Metformin use is associated with a lower risk of osteoporosis/vertebral fracture in Taiwanese patients with type 2 diabetes mellitus

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Abstract

Objectives: To investigate the metformin effect on the risk of osteoporosis (OS) and/or vertebral fracture (VF).

Methods: We enrolled 14 611 pairs of metformin ever and never users matched on propensity score (PS) from Taiwan's National Health Insurance database. All patients had new-onset type 2 diabetes mellitus (T2DM) during 1999–2005 and were free from OS and/or any fracture at the start of follow-up on January 1, 2006. They were followed up until December 31, 2011 for the incidence of OS/VF. Cox regression incorporated with the inverse probability of treatment weighting using PS was used in the main analyses.

Results: New-onset OS/VF was diagnosed in 1757 never users (median follow-up 5.0 years) and 1143 ever users (median follow-up 5.3 years). The respective incidence rates were 2870.97 and 1713.20 per 100 000 person-years. Two-thirds of the incident cases had OS without VF and the other third had VF. In main analyses, the hazard ratio for ever vs never users was 0.592 (95% CI: 0.550–0.638). In either sex, a dose-response pattern was noted and metformin therapy > 2 years was consistently associated with a lower risk. The protective effect attenuated with increasing age but remained significant in patients aged ≥ 80 years. In sensitivity analyses, metformin significantly reduced the risk of both OS and VF (with or without a prior OS) by 30–40%. Additional analyses showed a null association for other antidiabetic drugs, but significant interactions between metformin and insulin, sulfonylurea and pioglitazone, respectively, were noted.

Conclusion: Metformin use is associated with a lower risk of OS/VF.

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Introduction

Patients with diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), suffer from a significantly higher risk of osteoporosis, putting them at a high risk of vertebral fracture (1, 2, 3, 4, 5). However, the pathophysiology of bone changes associated with T1DM and T2DM may not be the same (1, 6). Insulin exerts osteogenic effects (7) and patients with T1DM, which mainly manifests in

adolescence, may have impaired bone formation because of inadequate accrual of peak bone mass resulting from insulin deficiency (1). On the other hand, T2DM mainly affects adult populations and patients with T2DM may have a higher bone mineral density than non-diabetic people because of the bone anabolic effect of hyperinsulinemia resulting from insulin resistance (1,

2). Despite the normal or higher levels of bone mineral density, patients with T2DM have a higher risk of fracture because of poor bone quality and increased adipogenicity in bone tissue (1).

Patients who use antidiabetic drugs such as insulin (8, 9, 10), thiazolidinediones (9, 10, 11, 12) and canagliflozin (13) may have a higher risk of fracture. The higher risk in insulin users may be explained by the increased incidence of hypoglycemia-induced falls (10). Thiazolidinediones increase fracture risk because it may shift the differentiation of mesenchymal stem cells to adipocytes via the activation of peroxisome proliferator-activated receptor gamma (1, 2). Diabetes patients with chronic microvascular complications may suffer from a higher risk of fracture because chronic renal insufficiency can affect bone metabolism (14) and retinopathy or neuropathy may increase the risk of fall because of visual impairment and/or frailty (1, 2, 3, 4, 5, 15, 16).

Some studies from the USA (8) and Denmark (17, 18) suggested that metformin users might have a lower risk of fracture (8, 17). However, a lack of association was observed in a case-control study in Italy (19), a cross-sectional study in Japan (9) and the Osteoporotic Fractures in Men study in the USA (20). Two meta-analyses were published in 2019 (10, 21). The first estimated relative risk of 0.86 (95% CI: 0.75–0.99) for any fracture for metformin users, but no significant risk reduction of vertebral fracture was observed (10). The other meta-analysis estimated a pooled relative risk of 0.82 (95% CI: 0.72–0.93) for any fracture associated with metformin use, but the site-specific fracture was not evaluated (21). Therefore, whether metformin use may reduce the risk of vertebral fracture has not been extensively investigated and the findings are not conclusive. Furthermore, no previous studies have ever investigated the effect of metformin on the risk of osteoporosis.

By using a nationwide reimbursement database of Taiwan's National Health Insurance (NHI), the present study compared the risk of osteoporosis and/or vertebral fracture in ever users vs never users of metformin in a well-matched cohort based on propensity score (PS) in patients with T2DM.

Subjects and methods

The national health insurance

The NHI is a universal and compulsory healthcare system implemented in Taiwan since March 1995. It covers >99% of the population and the Bureau of the NHI has contracts

with all hospitals and 93% of all medical settings. The NHI reimbursement database was described in more detail in a previously published paper (22). In brief, it keeps all disease diagnoses, medication prescriptions and clinical procedures as computer records that can be used for academic research after ethics review and approval. The present study was granted approval number 99274 by the National Health Research Institutes.

