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ORIGINAL ARTICLE

Metformin and the risks of cellulitis, foot infections, and amputation in patients with type 2 diabetes

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Abstract

Background: Patients with diabetes tend to have cellulitis, foot infections, and amputation. We conducted this research to compare the risks of cellulitis, foot infections, and amputation between metformin no-use and use in persons with type 2 diabetes.

Methods: Using propensity score matching, we identified 23 234 pairs of metformin nonusers and users from the National Health Insurance Research Database of Taiwan, since January 1, 2000, to December 31, 2017. Cox proportional hazards models were adopted to examine the risks of incident cellulitis, recurrent cellulitis, foot infections, and amputation between metformin use and no-use.

Results: The mean follow-up period of metformin use and no-use was 6.31 (3.93) and 5.54 (3.97) years, respectively. Compared with metformin no-use, the adjusted hazard ratio and 95% confidence interval for metformin use in cellulitis development, recurrent cellulitis, foot infections, and amputation were 1.08 (1.04-1.12), 1.33 (1.14-1.55), 1.91 (1.75-2.09), and 1.88 (1.35-2.62), respectively. The longer cumulative duration of metformin usage had association with higher risks of these outcomes than metformin no-use.

Conclusion: This population-based cohort study revealed that metformin use had association with significantly higher risks of incident cellulitis, recurrent cellulitis, foot infections, and amputation than metformin no-use in patients with type 2 diabetes.

Keywords: Amputation; Food infection; Incident cellulitis; Recurrent cellulitis

1. INTRODUCTION

Infection is an emerging complication of type 2 diabetes (T2D) in the 21st century.[1] Chronic hyperglycemia and increased accumulated reactive oxygen species may deteriorate the immune function of patients with T2D and exacerbate the risk and severity of infection.[1] Reports show that T2D is associated with 1.8 to 2.0 folds of cellulitis, 1.2 to 2.6 folds of pneumonia, 3.0 to 4.3 folds of urinary tract infection, and 2.0 to 3.3 folds of sepsis.[2] Cellulitis is the deep dermal and subcutaneous infection caused by bacterial invasion through an impaired skin barrier. It is a common, potentially severe infection that has plagued humans for a long time.[3,4] Old age, obesity, and diabetes increase the risk of cellulitis.[4] The global number of deaths due to cellulitis increased 1.66 times from 42 555 in 1999 to 70 526 in 2019.[5] About 60% of cellulitis occurs in the foot.[6–8] Without proper treatment, foot infections may lead to foot ulcers; cellulitis may also spread to the bone leading to osteomyelitis, bacteremia, sepsis, and even leg amputation.[7,8] Patients with T2D are reported to be at higher risk for foot infections and leg amputations.[9] Appropriate treatment of cellulitis, foot ulcers, and infections through pharmacological or surgical methods can reduce the risk of sepsis and amputation, and improve patients' quality of life.[10,11]

Metformin has been tested and used as an anti-malarial and anti-influenza agent since the 1940s.[12] Preclinical researches have demonstrated that metformin can enhance the function of neutrophil and T cells and decrease the amount of proinflammatory cytokines by stimulating the adenosine monophosphate-activated protein kinase (AMPK), thus producing anti-inflammatory and antibacterial effects.[13] Human studies

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have demonstrated that metformin may attenuate the risk of pneumonia, mycobacterial infection, sepsis, hospitalization, and mortality due to infection.[2,13–16] No study has explored the effect of metformin on the risk of cellulitis and foot infections. We hypothesize that metformin may have an impact on the risk of cellulitis, foot infections, and leg amputation in patients with T2D. Therefore, we performed this cohort study to determine the risks of cellulitis, recurrent cellulitis, foot infections, and amputation between metformin use and no-use in patients with T2D.

2. METHODS

2.1. Data source

We recruited persons with new diagnosis of T2D from Taiwan's National Health Insurance Research Database (NHIRD) since January 1, 2000, to December 31, 2017. The NHIRD is described in our previous study.[17] Information of the insured on sex, age, residential areas, premiums, diagnoses, laboratory tests, medications, and clinical procedures are written in the NHIRD. Disease diagnosis is according to the International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9 and 10-CM). This dataset switched from ICD-9 to ICD-10 coding in 2016. The NHIRD has linkage to the National Death Registry to get mortality data. We confirmed that all methods used were performed according to the Declaration of Helsinki. This research was approved by the Research Ethics Committee of China Medical University and Hospital [CMUH109-REC2-031(CR-2)]. The identifiable data of care providers and patients was enciphered and scrambled before release to avoid data leakage. Our study was permitted by the Research Ethics Committee to exempt for the informed consent of patients.

