J Chin Med Assoc

ORIGINAL ARTICLE

Dipeptidyl peptidase-4 inhibitors attenuates osteoporosis in patients with diabetes: A nationwide, retrospective, matched-cohort study in Taiwan

Chia-Hao Chang[a], Chieh Hua Lu[b,c], Chi-Hsiang Chung[d,e], Sheng-Chiang Su[b], Feng-Chih Kuo[b], Jhih-Syuan Liu[b], Peng-Fei Li[b,f], Chia-Luen Huang[b], Kuan-Chan Chen[b], Li-Ju Ho[b], Chih-Chun Kuo[b], Chun-Yung Chang[b], Ming-Shiun Lin[b], Yi-Chen Liu[b], Nain-Feng Chu[b], Chien-Hsing Lee[b,c], Yi-Jen Hung[b,g], Po-Shiuan Hsieh[g,h], Fu-Huang Lin[d], Chang-Hsun Hsieh[b], Wu-Chien Chien[c,d,e,*]

[a]Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Armed Forces General Hospital, Taichung, Taiwan, ROC; [b]Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, School of Medicine, National Defense Medical Center, Taipei, Taiwan, ROC; [c]Department of Medical Research, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC; [d]School of Public Health, National Defense Medical Center, Taipei, Taiwan, ROC; [e]Taiwanese Injury Prevention and Safety Promotion Association, Taipei, Taiwan, ROC; [f]Graduate Institute of Applied Science and Engineering, Fu-Jen Catholic University, New Taipei City, Taiwan, ROC; [g]Institute of Preventive Medicine, National Defense Medical Center, Taipei, Taiwan, ROC; [h]Department of Physiology and Biophysics, National Defense Medical Center, Taipei, Taiwan, ROC

Abstract

Background: Patients with diabetes have a relatively high risk of fracture due to osteoporosis. However, the risk of osteoporosis associated with the use of oral hypoglycemic drugs and dipeptidyl peptidase-4 inhibitor (DPP-4i) by patients with diabetes is unclear. This study aimed to explore the effect of DPP-4i on the risk of osteoporosis in Taiwanese patients with type 2 diabetes mellitus (T2DM).

Methods: This study enrolled 6339 patients on DPP-4i (DPP-4i group) and 25356 patients without DPP-4i (non-DPP-4i group). They were matched by 1:4 propensity score matching, using confounding variables including sex, age, comorbidities, medication, and index year. Cox proportional hazards analysis was used to compare hospitalization and mortality during an average follow-up period of 7 years.

Results: The mean age of patients in the two groups was 66 years. Men were slightly higher in number (51.79%) than women. At the end of the follow-up period, 113 (0.36%) patients had osteoporosis, of which 15 (0.24%) were in the case group and 98 (0.39%) in the control group. The risk of all-cause osteoporosis was significantly lower in the DPP-4i group than in the non-DPP-4i group (adjusted hazard ratio [HR] 0.616; 95% confidence interval [CI] 0.358–0.961; $p = 0.011$). Kaplan–Meier analysis showed that the preventive effect on osteoporosis was positively correlated with the cumulative dose of DPP-4i (log-rank, $p = 0.039$) with the class effect.

Conclusion: Compared with not using DPP-4i, the use of DPP-4i in Taiwanese T2DM patients was associated with a lower risk of osteoporosis due to the class effect, and the preventive effect was dose-dependent. However, larger prospective studies are needed to validate this finding and to explore the possible mechanism of the preventive effect of DPP-4i.

Keywords: Bone mass density; Diabetes mellitus; DPP-4 inhibitor; National Health Insurance Research Database; Osteoporosis

1. INTRODUCTION

As the world gradually enters an era of an increasingly aging society and modern lifestyle changes, the number of patients with diabetes and osteoporosis is observed to be increasing,[1] especially in the older population and postmenopausal women.[2] Osteoporosis pertains to bone loss caused by aging. More than 8.9 million people suffer from bone fractures each year worldwide, with hip fractures being the most common.[2] From 1996 to 2000, other treasury cabinets in Taiwan reported the annual incidence rate of fractures to be 225 and 505 per 100000 in men and women over 65 years of age, respectively.[3]

Previous studies have explored the association between diabetes and osteoporosis.[4] According to these studies, patients with diabetes have a relatively high risk of fracture.[5–7] The pathophysiological mechanism behind this association is partially understood, yet inconclusive. Patients with type 2 diabetes mellitus (T2DM) have reduced bone mass density (BMD) and an increased risk of fracture. T2DM is considered to be one of the risk factors for reducing BMD, osteoporosis, and fractures.[8] Few previous clinical studies and experimental data have shown that some hypoglycemic drugs, such as metformin or sulfonylurea, can increase or reduce the risk of fractures,[9] whereas insulin treatment has no significant effect on bone mineral density.[10]

*Address correspondence: Dr Wu-Chien Chien, Department of Medical Research, Tri-Service General Hospital, National Defense Medical Center, 325, Section 2, Cheng-Kung Road, Taipei 114, Taiwan, ROC. E-mail address: chienwu@mail.ndmctsgh.edu.tw (W.-C. Chien).