Outcome definitions

During the study period, disease diagnoses were coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The ICD-9-CM codes for the disease diagnoses used in the present study are provided in Supplementary Table 1 (see section on [supplementary materials](#) given at the end of this article).

We considered osteoporosis and/or vertebral fracture diagnosed at outpatient clinics or during hospitalization as a composite outcome investigated in the main analyses. The ICD-9-CM codes for osteoporosis included 733.00 (osteoporosis unspecified), 733.01 (senile osteoporosis), 733.02 (idiopathic osteoporosis), 733.03 (disuse osteoporosis) and 733.09 (other osteoporosis). Vertebral fracture was based on the ICD-9-CM codes of 805 (fracture of vertebral column without mention of spinal cord injury) and 806 (fracture of vertebral column with spinal cord injury).

In sensitivity analyses, osteoporosis/vertebral fracture as a composite outcome or osteoporosis and vertebral fracture separately (either diagnosed at outpatient clinics and/or during hospitalization or during hospitalization only) were considered as the outcome. Because a primary diagnosis made during hospitalization should have been supported by laboratory examinations for reimbursement purpose, it was considered more accurate than a diagnosis made at outpatient clinics.

Study population

A PS-matched cohort of ever and never users of metformin were enrolled according to the procedures shown in Fig. 1. At first, 423 949 newly diagnosed diabetes patients during 1999–2005 who had been followed up in the outpatient clinics with prescriptions of antidiabetic drugs for two or more times were identified from the whole nationwide database. Ineligible patients were then excluded: (1) metformin ever users who had been treated with other antidiabetic drugs before metformin was first prescribed

Figure 1

Flowchart showing the procedures in creating a cohort of 1:1 propensity score-matched pairs of ever and never users of metformin from the reimbursement database of the National Health Insurance. Outcomes investigated in the main analyses include osteoporosis (OS) and/or vertebral fracture (VF) diagnosed at outpatient clinics or during hospitalization.

($n=183\,837$, to avoid the carry-over effects of other antidiabetic drugs); (2) patients with T1DM ($n=2062$, these patients may have pathophysiological bone changes different from patients with T2DM and metformin is not indicated for use in patients with T1DM); (3) patients with missing data ($n=422$); (4) patients with a history of osteoporosis at entry ($n=43\,255$, these patients were excluded because osteoporosis was one of the outcomes investigated), (5) patients with a history of any bone fracture at entry ($n=30\,829$, these patients were excluded because vertebral fracture was one of the outcomes investigated); (6) patients with any cancer at entry or within 6 months of diabetes diagnosis ($n=16\,265$, these patients were excluded because cancer may affect bone fracture and the estimation of follow-up person-years could be biased because of shortened lifespan); and (7) patients who had been followed up for < 6 months ($n=13\,823$, to exclude the immortal time bias resulting from the short follow-up period of the initial 6 months). As a result, 118 771 ever users and 14 685 never users of metformin were identified

as an unmatched original cohort. Logistic regression was used to create PS from all characteristics listed in Table 1 plus the date of entry. A matched cohort of 14 611 pairs of ever users and never users was then created from the unmatched original cohort by matching the PS using the Greedy 8 --> 1 digit match algorithm (23).

Data collection

The following categories of variables were considered as factors that might potentially lead to confounding by indication and were included in the estimation of PS used in the above matching procedures and in the estimation of hazard ratios by Cox regression incorporated with the inverse probability of treatment weighting (IPTW) using the PS (described in the Supplementary document). They were also treated as potential confounders in traditional multiple Cox regression and in multiple logistic regression. The ICD-9-CM codes of the related disease diagnoses can be seen in Supplementary Table 1. The accuracy of

Table 1 Characteristics in never and ever users of metformin. Data are present as *n* (%).

