Original Article

DOI: 10.6966/EDMJ.202103_8(1).0001

Association between Current Metformin Use and Tuberculosis Infection in Patients with Diabetes Mellitus: A Nationwide Population-Based Study

Chia-Ta Tsai[1,2,], Jia-Ling Wu[3], Chung-Hsu Lai[1,2]*

Objective: Tuberculosis (TB) is a widespread infectious disease. Metformin is a first-line agent for patients with type 2 diabetes mellitus (DM) and has been reported to have potential protective effect against TB infection. This study examined the possible protective effect of metformin against TB infection in patients with DM.

Methods: We used time-density sampling to match TB cases with non-TB controls out of 97,487 patients with type 2 DM from 1998 to 2013. Conditional logistic regression was used to assess the odds ratios (OR) for the two groups.

Results: A total of 3,642 patients with TB and 34,837 non-TB controls with type 2 DM were enrolled. The crude OR of TB infection in a current metformin user was 0.55 (95% CI: 0.48 – 0.63, $p < 0.001$) in comparison with a non-metformin user. Adjusted OR was 0.66 (95% CI: 0.57 – 0.76, $p < 0.001$) after adjusting for duration of diagnosis of DM, severity of DM, and associated comorbidities. In a metformin dose analysis, the OR for TB infection with medium and high doses were 1.03 (95% CI: 0.62 – 1.71) and 0.85 (95% CI: 0.54 – 1.32), respectively, compared with that with a low dose.

Conclusions: The findings suggest a possible dose-independent protective effect of metformin against TB infection.

Key words: tuberculosis, metformin, diabetes mellitus

Introduction

Tuberculosis (TB), which is a widespread communicable disease, remains a critical public health concern.[2] According to a 2016 report by the World Health Organization, there were approximately 10.4 million new cases globally and an estimated 1.4 million deaths from TB in 2015.[1] It is also an endemic disease in Taiwan. In 2012, there were 12,338 cases (53.0 cases per 100,000 population) and 626 TB-related deaths (2.7 cases per 100,000 population). Age, male sex, smoking habit, type 2 diabetes mellitus (DM), human immunodeficiency infection (HIV), immunosuppressive therapy, being a transplantation recipient, and chronic renal failure are risk factors associated with TB infection.[3-5]

Type 2 DM (T2DM) is one of the most

From the [1]Division of Infectious Diseases, Department of Internal Medicine and [2]Department of Infection Control, E-Da Hospital, I-Shou University, Kaohsiung; [3]Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Received: March 2, 2019 Accepted: June 10, 2020

* Address reprint request and correspondence to: Chia-Ta Tsai, Division of Infectious Diseases, Department of Internal Medicine, E-Da Hospital, No.1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City, 82445, Taiwan
Tel: +886-7-615-0011 ext. 5555, E-mail: protass0203@gmail.com

common medical disorders that affected up to 451 million people worldwide in 2017. In Taiwan, DM is one of the top 10 causes of death. Nearly 10,000 people die each year because of diabetes.[6] Since DM reduces both adaptive and innate immune responses to TB, patients with DM are more susceptible to TB infection.[5,7-9] An estimated 16% of TB cases worldwide were attributable to DM in a systematic review.[10] In addition, DM is associated with poor outcomes, including relapse, reinfection, treatment failure, and death in TB patients.[5,10]

Since its approval in the United States in 1995, metformin has become one of the most commonly prescribed drugs for T2DM.[11] It is currently the first-line treatment for patients with T2DM. In addition to blood sugar control, several studies have reported novel effects of metformin, such as its protective effect against dementia, cardiac vascular diseases, and cancer.[12] In 2014, Singhal et al. reported that metformin enhances adenosine monophosphate-activated protein kinase (AMPK) activation and inhibits the intracellular growth of TB.[13] In a mouse model, metformin reduced inflammation and increased the specific immunity and efficacy of anti-TB agents. The authors concluded that metformin might be suitable as an adjunctive treatment for TB infection.[13]

Preliminary studies have suggested that metformin has protective effects against TB infection,[13-15] justifying an investigation into its use in the setting of diabetes.[13-14] We conducted a population-based nested case-control study to investigate the effect of current metformin use on the risk of contracting TB in patients with DM and to compare its effectiveness with other anti-diabetic agents.

