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Comparative risk of musculoskeletal adverse reactions among new users of dipeptidyl peptidase-4 inhibitors: A retrospective cohort study

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ARTICLE INFO

ABSTRACT

Background: The effects of dipeptidyl peptidase-4 inhibitors (DPP4Is) on joint pain have been controversial.
Objective: To assess the comparative musculoskeletal (MSk) risk of DPP4Is vs. non-DPP4Is.
Methods: This study used a national claims database from January 2007 to December 2014. Exposure included the initiation of DPP4Is against the initiation of non-DPP4Is: metformin, sulfonylureas, thiazolidinediones, meglitinides, and glucagonlike peptide-1 receptor agonists (GLP-1 RAs). Insulin was not included in this study. Outcomes were newly diagnosed MSk conditions (arthralgia, arthropathy, and rheumatoid arthritis or other inflammatory polyarthropathies). Individuals exposed to DPP4Is were matched to those exposed to non-DPP4Is using a propensity score (PS). Balance between the DPP4I's group and the non-DPP4Is group was assessed using standardized differences for both continuous and categorical variables. Cox regressions were used to estimate hazard ratios (HRs) for MSk conditions.
Results: Among PS-matched cohorts, incidence rates (IRs) for MSk conditions did not differ between DPP4I initiators and non-DPP4I initiators (HR = 1.01, 95% CI: 0.97–1.05). After stratifying non-DPP4Is by drug class, the results still showed that DPP4I initiators had similar MSk risk when compared to initiators of metformin, sulfonylureas, meglitinides, and GLP-1 RAs. However, thiazolidinedione initiators had higher risk of MSk conditions than DPP4I initiators (HR = 1.05, 95% CI: 1.00–1.10).
Conclusions: This head-to-head comparison study estimated comparative MSk risks among different antidiabetic drugs. The risk of MSk conditions among DPP4I initiators were not significantly higher than non-DPP4I initiators.

1. Introduction

Dipeptidyl peptidase-4 inhibitors (DPP4Is) are a class of oral drugs that treat type 2 diabetes mellitus (T2DM). Dipeptidyl peptidase-4 (DPP4) is an enzyme that degrades incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin-tropic polypeptide (GIP). The incretin hormones lower blood glucose levels by stimulating insulin secretion in response to glucose such as food or beverage intake. By blocking the degradation of GLP-1, DPP4Is enhance the incretin effects, thereby lowering glucose levels.[1,2] The pharmacological inhibition of DPP4, however, may be associated with adverse events characterized by cytokine-induced inflammation.[3] Accordingly, there have been concerns about immunological adverse reactions such as joint inflammation among DPP4I users.

Previous studies have assessed the musculoskeletal (MSk) safety of DPP4Is. However, the effects of DPP4Is on joint pain have not been

definitively concluded. A meta-analysis revealed that vildagliptin use was associated with an increased risk of arthralgia compared with other antidiabetic agents (odds ratio (OR) = 1.23, 95% CI: 1.02–1.48).[4] Another study also reported the association between the use of DPP4Is and arthralgia (OR = 2.69, 95% CI: 1.38–5.24).[5] Clinical cases demonstrating the onset of joint pain after initiating DPP4Is have been reported in the literature.[6] In line with these findings, the U.S. Food and Drug Administration (FDA) announced warnings for using DPP4Is related to the risk of joint pain[7] based on several case reports.[8–11] In contrast, a pivotal clinical study showed that incidence rates (IRs) of arthralgia and pain in the extremities were not significantly between patients treated with DPP4Is and a placebo group.[12] Moreover, a pooled analysis from 10,246 patients in 19 clinical studies reported no association between sitagliptin use and incidence of arthralgia.[13] Another study demonstrated that DPP4Is were not associated with the risk of rheumatoid arthritis (RA).[14] To add perspective,

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this study aimed to evaluate the comparative musculoskeletal risk of DPP4Is vs. non-DPP4Is using real-world data obtained from patients receiving routine care.

