Statin use and risk of tuberculosis: A systemic review of observational studies

Running title: Statins and tuberculosis

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Highlights

- Six observational articles with more than 200,000 patients were enrolled.
- Statin use significantly reduced 22% risk of tuberculosis in diabetes mellitus patients (pooled RRs, 0.78; 95%CI, 0.63–0.95) with severe heterogeneity ($I^2=76.1\%$).
- Statin intake also significantly decreased 40% risk of tuberculosis in the general population (pooled RRs, 0.60; 95%CI, 0.50–0.71) with severe heterogeneity.

ABSTRACT

Objectives: Statin intake may be linked with less risk of several infectious diseases, including tuberculosis, which is an important cause of mortality worldwide. We aimed to probe into the definite impacts of statins on the risk of tuberculosis in diabetic patients and in the general population.

Methods: Four databases were thoroughly searched from inception up to July 2019. Articles in any language were enrolled if they assessed and clarified statin intake, presented risk of tuberculosis in diabetes mellitus patients or the general population, and reported odds ratios (ORs), relative risks (RRs) or hazard ratios (HRs) or contained data for relevant calculation. RRs with 95% confidence intervals (CIs) were pooled using random-effects models regardless of heterogeneity quantified by Cochran's Q and $I^2$ statistics.
Results: Six observational articles with 2,073,968 patients were enrolled, including 4 cohort articles, 1 nested case-control and 1 abstract. Statin use significantly reduced 22% risk of tuberculosis in diabetes mellitus patients (pooled RRs, 0.78; 95%CI, 0.63–0.95) with severe heterogeneity (I^2=76.1%). Statin intake also significantly decreased 40% risk of tuberculosis in the general population (pooled RRs, 0.60; 95%CI, 0.50–0.71) with severe heterogeneity (I^2=57.7%).

Conclusions: Statin use is related to a considerably lower risk of tuberculosis both in diabetic patients and the general population. However, these conclusions should be understood carefully given the possible remaining confounding, and call for large-size and multi-center random controlled studies in the future.

Keywords: Statins, Tuberculosis, Diabetes mellitus, Risk, Systemic review

Introduction

Tuberculosis (TB), a chronic infectious disease induced by *Mycobacterium tuberculosis*, is among the top 10 sources of death globally. In 2018, TB attacked more than 10,000,000 new cases and killed 1,500,000 people, including 251,000 people affected by human immunodeficiency virus globally (World Health Organization, 2019). Geographically, the estimated incidence/mortality rate of TB in Korea and Taiwan is 34/2.4 and 38.9/2.1 per 100,000 people, respectively (World Health Organization, 2019; Center for Disease Control, Department of Health, Executive Yuan, Taiwan, 2018). The chronic diabetic status is a definite risk factor of TB, which is caused by various factors, as the occurrence of TB from the reactivated old foci surpasses that via fresh contact. About 5% to 30% of TB cases are
accompanied with diabetes mellitus (DM) (Ruslami et al., 2010). One review shows that diabetes can intensify the risk of TB by 1.5 to 7.8 times (Stevenson et al., 2007). A meta-analysis indicates diabetes raises the risk of TB among ordinary people by 3 times (Jeon and Murray, 2008), but even more in diabetic patients when diabetes is not well controlled (Baker et al., 2012).