Materials and Methods

Data source

We used the National Health Insurance Research Database (NHIRD), a universal insurance program database established in Taiwan in 1995. The database contains comprehensive drug history and medical records of all Taiwanese residents with a coverage rate higher than 98%. The NHIRD is authorized to provide insured registration files and original reimbursement claims data during the period from 1998 through 2013.

For privacy and security purposes, the identity data of patients are encrypted in the NHIRD. Diagnosis and drug coding are based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved by the Ethics Committee of the E-Da Hospital.

Definition of tuberculosis infection

Diagnosis of active TB was defined as the ICD-9-CM codes for TB (010 – 018) and hospitalization or at least two ambulatory visits. The diagnosis was confirmed by the prescription of two or more anti-TB drugs for more than 60 days.[4] The anti-TB drugs included rifampicin, isoniazid, ethambutol, pyrazinamide, aminoglycosides (streptomycin, kanamycin, and amikacin), quinolone (moxifloxacin and levofloxacin), prothionamide, ethionamide, cycloserine, para-aminosalicylate, and capreomycin.

Definitions of diabetes mellitus and anti-diabetic drug user

The definition of current metformin use was metformin prescription of more than 28 days before and overlapping the index date (i.e., diagnosis of TB). The same definition was applied for other diabetes medications, including sulfonylurea, alpha-glucosidase inhibitors, and thiazolidinedione.

Study population

We used time-density sampling and individually matched each case regarding time of TB diagnosis.[16-17] Information on age, sex,

year of cohort entry, level of urbanization of area of residence, monthly income, Charlson Comorbidity Index score, adapted Diabetes Complications Severity Index (DCSI) score[18] and duration of diagnosis of DM was collected.

The urbanization level of townships in Taiwan was categorized as low, medium, or high according to the method developed by Liu.[19] Baseline associated risk factors of active TB were also identified. These included bronchiectasis (ICD-9-CM 494), acquired immune deficiency syndrome (ICD-9-CM 042), chronic obstructive pulmonary disease (COPD; ICD-9-CM 491, 492, 494, or 496), autoimmune disease (ICD-9-CM 710 and 714), malignancy (ICD-9-CM 140 – 208), organ transplantation (ICD-9-CM 996 and V042), hepatitis B virus (HBV; ICD-9-CM 070.2, 070.3, and V02.61), hepatitis C virus (HCV; ICD-9-CM 070.7, 070.41, 070.44, 070.51, 070.54, and V02.62), and liver cirrhosis (ICD-9-CM codes 571.2, 571.5, or 571.6). Certification in the Registry of Catastrophic Illness was also recorded.

We also estimated the protective effect among different daily dosages of metformin, which were divided into low (≤ 1,000 mg/day), medium (1,000 – 2,000 mg/day) and high (≥ 2,000 mg/day) doses.[20-21]

Statistical analysis

The continuous variables were summarized as means and standard deviations, and the categorical variables were listed as the number of cases and percentages with respect to the total group sample. Continuous between-group variables were compared using Student's t test, and the categorical variables were examined with either chi-square test or Fisher's exact test. Using conditional logistic regression, we calculated crude and adjusted odds ratios (ORs) as estimates of relative risk and 95% confidence intervals (CIs) to assess the association between metformin use and TB. All statistical analyses were performed with SAS version 9.4