Author contributions: Dr. Chia-Hao Chang and Dr. Chieh-Hua Lu have contributed equally to this work.

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 747-753.

Received December 24, 2021; accepted March 31, 2022.

doi: 10.1097/JCMA.0000000000000743.

Conversely, in the Canagliflozin Cardiovascular Assessment Study, canagliflozin increased the risk of fracture[11] and thiazolidinediones increased bone loss as well as fracture risk.[12]

Metformin is an effective drug for the treatment of T2DM, and additive treatment is recommended.[13] Dipeptidyl peptidase-4 inhibitors (DPP-4i) should be neutral to the risk of cardiovascular disease in all patients with T2DM, and should not increase or decrease the same.[14,15] In a large comprehensive analysis study, it was found that the use of DPP-4i can relatively reduce the patient's risk of fracture.[16] However, in another retrospective generational study, the database UK Clinical Practice Research Datalink was used to analyze data from 2007 to 2012, and it was found that DPP-4i was not associated with fracture risk.[17]

Based on the current evidence, the effect of DPP-4i on osteoporosis is inconclusive. In addition, whether the association between DPP-4i and osteoporosis is a class effect or affected by other factors (such as treatment duration) remains to be clarified. The purpose of this study was to use data from the National Health Insurance Research Database (NHIRD) of Taiwan, a national health insurance database, to determine the potential of DPP-4i in reducing the incidences of osteoporosis in patients with diabetes.

2. METHODS

2.1. Data sources

In this study, we used 7 years of data from the NHIRD, based on two million (2008–2015) in Taiwan's Longitudinal Health Insurance Database (LHID). The National Health Insurance (NHI) program was launched in Taiwan in 1995. As of June 2009, it had signed contracts with 97% of medical providers and approximately 23 million beneficiaries, accounting for more than 99% of the total population.[18] The NHIRD uses International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to record diagnoses. All diagnoses of T2DM and osteoporosis were made by physicians, endocrinologists, or other experts certified by the committee. The NHI management department periodically reviewed the records of outpatient visits and hospitalization claims to verify the accuracy of the diagnosis. Therefore, the NHIRD was considered suitable for this study on the association between osteoporosis and DPP-4i use.

2.2. Research design and sampling participants

Sitagliptin was the first DDP-4i approved by the United States Food and Drug Administration. Approved on October 16, 2006, it has been marketed in Taiwan since 2008. This study had a retrospective matched-cohort design and was conducted between January 1, 2008 and December 31, 2015. Using the LHID, we identified and selected 57 054 patients with diabetes (ICD-9-CM 250.XX), who were consecutively administered oral hypoglycemic drugs for more than 90 days. Each enrolled patient was required to have made at least three outpatient visits during the study period. Diabetic patients younger than 20 years, those with previously diagnosed osteoporosis, and those who were on DPP-4i before the index date were excluded. In addition, patients who received glucagon-like peptide 1 receptor agonist (GLP-1 RA), thiazolidinedione, or canagliflozin before tracking were excluded.

Data on the use of DPP-4i, including sitagliptin, linagliptin, saxagliptin, vildagliptin, and alogliptin were collected. This study recruited 6339 patients on DPP-4i use (DPP-4i group), and 25 356 patients without DPP-4i use (non-DPP-4i group), who were then matched by 1:4 propensity score matching using confounding variables, including sex, age, comorbidities, medication, and index year (Fig. 1).

2.3. Comorbidity

Comorbidities included hyperthyroidism, hyperparathyroidism, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA), Cushing's syndrome, hypogonadism, acromegaly, vitamin D deficiency, hypercalciuria, alcoholism, and multiple myeloma. The Charlson comorbidity index was used to categorize comorbidities based on the ICD-9-CM codes, and the scores for each comorbidity-category were combined into a single comorbidity score. A score of zero indicated that no comorbidities were found, and a higher score indicated a higher burden of comorbidities.

2.4. Outcome measurements

All study participants were followed up, from the index date until the diagnosis of osteoporosis (ICD-9-CM codes: 733.00), until withdrawal from the NHI program, or until the end of 2015.

