, and 20.2% were smear-negative and culture-positive. The male to female ratio was 3.2:1. All were farmers, salaried persons or unemployed, with an average age of 42.7 years. This project was approved by the ethics committee of Shanghai Pulmonary Hospital, China.

Among these TB patients, 203 (9.5%) were complicated by DM (type 1, 7; type 2, 196). Of these, 114 patients were smear- and culture-positive and 47 were smear-negative and culture-positive. The blood glucose range of these patients was 200 - 700 mg/dl. After the DM patients had been hospitalized for 2 to 4 weeks, those with type 1 DM were treated by subcutaneous injection of recombinant insulin, and those with type 2 DM received oral medication including metformin hydrochloride and gliclazide. Thereafter, they received standardized regimens consisting of isoniazid, rifampicin, pyrazinamide, ethambuthol or streptomycin. We then examined the drug susceptibility of *M. tuberculosis* isolates cultured from the TB patients with DM by the proportional method (14). As shown in Table 1, 36 (17.7%) of the patients with DM had multidrug-resistant (MDR)-TB, the proportion being significantly higher than that of non-diabetics with TB (9.3%) ($P < 0.01$). Furthermore, the proportion of MDR-TB patients was much higher in the group with poorly controlled DM (32 versus 4). Of 167 patients who had received standardized chemotherapy, 20 (12.0%) relapsed within 2 years after being discharged from the hospital. There are several reasons that the incidence of MDR-TB and the relapse rate are higher in patients with DM than in non-diabetics. First, the DM patients have moderate to severe TB, and it takes longer period to treat them sufficiently with chemotherapy. Their drug compliance is often poor, and they suffer adverse reactions more frequently. They take anti-TB drugs irregularly. Second, some patients cannot pay for their medical expenses, and so their chemotherapy has to be discontinued for short periods of time until they earn enough money to restart the chemotherapy. Third, some patients do not take anti-DM drugs regularly, and their blood glucose levels are not well controlled, until eventually their TB becomes refractory. Lastly, these DM patients may be reinfected with new MDR-TB strains due to their lowered immunity.

Table 1. Drug sensitivity of tubercle bacilli cultured from TB patients with DM

	Drug-susceptible	MDR[1)]	Total
Diabetics (n = 203)[2)]	82.3%	36 (17.7%)	100%
FBS ≧ 200 mg/dl		32 (15.7%)	
126 ≦ FBS ≦ 199		4 (2.0%)	
Non-diabetics (n = 1,938)	90.7%	9.3%	100%

[1)]: $P < 0.01$.
[2)]: The detailed profiles of 203 diabetics and 1,938 non-diabetics are as follows: 67 (FBS ≧ 200 mg/dl) (51 - 78 years old, man:woman = 5.5:1), 136 (126 ≦ FBS ≦ 199) (30 - 82 years old, man:woman = 5.5:1), and 1,938 (FBS≦125) (2 - 96 years old, man:woman = 3:1).
MDR, multidrug-resistant; FBS, fasting blood sugar (mg/dl).

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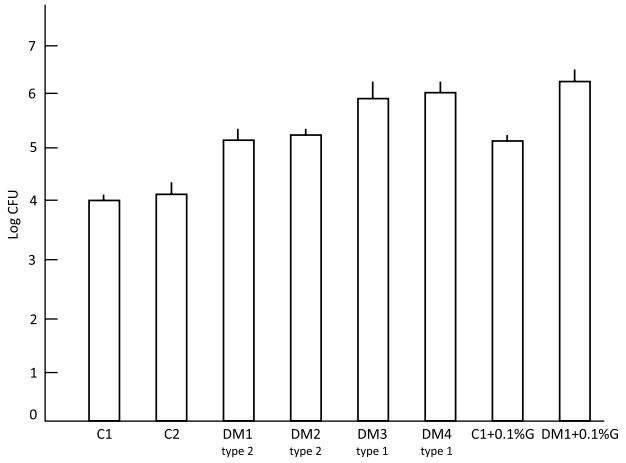

Fig. 1. The effect of serum from DM patients on growth of *M. tuberculosis* H37Rv. C, healthy volunteer; DM, diabetes mellitus; G, glucose.

There have been two reports of pulmonary TB complicated by DM in Japan (12,13). Kameda et al. analyzed 116 TB patients with DM among 644 TB patients. MDR-TB patients with DM accounted for 6.0% of the total, which was a significantly lower proportion than that in our present series. Their relapse rate within 30 months after discharge was 10.3%, which was not significantly different from the result in our series. Wada et al. also reported 54 TB patients with DM among 620 patients with TB, and the relapse rate within 24 months after discharge was 11.1%, compared with 1.3% in non-diabetics. This difference was statistically significant ($P < 0.01$). Thus, it is worthwhile to examine the TB relapse rate in diabetics on the basis of large samples.

We have recently reported that 0.1% glucose increased mycobacterial growth in vitro and that insulin treatment resulted in a significant reduction of tubercle bacilli in infected KDP rats (13). Therefore, it is useful to examine the effects of serum samples from DM patients on mycobacterial growth in vitro. We collected two serum samples from healthy subjects (C1 and C2), two samples from type 2 DM patients (DM1 and DM2) and two samples from type 1 DM patients (DM3 and DM4). Blood glucose levels and immunoreactive insulin (IRI) levels in DM1, DM2, DM3 and DM4 were 520 mg/dl and 5 μU/ml, 660 mg/dl and 5 μU/ml, 610 mg/dl and <1 μU/ml, and 705 mg/dl and <1 μU/ml, respectively. The reference value ranges of fasting blood glucose and IRI were 100-125 mg/dl and 5-15 μU/ml, respectively, in this hospital. The patients' serum (0.5 ml each) was added to 0.5 ml of 7H9 liquid medium and cultured in the presence of *M. tuberculosis* H37Rv (1,000 CFU) for 1 week. Thereafter, serially diluted samples were cultured on 1% Ogawa solid agar slants in triplicate, and the colonies that appeared were counted 4 weeks later. In some experiments, 0.1% glucose was added to C1 and DM1 serum samples. As shown in Fig. 1, the growth of tubercle bacilli was facilitated in the patients' sera. Moreover, the sera from type 1 DM patients enhanced mycobacterial growth significantly ($P < 0.01$). When 0.1% glucose was added to C1 and DM1 serum samples, the growth of tubercle bacilli was better facilitated ($P < 0.01$). Although the sample numbers were small, the results suggested that glucose stimulates mycobacterial growth, whereas insulin reduces mycobacterial colonies.

We then conducted a retrospective analysis of 2,141 patients with pulmonary TB newly diagnosed during the period from 2008 to 2009 to evaluate the influence of DM (203 cases) on the drug response rate and the long-term TB relapse rate. The cases of TB complicated by DM showed a poor prognosis if relapse occurred within 2 years. Thus, it appears that a longer treatment period is required for TB patients with DM. At the same time, as there were more MDR-TB patients with DM in this series, there is a need to devise a new chemotherapy regimen to achieve a more effective treatment.

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