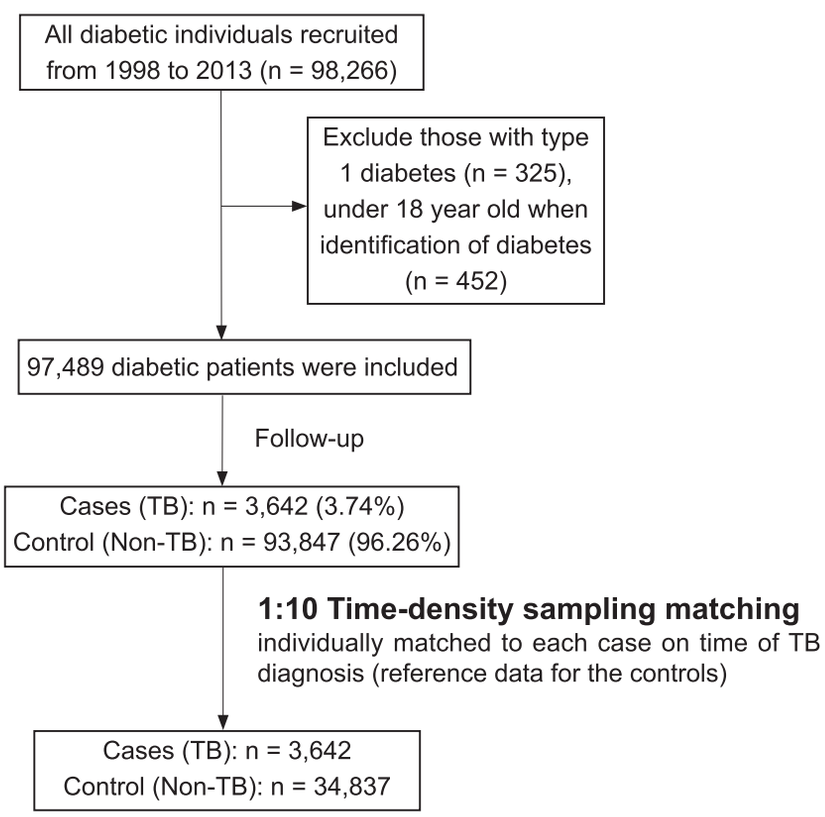

Fig. 1 Flowchart of identifying patients with diabetes with and without tuberculosis infection.

(SAS Institute, Cary, NC, USA). Two-sided *p* values of < 0.05 were considered statistically significant.

Results

The study population consisted of 98,266 patients with DM from 1998 to 2013; 97,489 patients with T2DM were enrolled after exclusion of patients with type 1 DM and of those under 18 years of age. TB was diagnosed in 3,642 (3.74%) of these patients. After 1:10 time-density sampling, 34,837 controls were enrolled in the non-TB group (Fig. 1).

Table 1 presents the demographic characteristics of patients in the TB and control groups. Patients with TB infection had a lower monthly income, lower residence urbanization level, higher DCSI score, and higher percentage of comorbid like HIV infection, COPD, malignancy, organ transplant, HBV infection, HCV infection, liver cirrhosis, and bronchiectasis compared with those in the control group.

Table 2 details the association between metformin use and TB infection in comparison with other diabetes medications in patients with T2DM. Metformin was prescribed in 14.0% of patients (510/3,642) in the TB group and 24.11% (8,399/34,837) in the control group. Metformin use was associated with decreased odds of developing TB (crude OR 0.55, 95% CI: 0.48 – 0.63, $p < 0.001$), and the adjusted OR was 0.66 (95% CI: 0.57 – 0.76, $p < 0.001$) after adjusting for duration of diagnosis of DM, severity of DM, and associated comorbidities.

Results regarding the correlation between the daily dose of metformin and TB infection were presented in Table 3. TB infection was diagnosed in 16.3%, 25.7%, and 58% of patients with T2DM taking low, medium, and

Table 1. Demographics and disease status of study patients.

	TB n = 3,642		Non-TB n = 34,837		*p*-value
Variable	N	%	N	%	
Age (SD)	66.28	14.59	64.56	14.78	
Gender (Male) (%)	2,567	70.5	16,579	47.65	< 0.0001
Monthly income (SD)	9,175 (12,663.6)		11,260 (14,907.5)		< 0.0001
Urbanization (%)					< 0.0001
Low	217	10.46	749	4.27	
Medium	343	16.53	2,110	12.04	
High	1,515	73.01	14,672	83.69	
Duration of diagnosis of diabetes mellitus,months (SD)	45.6 (43.84)		52.40 (42.88)		< 0.0001
DCSI	1.11	1.51	0.51	0.99	< 0.0001
Baseline comorbidities (%)					
HIV	6	0.16	3	0.01	< 0.0001
COPD	1,199	32.92	6,125	17.58	< 0.0001
Autoimmune disease	173	4.75	1,515	4.35	0.2605
Cancer	444	12.19	2,214	6.36	< 0.0001
Organ transplantation	100	2.75	599	1.72	< 0.0001
HBV	136	3.73	910	2.61	< 0.0001
HCV	128	3.51	743	2.13	< 0.0001
Liver cirrhosis	217	5.96	839	2.41	< 0.0001
Bronchiectasis	185	5.08	365	1.05	< 0.0001

TB: tuberculosis, DCSI: adapted Diabetes Complications Severity Index, HIV: human immunodeficiency viral infection, COPD: chronic obstructive pulmonary disease, HBV: hepatitis B viral infection, HCV: hepatitis C viral infection

Table 2. Associations between metformin use and risk of tuberculosis in study groups.

