The impact of diabetes mellitus on drug resistance in patients with newly diagnosed tuberculosis: a systematic review and meta-analysis

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Background: Tuberculosis and diabetes mellitus are both important global health problems now. Previous studies have drawn different conclusions about the impact of diabetes on drug resistance in patients with newly diagnosed tuberculosis.

Methods: We conducted a systematic search in four databases: PubMed, EMBSE, Cochrane Library, and Web of Science. The relative risk (RR) was applied to assess the association of diabetes with drug resistance and the STATA version 12.0 was used for data synthesis.

Results: A total of 13 studies involving 33,747 patients were included in our study. The pooled results revealed that presence of diabetes was significantly associated with isoniazid resistance (RR = 1.22, 95% CI: 1.04–1.43) in patients with newly diagnosed tuberculosis. However, no significant impact of diabetes on rifampicin resistance (RR = 0.67, 95% CI: 0.41–1.11) or multi-drug resistance (MDR) (RR = 1.28, 95% CI: 0.93–1.75) was observed. The results of subgroup analysis were similar to the pooled results. No significant publication bias for the results of MDR was found.

Conclusions: In patients with newly diagnosed tuberculosis, diabetes is associated with isoniazid resistance. However, there is no significant impact of diabetes on the rifampicin resistance or MDR. However, these findings still need to be verified in the future.

Keywords: Tuberculosis (TB); diabetes mellitus; drug resistance; meta-analysis

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Introduction

There were 10.4 million new cases of tuberculosis (TB) and 1.7 million deaths from tuberculosis globally in 2016 (1). Although this number has decreased dramatically in the last few decades, tuberculosis is still the top cause of death among infectious diseases now and a great challenge to global health security (2). Some risk factors are associated with tuberculosis infection or latent tuberculosis reactivation, such as smoking, alcohol intake, poor living conditions, malnutrition, contacts with sputum smear positive patients, HIV, kidney dialysis, organ transplantation, etc. (3,4). On the other hand, lack of systems and tools to monitor and treat TB patients in some high-incidence countries and international migration flows might both increase the global TB incidence rate (5,6). Drug-resistant tuberculosis (DR-TB) has generated lots of
concerns and discussion over recent years. In 2006, about 600,000 new cases were resistant to rifampicin, the most powerful and commonly used first-line drug (1). About 4.1% of new tuberculosis cases and 19% of retreatment cases experience multidrug-resistant tuberculosis (MDR-TB) globally now (7). It is generally recognized that the genetic selection of drug resistance strains makes mycobacterium tuberculosis (M. tuberculosis) unresponsive to drugs (8). Some man-related factors such as misdiagnosis and mismanagement could also contribute to this problem (9). It is noticeable that DR-TB patients generally require longer treatment regimens and more costly, toxic second-line drugs, which might cause more complications (10).

Diabetes mellitus is also one of the most important global health problems now (11). The diabetes prevalence, health expenditure and deaths due to diabetes would continue to rise in the next decades (12). One of the biggest threats caused by diabetes is the complications. Microvascular complications, macrovascular complications, as well as miscellaneous complications affect nearly every organ system (13).

Some previous studies have revealed that DR-TB might be associated with diabetes. For example, some researchers found there was a significant correlation between diabetes and DR-TB or MDR-TB development and adverse clinical outcomes (14,15). The renal lesions, effects of blood glucose on plasma concentration of antituberculosis drugs, influences of reactive oxygen species (ROS) on drug resistance mutations (16) are all potential mechanisms. However, some other studies showed opposite results (17,18). The differences of population, history of tuberculosis and treatment strategy might cause the inconsistency of conclusions. Thus, this issue is worth exploring further.

Given the uncertain relationship between diabetes mellitus and DR-TB, we conducted this systematic review and meta-analysis to clarify the impact of diabetes mellitus on drug resistance in patients with newly diagnosed tuberculosis.

**Methods**

**Search strategy**

We conducted a systematic search in four databases: PubMed, EMBASE, Cochrane Library, and Web of Science. We aimed to identify all potentially related studies which were published from January 1, 1966 to July 1, 2019. We used both MeSH terms and free-text words to increase sensitivity.

