Diabetes mellitus (DM) is a high-risk factor for tuberculosis (TB). An association between diabetes and 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.

<table>
<thead>
<tr>
<th>Drug-susceptible</th>
<th>MDR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetics (n = 203)</td>
<td>82.3%</td>
<td>36 (17.7%)</td>
</tr>
<tr>
<td>FBS ≥ 200 mg/dl</td>
<td>32 (15.7%)</td>
<td></td>
</tr>
<tr>
<td>126 ≤ FBS ≤ 199</td>
<td>4 (2.0%)</td>
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</tr>
<tr>
<td>Non-diabetics (n = 1,938)</td>
<td>90.7%</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

*P < 0.01.

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).
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.

**REFERENCES**