	TB (n = 3,642)		Non-TB (n = 34,837)		OR (95% CI)	
	N	%	N	%	Crude	Adjusted
Absent (non-metformin)	3,132	85.9	26,438	75.9	1.00	1.00
Present (metformin)	510	14.0	8,399	24.1	0.55 (0.48 – 0.63)	0.66 (0.57 – 0.76)

TB: tuberculosis, OR: odds ratio, CI: confidence interval
*Adjust factors in Table 1

high doses of metformin, respectively. In the control group, the percentage of patients diagnosed with TB infection was 13.4%, 24.7%, and 61.9% for low, medium, and high doses, respectively. The crude OR was 1.03 (95% CI: 0.62 – 1.71) for a medium dose and 0.85 for a high dose (95% CI: 0.54 – 1.32) in comparison with that in the low dose group. The adjusted OR was 1.16 (95% CI: 0.66 – 2.05) for a medium dose and 0.86 for a high dose (95% CI: 0.53 – 1.41) in comparison with that in the low dose group.

Discussion

This is a population-based nested case-control study to investigate the possible protection effect of current metformin use against active TB infection in comparison with non-metformin users with diabetes. We found that current metformin use was associated with a significantly lower risk of active TB infection in comparison with that in non-metformin users after the adjustment of associated confounding factors but the protective effect is not significantly related to the dosage of metformin.

Our study of the demographic characteristics of patients indicated that those with advanced age, male sex, COPD, malignancy, organ transplant, viral hepatitis (i.e., HBV, HCV), and liver cirrhosis appeared to be at a higher risk of contracting active TB. This is compatible with prior well-known risk factors.[3-6,9] We excluded chronic kidney disease not only because it is a known risk factor for TB infection but also due to the fact that metformin is contraindicated in patients with renal failure.[22] Although HIV infection is a major risk for TB infection,[3] our study had a low number of HIV cases. A possible explanation might be the prevalence of HIV infection among relatively young individuals in whom DM is uncommon.

Not only is poor diabetes control known to increase the risk of TB infection but it is also associated with a poor outcome.[5] Glycated hemoglobin (HbA1c) is a key marker for chronic sugar control that has a strong correlation with long-term complications of diabetes. However, data on blood sugar level and HbA1c were not available in the NHIRD. Therefore, instead

Table 3. Correlations among daily doses of metformin and risk of tuberculosis in study groups.

	TB (n = 3,642)		Non-TB (n = 34,837)		OR (95% CI)	
	N	%	N	%	Crude	Adjusted
Metformin (ref. ≤ 1000 mg/day)	83	16.3	1,121	13.4	1.00	1.00
Medium dose (1000 – 2000 mg/day)	131	25.7	2,072	24.7	1.03 (0.62 – 1.71)	1.16 (0.66 – 2.05)
High dose (≥ 2000 mg/day)	296	58.0	5,206	61.9	0.85 (0.54 – 1.32)	0.86 (0.53 – 1.41)

TB: tuberculosis, OR: odds ratio, CI: confidence interval
*Adjust factors in Table 1

of blood sugar level and HbA1c, we adopted the DCSI scores to assess the severity of DM without relying on laboratory data. DCSI has been found to be a reliable measure of diabetes severity in previous research.[18,23] Our findings also indicated that patients with TB infection had significantly higher DCSI scores (Table 1).

Metformin, which is a biguanide that has become one of the most widely used agents in the treatment of T2DM since its approval in the United Kingdom in 1958 and in the United States in 1995,[11-12] induces glucose uptake by the liver and inhibits gluconeogenesis through its effects on mitochondrial enzymes. The dosage range is from 500 to 2,500 mg/day. Recently, several novel effects of metformin have been discovered in addition to its role as a hypoglycemic drug, including antitumor, cardiovascular, anti-aging, and anti-TB effects.[12-13] Singhal et al. revealed that metformin could suppress the intracellular growth of TB via an AMPK-dependent pathway. In their research, metformin also reduced chronic pulmonary inflammation and enhanced immune response and the efficacy of anti-TB drugs in TB-infected mice.[13]

Our study is a nationwide, population-based, nested case-control study to examine the relationship between current metformin use and the risk of TB infection in patients with T2DM. We found that current metformin use was associated with a 0.55 crude OR for the development of TB infection in patients with DM compared with that in the control group and a 0.66 crude OR after adjusting for age, sex, urbanization level, monthly income, duration of diagnosis of DM, DSCI score, and comorbidities (Table 2).

