Metformin use and post-exposure incident tuberculosis: a nationwide tuberculosis-contact cohort study in Taiwan

To the Editor:

Patients with diabetes mellitus are susceptible to active tuberculosis (TB) and latent TB infection (LTBI) [1–3]. Close contact with patients with infectious TB is associated with an increased risk of having coprevalent TB or developing incident TB [4, 5]. However, information on the burden of incident TB in contacts with underlying diabetes is limited. Considering post-exposure TB in patients with diabetes, metformin has demonstrated anti-TB effects in preclinical studies and association with a low LTBI prevalence in a cross-sectional survey [6, 7]. Despite metformin’s wide use and correlation with a lower TB risk in patients with type 2 diabetes (T2D) [8], the impact of metformin use during TB exposure on subsequent TB risk has not been thoroughly investigated. We aimed to obtain the rate of post-exposure incident TB, but not coprevalent TB, in T2D patients and evaluate whether TB risk can be modified by metformin use during the TB-exposure period.

This retrospective cohort study in TB contacts used the National Health Insurance Research Database (with approval from Taipei City Hospital: TCHIRB-10704109-W), in a manner as previously used by Yen et al. [9]. This database includes longitudinal claims data of >23 million beneficiaries in Taiwan and has contributed to numerous validated reports [4, 8]. We identified TB contacts by diagnostic International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) code of V01.1 plus chest radiography orders in outpatient records from 2008 to 2014, when TB-contact investigation is mandatory in Taiwan [4]. The index date was the date of coding of V01.1. To minimise confounding variables, we excluded subjects with a prior TB history, preventive therapy for LTBI, type 1 diabetes and those with chronic kidney disease, in who metformin is contraindicated [8].

We defined T2D patients by the presence of 250.x0 and 250.x2 ICD-9 codes (one inpatient or more than three outpatient records in the 6 months before and after the index date) [8]. Using the defined daily dose (DDD) of metformin [8], i.e. 2000 mg, we defined a T2D subject as having metformin use during TB exposure (T2D-useMet) if the cumulative DDD of metformin was >30 within 6 months before the index date; the others were T2D without metformin (T2D-nonMet). The outcome, after excluding subjects with coprevalent TB occurring within 6 months, was post-exposure incident TB developing after the initial 6 months [5]. We identified TB by codes 010–018 plus prescription of anti-TB drugs in all subjects until December 2016, death or 3 years [8]. We recorded potential confounders including diabetes severity as indicated by the adapted diabetes complication severity index (aDCSI) score (table 1) [8]. We used SAS (version 9.4; SAS Institute, Cary, NC, USA) for data extraction and analysis, and Cox regression analysis to assess predictors for incident TB.

We identified 234,373 adult TB contacts aged >20 years during 2008–2014. We excluded 3308 (1.4%) participants with prior TB, 1414 (0.6%) with coprevalent TB within 6 months after the index dates and

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This TB contact cohort study showed that the risk of incident TB, not coprevalent TB, was highest in the diabetes group without metformin use during TB exposure, followed by the nondiabetes population, and was lowest in the diabetes group with metformin use https://bit.ly/3fpJyF0

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Table 1: Demographic data of the whole cohort and analysis of the risk factors for post-exposure incident tuberculosis (TB) in patients with type 2 diabetes (T2D)