2.2. Study design and participants

In Taiwan, doctors will test the patient's blood glucose and glycated hemoglobin according to the patient's description. If the results are consistent with a diagnosis of T2D patients will be diagnosed with T2D and will receive diabetes education, medications, and regular follow-up. The Diabetes association of the Republic of China has established guidelines for T2D, including criteria for diagnosing T2D and recommending that patients' hemoglobin A1c be monitored every 3 months and that low-density cholesterol, fundus, neurological, renal function, and microalbuminuria be checked at least once a year. We recruited patients from the NHIRD. They were diagnosed with T2D and taking antidiabetic drugs. T2D was diagnosed according to the ICD codes (Supplementary Table S1, http://links.lww.com/JCMA/A240) for ≧3 outpatient claims or 1 hospitalization. The method of taking ICD codes to define T2D was validated by previous research in Taiwan with acceptable accuracy (74.6%).[18] Patients with the following conditions were excluded (Fig. 1): (1) missing gender or age, (2) age <20 or >80 years, (3) diagnosed type 1 diabetes, cellulitis, foot infections, or amputation at baseline, malignant cancers of the urinary tract, hematopoietic and lymphatic tissue, dialysis, hepatic failure, or immunosuppressant administered during the study, (4) index years not between enrollment dates and end of the research.

2.3. Study procedures

When a patient finishes an office visit, he goes to the pharmacy to fill the prescription. The drug coverage is available for all ages within the Taiwan's National Health Insurance. Patients who used metformin for ≧28 days within 1 year were defined as the metformin use study group, and those who did not use metformin during the study period were defined as the metformin nonuse control group. The first day of metformin use after the diagnosis of T2D was set as the index date, and the index date for the comparison group was set as the same time from T2D diagnosis to the index date of metformin usage. Some crucial variables assessed and matched between metformin use and no-use were age, sex, smoking, obesity, alcohol-related disorders, hypertension, dyslipidemia, stroke, coronary artery disease, atrial fibrillation, heart failure, chronic kidney disease, peripheral arterial disease, retinopathy and other retinal disorders, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, systemic lupus erythematosus, liver cirrhosis, psychosis, depression, cancers, and dementia diagnosed within 1 year before the index date. Prescriptions, such as the number and item of oral antidiabetic drugs, glucagon-like peptide-1 receptor agonists (GLP-1RAs), insulin, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), statins, and aspirin, were also recorded before or during the index date. We counted the Diabetes Complication Severity Index (DCSI) and Charlson Comorbidity Index (CCI) scores to assess the disease burden of patients.[19,20] But about the information of patient's persistence and adherence to doctor's prescribed medication is incomplete in this dataset.

2.4. Main endpoints

We assessed and compared the risk of cellulitis development, recurrent cellulitis, foot infections, and leg amputation between metformin use and no-use during the follow-up time.[21] Cellulitis was diagnosed with the ICD codes for ≧3 outpatient claims or one hospitalization. Recurrent cellulitis was characterized by the second episode of cellulitis occurring more than 30 days after the initial event. The foot infections included gangrene, osteomyelitis, and cellulitis or abscess of the leg. Amputation was characterized by at least one hospitalization for amputation, excluding traumatic cases.

2.5. Statistical analysis

Propensity score matching was adopted for matching related variates between metformin use and no-use.[22] Nonparsimonious multivariable logistic regressions were used to estimate the propensity score for every patient, with metformin use as the dependent variate, 42 clinical variates, including gender, age, obesity, smoking, comorbidities, DCSI, CCI scores, prescriptions, and duration of T2D, as the independent variates (Table 1). The nearest-neighbor algorithm was adopted to select pairs, and the control group was matched without replacement. We assumed the standardized mean difference (SMD) of ≦0.1 as a negligible difference between the study and comparison groups.

The incidence rate of endpoints was calculated by the timescale of 1000 person-years during the traced period. Crude and multivariable adjusted Cox proportional hazards models with robust sandwich standard error estimates were used to compare outcomes between metformin use and no use. The results are displayed as hazard ratio (HR), adjusted hazard ratio (aHR) and 95% CI for metformin use versus no-use. To assess the observed risk, we traced patients till the date of respective endpoints, mortality, or at the end of follow-up time on December 31, 2017, whichever happened first. Log-rank test and Kaplan-Meier method were utilized to describe and measure the cumulative incidence of incident cellulitis, foot infections, and amputation between metformin use and no-use during the traced time. We also evaluated the average cumulative duration of metformin usage for the risk of cellulitis, recurrent cellulitis, foot infections, and amputation compared with metformin no-use. We have performed a sensitivity analysis by using full cohort of unmatched patients through inverse probability of treatment weighting (IPTW). Time-varying exposure of metformin analysis was done to account for the changes of metformin use over time in practice. We also included "cellulitis and oral soft tissue abscess" in the definition of cellulitis,

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Fig. 1 The flowchart of patient's selection in this research. T2DM = type 2 diabetes mellitus.