Similar to our study, a retrospective single-center case control study by Marupuru et al. on 451 patients with diabetes (152 TB and 299 non-TB) reported a potential 3.9-fold protective effect of metformin against TB infection.[24] One strength of our study was the analysis of a large number of cases from 1998 to 2013, including 3,642 patients with TB and 93,847 without. We minimized referral and selection bias by forming a study cohort using a population-based database that uniquely identified all cases of TB infection by means of a national identification number and anti-TB drug prescription, supplemented with a control group selected from a density sample of the study cohort. Additionally, data were obtained from computerized health insurance claims, which reduced recall bias. Consistently, two previous national cohort studies based on the NHIRD database demonstrated a negative association between metformin use and the risks of TB infection among DM patients.[25-26] Since the designs of these studies were different from the nested case-control approach in the current investigation to avoid misclassification bias of exposure, our study provided additional evidence to support metformin use against TB infection.

The study by Marupuru et al. that examined the possible dosage-related protective effect of metformin against TB infection demonstrated no difference between daily doses of 1,000 mg and 500 mg.[24] However, a daily dose of 500 to 1,000 mg is relatively low for metformin.[21] Other studies have suggested that metformin dosage may affect glycemic and lipid control,[20] suggesting the possibility of a dose effect. A previous cohort study using cumulative defined daily doses of metformin to examine the protective effect against TB infection showed a dose-dependency.[26] To clarify the influence of dose on the protective effect of current metformin use against TB infection, we divided the dosages into low, medium, and high (Table 3). In comparison with a low dose of metformin, medium and high doses did not demonstrate better protective effects in the current study. Another cohort study found non-significant effect of metformin against TB infection for a cumulative duration of metformin less than 27 months in comparison with non-users,[25] implying that the cumulative duration

of metformin use might play an important role in the potential protective effect of metformin against TB infection.

Limitations

The current study had some limitations. First, a major concern is the precision of the coding of DM and TB. However, we used diagnosis codes together with TB drug prescription to confirm the diagnoses and reduce the errors caused by using only diagnostic codes.[4] Second, TB contact history and lifestyle information such as smoking habit, diet, and alcohol consumption are unavailable in the NHIRD. Third, new antidiabetic agents such as sodium-glucose cotransporter 2 inhibitors (introduced in Taiwan in 2014) were unavailable in our database for the current analysis.

Conclusion

Metformin use was associated with a lower incidence of active tuberculosis infection in patients with diabetes regardless of the daily dose in comparison with other antidiabetic agents, implying a potential protective effect. The findings emphasize a novel benefit of metformin in patients with diabetes beyond the indications highlighted in the diabetes treatment guidelines. Further prospective studies are warranted to provide additional evidence supporting the protective effects of metformin against tuberculosis infection and to verify its suitability for being used as an adjuvant therapy in this patient population.