Variables	Never users (<i>n</i> = 14,611)	Ever users (<i>n</i> = 14,611)	S.D.
Basic information			
Age* (years)	62.17 ± 13.32	62.01 ± 12.29	−0.66
Years since diabetes diagnosis*	4.10 ± 2.48	4.10 ± 2.10	−0.16
Sex (men)	9073 (62.10)	9062 (62.02)	−0.18
Occupation			
I	5571 (38.13)	5688 (38.93)	
II	2597 (17.77)	2607 (17.84)	0.08
III	3210 (21.97)	3240 (22.18)	0.57
IV	3233 (22.13)	3076 (21.05)	−2.58
Living region			
Taipei	5187 (35.50)	5171 (35.39)	
Northern	1550 (10.61)	1545 (10.57)	−0.10
Central	2468 (16.89)	2467 (16.88)	0.00
Southern	2466 (16.88)	2561 (17.53)	1.79
Kao-Ping and Eastern	2940 (20.12)	2867 (19.62)	−1.25
Major comorbidities			
Hypertension	10,966 (75.05)	10,909 (74.66)	−0.79
Dyslipidemia	8536 (58.42)	8553 (58.54)	0.31
Obesity	264 (1.81)	268 (1.83)	0.10
Diabetes-related complications			
Nephropathy	3587 (24.55)	3459 (23.67)	−2.30
Eye diseases	1355 (9.27)	1372 (9.39)	−0.03
Diabetic polyneuropathy	3920 (26.83)	3845 (26.32)	−1.11
Stroke	1471 (10.07)	1466 (10.03)	−0.44
Ischemic heart disease	5757 (39.40)	5700 (39.01)	−0.80
Peripheral arterial disease	2218 (15.18)	2193 (15.01)	−0.59
Antidiabetic drugs			
Insulin	1171 (8.01)	1144 (7.83)	−2.64
Sulfonylurea	10728 (73.42)	11039 (75.55)	4.00
Meglitinide	1222 (8.36)	1231 (8.43)	−0.17
Acarbose	1563 (10.70)	1640 (11.22)	−0.17
Rosiglitazone	443 (3.03)	432 (2.96)	−1.38
Pioglitazone	346 (2.37)	350 (2.40)	−0.69
Common comorbidities			
COPD	5872 (40.19)	5906 (40.42)	0.62
Tobacco abuse	194 (1.33)	185 (1.27)	−0.56
Alcohol-related diagnoses	713 (4.88)	661 (4.52)	−1.75
Medications used by diabetes patients			
ACE inhibitor/angiotensin receptor blocker	8907 (60.96)	8828 (60.42)	−1.21
Calcium channel blocker	8322 (56.96)	8208 (56.18)	−1.42
Statin	5602 (38.34)	5525 (37.81)	−1.28
Fibrate	3816 (26.12)	3738 (25.58)	−1.32
Aspirin	7100 (48.59)	7075 (48.42)	−0.26
Other potential confounders			
Heart failure	2409 (16.49)	2409 (16.49)	−0.84
Parkinson's disease	401 (2.74)	378 (2.59)	−0.86
Dementia	843 (5.77)	819 (5.61)	−0.67
Head injury	123 (0.84)	107 (0.73)	−1.33
Valvular heart disease	1301 (8.90)	1281 (8.77)	−0.36
Hypoglycemia	240 (1.64)	216 (1.48)	−1.36
<i>H. pylori</i> infection	3041 (20.81)	2903 (19.87)	−2.36
Epstein-Barr virus infection	66 (0.45)	78 (0.53)	1.13
Hepatitis B virus infection	245 (1.68)	247 (1.69)	0.06
Hepatitis C virus infection	508 (3.48)	480 (3.29)	−1.09
HIV disease	9 (0.06)	5 (0.03)	−1.55
Cirrhosis of liver without mention of alcohol	672 (4.60)	680 (4.65)	0.12
Other chronic nonalcoholic liver disease	1024 (7.01)	1048 (7.17)	0.53

(Continued)

Table 1 Continued.

Variables	Never users (n = 14,611)	Ever users (n = 14,611)	s.d.
Autoimmune diseases	948 (6.49)	868 (5.94)	-2.28
Organ transplantation	79 (0.54)	62 (0.42)	-1.93
Insomnia	2944 (20.15)	2954 (20.22)	0.33
Malaise and fatigue	500 (3.42)	522 (3.57)	0.98
History of some disorders of the CNS	2752 (18.84)	2711 (18.55)	-0.60
Immunosuppressants	655 (4.48)	623 (4.26)	-1.17
Hyperthyroidism	487 (3.33)	494 (3.38)	0.23

Refer to 'Subjects and methods' for the classification of occupation.

*Data presented as mean $\pm$ s.d.

ACE, angiotensin converting enzyme; COPD, chronic obstructive pulmonary disease.

disease diagnoses in the NHI database has been studied previously. Agreements between claim data and medical records are moderate to substantial, with Kappa values ranged from 0.55 to 0.86 (24).