2.5. Statistical analysis

All analyses were performed using the SPSS software version 22 (SPSS Inc., Chicago, IL, USA). The χ^2 and Student's *t*-tests were used to evaluate the distribution of categorical and continuous variables, respectively. Fisher's exact test was used to analyze the differences in categorical variables between the two cohorts. Multivariate Cox proportional hazards regression analysis was used to determine the risk of osteoporosis, and the results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The difference in the risk of osteoporosis between the DPP-4i and non-DPP-4i groups was estimated using the Kaplan–Meier method with the log-rank test. Statistical significance was defined as a two-tailed p-value < 0.05.

2.6. Ethics approval

This study was conducted in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Board of the Tri-Service General Hospital approved this study (TSGH IRB No.2-105-05-082).

3. RESULTS

Table 1 presents the demographic data of the study participants. There were 6339 patients in the DPP-4i group and 47 989 in the non-DPP-4i group. After propensity score matching at a ratio of 1:4, 25 356 pairs remained. Both groups had a mean age of 66 years, mild male preponderance (51.79%), and were followed up for a mean duration of 7 years. Fig. 2 shows the Kaplan–Meier analysis for the cumulative risk of osteoporosis in the case and control groups, with a statistically significant difference (log-rank, $p = 0.039$).

Table 2 shows that at the end of the follow-up, 113 (0.36%) of all enrolled subjects had osteoporosis, including 15 (0.24%) in the case group and 98 (0.39%) in the control group. The results of the Cox regression analysis of factors related to the incidence of osteoporosis. Cox proportional hazards regression analysis showed that patients receiving DPP-4i treatment were associated with a lower incidence of osteoporosis (adjusted HR, 0.616 [95% CI, 0.358-0.961, $p = 0.011$]) than those not receiving the treatment. The study subjects with female, increasing age, and comorbidity free of diseases such as hyperthyroidism, hyperparathyroidism, Cushing's syndrome, hypogonadism, acromegaly, vitamin D deficiency, hypercalciuria, RA, COPD, alcoholism, and multiple myeloma were associated with a higher rate of osteoporosis in those without DPP4i therapy groups. The reduction in the risk of osteoporosis in the DPP-4i group was independent of sex or age.