References

1. World Health Organization: Global tuberculosis report 2016. World Health Organization, 2016. https://apps.who.int/iris/handle/10665/250441.
2. Centers for Disease Control, Ministry of Health and Welfare, R.O.C. (Taiwan): Taiwan Tuberculosis Control Report 2013. Centers for Disease Control, Ministry of Health and Welfare, R.O.C. (Taiwan) 2014.
3. Lawn SD, Zumla AI: Tuberculosis. Lancet 2011;378:57-72. doi: 10.1016/S0140-6736(10)62173-3.
4. Lin YT, Wu PH, Lin CY, et al: Cirrhosis as a risk factor for tuberculosis infection--a nationwide longitudinal study in Taiwan. Am J Epidemiol 2014;180:103-10. doi: 10.1093/aje/kwu095.
5. Restrepo BI: Diabetes and tuberculosis. Microbiol Spectr 2016;4:10.1128 /microbiolspec.TNMI7-0023-2016. doi: 10.1128/microbiolspec.TNMI7-0023-2016
6. Cho NH, Shaw JE, Karuranga S, et al: IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018;138:271-81. doi: 10.1016/j.diabres.2018.02.023.
7. Martinez N, Kornfeld H: Diabetes and immunity to tuberculosis. Eur J Immunol 2014;44:617-26. doi: 10.1002/eji.201344301.
8. Ferrara G, Murray M, Winthrop K, et al: Risk factors associated with pulmonary tuberculosis: smoking, diabetes and anti-TNFalpha drugs. Curr Opin Pulm Med 2012;18:233-40. doi: 10.1097/MCP.0b013e328351f9d6.
9. Kuo MC, Lin SH, Lin CH, et al: Type 2 diabetes: an independent risk factor for tuberculosis: a nationwide population-based study. PLoS One 2013;8:e78924. doi: 10.1371/journal.pone.0078924.
10. Baker MA, Harries AD, Jeon CY, et al: The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med 2011;9:81. doi: 10.1186/1741-7015-9-81.
11. Thomas I, Gregg B: Metformin; a review of its history and future: from lilac to longevity. Pediatr Diabetes 2017;18:10-6. doi: 10.1111/pedi.12473.
12. Wang YW, He SJ, Feng X, et al: Metformin: a review of its potential indications. Drug Des Devel Ther 2017;11:2421-9. doi: 10.2147/DDDT.S141675.
13. Singhal A, Jie L, Kumar P, et al: Metformin as adjunct antituberculosis therapy. Sci Transl Med 2014;6:263ra159. doi: 10.1126/scitranslmed.3009885.
14. Vashisht R, Brahmachari SK: Metformin as a potential combination therapy with existing front-line antibiotics for Tuberculosis. J Transl Med 2015;13:83. doi: 10.1186/s12967-015-0443-y.
15. Restrepo BI: Metformin: candidate host-directed therapy for tuberculosis in diabetes and non-diabetes patients. Tuberculosis (Edinb) 2016;101S:S69-72. doi: 10.1016/j.tube.2016.09.008.
16. Lubin JH, Gail MH: Biased selection of controls for case-control analyses of cohort studies. Biometrics 1984;40:63-75.
17. Prentice RL: On the design of synthetic case-control studies. Biometrics 1986;42:301-10.
18. Chang HY, Weiner JP, Richards TM, et al: Validating the adapted diabetes complications severity index in claims data. Am J Manag Care 2012;18:721-6.
19. Liu CY, Hung YT, Chuang YL, et al: Incorporating development stratification of Taiwan townships into sampling design of large scale health interview

survey. J Health Manag 2006. doi: 10.29805/JHM.200606.0001.
20. Grant PJ: The effects of high- and medium-dose metformin therapy on cardiovascular risk factors in patients with type II diabetes. Diabetes Care 1996;19:64-6. doi: 10.2337/diacare.19.1.64.
21. Gregorio F, Ambrosi F, Marchetti P, et al: Low dose metformin in the treatment of type II non-insulin-dependent diabetes: clinical and metabolic evaluations. Acta Diabetol Lat 1990;27:139-55. doi: 10.1007/BF02581286.
22. Chaudhury A, Duvoor C, Reddy Dendi VS, et al: Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Front Endocrinol (Lausanne) 2017;8:6. doi: 10.3389/fendo.2017.00006.
23. Young BA, Lin E, Von Korff M, et al: Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. Am J Manag Care 2008;14:15-23.
24. Marupuru S, Senapati P, Pathadka S, et al: Protective effect of metformin against tuberculosis infections in diabetic patients: an observational study of south Indian tertiary healthcare facility. Braz J Infect Dis 2017;21:312-6. doi: 10.1016/j.bjid.2017.01.001.
25. Tseng CH: Metformin decreases risk of tuberculosis infection in type 2 diabetes patients. J Clin Med 2018;7:264. doi: 10.3390/jcm7090264.
26. Lee MC, Chiang CY, Lee CH, et al: Metformin use is associated with a low risk of tuberculosis among newly diagnosed diabetes mellitus patients with normal renal function: a nationwide cohort study with validated diagnostic criteria. PLoS One 2018;13:e0205807. doi: 10.1371/journal.pone.0205807.