| Variables                      | TB contact cohort | Nondiabetes participants | T2D participants | Cox analysis of risk factors for TB in T2D population |
|-------------------------------|------------------|--------------------------|------------------|-------------------------------------------------------|
|                               |                  | Non-metformin | Metformin use | | Univariate analysis | Multivariate analysis |
|                               |                  | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Subjects n                    | 205797           | 185189       | 9851     | 10757       | 1.01 (1.00-1.02) | 0.088 | 1.00 (0.99-1.02) | 0.455 |
| Age years                     | 46.24±15.17      | 44.90±14.44  | 59.10±16.74 | 57.49±15.70 | 1.01 (1.00-1.02) | 0.088 | 1.00 (0.99-1.02) | 0.455 |
| Male sex                      | 106301 (51.6%)   | 94523 (51.04%) | 5719 (58.06%) | 6059 (56.33%) | 1.70 (1.19-2.43) | 0.004 | 1.71 (1.18-2.47) | 0.005 |
| Income level                  |                  |              |          |             |                     |      |                     |      |
| Low                           | 39865 (19.37%)   | 34088 (18.41%) | 2970 (30.15%) | 2807 (26.09%) | 1.00 |                     |      |
| Intermediate                  | 112053 (54.45%)  | 101464 (54.79%) | 4832 (49.05%) | 5757 (53.52%) | 0.84 (0.58-1.22) | 0.372 | 1.01 (0.68-1.51) | 0.942 |
| High                          | 53879 (26.18%)   | 49637 (26.80%) | 2049 (20.80%) | 2193 (20.39%) | 0.69 (0.42-1.13) | 0.141 | 0.89 (0.52-1.52) | 0.669 |
| Urbanisation                  |                  |              |          |             |                     |      |                     |      |
| Urban                        | 114124 (55.45%)  | 103798 (56.05%) | 4951 (50.26%) | 5375 (49.97%) | 1.00 |                     |      |
| Suburban                      | 70748 (34.38%)   | 63307 (34.19%) | 3529 (35.82%) | 3912 (36.37%) | 1.16 (0.80-1.69) | 0.441 | 1.11 (0.75-1.63) | 0.601 |
| Rural                         | 20925 (10.17%)   | 18084 (9.77%) | 1371 (13.92%) | 1470 (13.67%) | 1.99 (1.30-3.06) | 0.002 | 1.83 (1.17-2.88) | 0.008 |
| Comorbidities                 |                  |              |          |             |                     |      |                     |      |
| COPD or asthma                | 24763 (12.03%)   | 19316 (10.43%) | 3039 (30.85%) | 2408 (22.39%) | 1.49 (1.05-2.12) | 0.027 | 1.24 (0.85-1.80) | 0.261 |
| Malignancy                    | 6712 (3.26%)     | 5080 (2.74%) | 869 (8.82%) | 763 (7.09%) | 1.19 (0.66-2.15) | 0.565 | 1.03 (0.57-1.89) | 0.913 |
| Liver cirrhosis               | 1966 (0.96%)     | 1281 (0.69%) | 396 (4.02%) | 289 (2.69%) | 2.81 (1.52-5.20) | 0.001 | 2.00 (1.02-3.92) | 0.042 |
| Alcoholism                    | 1498 (0.73%)     | 1151 (0.62%) | 214 (2.17%) | 133 (1.24%) | 3.24 (1.52-6.94) | 0.002 | 1.94 (0.84-4.47) | 0.119 |
| Autoimmune disease            | 5508 (2.68%)     | 4450 (2.40%) | 532 (5.40%) | 526 (4.89%) | 0.80 (0.35-1.81) | 0.594 | 0.72 (0.32-1.65) | 0.440 |
| AIDS#                         | 234              | 164 (0.09%) | 8 (0.08%) | 4 |                     |      |                     |      |
| Organ Transplant#             | 48 (0.03%)       | 10 (0.10%) |                     | |                     |      |                     |      |
| Steroid use#                  | 1408 (0.68%)     | 1093 (0.59%) | 172 (1.75%) | 143 (1.33%) | 2.25 (0.83-6.09) | 0.110 | 1.88 (0.69-5.12) | 0.220 |
| Statin use#                   | 9453 (4.69%)     | 4256 (2.30%) | 1639 (16.6%) | 3758 (34.94%) | 0.66 (0.44-1.00) | 0.049 | 0.77 (0.51-1.18) | 0.236 |
| Insulin use#                  | 1747 (0.85%)     | 5 (0.00%) | 808 (8.20%) | 934 (8.68%) | 1.16 (0.66-2.05) | 0.612 | 1.11 (0.62-2.00) | 0.723 |
| aDCSI score                   | 0.64±1.24        | 0.46±0.96 | 2.27±2.04 | 2.30±1.96 | 1.06 (0.98-1.15) | 0.153 | 1.03 (0.94-1.12) | 0.542 |
| Follow-up duration years      | 2.93±0.35        | 2.94±0.30 | 2.71±0.68 | 2.83±0.51 |                     |      |                     |      |
| Incident TB events            | 912 (0.44%)      | 771 (0.42%) | 82 (0.83%) | 59 (0.55%) |                     |      |                     |      |

Data are presented as n (%) or mean±SD, unless otherwise stated. HR: hazard ratio; aDCSI: adapted diabetes complication severity index. # : because the numbers of AIDS and organ transplant patients were too small to be publicly disclosed in the table, the two factors were combined into autoimmune disease for the univariate and multivariate Cox regression analyses. ¶: use of a comedication during TB exposure period is defined as taking a drug for >30 cumulative defined daily doses within 6 months before the index date.
6161 (2.6%) receiving isoniazid preventive therapy for LTBI. After excluding subjects with chronic kidney disease and/or type 1 diabetes (n=5172) and T2D developed during 3-year follow-up (n=12521), we finally included 205797 participants for the analysis: 185189 (90%) nondiabetes, 9851 (4.8%) T2D-nonMet and 10757 (5.2%) T2D-useMet subjects. Compared with the nondiabetes group, the T2D groups were older and had more comorbidities and comedications, including statins. After a mean±SD follow-up of 2.93±0.35 years, we observed 912 (0.44%) incident TB events: 771 (0.42%), 82 (0.83%) and 59 (0.55%) in the nondiabetes, T2D-nonMet and T2D-useMet groups (p<0.001), respectively. The corresponding incidences of TB were 1.4, 3.1 and 1.9 cases per 1000 person-years in the three groups (table 1). The Kaplan–Meier curves of probabilities of incident TB after the initial post-exposure 6 months for the three groups were significant different (log-rank p<0.001).

In the T2D population, metformin use during TB exposure significantly predicted incident TB in univariate analysis (p=0.007). Notably, T2D-useMet was negatively associated with TB after adjustment by cofactors with univariate p<0.05 (adjusted hazard ratio (aHR) 0.69, 95% CI 0.49–0.98; p=0.037). In the fully adjusted model, T2D-useMet remained correlated with lower risk for TB development (aHR 0.69, 95% CI 0.49–0.98; p=0.036) (table 1). Furthermore, compared with T2D-nonMet subjects, T2D-useMet subjects receiving a high dose of metformin had further declined risks of TB: aHR 0.87 (95% CI 0.56–1.37, p=0.558) in the subgroup receiving 30–90 DDD and 0.59 (95% CI 0.39–0.90, p=0.013) in that taking >90 DDD within 6 months before the index date. While incorporating nondiabetes data into the analysis, we found that TB risk was highest in the T2D-nonMet group (aHR 1.41, 95% CI 1.01–1.97; p=0.045), followed by the nondiabetes (aHR 1.15, 95% CI 0.86–1.52; p=0.342), and was lowest in T2D-useMet reference groups after adjusting for age, sex, income, residence, all comorbidities, steroid and insulin use (all factors with univariate p<0.05 in the whole-population analysis; statins not included due to p=0.917 in the univariate analysis).

In summary, our diabetes subjects with metformin use during TB exposure had a 31% lower risk of incident TB than those without and a similar risk to the controls without diabetes. These results may provide rationales for researching metformin’s potential in preventive therapy after TB exposure.

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