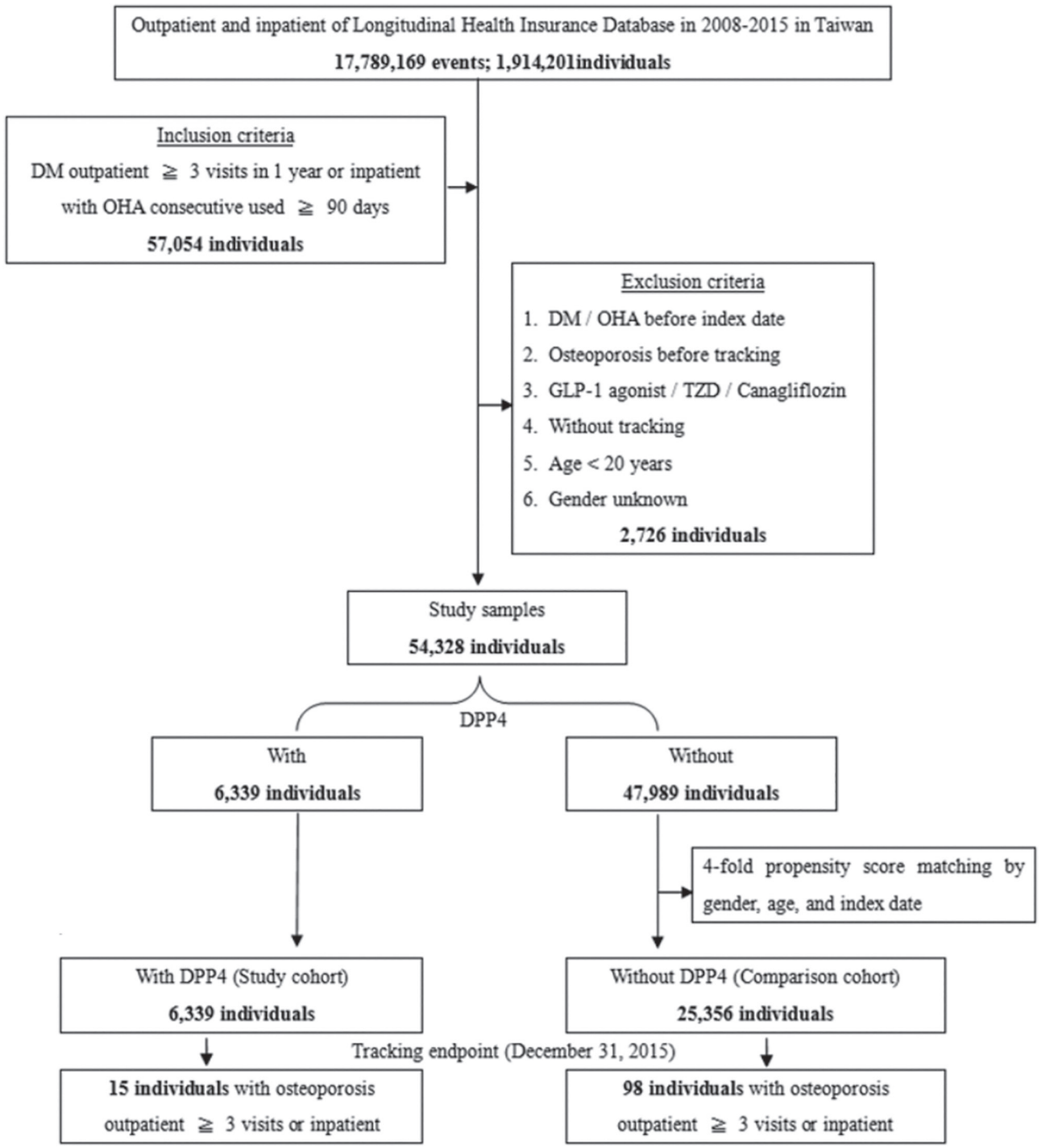

Fig. 1 Flow chart of the sample selection process. DM = diabetes mellitus; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1 receptor agonist = glucagon-like peptide 1 receptor agonist; OHA = oral hypoglycemic agents.

Table 3 shows a comparison of the risk of osteoporosis among the different combinations of DDP-4i. Various DPP-4i are observed to significantly protect against the development of osteoporosis. Cumulative protective effects of all types of DPP-4i were observed, especially when the treatment duration was greater than 6 months and persisted for more than 1 year. In patients treated with alogliptin, saxagliptin, and vildagliptin, it was observed that the use of these DPP-4 for more than 1 year reduced the risk of osteoporosis.

4. DISCUSSION

Our study demonstrated that compared with no DPP-4i use, the use of DPP-4i was associated with a 38.4% lower risk of developing osteoporosis in patients with T2DM. As the duration of treatment increased from 181 to 364 days and to more than 365 days, we found that DPP4i therapy such as alogliptin, saxagliptin, and vildagliptin decreased the risk of osteoporosis. This information may be important for physicians when choosing optimal antidiabetic medications to prevent osteoporosis

Table 1

Characteristics of study in the baseline

Variables	With DPP-4i use n %	Without DPP-4i use n %	*p*
Total	6339	25,356	
Number of men (percentage)	3283 (51.79%)	13132 (51.79)	0.999
Age (years)	66.02 ± 11.96	66.04 ± 11.82	0.923
Age groups (years)			0.999
18-49	731 (11.53%)	2924 (11.53%)	
50-64	1746 (27.54%)	6984 (27.54%)	
≧65	3862 (60.92%)	15448 (60.92%)	
Hyperthyroidism	13 (0.21%)	64 (0.25%)	0.563
Hyperparathyroidism	0 (0%)	4 (0.02%)	0.59
Cushing's syndrome	52 (0.82%)	181 (0.71%)	0.368
Hypogonadism	0 (0%)	1 (0%)	0.817
Acromegaly	6 (0.09%)	26 (0.10%)	0.86
Vitamin D deficiency	0 (0%)	1 (0%)	0.817
Hypercalciuria	10 (0.16%)	38 (0.15%)	0.857
Rheumatoid arthritis	16 (0.25%)	38 (0.15%)	0.088
Chronic obstructive pulmonary disease	617 (9.73%)	2315 (9.13%)	0.126
Alcoholism	20 (0.32%)	73 (0.29%)	0.707
Multiple myeloma	5 (0.08%)	13 (0.05%)	0.383
CCI_R	0.80 ± 1.73	0.78 ± 1.77	0.411

P: Chi-square/Fisher exact test on category variables and t-test on continue variables

development in patients with T2DM without osteoporosis. We also observed that the effect was seen in both sexes but only among subjects 50–64 years old.