The following search terms were used: “diabetes” or “diabetes mellitus” or “diabetics mellitus” or “diabetic” or “diabete” and “tuberculosis” or “tuberculoses” or “tuberculosis” or “pulmonary tuberculosis” and “drug resistance” or “drug-resistance” or “drug resistant” or “DR”. All searched results were evaluated according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (19). Firstly, titles and abstracts were screened to recognize relevant studies. Then, full texts were evaluated carefully. Both search and selection were completed by two independent investigators (Dong Huang and Yan Wang).

**Inclusion and exclusion criteria**

The following inclusion criteria were used: (I) adults (18 years or older); (II) newly diagnosis of tuberculosis with or without diabetes mellitus; (III) received antituberculotic therapy and follow-up; (IV) outcomes included but not limited to: DR [M. tuberculosis resistant to any first-line anti-TB drug (isoniazid, rifampicin, pyrazinamide and ethambutol)] or MDR (M. tuberculosis resistant to at least isoniazid and rifampin).

The following exclusion criteria were used: (I) previous history of TB, TB treatment, DR-TB or MDR-TB; (II) editorials, expert opinions, case reports and reviews or studies with insufficient data; (III) nonhuman studies.

**Data collection**

Two researchers (Dong Huang and Yan Wang) collected data from each article by using an Excel sheet (Microsoft Corporation) independently. Any disagreement was resolved through team discussion until consensus reached. The following information was extracted from all included studies: first author of the study, publication year, the country where the study was performed, sample size, number of diabetes patients, type of diabetes, number of DR, number of MDR, type of drug-resistance.

**Statistical analyses**

Data synthesis was accomplished by STATA (version 12.0; Stata Corporation) and the results were displayed by forest plots. We rendered statistical significance as P.
value <0.05. Statistical heterogeneity between studies was evaluated using Cochran’s Q test and Higgins I² statistic (20). The significant heterogeneity was defined as P<0.1 and (or) I² >50%. We used random-effects model to calculate the pooled effects if significant heterogeneity was observed, or used the fixed-effects model when there was no significant heterogeneity. We calculated mean difference (MD) and 95% confidence interval (CI) for continuous data, while calculated risk ratio (RR) and 95% CI for dichotomous data. We also performed a subgroup analysis investigating whether country, sample size, type of drug-resistance, location of tuberculosis affected results of our study. We performed the sensitivity analysis to further verify conclusions of our study by removing the data of an individual study in turn each time. We evaluated publication bias by the Beggs funnel plot and Egger’s linear regression tests (21).

Quality assessment

The quality of the included studies was assessed with the NOS (Newcastle-Ottawa quality assessment scale) (22). The NOS included three parameters: selection, comparability, and outcome. Studies which earned at least 6 points were regarded as high-quality studies. Quality assessment was also completed by two independent researchers (Dong Huang and Yan Wang).

Results

Characteristics of included studies

As shown in Figure 1, the electronic search yielded 1,124 records. After duplicates were removed, there were 877 records left. Then we screened titles and abstracts carefully, and assessed 34 full-text articles for eligibility. At last, 13 articles (17,18,23-33) including 33,747 patients were included in this meta-analysis, among which 6,365 patients suffered from diabetes. In these 13 studies, 959 patients were found with isoniazid resistance, and 188 patients were found with rifampicin resistance, and only one patient were reported resistant to ethambutol. Moreover, a total of 641 patients had MDR-TB. There were 8 studies which focused on pulmonary tuberculosis exclusively. Only some of included studies reported the type of diabetes and type of drug resistance. As for quality assessment, all studies earned at least 6 points. Other details of characteristics of included studies were shown in Table 1.

Impact of diabetes on drug resistance of tuberculosis

There were 5 studies which explored the impact of diabetes on isoniazid resistance. The fixed-effects model was applied because no significant heterogeneity was observed (I² =0%, P=0.471). The pooled results revealed a significant trend towards more resistance to isoniazid in diabetes patients compared with non-diabetes patients (RR =1.22, 95% CI: 1.04–1.43) (Figure 2).

There were 5 studies which explored the impact of diabetes on rifampicin resistance. At last 3 studies were included in our meta-analysis because the data of other 2 studies could not be used to calculate the RR in STATA. We used fixed-effects model because of the non-significant heterogeneity (I² =0%, P=0.712). There was no significant impact of diabetes on rifampicin resistance (RR =0.67, 95% CI: 0.41–1.11) (Figure 3).