- I. Basic information: age, time-elapsed since diabetes diagnosis, sex, occupation and living region. The classifications of living region and occupation were detailed elsewhere (25). In brief, the living region was classified as Taipei, Northern, Central, Southern, and Kao-Ping/Eastern. Occupation was classified as class 1 (civil servants, teachers, employees of governmental or private businesses, professionals and technicians), class 2 (people without a specific employer, self-employed people or seamen), class 3 (farmers or fishermen) and class 4 (low-income families supported by social welfare, or veterans).
- II. Major comorbidities: hypertension, dyslipidemia and obesity.
- III. Diabetes-related complications: nephropathy, eye diseases, diabetic polyneuropathy, stroke, ischemic heart disease and peripheral arterial disease.
- IV. Antidiabetic drugs: insulin, sulfonylurea, meglitinide, acarbose, rosiglitazone and pioglitazone.
- V. Commonly encountered comorbidities: chronic obstructive pulmonary disease (a surrogate for smoking), tobacco abuse and alcohol-related diagnoses.
- VI. Commonly used medications in diabetes patients: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, calcium channel blocker, statin, fibrate and aspirin.
- VII. Other potential confounders: heart failure, Parkinson's disease, dementia, head injury, valvular heart disease, hypoglycemia, history of *Helicobacter pylori* (HP) infection (defined below), Epstein-Barr virus infection, hepatitis B virus infection, hepatitis C virus infection, human

immunodeficiency virus disease, cirrhosis of liver without mention of alcohol, other chronic nonalcoholic liver disease, autoimmune diseases, organ transplantation, insomnia, malaise and fatigue, history of some disorders of the CNS, immunosuppressants (consistent use $\geq$ 90 days and included corticosteroids, calcineurin inhibitors and/or inosine-5'-monophosphate dehydrogenase inhibitors) and hyperthyroidism. History of HP infection was defined in patients who met one of the following two criteria: (1) patients receiving an HP eradication therapy (detailed previously (26), defined in brief as a combination use of proton pump inhibitor or H₂ receptor blockers, plus clarithromycin, metronidazole or levofloxacin, plus amoxicillin or tetracycline, with or without bismuth, in the same prescription order for 7–14 days); and/or (2) ICD-9-CM code of HP infection.

- VIII. In sex-specific analyses that included women only, two additional covariates were included in the estimation of PS or as covariates for adjustment in regression analyses, that is, 'symptomatic menopausal or female climacteric states' and 'use of estrogen'.

Statistical analysis

Statistical analysis are described in detail in the Supplementary document. SAS statistical software, version 9.3 (SAS Institute, Cary, NC) was used. $P < 0.05$ was considered statistically significant. In brief, standardized difference was calculated for each covariate (27), incidence density was calculated and cumulative duration of metformin therapy was used as an indicator of dose-response relationship. Cox regression incorporated with the inverse probability of treatment weighting (28) was used to estimate HRs

and their 95% CIs in main analyses and in sensitivity analyses. Traditional Cox regression was used to investigate the interactions between metformin and other antidiabetic drugs. To examine the consistency of the findings, multiple logistic regression was used to analyze the database cross-sectionally. To reduce the risk of overadjustment or unnecessary adjustment (29), additional logistic regression models were created by restricting adjusted variables to those with significant *P*-values between metformin users and non-users and between patients with and without the outcome.

Results

As shown in Fig. 1, 1143 (7.8%) of the 14 611 ever users of metformin and 1757 (12.0%) of the 14 611 never users of metformin in the matched cohort developed osteoporosis and/or vertebral fracture. Osteoporosis without vertebral fracture was the most common diagnosis, representing approximately two-thirds of the incident cases in either the ever users (761 cases or 66.6%) or the never users of

metformin (1162 cases or 66.1%). Vertebral fracture could happen either without a diagnosis of osteoporosis (178 cases or 15.6% in ever users and 281 cases or 16.0% in never users), at the same time of a diagnosis of osteoporosis (77 cases or 6.7% in ever users and 98 cases or 5.6% in never users) or before the diagnosis of osteoporosis (69 cases or 6.0% in ever users and 100 cases or 5.7% in never users). Only a small proportion of the incident cases (58 cases or 5.1% in ever users and 116 cases or 6.6% in never users) would have a prior diagnosis of osteoporosis before vertebral fracture occurred.

The characteristics in never users and ever users of metformin are shown in Table 1. The two groups were well matched because all covariates had values of standardized difference < 10%.

Table 2 shows the incidence of osteoporosis/vertebral fracture and the HRs by metformin exposure in both sexes together and in men and women separately in the main analyses. For a median follow-up of 5.0 years in never users and 5.3 years in ever users, 1757 and 1143 cases developed an outcome of osteoporosis/vertebral fracture, and the respective incidence rates were 2870.97

Table 2 Incidence of osteoporosis/vertebral fracture diagnosed at outpatient clinics or during hospitalization and hazard ratios by metformin exposure in main analyses.