DPP-4i is a type of incretin-based therapy that can increase the concentration of circulating GLP-1, has a relatively low risk of causing hypoglycemia, and is often used to treat T2DM.[19] A recent meta-analysis found that there was no difference in fracture risk among DPP-4i users compared to placebo or active comparator.[20] Similarly, observational data examining the association between DPP-4 inhibitors and fragility fractures do not support an increase or decrease in the fracture risk.[21] These results were inconsistent with those of the previous human studies.[17,22] The differences between the studies may be attributed to the population and number of study participants, study design, duration of follow-up, efficacy, and analysis of previous observational studies.

Several previous human studies reported that DPP-4i is beneficial for bone metabolism, which is consistent with our findings.[23–25] DPP-4i is associated with fewer fracture events than placebo or control treatments, the basis of which could be explained by the protective effect of DPP-4i on bones.[16] DPP-4i may promote bone formation and reduce bone resorption through a variety of mechanisms that inhibit DPP-4, while possibly promoting bone metabolism by lowering glucose levels. Also, the energy metabolism associated with DPP-4 substrate and DPP-4 may affect bone metabolism. The DPP-4i may increase the serum concentration of 25-hydroxy vitamin D3, which affects the risk of bone fracture, BMD, and bone

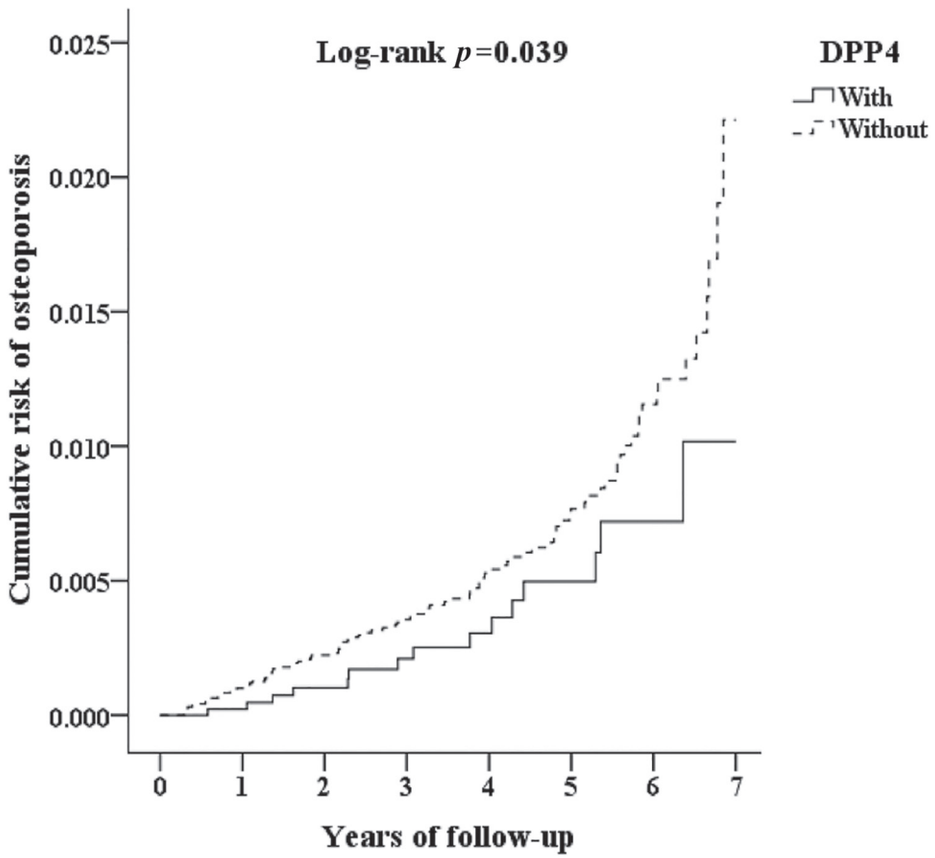

Fig. 2 Kaplan–Meier curve for the cumulative risk of osteoporosis in patients with DM on OHA (≥20) stratified by DPP-4i with log-rank test. DM + diabetes mellitus; DPP-4i = dipeptidyl peptidase-4 inhibitor; OHA = oral hypoglycemic agents.