"necrotizing fasciitis," and "pyomyositis" in the broad definition of foot infections, and performed the multivariable adjusted analysis (Supplementary Table S2, http://links.lww.com/JCMA/A240). Using the outcome-related risk factors as adjustment variables, we performed multivariate analysis of different models. That is, model I to adjust for age and sex, model II to adjust for age, sex, obesity, smoking and alcohol, model III to adjust for age, sex, obesity, smoking, alcohol disorders, peripheral arterial disease, chronic kidney disease, retinopathy and other retinal disorders, COPD, liver cirrhosis, rheumatoid arthritis, systemic lupus erythematosus, corticosteroids, duration of T2D (Supplementary Table S2, http://links.lww.com/JCMA/A240). To avoid confounding by the high risk of cardiovascular mortality in diabetes. We used mortality as a competing risk to perform the competing risk analysis for the risks of cellulitis, foot infections, and amputation between metformin use and no use (Supplementary Table S3, http://links.lww.com/JCMA/A240).

We considered a two-tailed *p* value less than 0.05 as statistically significant. Statisticians, Kai-Chieh Hu and Teng-Shun Yu, performed data organization, and used SAS (version 9.4; SAS Institute, Cary, NC) for statistical analysis.

3. RESULTS

3.1. Study population

From January 1, 2000, to December 31, 2017, we found 276 415 patients with newly diagnosed T2D; 206 046 patients used metformin, and 70 369 patients did not use metformin (Fig. 1). After excluding unsuitable participants, one to one propensity score matching was adopted to select 23 234 pairs of patients with metformin use and no-use. All critical variables were matched well between the study and comparison groups with the SMD ≦0.1 (Table 1). In matched cohorts, 51.03% of patients were female. The mean (SD) age of patients with metformin use and no-use was 59.28 (12.03) and 58.74 (12.27) years, and the mean follow-up period was 6.31 (3.93) and 5.54 (3.97) years, respectively.

3.2. Main endpoints

After propensity score matching, 6310 (27.16%) metformin users and 5070 (21.82%) nonusers had cellulitis during the follow-up period (incidence rate: 49.99 vs 45.00 per 1000 person-years; Table 2). The multivariable models presented that metformin users had a significantly (8%) higher risk of incident cellulitis (aHR, 1.08; 95% CI, 1.04-1.12) than nonusers (Table 2). Patients with male sex, young age (20-39 years), alcohol-related disorders, heart failure, coronary artery disease, retinopathy and other retinal disorders, liver cirrhosis, rheumatoid arthritis, chronic kidney disease, psychosis, COPD, dementia, CCI ≧2, DCSI score ≧2, insulins, and NSAIDs use had a significantly higher risk of cellulitis; while patients with dyslipidemia, and statin use showed a significantly lower risk of cellulitis (Supplementary Table S4, http://links.lww.com/JCMA/A240). Multivariable models also showed that metformin use had a 33% higher risk of recurrent cellulitis (aHR, 1.33;

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Table 1

Baseline characteristics, comorbidities, and prescriptions in patients with T2D with and without metformin use