Metformin use	Incident case number	Cases followed	Person-years	Incidence rate (per 100 000 person-years)	Hazard ratio	95% CI	P value
Both sexes							
Never users	1757	14 611	61 198.80	2870.97	1.000		
Ever users	1143	14 611	66 717.12	1713.20	0.592	0.550–0.638	<0.0001
Tertiles of cumulative duration of metformin therapy (months)							
Never users	1757	14 611	61 198.80	2870.97	1.000		
<25.5	548	4813	16 403.15	3340.82	1.145	1.039–1.260	0.0060
25.5–54.8	384	4829	22 559.85	1702.14	0.584	0.523–0.652	<0.0001
>54.8	211	4969	27 754.12	760.25	0.263	0.228–0.304	<0.0001
Men							
Never users	680	9073	38 730.85	1755.71	1.000		
Ever users	439	9073	41 638.99	1054.30	0.596	0.529–0.672	<0.0001
Tertiles of cumulative duration of metformin therapy (months)							
Never users	680	9073	38 730.85	1755.71	1.000		
<24.9	201	2991	10 317.83	1948.08	1.086	0.928–1.273	0.3037
24.9–53.9	157	2995	14 071.85	1115.70	0.624	0.525–0.743	<0.0001
>53.9	81	3087	17 249.30	469.58	0.265	0.210–0.334	<0.0001
Women*							
Never users	1079	5516	22 363.36	4824.86	1.000		
Ever users	689	5516	24 903.84	2766.64	0.568	0.517–0.625	<0.0001
Tertiles of cumulative duration of metformin therapy (months)							
Never users	1079	5516	22 363.36	4824.86	1.000		
<25.7	326	1822	6147.16	5303.26	1.085	0.958–1.228	0.2002
25.7–55.0	226	1812	8342.91	2708.89	0.552	0.478–0.638	<0.0001
>55.0	137	1882	10 413.77	1315.57	0.270	0.226–0.322	<0.0001

Hazard ratios were estimated by Cox regression incorporated with the inverse probability of treatment weighting using propensity score.

*Models conducted in women included two additional covariates in the estimation of propensity score, that is 'symptomatic menopausal or female climacteric states' and 'use of estrogen'.

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Table 3 Sensitivity analyses estimating hazard ratios for osteoporosis/vertebral fracture for ever vs never users of metformin.

Models	Hazard ratio	95% CI	P value
I. Men aged < 60 years	0.491	0.391–0.616	<0.0001
II. Men aged 60–69 years	0.587	0.464–0.743	<0.0001
III. Men aged 70–79 years	0.640	0.513–0.799	<0.0001
IV. Men aged ≥ 80 years	0.673	0.467–0.970	0.0338
V. Women aged < 60 years*	0.469	0.380–0.579	<0.0001
VI. Women aged 60–69 years*	0.526	0.444–0.623	<0.0001
VII. Women aged 70–79 years*	0.654	0.552–0.775	<0.0001
VIII. Women aged ≥ 80 years*	0.703	0.526–0.940	0.0173
IX. Excluding two consecutive prescriptions of metformin spanning more than 4 months	0.575	0.515–0.642	<0.0001
X. Excluding patients treated with incretin-based therapies during follow-up	0.693	0.642–0.748	<0.0001
XI. Excluding patients treated with insulin at entry and/or during follow-up	0.584	0.532–0.640	<0.0001
XII. Excluding patients treated with sulfonylurea at entry and/or during follow-up	0.595	0.334–1.059	0.0777
XIII. Excluding patients treated with meglitinide at entry and/or during follow-up	0.597	0.545–0.653	<0.0001
XIV. Excluding patients treated with acarbose at entry and/or during follow-up	0.618	0.561–0.681	<0.0001
XV. Excluding patients treated with thiazolidinediones at entry and/or during follow-up	0.639	0.582–0.700	<0.0001
XVI. Excluding patients with a diagnosis of cancer during follow-up	0.600	0.555–0.648	<0.0001
XVII. Defining primary outcome as osteoporosis only diagnosed at outpatient clinics or during hospitalization	0.614	0.566–0.667	<0.0001
XVIII. Defining primary outcome as vertebral fracture only diagnosed at outpatient clinics or during hospitalization	0.622	0.547–0.708	<0.0001
XIX. Defining primary outcome as vertebral fracture without a prior diagnosis of osteoporosis diagnosed at outpatient clinics or during hospitalization	0.659	0.564–0.770	<0.0001
XX. Defining primary outcome as osteoporosis and/or vertebral fracture as a primary diagnosis during hospitalization	0.641	0.530–0.775	<0.0001
XXI. Defining primary outcome as vertebral fracture with or without a prior diagnosis of osteoporosis during hospitalization	0.700	0.541–0.907	0.0069
XXII. Defining primary outcome as vertebral fracture without a prior diagnosis of osteoporosis during hospitalization	0.586	0.419–0.819	0.0018