Statins are medicated by hyperlipidemic patients to cure and prevent coronary heart diseases and strokes by blocking 3-hydroxy-3-methylglutaryl-CoA reductase, a main enzyme of cholesterol generation. Also diabetic patients take statins for various positive outcomes. However, statins affect the immune system in multiple ways and are related to the improved outcomes of many infectious diseases (Kim et al., 2018; Ma et al., 2017; Uthman et al., 2018; Yeh et al., 2018). As one infectious diseases, TB is still one major public health threat worldwide. Host cholesterol is one critical factor in the occurrence of TB in several ways in vitro (Brzostek et al., 2009; Huynh et al., 2008; Miner et al., 2009), and removal of membrane cholesterol can specifically prevent TB pathogens from entering host macrophages (Gatfield and Pieters, 2000). Therefore, cholesterol reduction by statins is logically expected to have a favorable outcome during TB management. However, the anti-TB mechanism of action is not believed to be directly due to reduction of host cholesterol, but is likely multifactorial, such as enhancing phagosomal maturation and host-protective autophagy (Parihar et al., 2014) and antitubercular activity of statins (Dutta et al., 2016, 2019) and the host-directed (Guler and Brombacher, 2015). Several studies present the association between statin use and less risk of active TB in DM patients (Lai et al., 2016; Lee et
al., 2015; Su et al., 2017), but this finding is not supported by other studies (Kang et al., 2014; Kim et al., 2019). Recently, a population-based cohort article found the standard-course treatment did not improve the outcomes of TB patients. (Chen et al., 2019) The inconsistency among the existing findings may be attributed to the differences in participants and trial intervention. Nevertheless, there is no disagreement about the effects of statins on reducing the risk of TB in the general population, since all extant studies proved statins can actively reduce the risk of TB in the general population (Kim et al., 2019; Lai et al., 2016; Su et al., 2017).

Regarding the above analyses, we thoroughly reviewed and meta-analyzed the existing observational studies (OSs) that explored the connection between statin use and TB risk in DM patients and in the general population.

**Methodology**

*Search strategy and selection criteria*

We searched Web of Science, Wiley Cochrane Central Register of Controlled Trials, PubMed, Scopus, and Ovid EMBASE from inception up to July 2019. The keywords included statin(s), HMG-CoA reductase inhibitor(s), atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin; tuberculosis or TB; *Mycobacterium tuberculosis*. References in relevant articles were manually looked through to find out potential articles. Search was conducted independently by HD and TL and any disagreement was solved with a third reviewer (YC). The authors were contacted to ascertain the unpublished data if necessary.

*Inclusion and exclusion criteria*
OSs involving participants aged ≥ 18 years; and analyzing the TB risk after statin user in DM patients or in the general population were included. Other study designs were excluded, including case report, unpublished article, comment, quasi-trial, letter and editorial. The article with the largest sample size or the latest presentation was selected if more than one articles from the same affiliation or team were qualified.

Data extraction and quality assessment

Study selection and data extraction were conducted as per the Cochrane instruction. Demographic information and Charlson comorbidity parameter were extracted in standardized forms. Data about type of study, statin use (A standardized data abstraction case report form was developed for statin use, duration, frequency, dose, and so on), and trial properties (exclusion and inclusion criteria) were also collected. The characteristics and clinical relevance of potential articles were reviewed by HD and TL independently. Any conflict between them was addressed by discussing with YC.

The quality of each OS was evaluated by HD and TL independently using the nine-star Newcastle-Ottawa scale (NOS). A score of over six stars was indicative of high quality(Gu et al., 2015). The strength of evidence (SOE) of each outcome was graded as high, moderate, low or inadequate by HD and TL independently as per the Grading of Recommended Assessment, Development and Evaluation (GRADE)(Berkman et al., 2015). Any conflict was handled by a joint reassessment of the corresponding article with YC.

Statistical analysis
The primary and secondary end points were the risk of TB in DM patients and in the general population respectively. Since the absolute risk of TB is low in diabetic or general population, the odds ratio (OR), relative risk (RR) and hazard ratio (HR) of association can ensure similar estimates of RR (Siristatidis et al., 2013). Dichotomous data were gathered by using RR and 95% confidence interval (CI) on random-effect models.

Between-study heterogeneity was quantified as severe ($I^2 \geq 50\%$), moderate (25%–50%) or low (<25%). Any detectable source of heterogeneity was identified via sensitivity analysis by removing the articles one by one. Subanalyses by region (Korea and Taiwan) and mean age (<60 and ≥60 years old) were also done.

Publication bias was judged based on visual interpretation of the asymmetry of funnel curves and on Begg's and Egger's tests. All data were analyzed on STATA 14.0 with significant level at $P <0.05$, except for the publication bias test ($P<0.10$).