	Before PSM			After PSM		
	Nonmetformin users	Metformin users		Nonmetformin Users	Metformin users	
Variable	n (%)/mean ± SD		SMD	n (%)/mean ± SD		SMD[a]
All	25 615	78 581		23 234	23 234	
Gender			0.1369			0.0079
Female	13 226 (51.63)	35 212 (44.81)		11 811 (50.83)	11 903 (51.23)	
Male	12 389 (48.37)	43 369 (55.19)		11 423 (49.17)	11 331 (48.77)	
Age group (y)						
20-39	1928 (7.53)	6222 (7.92)	0.0147	1749 (7.53)	1553 (6.68)	0.0328
40-59	10 600 (41.38)	41 213 (52.45)	0.2231	9928 (42.73)	9660 (41.58)	0.0234
60+	13 087 (51.09)	31 146 (39.64)	0.2316	11 557 (49.74)	12 021 (51.74)	0.0400
Age (y)	59.10 ± 12.40	56.25 ± 11.62	0.2371	58.74 ± 12.27	59.28 ± 12.03	0.0440
Comorbidities						
Obesity			0.0050			0.0164
Yes	266 (1.04)	856 (1.09)		252 (1.08)	293 (1.26)	
Smoking status			0.0237			0.0125
Yes	393 (1.53)	987 (1.26)		347 (1.49)	383 (1.65)	
Alcohol disorders			0.0463			0.0097
Yes	715 (2.79)	1633 (2.08)		632 (2.72)	669 (2.88)	
Hypertension			0.0657			0.0735
Yes	14 771 (57.67)	42 754 (54.41)		13 414 (57.73)	14 252 (61.34)	
Dyslipidemia			0.2194			0.0711
Yes	14 666 (57.26)	36 427 (46.36)		13 190 (56.77)	14 003 (60.27)	
Coronary artery disease			0.1922			0.0370
Yes	7415 (28.95)	16 254 (20.68)		6532 (28.11)	6922 (29.79)	
Stroke			0.1884			0.0225
Yes	4170 (16.28)	7817 (9.95)		3551 (15.28)	3741 (16.10)	
Atrial fibrillation			0.0923			0.0085
Yes	649 (2.53)	1001 (1.27)		533 (2.29)	563 (2.42)	
Heart failure			0.1225			0.0065
Yes	1569 (6.13)	2756 (3.51)		1325 (5.70)	1360 (5.85)	
Peripheral arterial disease			0.0729			0.0017
Yes	663 (2.59)	1219 (1.55)		567 (2.44)	561 (2.41)	
Chronic kidney disease			0.2303			0.0116
Yes	2105 (8.22)	2327 (2.96)		1569 (6.75)	1502 (6.46)	
Retinopathy and other retinal disorders			0.0589			0.0173
Yes	1587 (6.20)	3812 (4.85)		1426 (6.14)	1524 (6.56)	
COPD			0.1801			0.0166
Yes	4526 (17.67)	8920 (11.35)		3867 (16.64)	4012 (17.27)	
Rheumatoid arthritis			0.0654			0.0026
Yes	497 (1.94)	893 (1.14)		417 (1.79)	425 (1.83)	
Systemic lupus erythematous			0.0469			0.0019
Yes	73 (0.28)	66 (0.08)		48 (0.21)	46 (0.20)	
Liver cirrhosis			0.0953			0.0025
Yes	688 (2.69)	1059 (1.35)		583 (2.51)	592 (2.55)	
Cancers			0.1478			0.0000
Yes	1295 (5.06)	1795 (2.28)		1041 (4.48)	1041 (4.48)	
Psychosis			0.0353			0.0035
Yes	501 (1.96)	1176 (1.50)		426 (1.83)	437 (1.88)	
Depression			0.1318			0.0056
Yes	1479 (5.77)	2412 (3.07)		1232 (5.30)	1203 (5.18)	
Dementia			0.1292			0.0043
Yes	705 (2.75)	788 (1.00)		539 (2.32)	524 (2.26)	
CCI						
0	18 062 (70.51)	64 888 (82.57)	0.2876	16 775 (72.20)	16 435 (70.74)	0.0324
1	3000 (11.71)	7276 (9.26)	0.0801	2711 (11.67)	2909 (12.52)	0.0261
2+	4553 (17.77)	6417 (8.17)	0.2890	3748 (16.13)	3890 (16.74)	0.0165
DCSI						
0	9102 (35.53)	39586 (50.38)	0.3033	8559 (36.84)	7859 (33.83)	0.0631
1	4912 (19.18)	14 361 (18.28)	0.0231	4521 (19.46)	4746 (20.43)	0.0242
2+	11 601 (45.29)	24 634 (31.35)	0.2898	10 154 (43.70)	10 629 (45.75)	0.0411

(Continued)

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Table 1

(Continued.)

Variable	Before PSM			After PSM		
	Nonmetformin users	Metformin users	SMD	Nonmetformin Users	Metformin users	SMD[a]
	n (%)/mean ± SD			n (%)/mean ± SD		
Medications						
Numbers of oral antidiabetic agents						
<2	25 199 (98.38)	75 659 (96.28)	0.1302	22 821 (98.22)	22 692 (97.67)	0.0391
2-3	411 (1.60)	2904 (3.70)	0.1305	408 (1.76)	535 (2.30)	0.0388
>3	5 (0.02)	18 (0.02)	0.0023	5 (0.02)	7 (0.03)	0.0054
GLP-1RAs			0.0097			0.0131
No	25 615 (100.00)	78 581 (100.00)		23 234 (100.00)	23 234 (100.00)	
Insulins			0.2097			0.0391
Yes	5340 (20.85)	10 234 (13.02)		4775 (20.55)	5147 (22.15)	
Corticosteroids			0.4994			0.0403
Yes	12 025 (46.95)	18 686 (23.78)		10 448 (44.97)	10 914 (46.97)	
Statins			0.2611			0.0477
Yes	7232 (28.23)	13 649 (17.37)		6377 (27.45)	6877 (29.60)	
NSAIDs			0.8137			0.0830
Yes	21 078 (82.29)	36 272 (46.16)		18 709 (80.52)	19 447 (83.70)	
Aspirin			0.2571			0.0477
Yes	6911 (26.98)	12 937 (16.46)		6119 (26.34)	6613 (28.46)	
Duration of T2D (y)	3.92 ± 3.54	1.91 ± 2.94	0.6157	3.74 ± 3.39	3.91 ± 3.76	0.0470