Hazard ratios were estimated by Cox regression incorporated with the inverse probability of treatment weighting using propensity score.

*Models conducted in women included two additional covariates in the estimation of propensity score, that is, 'symptomatic menopausal or female climacteric states' and 'use of estrogen'.

and 1713.20 per 100 000 person-years. For ever vs never users, a significant 40% risk reduction was consistently observed in both sexes together (HR: 0.592, 95% CI: 0.550–0.638), in men (HR: 0.596, 95% CI: 0.529–0.672) and in women (HR: 0.568, 95% CI: 0.517–0.625). In the tertile analysis, patients who used metformin for < 25.5 months in the first tertile had a slightly increased risk (HR: 1.145, 95% CI: 1.039–1.260, $P < 0.01$) when both sexes were analyzed together. However, significantly lower risk was observed for patients who had used metformin for a longer duration in the second tertile of 25.5–54.8 months (HR: 0.584, 95% CI: 0.523–0.652, $P < 0.001$) and third tertile of > 54.8 months (HR: 0.263, 95% CI: 0.228–0.304, $P < 0.001$). The analyses conducted in men and women separately showed similar results but the HRs in the first tertiles were not significant.

The sensitivity analyses shown in Table 3 all consistently supported a lower risk of osteoporosis/vertebral fracture associated with metformin use. The significant risk reduction could be similarly demonstrated in all four age subgroups of <60, 60–69, 70–79 and ≥80 years in either sex, but the risk reduction attenuated with increasing age (Models I–VIII). The benefit of metformin could be similarly demonstrated after excluding patients who did not refill regularly (Model IX) and the protection of metformin was not affected by the use of other antidiabetic drugs (Models X–XV). Although cancer may affect fracture risk and shorten lifespan, the beneficial effect of metformin remained significant after excluding patients with a diagnosis of cancer (Model XVI). The risk reduction associated with metformin use could be similarly demonstrated for osteoporosis (Model XVII)

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and vertebral fracture (Models XVIII, XIX, XXI and XXII), respectively, and for vertebral fracture without a prior diagnosis of osteoporosis (Model XIX for diagnoses made at outpatient clinics or during hospitalization and Model XXII for diagnoses made during hospitalization). Diagnoses of osteoporosis/vertebral fracture made during hospitalization (Model XX) slightly moved the HR toward unity but remained significant (HR: 0.641, 95% CI: 0.530–0.775, $P < 0.0001$) when compared to the corresponding overall HR when diagnoses were made at the outpatient clinics or during hospitalization (HR: 0.592, 95% CI 0.550–0.638, $P < 0.0001$, Table 2).

Table 4 shows the multivariate-adjusted HRs created by traditional Cox regression for osteoporosis/vertebral fracture (diagnosed at outpatient clinics or during hospitalization) for users vs non-users of insulin, sulfonylurea, meglitinide, acarbose, rosiglitazone, pioglitazone, immunosuppressants and estrogen (in women only) and for metformin ever vs never users in the respective subgroups of these drugs and their P -values for interaction. The use of other antidiabetic

drugs or estrogen (women only) had a neutral effect but the use of immunosuppressants was associated with an increased risk (HR: 1.383, 95% CI: 1.184–1.617, $P < 0.0001$). Metformin was significantly associated with a lower risk in all subgroups of use and non-use of the other drugs except in users of insulin and rosiglitazone. Significant interactions between metformin and insulin, sulfonylurea and pioglitazone could be seen (P -values for interaction < 0.05). The protective effect of metformin was not observed among users of insulin but could be stronger among users of sulfonylurea or pioglitazone than non-users.