2. Methods

This was a retrospective cohort study using a nationally representative sample of individuals with T2DM. Data were obtained from a large commercial claims database (Symphony Health Solutions database) that captured patients participating in commercial health plans and public insurance programs (e.g., Medicare and Medicaid). Individuals who initiated an antidiabetic agent in the first-line setting between 1 January 2007 and 31 December 2014 were identified. Of those identified, patients were selected if they (a) were aged 18 or older at the time they started an antidiabetic agent; (b) had at least one diagnosis of type 2 diabetes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (Appendix A shows the list of ICD-9-CM codes for diabetes); (c) had 12 months of continuous health plan enrollment prior to the index date; and (d) had not used any antidiabetic drug for the 12-month period before the index date to eliminate the effects of the drug used before the index date. The following subjects were excluded: (a) women with gestational diabetes during 12 months before the index date; (b) women with a history of polycystic ovary syndrome (because metformin is used not only for T2DM but also for this syndrome); (c) patients using insulin-containing drugs or pramlintide during any study period (because these drugs are used for both type 1 and type 2 diabetes); (d) those diagnosed with MSk conditions during the 12 months before the index date; and (e) those who received combination therapy for diabetes. The index date was defined as the earliest date of initiating antidiabetic agents. One year before the index date was kept as baseline for continuous enrollment and medication use assessment. Exposure of interest was the initiation of DPP4Is against the initiation of other antidiabetic agents – i.e., metformin, sulfonylureas, thiazolidinediones, meglitinides, and GLP-1 receptor agonists (GLP-1 RAs). Insulin was not included in this study. Each patient was followed from the day after the index date until the occurrence of study outcomes or censoring events, whichever came first. The primary outcome was a composite of MSk conditions comprising arthralgia, arthropathy, and RA or other inflammatory polyarthropathies, defined by ICD-9-CM codes in Appendix A. The secondary outcomes were the individual components of the primary outcome. Censoring events included discontinuation or switching of a study drug, loss of health plan coverage, or the end of the study period. Drug discontinuation was defined as having gaps more than 45 days after the expiration of the last prescription supply. Drug switching was also defined as having gaps more than 45 days after the expiration of the last prescription supply. Patients were allowed to enter the analyses only one time.

A propensity score (PS) matching was performed using age, gender, index year (2007 through 2014), geographic region (Northeast, Midwest, South, and West), comorbidities (hypertension, lipid metabolism disorder, obesity, smoking status, and Charlson comorbidity score), diabetes complications severity score, and use of medication (antihypertensive, antihyperlipidemic, steroids, and anti-inflammatory). Patients exposed to DPP4Is were matched to those exposed to non-DPP4Is based on a PS at a fixed ratio of 1:1 using a nearest neighbor method with a caliper of 0.05. Balance between the DPP4I's group and the non-DPP4Is group was assessed using standardized differences, which is a common approach in PS-matching studies.[15–18] The standardized differences are calculated using the mean and standard deviation for continuous variables and the proportion for categorical variables. A standardized difference of less than 0.1 has been considered negligible imbalance between groups.[16] Cox proportional hazards regression models were used to estimate hazard ratios (HRs) for MSk conditions between DPP4I initiators and non-DPP4I initiators. Additional Cox regression analyses were conducted after stratifying non-DPP4Is by drug class. Furthermore, the maximum follow-up periods were varied up to six months, one year, and two years after the index

event in sensitivity analyses. All analyses were conducted using SAS 9.4 Statistical Software (SAS Institute Inc., Cary, NC, USA).

This study was reviewed and approved by Saint Louis University Institutional Review Board.

3. Results

There were 8,753,536 individuals between January 2007 and December 2014 in the dataset. After applying inclusion and exclusion criteria, the cohort consisted of 50,409 DPP4I initiators and 1,074,062 non-DPP4I initiators (Fig. 1).