CCI = Charlson comorbidity index; COPD = chronic obstructive pulmonary disease; DCSI = Diabetes complications severity index; GLP-1RAs = glucagon-like peptide-1 receptor agonists; NSAIDs = nonsteroidal anti-inflammatory drugs; PSM = propensity score matching; SMD = standardized mean difference; T2D = type 2 diabetes.

[a]A SMD ≤0.1 indicates a negligible difference between the two cohorts.

Table 2

Incidence and risk of outcomes associated with metformin use in patients with T2D

Variable	Nonmetformin users			Metformin users			Crude		Adjusted[a]	
	Event	Person-years	IR	Event	Person-years	IR	HR (95% CI)	*p*	HR (95% CI)	*p*
Cellulitis	5070	112 654	45.00	6310	126 227	49.99	1.11 (1.07-1.15)	<0.0001	1.08 (1.04-1.12)	<0.0001
Recurrent cellulitis	254	134 455	1.89	452	155 231	2.91	1.48 (1.27-1.73)	<0.0001	1.33 (1.14-1.55)	0.0003
Foot infections	711	132 688	5.36	1622	149 078	10.88	2.02 (1.85-2.21)	<0.0001	1.91 (1.75-2.09)	<0.0001
Amputation	51	135 067	0.38	124	156 232	0.79	2.07 (1.50-2.87)	<0.0001	1.88 (1.35-2.62)	0.0002

HR = hazard ratio; IR = incidence rate (per 1000 person-years); T2D = type 2 diabetes.

[a]Adjusted HR estimated by the Cox proportional hazards model, including the variates of metformin, gender, age, comorbidities, medications, enrollment years 2000-2005, 2006-2011, 2012-2017, and duration of T2D.

95% CI, 1.14-1.55), a 91% higher risk of foot infections (aHR, 1.91; 95% CI, 1.75-2.09), and an 88% higher risk of amputation (aHR, 1.88; 95% CI, 1.35-2.62) than metformin no-use (Table 2).

The Kaplan-Meier method depicted that cumulative incidences of incident cellulitis, foot infections, and amputation were significantly higher in patients with metformin use than no-use (log-rank test p value < 0.0001; Fig. 2).

3.3. Cumulative use of metformin

We evaluated the association between the average cumulative duration of metformin usage and the risks of cellulitis development, recurrent cellulitis, foot infections, and amputation (Table 3). The longer average cumulative duration of metformin usage had higher risks of these outcomes than no use of metformin (Table 3).

3.4. Additional analysis

The IPTW analysis disclosed that metformin use was associated with a significantly higher risk of cellulitis (aHR, 1.03; 95% CI, 1.00-1.05), recurrent cellulitis (aHR, 1.21; 95% CI, 1.09-1.34), foot infections (aHR, 1.79; 95% CI, 1.69-1.90), and amputation (aHR, 1.56; 95% CI, 1.27-1.92) than metformin no-use (Supplementary Table S5, http://links.lww.com/JCMA/A240). The time-varying exposure of metformin analysis showed that metformin use had association with significantly higher risk of cellulitis (aHR, 1.12; 95% CI, 1.03-1.22), and foot infections (aHR, 2.25; 95% CI, 1.78-2.83) than metformin no-use (Supplementary Table S5, http://links.lww.com/JCMA/A240). Using the broader definition of cellulitis and foot infections, there was no change in cellulitis events, but there was a significant increase in foot infection events, with HRs similar to the original study (Supplementary Table S2, http://links.lww.com/JCMA/A240). The three models of Cox proportional hazards analysis showed a consistently and slightly gradual decrease in the adjusted HRs from model I to model III (Supplementary Table S2, http://links.lww.com/JCMA/A240). The competing risk analysis using mortality as a competing risk showed that metformin use had a significantly higher risk of cellulitis (aHR, 1.21; 95% CI, 1.17-1.25), recurrent cellulitis (aHR, 1.59; 95% CI, 1.36-1.85), foot infections (aHR, 1.38, 95% CI, 1.31-1.45), and amputation (aHR, 2.27; 95% CI, 1.64-3.14) than metformin no-use (Supplementary Table S3, http://links.lww.com/JCMA/A240). These additional analyses seem to be consistent with the original analysis.