Totally, 13 studies reported the association between diabetes and MDR-TB. Similarly, 10 studies with valid data were included in our meta-analysis. The random-effects model was applied because of significant heterogeneity.
Table 1 Basic characteristics of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Sample size</th>
<th>Diabetes, No.</th>
<th>Type of diabetes</th>
<th>Isoniazid resistance, No.</th>
<th>Rifampicin resistance, No.</th>
<th>Ethambutol resistance, No.</th>
<th>MDR, No.</th>
<th>Type of drug-resistance</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singla</td>
<td>2006</td>
<td>India</td>
<td>500</td>
<td>125</td>
<td>Type 1/2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Zhang</td>
<td>2009</td>
<td>China</td>
<td>2141</td>
<td>203</td>
<td>Type 1/2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>216</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Chang</td>
<td>2011</td>
<td>China (Taiwan)</td>
<td>192</td>
<td>60</td>
<td>Type 2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4</td>
<td>Primary</td>
<td>7</td>
</tr>
<tr>
<td>Jiménez-Corona</td>
<td>2013</td>
<td>Mexico</td>
<td>796</td>
<td>275</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>17</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Duangrithi</td>
<td>2013</td>
<td>Thailand</td>
<td>227</td>
<td>37</td>
<td>–</td>
<td>15</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>Primary</td>
<td>8</td>
</tr>
<tr>
<td>Hsu</td>
<td>2013</td>
<td>China (Taiwan)</td>
<td>869</td>
<td>204</td>
<td>Type 1/2</td>
<td>97</td>
<td>34</td>
<td>1</td>
<td>29</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Mi</td>
<td>2014</td>
<td>China</td>
<td>422</td>
<td>144</td>
<td>Type 2</td>
<td>37</td>
<td>5</td>
<td>–</td>
<td>26</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Magee</td>
<td>2015</td>
<td>Republic of Georgia</td>
<td>318</td>
<td>37</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>52</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>Baghaei</td>
<td>2016</td>
<td>Iran</td>
<td>126</td>
<td>62</td>
<td>–</td>
<td>11</td>
<td>2</td>
<td>–</td>
<td>2</td>
<td>Primary</td>
<td>6</td>
</tr>
<tr>
<td>Salindri</td>
<td>2016</td>
<td>Georgia</td>
<td>268</td>
<td>36</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>52</td>
<td>Primary</td>
<td>6</td>
</tr>
<tr>
<td>Abdelbary</td>
<td>2017</td>
<td>America</td>
<td>8431</td>
<td>2121</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>55</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Leung</td>
<td>2017</td>
<td>China</td>
<td>19279</td>
<td>3005</td>
<td>–</td>
<td>799</td>
<td>145</td>
<td>–</td>
<td>90</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>Li</td>
<td>2017</td>
<td>China</td>
<td>178</td>
<td>56</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>89</td>
<td>Primary</td>
<td>7</td>
</tr>
</tbody>
</table>

MDR, multidrug resistance; NOS, Newcastle-Ottawa quality assessment scale; –, not reported; No., number.

Figure 2 Forest plot for the association between diabetes and isoniazid resistance in newly diagnosed tuberculosis patients.
Figure 3 Forest plot for the association between diabetes and rifampicin resistance in newly diagnosed tuberculosis patients.

Figure 4 Forest plot for the association between diabetes and multi-drug resistance (MDR) in newly diagnosed tuberculosis patients.

The pooled results showed that diabetes was not associated with MDR (RR = 1.28, 95% CI: 0.93–1.75) (Figure 4).

Subgroup analysis

We aimed to investigate whether country (China vs non-China studies), sample size (≥1,000 vs <1,000), type of drug-resistance (primary drug-resistance) and location of tuberculosis (pulmonary tuberculosis) would affect the results of MDR-TB. Most of the results of subgroup analysis were similar to pooled results. The sample size, type of drug-resistance and location of tuberculosis did not have significant effects on the association between...
diabetes and MDR-TB. However, the pooled results of 4 non-China studies showed diabetes could increase the risk of MDR-TB (RR = 1.62, 95% CI: 1.13–2.34) (Table 2).

**Sensitivity analysis and publication bias**

Because of the significant heterogeneity in the pooled results of MDR, we further conducted sensitivity analysis to assess the stability of the pooled results. We evaluated the exact influences of each study on the pooled RR by excluding every single study individually and gradually from the overall meta-analysis. The results showed that the pooled RR for the impact of diabetes on MDR were robust (Figure 5).