Table 1 presents the baseline characteristics comparing the DPP4I's group ($n = 50,409$) and the non-DPP4Is group ($n = 1,074,062$). Before PS-matching, there were significant imbalances (i.e., standardized differences ≥ 0.1) between these two groups for several characteristics, such as age, Northeast geographic region, comorbidities, diabetes severity, and anti-inflammatory drug use. For example, DPP4I initiators were older than non-DPP4I initiators. In addition, DPP4I initiators were more likely to have some comorbidities (e.g., hypertension and lipid disorders) with a higher Charlson comorbidity score. Diabetes complications severity index was also higher among DPP4I initiators. The proportion of anti-inflammatory drug use was higher among non-DPP4 initiators (22% vs. 17%). After the PS-matching at a 1:1 ratio, there were a total of 49,988 pairs of DPP4I and non-DPP4I initiators. Of these 49,988 individuals in the DPP4I's group, the majority started sitagliptin ($n = 29,160$, 58.33%) followed by saxagliptin ($n = 16,663$, 33.33%) and linagliptin ($n = 4165$, 8.33%). All baseline characteristics were well balanced between the two groups, with standardized differences of less than 0.1. The average ages of the PS-matched samples were 60.2 ± 10.7 and 60.5 ± 10.6 for the DDP4I group and the non-DPP4I group, respectively. About 71% and 65% of both groups had hypertension and lipid disorders. The DPP4I's group and the non-DPP4Is group had mean Charlson comorbidity scores of 2.4 ± 2.1 and 2.3 ± 2.1, respectively. Both groups had a diabetes complication severity index score of 3.0. The proportion of anti-inflammatory drug use was also similar between the DPP4I's group and the non-DPP4Is group (17% and 15%, respectively).

Comparative risk of MSk conditions among DPP4I initiators in the PS-matched samples is presented in Table 2. There was no significant difference in IRs for the primary outcome between the DPP4I's group and the non-DPP4Is group among PS-matched cohorts (11.52 per 100 person-years for both groups). HR for MSk conditions was 1.01 (95% CI: 0.97–1.05), indicating no significant difference in the risk of MSk conditions between the two groups. The secondary outcomes from stratified analyses confirmed this finding of no higher risk of MSk events among DPP4I initiators than non-DPP4I initiators. In other words, DPP4I initiators did not have a higher risk of each MSk event compared with initiators of metformin, sulfonylureas, meglitinides, and GLP-1 RAs. HRs for MSk events ranged from 0.91 (95% CI: 0.75–1.09) for GLP-1 RA initiators to 1.01 (95% CI: 0.97–1.05) for metformin initiators. However, the MSk risk was statistically different between DPP4I initiators and thiazolidinedione initiators. IRs for MSk conditions were 11.41 and 12.30 per 100 person-years among DPP4I initiators and thiazolidinedione initiators, respectively. The risk of MSk conditions was higher for thiazolidinedione initiators compared with DPP4I initiators, with HR of 1.05 (95% CI: 1.00–1.10).