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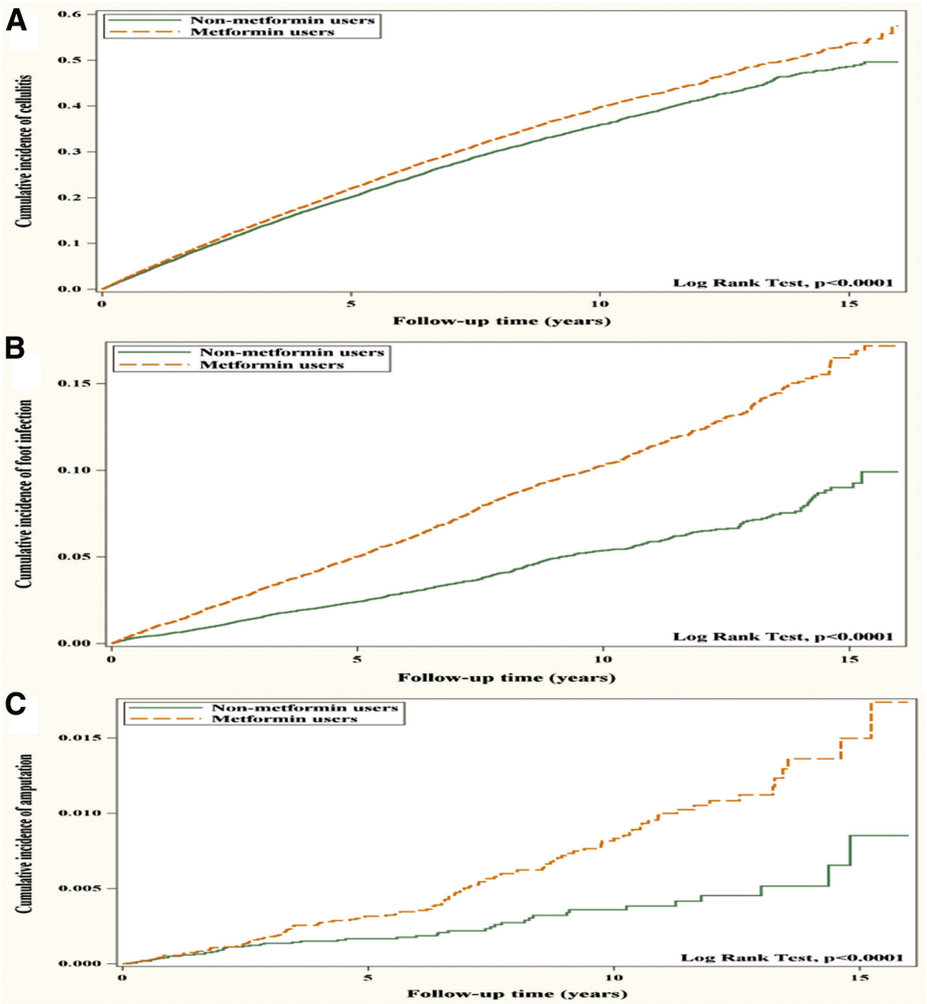

Fig. 2 Cumulative incidences of (A) new-onset cellulitis, (B) foot infection, and (C) amputation in T2D patients. T2D = type 2 diabetes.

4. DISCUSSION

This nationwide cohort study disclosed that metformin use had association with significantly higher risks of cellulitis, recurrent cellulitis, foot infections, and amputation than metformin no-use. Additionally, the longer cumulative duration of metformin usage was associated with further higher risks of these outcomes than no use of metformin.

The neutrophil function of mobilization toward chemotactic factors, adherence to the endothelium, and phagocytosis of invading pathogens may be impaired in patients with diabetes, leading to cellulitis.[1,23,24] Poor glycemic control has association with a higher risk of cellulitis development.[21] Recurrence of cellulitis is also common, with studies showing that about 22% to 49% of patients with cellulitis experience recurrence, and patients with obesity and diabetes are more prone to recurrence.[3,4,7] To our knowledge, our research is the first to observe the association between metformin use and cellulitis. However, it disclosed that metformin might increase the risks of new-onset and recurrent cellulitis, and longer cumulative duration of metformin usage was associated with higher risks of these outcomes. Furthermore, we well-matched the critical variables, such as age, gender, alcohol-related disorders, obesity, smoking, comorbidities, diabetes complications, items and numbers of antidiabetic medications, insulin, statins, aspirin, corticosteroids, NSAIDs, and the duration of diabetes, between metformin use and no-use. This study also disclosed that patients with alcohol-related disorders, heart failure, coronary artery disease, retinopathy and other retinal disorders, chronic kidney disease, liver cirrhosis, rheumatoid arthritis, and COPD (who may have compromised immune function, or vascular complications with affected vessel circulation) had association with an increased risk of cellulitis, which was concordant with previous research.[3,4,7]