Results

Study search and characteristics

The first search returned 634 potential articles, in which 39 articles were further assessed. Four articles published in abstracts involved the already included participants and thus were excluded. Finally, 6 OSs were enrolled, including 4 cohort articles (Kang et al., 2014; Kim et al., 2019; Lee et al., 2015; Su et al., 2017), 1 nested case-control article (Lai et al., 2016), and one abstract (SHENG-WEI PAN and WEI-JUIN SU, 2018) (Figure 1). Of the 6 OSs, the sample size varied from 13,981 to 840,899 patients, with a total of 2,073,968 patients, and the female percents ranged
from 31.2% to 54.0%. Three articles only included diabetic patients (Kang et al., 2014; Lee et al., 2015; SHENG-WEI PAN and WEI-JUIN SU, 2018), and three articles involved both diabetic patients and the general population (Kim et al., 2019; Lai et al., 2016; Su et al., 2017). Tables 1 list the main information of the 6 studies.

**Quality evaluation**

The 5 OSs were highly qualified, with NOS scores of ≥7 (mean, 9.0; Table S1).

**Effect of statin use on the TB risk of DM patients**

In the 6 OSs, statin use significantly decreased the occurrence rate of TB in DM patients by 22% (pooled RR, 0.78; 95%CI, 0.63–0.95; P=0.015), with severe heterogeneity ($I^2=76.1$%; P=0.001; Figure 2). The pooled RRs were widely consistent across Taiwan (P<0.001) and the elder population (≥60 years old, P=0.001), but not across Korea (P=0.703) or the younger population (<60 Years old, P=0.345) (Figures 3 and 4).

For sensitivity analysis, the removal of one study(Kang et al., 2014) gently changed the overall risk judgement (pooled RR 0.71; 95%CI,0.61–0.82), with no heterogeneity ($I^2=17.8$%; P=0.301).

No evident publication bias was revealed by funnel plot examination (Fig. S1) or Egger's test (P=0.123). The low GRADE implied that statins resisted TB.

**Effect of statin use on TB risk in the general population**

The statin-use versus non-statin use significantly lowered the risk of TB in general patients by 40% (pooled RR, 0.60; 95%CI, 0.50–0.71; P<0.001), with severe heterogeneity ($I^2=57.7$, P=0.094, Figure 5). The low GRADE proved that statins
protected the general population from TB.

**Discussion**

This review and meta-analysis involving 2,073,968 patients suggests statin use is related with a considerable 22% and 40% decrease in the TB risk among diabetic patients and the general population respectively. Whether risk of TB differed among regions and among ages was explored via subgroup analyses. The a-priori subgroup analysis by regions implied statin use versus non-statin use largely relieved the TB risk in the studies conducted in Taiwan, but not in Korea. Of the two trails(Kang et al., 2014; Kim et al., 2019) from Korea, one study only involved new cases of type 2 DM and presented no data on death(Kang et al., 2014), which can be a bias from the competing risks between death and TB that may lower the TB occurrence in statin users. The other study found statin intake relieved the risk of active TB in general people, but was weakened by diabetes (Kim et al., 2019). They thought the studies from Taiwan may have a major limitation of inadequate control of confounding factors, which may account for the disagreement regarding the TB risk depending on whether diabetes occurred. In terms of age, the risk of TB after statin use versus non-statin intake significantly decreased only in elder population, which may be because statins were often medicated for several positive outcomes in the elderly. Other drugs also have the anti-TB effect for elder population(Lee et al., 2015).

Besides regions and ages, some other key and potential confounders, including prior TB status, body mass index(BMI) or obesity, cholesterol levels, smoking status, validity of TB diagnosis, presence of cardiovascular disease (CVD), and mortality
which may play important roles in the association between statin use and TB, were not available because of limited data in the review. The lack of these confounding factors might deviate us from more accurate estimate for the association. Latent tuberculous infection was not evaluated by the most selected studies. Recently, Lin et al (Lin et al., 2018) reported that the protective effect of obesity on TB risk was weakened by a mediation effect of diabetes. The validity of TB diagnosis based on the ICD codes and the prescription criteria in most selected studies might be challenged since it might include TB cases that were not bacteriologically confirmed and cause misclassification for active TB. Meanwhile, comorbidities such as CVD, at least in part smoking-related, could be high risk factors for TB development among statin users, which might lead to an overestimation of the risk of TB among statin users.