The average length of time to censorship was 0.90 ± 1.13 (maximum follow-up: 6.92) years and 0.72 ± 0.99 (maximum follow-up: 6.95) years in the DPP4I group and the non-DPP4Is group, respectively. Reasons for censorship were discontinuation or switching of study drugs, loss of health plan coverage, or end of the study period. In sensitivity analyses, the maximum follow-up periods were limited to 6 months, one year, and two years from the index event. Results from the sensitivity analyses still showed no significant difference in the risk of MSk conditions between the two groups. HRs for MSk events ranged from 1.02 (95% CI: 0.96–1.08) to 1.03 (95% CI: 0.98–1.08) when the maximum follow-up periods were varied. The full results from sensitivity analyses are shown in Appendix B.
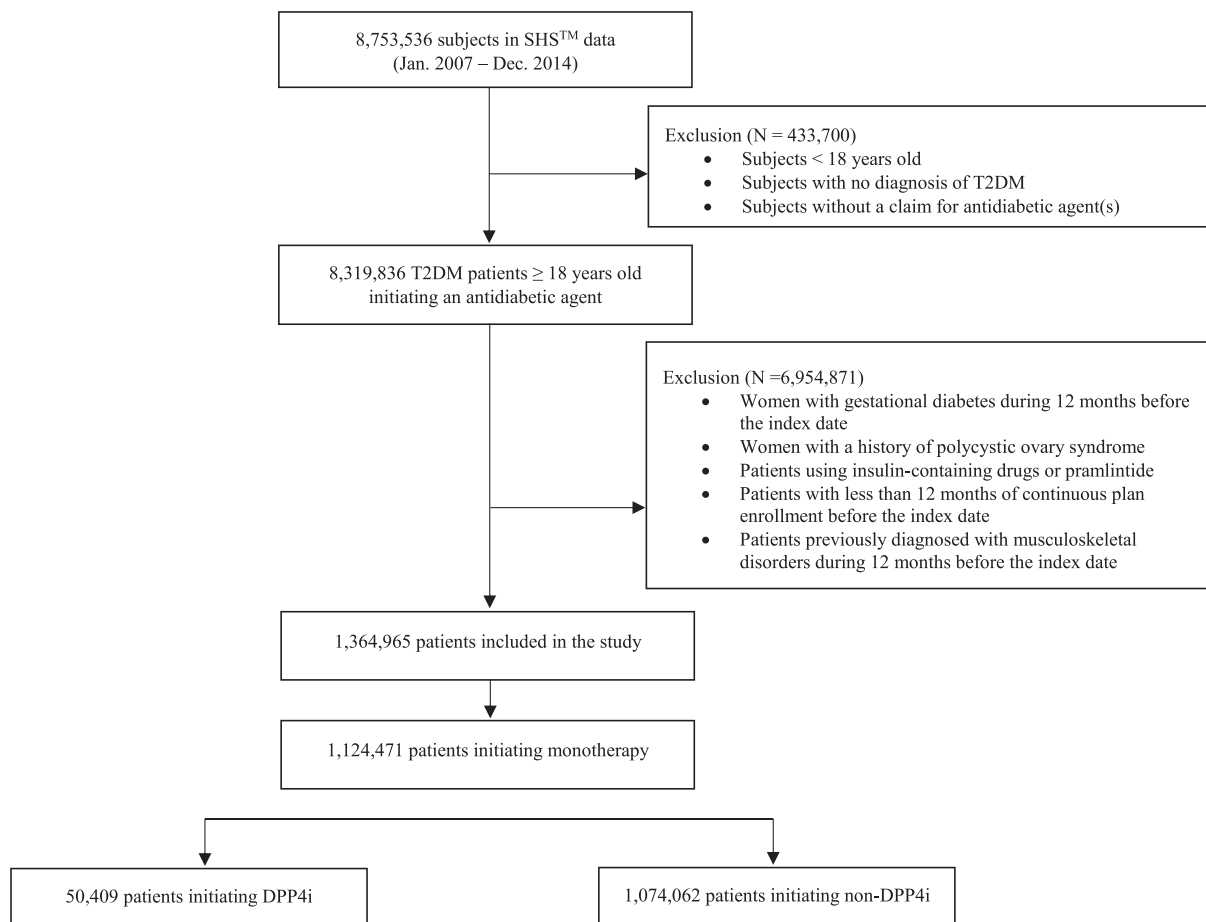
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┌─────────────────────────────────┐
│  8,753,536 subjects in SHSᵀᴹ data │
│     (Jan. 2007 – Dec. 2014)       │
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Exclusion (N = 433,700)
- Subjects < 18 years old
- Subjects with no diagnosis of T2DM
- Subjects without a claim for antidiabetic agent(s)

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┌─────────────────────────────────────────┐
│ 8,319,836 T2DM patients ≥ 18 years old    │
│      initiating an antidiabetic agent     │
└─────────────────────────────────────────┘
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Exclusion (N =6,954,871)
- Women with gestational diabetes during 12 months before the index date
- Women with a history of polycystic ovary syndrome
- Patients using insulin-containing drugs or pramlintide
- Patients with less than 12 months of continuous plan enrollment before the index date
- Patients previously diagnosed with musculoskeletal disorders during 12 months before the index date

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┌─────────────────────────────────────────┐
│  1,364,965 patients included in the study │
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┌─────────────────────────────────────────┐
│  1,124,471 patients initiating monotherapy │
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┌──────────────────────────────┐      ┌────────────────────────────────────┐
│ 50,409 patients initiating DPP4i │  │ 1,074,062 patients initiating non-DPP4i │
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Fig. 1. Selection of a study cohort.