The foot is the crossroad where microvascular and macrovascular complications of diabetes meet each other.[8] Diabetic neuropathy of the legs can make the skin arid, cracked, and prone to infection. Legs are prone to sprains or injury due to sensory disorders, and the injuries or inflammation may not be detected or optimally treated due to sensory retardation. Peripheral arterial disease complicates leg wound healing.[4,8] A US cohort study revealed that diabetes mellitus had association with a significantly increased risk of hospitalization for infections, and the risk was most prominent for foot infection (HR, 5.99; 95% CI, 4.38-8.19).[25] Without proper treatment, foot infections may progress from cellulitis to osteomyelitis; cellulitis may also lead to foot ulcers. A deteriorated foot infection may necessitate an amputation to save a life.[7,8] Surprisingly, our study disclosed that metformin might elevate the risk of foot infections and amputation, and the longer cumulative period of

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Table 3

Incidence and risk of outcomes associated with cumulative period of metformin use

Variable	Event	Person-years	IR	Crude		Adjusted[a]	
				HR (95% CI)	*p*	HR (95% CI)	*p*
Cellulitis							
Nonmetformin users	5070	112 654	45.00	1 (Reference)		1 (Reference)	
Metformin users							
1-68 d/y	1632	32 600	50.06	1.11 (1.05-1.18)	0.0002	1.05 (0.99-1.11)	0.1182
69-127 d/y	1248	35 056	35.60	0.79 (0.74-0.84)	<0.0001	0.78 (0.73-0.83)	<0.0001
128-170 d/y	1280	31 690	40.39	0.90 (0.84-0.95)	0.0005	0.88 (0.83-0.94)	<0.0001
>170 d/y	2150	26 882	79.98	1.78 (1.69-1.87)	<0.0001	1.74 (1.65-1.83)	<0.0001
Recurrent cellulitis							
Nonmetformin users	254	134 455	1.89	1 (Reference)		1 (Reference)	
Metformin users							
1-68 d/y	129	39 417	3.27	1.70 (1.37-2.10)	<0.0001	1.37 (1.11-1.70)	0.0040
69-124 d/y	107	40 660	2.63	1.32 (1.05-1.65)	0.0161	1.21 (0.96-1.52)	0.1007
125-160 d/y	76	37 553	2.02	1.06 (0.82-1.37)	0.6655	0.99 (0.77-1.28)	0.9521
>160 d/y	140	37 601	3.72	1.84 (1.49-2.26)	<0.0001	1.73 (1.40-2.12)	<0.0001
Foot infections							
Non-metformin users	711	132 688	5.36	1 (Reference)		1 (Reference)	
Metformin users							
1-68 d/y	392	38 270	10.24	1.91 (1.69-2.17)	<0.0001	1.68 (1.48-1.90)	<0.0001
69-125 d/y	323	40 045	8.07	1.50 (1.31-1.71)	<0.0001	1.43 (1.26-1.64)	<0.0001
126-162 d/y	291	35 643	8.16	1.52 (1.33-1.75)	<0.0001	1.48 (1.29-1.69)	<0.0001
>162 d/y	616	35 120	17.54	3.25 (2.91-3.62)	<0.0001	3.15 (2.82-3.51)	<0.0001
Amputation							
Nonmetformin users	51	135 067	0.38	1 (Reference)		1 (Reference)	
Metformin users							
1-68 d/y	42	39 682	1.06	2.81 (1.87-4.23)	<0.0001	2.19 (1.45-3.31)	0.0002
69-124 d/y	22	40 945	0.54	1.40 (0.85-2.31)	0.1885	1.29 (0.78-2.14)	0.3168
125-160 d/y	17	37 749	0.45	1.19 (0.69-2.06)	0.5322	1.16 (0.67-2.02)	0.5922
>160 d/y	43	37 856	1.14	2.91 (1.94-4.37)	<0.0001	2.84 (1.89-4.28)	<0.0001

HR = hazard ratio; IR = incidence rate (per 1000 person-years); T2D = type 2 diabetes.