The publication bias was evaluated by Begg’s funnel plot and Egger’s linear regression tests. The funnel plot was symmetric and we did not observe significant publication bias for the results of MDR (Begg’s: P=0.859; Egger’s: P=0.771) (Figure 6).

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Table 2 Meta-analyses for the association of diabetes mellitus with MDR in patients with newly diagnosed tuberculosis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of studies</th>
<th>RR (95% CI)</th>
<th>Log-rank P value</th>
<th>I² (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidrug resistance</td>
<td>10</td>
<td>1.28 (0.93–1.75)</td>
<td>0.125</td>
<td>62.2</td>
<td>0.005</td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>6</td>
<td>1.12 (0.70–1.77)</td>
<td>0.643</td>
<td>70.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Non-China</td>
<td>4</td>
<td>1.62 (1.13–2.34)</td>
<td>0.009</td>
<td>23.7</td>
<td>0.269</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1,000</td>
<td>3</td>
<td>1.32 (0.71–2.46)</td>
<td>0.376</td>
<td>77.6</td>
<td>0.012</td>
</tr>
<tr>
<td>&lt;1,000</td>
<td>7</td>
<td>1.24 (0.84–1.81)</td>
<td>0.276</td>
<td>50.6</td>
<td>0.059</td>
</tr>
<tr>
<td>Type of multidrug-resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary drug-resistance</td>
<td>2</td>
<td>1.22 (0.68–2.18)</td>
<td>0.498</td>
<td>69.3</td>
<td>0.071</td>
</tr>
<tr>
<td>Location of tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>8</td>
<td>1.35 (0.95–1.91)</td>
<td>0.092</td>
<td>60.6</td>
<td>0.013</td>
</tr>
</tbody>
</table>

MDR, multidrug resistance; No., number; RR, relative risk; CI, confidence interval.
Discussion

As far as we know, this is the first systemic review and meta-analysis investigating exclusively the impact of diabetes on drug resistance in newly diagnosed tuberculosis patients. We found that, compared with absence of diabetes, presence of diabetes was associated with resistance to isoniazid in newly diagnosed tuberculosis patients. However, diabetes did not have significant impact on the resistance to rifampicin or MDR.

We supposed that there might be several reasons why diabetes had significant effects on isoniazid rather than rifampicin. Firstly, the number of studies included in the meta-analysis for rifampicin resistance is smaller than that for isoniazid resistance. The pooled results might be insufficient to find a link between diabetes and rifampicin resistance. Secondly, isoniazid is one of the first known and most effective anti-TB drugs (34). It has strong early bactericidal activity and is long-term widely used. Numerous researchers believe resistance to isoniazid usually comes first during first-line chemotherapy regimens among new patients without HIV-infected in most settings (35-37). On the other hand, isoniazid resistance is even considered as the first step in development of MDR and extremely resistant (XDR) TB (38). Thirdly, the serum concentrations of isoniazid and rifampin are often affected by blood glucose level and become below the expected range (39,40). Furthermore, tuberculosis and the drugs used to treat tuberculosis might also lead to worse glycemic control in people with diabetes (41). Tuberculosis and diabetes might aggravate each other and this vicious circle could produce the effects similar to misadministration of anti-TB drugs, which is the most common reason for drug resistance (42). Heysell et al. have found the dosage adjustment of rifampin was more likely to elevate serum concentration to the target range than dosage adjustment of isoniazid (43), which might partly explain why isoniazid resistance is more common in patients with TB and diabetes. Moreover, the changed binding drugs in the blood due to glycosylation of plasma proteins and increased renal clearance of anti-TB drugs have both been reported in previous studies (44). However, these theories have not been been confirmed widely and the scientific mechanism is still unclear. The relationship between diabetes and DR-TB is worth discussing in the future. In addition to this, we have planned to explore if diabetes would increase the risks of resistance to pyrazinamide and ethambutol. Nevertheless, only 2 researches reported the incidence of ethambutol resistance. We abandoned this idea due to lack of data.