The odds ratios after adjustment for all covariates in Table 1 for prevalent users vs non-users of metformin were 0.629 (95% CI: 0.579–0.682) for both sexes, 0.639 (95% CI: 0.563–0.725) for men and 0.598 (95% CI: 0.537–0.666) for women. The odds ratios after adjustment for selected variables that differed significantly between metformin users and non-users and between patients with and without the outcome were 0.627 (95% CI: 0.579–0.679) for both sexes (adjusted for hypertension, sulfonylurea,

Table 4 Multivariate-adjusted hazard ratios (created by traditional Cox regression) for osteoporosis/vertebral fracture diagnosed at outpatient clinics or during hospitalization for users vs non-users of some medications other than metformin and for metformin ever vs never users in the respective subgroups of the other medications and their P -values for interaction.

Subgroups of other medications	Users vs non-users of other medications			Metformin ever vs never users in subgroups			P-interaction
	HR	95% CI	P value	HR	95% CI	P value	
Insulin							
No	1.000			0.577	0.533–0.623	<0.0001	<0.0001
Yes	0.980	0.824–1.166	0.8209	1.124	0.746–1.693	0.5758	
Sulfonylurea							
No	1.000			0.819	0.685–0.980	0.0288	<0.0001
Yes	1.057	0.939–1.190	0.3598	0.544	0.498–0.595	<0.0001	
Meglitinide							
No	1.000			0.598	0.553–0.646	<0.0001	0.5148
Yes	0.942	0.796–1.115	0.4894	0.615	0.462–0.820	0.0009	
Acarbose							
No	1.000			0.603	0.557–0.653	<0.0001	0.7953
Yes	0.938	0.823–1.070	0.3401	0.501	0.371–0.677	<0.0001	
Rosiglitazone							
No	1.000			0.602	0.558–0.650	<0.0001	0.8968
Yes	1.128	0.918–1.387	0.2514	0.668	0.394–1.135	0.1358	
Pioglitazone							
No	1.000			0.611	0.567–0.659	<0.0001	0.0125
Yes	1.018	0.777–1.334	0.8953	0.163	0.071–0.370	<0.0001	
Immunosuppressants use							
No	1.000			0.605	0.560–0.654	<0.0001	0.8481
Yes	1.383	1.184–1.617	<0.0001	0.576	0.421–0.789	0.0006	
Estrogen (women only)*							
No	1.000			0.613	0.545–0.689	<0.0001	0.0748
Yes	1.093	0.956–1.250	0.1923	0.489	0.411–0.581	<0.0001	

*Models conducted in women included an additional covariate of 'symptomatic menopausal or female climacteric states'.
HR, hazard ratio.

angiotensin converting enzyme inhibitor/angiotensin receptor blocker, calcium channel blocker and HP infection), 0.641 (95% CI: 0.566–0.726) for men (adjusted for stroke and dementia) and 0.596 (95% CI: 0.537–0.662) for women (adjusted for hypertension, sulfonylurea and statin). The corresponding odds ratios estimated after adjustment for all covariates and after adjustment for selected covariates were almost the same for both sexes, for men and for women, respectively, suggesting that the estimates would not be biased by the changes in the covariates used for adjustment.

Discussion

Main findings

This study showed a reduced risk of osteoporosis/vertebral fracture associated with metformin use in patients with T2DM in either sex (Table 2). A dose–response pattern could be seen and the beneficial effect was especially significant when metformin had been used for more than approximately 2 years (Table 2).

Interactions with other antidiabetic drugs

We did not observe an independent risk association with any other antidiabetic drugs (Table 4). However, we did observe significant interactions between metformin and insulin, sulfonylurea and pioglitazone, respectively (Table 4).

The beneficial effect of metformin could not be demonstrated in insulin users (Table 4), probably because of hypoglycemia-induced falls associated with insulin use (7). Fracture risk associated with sulfonylurea is not conclusive (9, 17, 30). Although the risk did not differ between users and non-users of sulfonylurea (Table 4), we did observe a shift of HR for metformin ever users vs never users away from unity in the subgroup of patients who used sulfonylurea (P -interaction < 0.0001, Table 4). Therefore, when sulfonylurea is used, it is better to include metformin as a combination therapy.

Increased fracture risk associated with thiazolidinediones is mainly observed in postmenopausal women and for fractures of long bones (7). In the present study, both rosiglitazone and pioglitazone had a neutral effect on osteoporosis/vertebral fracture (Table 4). However, a significant interaction with metformin was observed for pioglitazone but not for rosiglitazone (Table 4). The remarkable shift of HR away from unity among

pioglitazone users suggested that the protective effect of metformin would be more prominent when the patients were using pioglitazone.