As for the duration and dose response relationship between statin exposure and the incident TB disease risk, only two studies (Lai et al., 2016; Su et al., 2017) reported them respectively. Lai et al (Lai et al., 2016) suggested the length of statin therapy affected the TB protection and a trend toward having temporal association between the decreased TB risk and the time period after statin discontinuation by conducting a sensitivity analysis using different censoring cutoffs. Su et al (Su et al., 2017) revealed a dose-dependent benefit of statins on the TB risk and found that there was no protective effect on TB risk by statin use of < 180 cDDD.

There are some probable mechanisms underlying statin use may lower the risk of TB. Evidence implies that cholesterol metabolization by *M. tuberculosis* occurs throughout the tuberculosis infection in the human host. Such sterol metabolism is
crucial in the disease progression (Miner et al., 2009). Statins reduce macrophage cholesterol by multiple mechanisms, including the decreased cholesterol formation, activated efflux and blocked ester accumulation(Argmann et al., 2005; Qiu and Hill, 2008). Statin intake prevented phagocytosis in macrophages in vitro due to the cholesterol-lowering effect (Loike et al., 2004). Other than cholesterol reduction, statins may play beneficial roles, such as anti-inflammation and immune-modulatory for the host during tuberculosis. These potentially conflicting immune-modulating activities of statins include promotion of autophagy and phagosome maturation in macrophages(Dutta et al., 2019; Parihar et al., 2014), as well as induction of NKT cells and promotion of the secretion of pro-inflammatory cytokines, such as IL-1β and IL-12p70(Guerra-De-Blas et al., 2019). On the other hand, recent studies have suggested that statins may prevent induction of trained immunity(Bekkering et al., 2018), which is important in resistance to Mtb infection(Joosten et al., 2018).

Like other reviews and meta-analyses, the heterogeneity of OSs was unavoidable, given the discrepancy in study design, patient information and statistical method. With our strict criteria, the enrolled studies stand for a thorough try to pool relevant published and upcoming studies. Thus, we adopted the summary-level judgments of single study effects. Also the traditional statistical methods used in the OSs did not effectively handle the influence of undetected confounding factors on the overall effect judgement. We explored the origins of heterogeneousness through sensitivity analyses. The incorporated RR for TB of the six OSs in diabetic patients was smaller than that reported by Kang et al.(Yang et al., 2015)(0.78 vs. 0.98). The possible reason
was discussed above.

This review has some advances, such as the extensive search strategy, adoption of Cochrane instruction, and large sample size. However, it also has some disadvantages. Firstly, all the included studies were from Asia and did not involve RCT or unpublished article, which may bias our findings. Secondly, little data were found about the dose and duration effect of statins, case numbers, or person years for dose-reaction meta-analyses. As maybe expected, the risks of TB observed in diabetic patients were highly heterogeneous among the OSs. Furthermore, it was not blinded during quality assessment and study selection in the meta-analysis. In conclusion, statin use is linked with a less risk of TB both in diabetic patients and the general population. However, these conclusions should be understood carefully regarding the potential remaining confounding. Thus, large-size and multi-center RCTs are needed.

**Contributions**

XZ, AY, LZ and YZ done the statistical analysis, HD and TL performed the database research, YC reviewed the conflicts in the databases obtained by HD and TL. HD wrote the first draft of the manuscript; TL and YC reviewed the manuscript critically for contents. All authors are in agreement with the content of the manuscript and approved the final manuscript.

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**Ethical approval**
Not required.

**Conflict of interest**

The authors declare no competing interests.

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**References**


Figure legend
Figure 1. Flow diagram of study selection.

Figure 2. Forest plot for the association between statin use and the risk of tuberculosis (X-axis: log scale; solid square: relative risk; horizontal lines: 95% CIs. The same in other figures).
Figure 3. Forest plot for the association between statin use and the risk of tuberculosis according to regions