Table 2

Factors of osteoporosis stratified by variables listed in the table using Cox regression

DPP-4i	With		Without		With vs Without	
Group	**Events**	**Rate (%)**	**Events**	**Rate (%)**	**Adjusted HR**	***p***
Total	15	0.24	98	0.39	0.616 (0.358-0.961)	0.011
Sex						
Male	4	0.10	29	0.22	0.562 (0.322-0.878)	0.001
Female	11	0.36	69	0.56	0.638 (0.364-0.980)	0.029
Age gourps (years)						
18-49	0	0.00	4	0.18	0.000	0.785
50-64	2	0.13	15	0.25	0.521 (0.298-0.816)	<0.001
≧65	13	0.30	79	0.46	0.674 (0.391-1.043)	0.126
Disease free of						
Hyperthyroidism	15	0.24	97	0.38	0.622 (0.357-0.973)	0.018
Hyperparathyroidism	15	0.24	98	0.39	0.616 (0.358-0.961)	0.011
Cushing's syndrome	14	0.22	97	0.38	0.597 (0.362-0.909)	<0.001
Hypogonadism	15	0.24	98	0.39	0.616 (0.358-0.961)	0.011
Acromegaly	15	0.24	98	0.39	0.616 (0.358-0.961)	0.011
Vitamin D deficiency	15	0.24	98	0.39	0.616 (0.358-0.961)	0.011
Hypercalciuria	15	0.24	98	0.39	0.616 (0.358-0.961)	0.011
Rheumatoid arthritis	15	0.24	97	0.38	0.623 (0.362-0.968)	0.01
Chronic obstructive pulmonary disease	13	0.21	86	0.34	0.603 (0.299-0.943)	0.005
Alcoholism	15	0.24	98	0.39	0.616 (0.358-0.961)	0.011
Multiple myeloma	15	0.24	98	0.39	0.616 (0.358-0.961)	0.011

CI = confidence interval; adjusted HR = adjusted hazard ratio: adjusted for the variables listed in Table 2; PYs = person-years.

quality through vitamin D-related and other related signaling pathways.[26]

Systemic osteoporosis has several different causes and pathogenesis.[27] When assessing the underlying causes of osteoporosis, it was found that up to 30% of postmenopausal women and 50%-80% of men have factors that lead to osteoporosis, with glucocorticoid-induced osteoporosis being the most common form of secondary osteoporosis.[28,29] The term secondary applies to all patients with osteoporosis whose identifiable causes are not aging or menopause.[30] Our study also demonstrated that the incidence of osteoporosis development diminished among patients with co-existence of T2DM and underlying diseases that caused secondary osteoporosis, such as endocrine diseases, RA, COPD, and multiple myeloma. This was to analyze whether the use of DPP4i reduces the risk of osteoporosis. One should be cautious while interpreting the results. Owing to the limited number of cases, it is impossible to draw any firm conclusions. However, in patients with diabetes without these diseases, the use of DPP4i reduces the risk of osteoporosis compared to patients who do not use DPP4i.

One study showed that the use of DPP-4i significantly reduced the risk of lower extremity fractures in men and women aged 46-55 years and reduced the risk of all fractures only in women aged 45-54 years with diabetes.[25] Similarly, in our subgroup analysis, there was an association between the use of DPP-4i in patients with diabetes aged >50 years with a lower risk of osteoporosis; however, we found that the benefits of DPP-4i are weaker in people over 65 years of age. We are currently unable to explain the reasons for the differences between relevant age groups based on the results of previous literature studies and our study.

One study showed no association with increased fracture risk when stratified by the duration of current DPP-4i use >4.0-8.5 years.[31] Moreover, a previous meta-analysis of 28 randomized clinical trials concluded that DPP-4i treatment reduced fracture risk compared with placebo or other treatments (HR = 0.60, 95% CI, 0.37-0.99, $p = 0.045$).[16] These studies have shown that, as compared to linagliptin and saxagliptin, alogliptin and sitagliptin have beneficial effects on fractures.[24] Furthermore, in another study elucidating the effect of different classes of DPP-4i on bone metabolism, alogliptin may be associated with a lower risk of fracture compared to placebo, linagliptin, or saxagliptin, whereas other antidiabetic medications appear to be associated with fracture risk.[23] In our subgroup analysis, we found some