Differences from earlier studies

Metformin was associated with a reduced risk of any fracture of 20–30% in some studies (8, 17, 18) but not in others (9, 19, 20). It should be pointed out that the three studies showing a favorable effect studied any fracture and not vertebral fracture and were conducted mainly in Caucasians (8, 17, 18). Two of the three studies that did not show a favorable effect used either a cross-sectional design in the Japanese study (494 men and 344 postmenopausal women with T2DM) (9) or a nested case–control design in the Italian study (83 cases and 249 matched controls) (19). Prevalent user bias could not be excluded and both had small sample sizes. The third study was conducted in the USA (20). Although a prospective follow-up design was used, it enrolled only males and evaluated non-vertebral fracture in a small sample size of 779 participants with diabetes mellitus (20). Therefore, a non-significant result in these studies could probably be due to the inadequate study designs or the lack of sufficient statistical power.

Findings supporting early intervention in diabetes

Patients with T2DM have an increased risk of vertebral fracture and its occurrence indicates a significantly higher risk of non-vertebral fracture and mortality (31). The International Osteoporosis Foundation recommended to take action in the diabetes patients when a T-score is < -2.0 or when the patients develop hip or vertebral fracture (32). As shown in Fig. 1, the high proportion (approximately one-third) of an outcome of vertebral fracture, which is predictive for future fracture and mortality (31), indicated a need for early diagnosis and intervention of osteoporosis/vertebral fracture. Furthermore, only a small proportion of the incident cases would have a prior diagnosis of osteoporosis as a warning sign before the occurrence of vertebral fracture (5.1% in ever users and 6.6% in never users, Fig. 1) and a high proportion would suffer from vertebral fracture without a warning sign of osteoporosis (15.6% in ever users and 16.0% in never users, Fig. 1). These findings strongly implied either a late diagnosis of osteoporosis in current medical care or the requirement of a loosening of the diagnostic criteria for osteoporosis in patients with T2DM, for example, a T-score < -2.0 as recently recommended by the International Osteoporosis Foundation (32).

Perspectives

This observational study has some clinical implications. First, because metformin is safe and not expensive, it may be a good preventive agent for osteoporosis/vertebral fracture and may be used as an adjuvant therapy, in either the diabetes patients or non-diabetes people. Second, whether there can be synergistic effects of metformin and other antiosteoporosis medications are worthy of intensive investigation. Third, the more remarkable effect observed in the younger age groups (Models I–VIII, Table 3) suggested that prescription of metformin to younger patients would result in a more significant impact with better cost-effectiveness.

Potential mechanisms

Some biological actions of metformin could explain the reduced risk of osteoporosis/vertebral fracture associated with metformin use. First, metformin can reverse the deleterious effects of hyperglycemia on bone metabolism by lowering blood glucose levels (16). Second, metformin itself may exert osteogenic effects (33) and inhibit osteoclasts (15) through the activation of 5'-AMP-activated protein kinase. Third, type 1 collagen synthesis and osteocalcin expression are both stimulated by metformin (15, 16) and metformin may stimulate osteoprotegerin, which in turn inhibit the activity of osteoclasts and prevent bone loss (34). Fourth, insulin resistance and inflammation may disturb bone metabolism (16) and metformin may improve insulin resistance and reduce tissue inflammation (35). Fifth, osteoporosis and vertebral fracture are both age-related. Recent studies suggested that metformin has an anti-aging effect because it can target senescent cells and prevents the induction of senescence-associated secretory phenotype (36). An *in vitro* and *in vivo* study did show that metformin protected against intervertebral disc degeneration by attenuating apoptosis and senescence in nucleus pulposus cells via autophagy stimulation (37).

Strengths of the study

The strengths of the study has been extensively discussed in a previous paper that used a similar study design and statistical approach, with special attention to common methodological limitations seen in pharmacoepidemiological studies such as selection bias, prevalent user bias, immortal time bias and confounding by indication (38).

Study limitations

Study limitations may include a lack of biochemical, humoral and hormonal data, anthropometric factors, lifestyle, physical activity, menstruation history, cigarette smoking, alcohol drinking, dietary pattern, vitamin D and calcium supplements, family history and genetic parameters. Because only ICD-9-CM codes were used and no laboratory data such as dual-energy X-ray absorptiometry, spine X-ray or CT were available, misclassification of osteoporosis and/or vertebral fracture could not be excluded. However, the effects would only have been underestimated if the misclassifications were not differential in ever and never users of metformin (39).

Conclusions

The findings of the present study support a lower risk of osteoporosis/vertebral fracture associated with metformin use in patients with T2DM, disregarding sexes. Metformin should be especially considered in patients younger than 60 years of age because they can obtain the strongest protection than patients of older ages.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-20-0507>.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

Tseng C H researched data and wrote manuscript. The guarantor of this paper is Tseng C H.

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