Figure 4. Forest plot for the association between statin use and the risk of tuberculosis according to ages
Figure 5. Forest plot for the association between statin use and the risk of tuberculosis in general patients
<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Study Design</th>
<th>Baseline years</th>
<th>Sample size</th>
<th>Mean age (years)</th>
<th>Sex (%Female)</th>
<th>TB definition</th>
<th>Definition of statin user</th>
<th>Population</th>
<th>Effect estimates</th>
<th>Adjusting confounders (Yes or No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang, 2014</td>
<td>Korea</td>
<td>Cohort</td>
<td>2007-2010</td>
<td>840899</td>
<td>56.3</td>
<td>40.9</td>
<td>1*</td>
<td>At least one prescription of any type of statin during the study period</td>
<td>DM</td>
<td>aHR(95%CI): 0.98(0.89-1.07)</td>
<td>Yes</td>
</tr>
<tr>
<td>Lee, 2015</td>
<td>Taiwan</td>
<td>Cohort</td>
<td>1998-2009</td>
<td>13981</td>
<td>&gt;65 years</td>
<td>54.0</td>
<td>2*</td>
<td>NR</td>
<td>DM</td>
<td>aRR(95%CI): 0.76(0.60-0.97)</td>
<td>Yes</td>
</tr>
<tr>
<td>Lai, 2016</td>
<td>Taiwan</td>
<td>Nested case-control</td>
<td>1999-2011</td>
<td>817898</td>
<td>60.2</td>
<td>31.2</td>
<td>2*</td>
<td>Having statins prescription record ≥7 days(Current user status^α vs Recent user status^β vs Past user status^γ vs Chronic use status^δ)</td>
<td>General and DM</td>
<td>aRR(95%CI)[General]: 0.66(0.56-0.78); aRR (95%CI) [DM]: 0.70(0.54-0.91)</td>
<td>Yes</td>
</tr>
<tr>
<td>Su, 2017</td>
<td>Taiwan</td>
<td>Cohort</td>
<td>2000-2013</td>
<td>305142</td>
<td>58.02</td>
<td>49.3</td>
<td>2*</td>
<td>A cumulative prescription record for ≥30 days of one or more of the following compounds: simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, and pitavastatin</td>
<td>General and DM</td>
<td>aHR (95%CI)[General]: 0.53(0.47-0.61); aHR (95%CI)[DM]: 0.60(0.47-0.78)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
TB; tuberculosis; DM: diabetes mellitus; aHR, adjusted hazard ratio; aRR, adjusted risk ratios; CI, confidence interval; NR, not reported.

1. Both the use of ICD-10 codes for TB (A15–A19, U88.0–U88.1) to identify the disease and the satisfaction of prescription criteria, based on a prescription of at least one of the following: 1) isoniazid and rifamycin, 2) ethambutol, 3) pyrazinamide, 4) prothionamide, 5) cycloserine, or 6) paraaminosalicylic acid.

2. ICD-9-CM codes of TB plus the prescription of more than two anti-tuberculosis medications for more than 28 days.

3. ICD-10 codes, along with two or more anti-TB medications of 1) isoniazid and rifamycin, 2) ethambutol, 3) pyrazinamide, 4) prothionamide, 5) cycloserine, or 6) paraaminosalicylic acid that were prescribed within 3 months of the diagnosis of TB.

α referred to patients with a statin prescription that was filled within 30 days of the index date;  β Referred to patients with a statin prescription filled between 31 and 90 days prior to the index date;  γ Referred to patients with a statin prescription filled between 91 days and 1 year prior to the index date;  δ Referred to patients with a cumulative prescription length of more than 90 days in the year in which the TB diagnosis was made.

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Country</th>
<th>Cohort Period</th>
<th>n (Cases)</th>
<th>Age at Index (Median, IQR)</th>
<th>Gender</th>
<th>DM</th>
<th>aHR (95% CI)</th>
<th>aRR (95% CI)</th>
<th>Received prescriptions for statins continuously for at least 7 days</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan, 2018</td>
<td>Taiwan</td>
<td>2001-2013</td>
<td>40012</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Received prescriptions for statins continuously for at least 7 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Kim, 2019</td>
<td>Korea</td>
<td>2003-2013</td>
<td>56036</td>
<td>52.5</td>
<td>51.1</td>
<td>3</td>
<td>Received prescriptions for statins continuously for at least 7 days</td>
<td>General and DM</td>
<td>aHR (95% CI) (General): 0.67 (0.46-0.98); aHR (95% CI) (DM): 1.05 (0.66-1.67)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note: The table above highlights the differences in methodology and outcomes between the two studies, demonstrating the impact of specific drug regimens on TB and diabetes outcomes.