Table 3

Factors of osteoporosis among different DDP4 subgroups using Cox regression

	Events	PYs	Rate (per 10^5 PYs)	Adjusted HR	Lower CI	Higher CI	*p*
All DDP-4i	15	31223.90	48.04	0.616	0.358	0.961	0.011
All DDP-4i (90-180 days)	8	8657.38	92.41	1.186	0.690	1.847	0.283
Alogliptin	2	1820.22	109.88	1.410	0.823	2.195	0.394
Linagliptin	2	1836.12	108.93	1.394	0.808	2.173	0.373
Saxagliptin	1	1025.67	97.50	1.233	0.714	1.918	0.290
Sitagliptin	2	2425.11	82.47	1.017	0.613	1.622	0.275
Vildagliptin	1	1550.26	64.51	0.815	0.482	1.280	0.211
All DDP-4i (181-364 days)	4	10170.86	39.33	0.505	0.293	0.786	<0.001
Alogliptin	1	2091.9	47.80	0.613	0.355	0.957	0.018
Linagliptin	1	2108.95	47.42	0.609	0.352	0.949	0.009
Saxagliptin	1	1900.81	52.61	0.677	0.392	1.059	0.186
Sitagliptin	1	2571.41	38.89	0.498	0.290	0.777	<0.001
Vildagliptin	0	1497.79	0.00	0.000	-	-	0.989
All DDP-4i (≧365 days)	3	12395.66	24.20	0.311	0.181	0.484	<0.001
Alogliptin	1	2118.14	47.21	0.605	0.351	0.943	0.007
Linagliptin	0	2538.07	0.00	0.000	-	-	0.986
Saxagliptin	1	2009.42	49.77	0.624	0.364	0.913	<0.001
Sitagliptin	0	2590.42	0.00	0.000	-	-	0.994
Vildagliptin	1	3139.61	31.85	0.408	0.234	0.633	<0.001

CI = confidence interval; adjusted HR = adjusted hazard ratio: adjusted for the variables listed in Table 3; PYs = person-years.

kinds of DPP-4i in which alogliptin, saxagliptin, and vildagliptin were used, the treatment time was longer (more than 6 months and persisted for more than 1 year), and the risk of osteoporosis was reduced. Some possible reasons include different sample sizes and usage doses of DPP-4i in studies, making some of the results lack statistical power. Further large-scale RCT trials should be designed to clarify this issue.

There were several limitations to our study, including the lack of an analysis of the course of the disease, severity of the disease, and patient parameters. The pathophysiological mechanisms are partially understood, whereas common factors, such as sex and aging, can explain the increased risk of osteoporosis.[32] Furthermore, our study lacked laboratory data such as adjustment for renal function, as it was not available in the NHIRD. However, we compared the number of DPP-4i and non-DPP-4i users before and after propensity score matching and observed no significant differences. Other residual confounding factors, such as HbA1c or vitamin D levels, dietary factors, and BMI, were also not included in the NHIRD. This was a population-based study, and it was impossible to elucidate the actual mechanism of the association between DPP-4i use and osteoporosis in patients with T2DM.

In conclusion, compared with no DPP-4i use, DPP-4i use was associated with a lower risk of osteoporosis in patients with T2DM in Taiwan. Based on a longer follow-up period, further research on the effects of DPP-4i on bone remodeling, vitamin D level, and other mechanisms may be needed to verify the risk of osteoporosis using DPP-4i.

ACKNOWLEDGMENTS

This study was funded by the Tri-Service General Hospital Research Foundation (TSGH-C108-142, TSGH-B-110012, TSGH-D-110058, and TSGH-B-111246) and the Teh-Tzer Study Group for Human Medical Research Foundation. We also appreciate the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW), Taiwan, for providing the National Health Insurance Research Database (NHIRD).

REFERENCES

1. Rosen CJ, Feingold KR, Anawalt B, Boyce A, Chrousos G, Herder WW, et al. The epidemiology and pathogenesis of osteoporosis. *In: Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000–2020.
2. Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. *Eur J Rheumatol* 2017;**4**:46–56.
3. Chie WC, Yang RS, Liu JP, Tsai KS. High incidence rate of hip fracture in Taiwan: estimated from a nationwide health insurance database. *Osteoporos Int* 2004;**15**:998–1002.
4. Jackuliak P, Payer J. Osteoporosis, fractures, and diabetes. *Int J Endocrinol* 2014;**2014**:820615.
5. Wongdee K, Charoenphandhu N. Osteoporosis in diabetes mellitus: possible cellular and molecular mechanisms. *World J Diabetes* 2011;**2**:41–8.
6. Massé PG, Pacifique MB, Tranchant CC, Arjmandi BH, Ericson KL, Donovan SM, et al. Bone metabolic abnormalities associated with well-controlled type 1 diabetes (IDDM) in young adult women: a disease complication often ignored or neglected. *J Am Coll Nutr* 2010;**29**:419–29.
7. Dienelt A, zur Nieden NI. Hyperglycemia impairs skeletogenesis from embryonic stem cells by affecting osteoblast and osteoclast differentiation. *Stem Cells Dev* 2011;**20**:465–74.
8. Moseley KF. Type 2 diabetes and bone fractures. *Curr Opin Endocrinol Diabetes Obes* 2012;**19**:128–35.
9. Adil M, Khan RA, Kalam A, Venkata SK, Kandhare AD, Ghosh P, et al. Effect of anti-diabetic drugs on bone metabolism: evidence from preclinical and clinical studies. *Pharmacol Rep* 2017;**69**:1328–40.
10. Losada-Grande E, Hawley S, Soldevila B, Martinez-Laguna D, Nogues X, Diez-Perez A, et al. Insulin use and excess fracture risk in patients with type 2 diabetes: a propensity-matched cohort analysis. *Sci Rep* 2017;**7**:3781.
11. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–57.
12. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. *Arch Intern Med* 2008;**168**:820–5.