Compared with single drug-resistance, there were more researches which explored the association between diabetes and MDR. Liu et al. have conducted a meta-analysis of 13 studies and concluded that diabetes was an independent risk factor for MDR-TB (OR =1.71; 95% CI: 1.32–2.22) (45). However, their meta-analysis included both newly diagnosed patients and retreatment patients with history of TB. In their meta-analysis, only about half of included studies focused on newly diagnosed patients exclusively. We thought that it was necessary to analyze new patients separately because it has been reported that previously treated patients were at increased risk for drug resistance (46). Tsao et al. have also found that a history of pulmonary TB was a predictor for drug resistance (47). Furthermore, the emergence of MDR-TB is often related to abuse or non-standard use of anti-TB drugs, which mainly happens in retreatment patients with long-term medication. Tégegne et al. have also conducted a similar meta-analysis about the association between diabetes and MDR-TB (48). In their particular sub-analysis including only 5 studies of new TB, the pooled OR (95% CI) for MDR were 2.36 (1.59–3.51) when adjusted for at least one covariate and 1.64 (0.99–2.71) when not adjusted for covariates. The authors also deemed that there were inadequate number of studies which adjusted and adjusted results still suffered from unobserved confounding factors. This controversial conclusion needs to be clarified in future multi-center, large-scale and well-designed prospective studies. As for the results of subgroup analysis of non-China studies, we should be cautious about this conclusion. As reported the number of TB in China is 900,000 in 2016, only less than India and Indonesia (49). However, after consulting relative references, we did not find distinct differences of population, treatments or follow-
up systems between China and other countries. It needs to be further explored. To sum up, we believe the current evidence is not enough to certify the association between diabetes and MDR in newly diagnosed TB patients. Physicians should pay more attention to the level of blood glucose in patients with history of TB or retreatment patients specially to minimize the risks of MDR-TB. This measure would decrease mutual impact of diabetes and tuberculosis (50) and is cost-effective for these patients (51).

Apart from the direct effects of diabetes on drug resistance, now evidence is growing that diabetes could affect the occurrence and prognosis of tuberculosis. Previous studies have ever found that diabetic patients have increased risk of developing TB compared with people without DM (52,53). Moreover, the risks of developing TB are especially high in young, low BMI, and poorly controlled diabetes patients (54). Diabetes might cause immune dysfunction, altered levels of cytokines and changed activation state of the macrophages (55,56). Meanwhile, the acid environment of high glucose may be in favor of growth of *M. tuberculosis*. This mechanism would decrease efficacy of anti-TB drugs and increase the risks of drug resistance. Baker *et al.* have conducted a systemic review and revealed diabetes increased the risk of treatment failure, relapse and death among TB patients (57). Meanwhile, the time of sputum culture conversion is longer in diabetes patients compared with non-diabetes patients (58). Recently oxidative stress is also considered as a major underlying mechanism adversely impacting TB treatment outcomes of diabetes patients (59). However, these findings have not been confirmed in other studies. It is reported that diabetes is not associated with higher OR of unsuccessful treatment outcome in MDR/XDRTB patients (60). Some researchers even found diabetes appeared as a protective factor for death in TB patients (61). Future studies should obtain more information about the characteristics of population, comorbidities (especially HIV infection and kidney diseases) and treatments in order to draw relatively fair conclusions.

The effects of glycemic control conditions and types of diabetes on TB is also a matter of concern. Previous studies got different results. Shewade HD once conducted a systemic review and concluded that optimal glycemic control was associated with more successful treatment outcomes, fewer odds of recurrence, faster culture conversion (62). As for the types of diabetes, it was reported that the blood concentration of drugs and therapy outcomes of TB were more favorable in patients with type 1 diabetes mellitus compared with type 2 (63). Researchers speculated that the significant slower inactivation process and slighter inactivation of anti-TB drugs in type 1 diabetes patients were main reasons. We have also planned to explore whether glycemic control conditions and diabetes type could influence drug resistance. Similarly, we abandoned this idea because lack of available data in included studies. However, we believe it is worth exploring in the future. After understanding more specific relationships between diabetes and TB, physicians could make more detailed treatment plans, which might lead to better prognosis for TB patients with diabetes.

There are still several limitations in the study. Firstly, significant heterogeneity exists in this meta-analysis. But we did not find any single study which could increase heterogeneity prominently in sensitivity analysis. Then, the included patients in these studies has different types and therapy methods of diabetes. However, we were not able to perform more subgroup analyses or adjust results in terms of these confounding factors due to lack of original data. Thirdly, all studies were published in English in our meta-analysis, which means that some eligible studies might have been excluded because of language restrictions.

**Conclusions**

In newly diagnosed tuberculosis patients, presence of diabetes is associated with more resistance to isoniazid compared with absence of diabetes. However, there is no significant impact of diabetes on the rifampicin resistance or MDR. These findings need to be confirmed in the future.

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**Footnote**

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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