[a]Adjusted HR estimated by the Cox proportional hazards model, including the variables of metformin, gender, age, comorbidities, medications, enrollment years 2000-2005, 2006-2011, 2012-2017, and duration of T2D.

metformin usage was associated with a further increased risk of these outcomes. Previous meta-analyses of metformin use did not show a risk of amputation.[26,27] However, a case report describes metformin use in type 1 diabetes resulting in diabetic ketoacidosis, multiorgan failure, and leg amputation.[28] A study by Ochoa-Gonzalez et al[28] disclosed that metformin use could decrease the proliferation of keratinocytes and decrease the rate of wound healing in animal models. Their study also revealed that metformin use could enlarge ulcer size in patients with deep foot ulcers but with a significantly lower risk of amputation.[29] Charcot foot is a serious diabetic foot lesion that is not easy to diagnose early. The deformity of Charcot foot may be treated by the use of minimally invasive surgery for tibiotalocalcaneal arthrodesis with intramedullary nail to prevent future foot ulcers, infections or even amputations.[30] More prospective studies are warranted to delineate the relationship between metformin use, foot infections, wound healing, and leg amputation. Additionally, it would be very interesting to observe other antidiabetic drugs in the risks of diabetic foot diseases.

The potential explanations for increased risk of cellulitis, foot infections, and amputation associated with metformin use are as follows: (1) longer period of metformin use may cause vitamin B12 deficiency and affect sensation in the limbs, increasing patient susceptibility to injury and infection[8,31]; (2) metformin can reduce ATP production by inhibiting the complex one of the electron transport chain and mitochondrial respiration. Wounds healing would be slowed down as tissue energy is restricted. In addition, the restriction of tissue energy can lead to hypoxia, which is also detrimental to wound healing.[4,32] The hypoxic tissue shows mild chronic inflammation with immune defects and increased susceptibility to cellulitis.[4,8,32] Longstanding foot infections are usually a mixture of aerobic and anaerobic infections, and wounds with hypoxic conditions may promote the growth of anaerobic bacteria[8]; (3) metformin can decrease cell proliferation and alter the cell cycle of keratinocytes via the activation of AMPK and inhibition of the mammalian target of rapamycin (mTOR), decrease protein synthesis, delay the rate of wound healing, enlarge foot ulcers, and worsen foot infections.[29,33] More researches are required to explore the mechanisms of metformin on cellulitis, wound healing, and foot infections.

The advantage of this study is that this is a population-based study with a large number of patients; both inpatient and outpatient data are available, reducing selection bias. This study has been traced from 2000 to 2017, spanning 17 years, providing an adequate sample size and time to investigate the outcomes.

This research also has some limitations. First, we utilized ICD codes to define cellulitis, and some patients with abscess or deep skin infection could have been diagnosed with cellulitis. Besides, we used ICD codes for ≧3 outpatient claims or one hospitalization to identify cellulitis. The accuracy of the approach needs verification. Second, this administrative database lacked complete information on patient lifestyle, family history, marital status, alcohol consumption, and occupation. The study also lacked data on hemoglobin A1C, liver and renal functional tests, blood cultures, and immunological tests,

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which precluded a detailed assessment of immune function and diabetes status. However, we used age, gender, obesity, smoking status, comorbidities, CCI, and prescriptions as proxies to assess the overall health status of patients. We used DCSI scores, duration of T2D, number of oral antidiabetic drugs, and insulin as a proxy to evaluate the severity of T2D. Third, the preferred prescriptions of doctors, patient preference for medications, patient's persistence and adherence to prescribed medications were unavailable in this dataset, which may also affect the results of this study. Fourth, most patients in this study were Chinese. Therefore, the results of this study may not be applicable to other ethnic groups. Fifth, this study did not analyze the association between cellulitis, foot infection, and amputation with the cumulative dose and average daily dose of metformin which may cause some bias to this study. Finally, a retrospective cohort study usually has some unmeasured or unknown confounding factors. Therefore, our study can only show an association between the use of metformin and cellulitis, foot infections and amputation, and not a cause-and-effect relationship. A randomized controlled trial is needed to verify our findings.

In conclusion, some studies have demonstrated that metformin may decrease the risk of infections. However, our study revealed that metformin could increase the risk of cellulitis, foot infection, and amputation. We attempted to match the possible confounding factors well, and the longer cumulative period of metformin usage had association with further higher risks of these outcomes. Another animal and human study also showed that metformin delayed wound healing and increased the risk of foot infections.[29] More clinical and basic studies are needed to clarify the relationship among metformin, cellulitis, and foot infections.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A240.

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