13. Holman R. Metformin as first choice in oral diabetes treatment: the UKPDS experience. *Journ Annu Diabetol Hotel Dieu* 2007:13–20.
14. Khalse M, Bhargava A. A review on cardiovascular outcome studies of dipeptidyl peptidase-4 inhibitors. *Indian J Endocrinol Metab* 2018;**22**:689–95.
15. Santamarina M, Carlson CJ. Review of the cardiovascular safety of dipeptidyl peptidase-4 inhibitors and the clinical relevance of the CAROLINA trial. *BMC Cardiovasc Disord* 2019;**19**:60.
16. Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. *Diabetes Care* 2011;**34**:2474–6.
17. Driessen JH, van Onzenoort HA, Henry RM, Lalmohamed A, van den Bergh JP, Neef C, et al. Use of dipeptidyl peptidase-4 inhibitors for type 2 diabetes mellitus and risk of fracture. *Bone* 2014;**68**:124–30.
18. Chamberlain JJ, Herman WH, Leal S, Rhinehart AS, Shubrook JH, Skolnik N, et al. Pharmacologic therapy for type 2 diabetes: synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes. *Ann Intern Med* 2017;**166**:572–8.
19. Karagiannis T, Boura P, Tsapas A. Safety of dipeptidyl peptidase 4 inhibitors: a perspective review. *Ther Adv Drug Saf* 2014;**5**:138–46.
20. Mamza J, Marlin C, Wang C, Chokkalingam K, Idris I. DPP-4 inhibitor therapy and bone fractures in people with Type 2 diabetes - a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2016;**116**:288–98.
21. Majumdar SR, Josse RG, Lin M, Eurich DT. Does sitagliptin affect the rate of osteoporotic fractures in type 2 diabetes? Population-based cohort study. *J Clin Endocrinol Metab* 2016;**101**:1963–9.
22. Driessen JH, van Onzenoort HA, Starup-Linde J, Henry R, Neef C, van den Bergh J, et al. Use of dipeptidyl peptidase 4 inhibitors and fracture risk compared to use of other anti-hyperglycemic drugs. *Pharmacoepidemiol Drug Saf* 2015;**24**:1017–25.
23. Yang Y, Zhao C, Liang J, Yu M, Qu X. Effect of dipeptidyl peptidase-4 inhibitors on bone metabolism and the possible underlying mechanisms. *Front Pharmacol* 2017;**8**:487.
24. Yang J, Huang C, Wu S, Xu Y, Cai T, Chai S, et al. The effects of dipeptidyl peptidase-4 inhibitors on bone fracture among patients with type 2 diabetes mellitus: a network meta-analysis of randomized controlled trials. *PLoS One* 2017;**12**:e0187537.
25. Hou WH, Chang KC, Li CY, Ou HT. Dipeptidyl peptidase-4 inhibitor use is associated with decreased risk of fracture in patients with type 2 diabetes: a population-based cohort study. *Br J Clin Pharmacol* 2018;**84**:2029–39.
26. Barchetta I, Cimini FA, Bloise D, Cavallo MG. Dipeptidyl peptidase-4 inhibitors and bone metabolism: is vitamin D the link? *Acta Diabetol* 2016;**53**:839–44.
27. Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J Clin Invest* 2005;**115**:3318–25.
28. Harper KD, Weber TJ. Secondary osteoporosis. Diagnostic considerations. *Endocrinol Metab Clin North Am* 1998;**27**:325–48.
29. Nih consensus development panel on osteoporosis prevention D, therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001;**285**:785–95.
30. Mirza F, Canalis E. Management of endocrine disease: secondary osteoporosis: pathophysiology and management. *Eur J Endocrinol* 2015;**173**:R131–51.
31. Driessen JH, van den Bergh JP, van Onzenoort HA, Henry RM, Leufkens HG, de Vries F. Long-term use of dipeptidyl peptidase-4 inhibitors and risk of fracture: a retrospective population-based cohort study. *Diabetes Obes Metab* 2017;**19**:421–8.
32. Fitzpatrick LA. Secondary causes of osteoporosis. *Mayo Clin Proc* 2002;**77**:453–68.