4. Discussion

This study assessed real-world joint pain safety of antidiabetic agents using a large database. The study findings indicated no significant difference in the risk of MSk conditions between DPP4I initiators and non-DPP4I initiators. Of note, DPP4I initiators had lower MSk risk than thiazolidinedione initiators. This finding is consistent with previous studies showing no significant association of using DPP4Is with the risk of MSk conditions (e.g., arthralgia, pain in extremes, and RA).[12–14] Specifically, HRs ranging from 0.66 to 0.74 for RA among DPP4I initiators reported in a previous study[14] were comparable to those ranging from 0.91 to 1.05 for MSk conditions in this study. On the contrary, other prior studies suggested the potential association between the use of DPP4Is and MSk disorders.[4–6,8–11] These studies propose that joint pain among patients starting DPP4Is may result from the effects of DPP4Is on immune systems. DPP4 degrades not only incretin hormones but also several cytokines and chemokines. Furthermore, DPP4 is expressed in several cell types including fibroblasts, leukocyte subsets, T lymphocytes, and macrophages. Accordingly, inhibition of DPP4 may cause changes to inflammatory homeostasis, thereby influencing bone and joints. These findings, however, indicate that the effects of DPP4Is on the immune system may not be significantly higher compared with those of non-DPP4Is.

This study has several strengths. To the authors' best knowledge, this is the first study evaluating the comparative risk of the comprehensive MSk conditions such as arthralgia, arthropathy, and inflammatory polyarthropathies among DPP4I initiators. Moreover, this study performed head-to-head comparisons using large real-world data. Based on such direct comparisons, this study could estimate real-world MSk risk in the DPP4I group compared with each non-DPP4Is group. Furthermore, this study used propensity score matching to reduce selection bias. This rigorous study design accommodated the unbalanced distributions in characteristics between the DPP4I's group and the non-DPP4Is groups.

Several limitations of this study should also be noted. First, although several covariates were adjusted for in the regression models, residual confounding may exist by unmeasured factors such as family history, lifestyle factors, or the initiation of other medications after the index date that may have related to MSk conditions. This limitation is inherent in any observational study. To the extent that unmeasured confounders affect the comparative risk of DPP4Is, the results will be biased. In addition, most research, including this study, that uses a claims database or administrative database relies on billing codes to capture the diagnosis of conditions. As such, these studies are not free from coding inaccuracy caused by code ambiguity or coder errors. Furthermore, DPP4Is are widely used as combination therapy with metformin or insulin. Nevertheless, this study was limited to patients using DPP4Is as first-line monotherapy to isolate the effects of DPP4Is alone on MSk conditions. Accordingly, the study findings should be interpreted with caution. The study results may not be generalizable to those who use more than one antidiabetic agent or initiate DPP4I as the second-line therapy. Moreover, this study did not account for genetic factors that may play an important role in MSk conditions. For example, the human leukocyte antigen (HLA) is the genetic factor associated with the pathogenesis of RA. A prior study suggested that sitagliptin may trigger RA in individuals with shared epitope (SE)-positive HLA-DRB1 alleles.[19] However, such genetic factors were not considered in this study as they were beyond the scope of this study. Finally, this study was not able to assess the MSk risk of sodium-glucose co-transporter 2 (SGLT2) inhibitors within the study period. Future research is warranted to determine the MSk safety of this drug class.

Table 1

Baseline characteristics of study population before and after propensity score matching.

	Before PS matching			After PS matching		
	DPP4I initiators (N = 50,409)	Non-DPP4I initiators (N = 1,074,062)[a]	Standardized difference	DPP4I initiators (N = 49,988)[b]	Non-DPP4I initiators (N = 49,988)[c,d]	Standardized difference
Age (yr), mean ± SD	60.24 ± 10.68	56.84 ± 12.07	−0.298*	60.24 ± 10.67	60.54 ± 10.61	0.028
Female, n(%)	23,223 (46.07)	505,685 (47.08)	0.020	23,032 (46.08)	22,942 (45.90)	−0.004
Index year, n(%)						
2007	1 (0.00)	691 (0.06)	0.034	–	–	
2008	5427 (10.77)	119,639 (11.14)	0.012	5382 (10.77)	5407 (10.82)	0.002
2009	9855 (19.55)	225,400 (20.99)	0.036	9796 (19.60)	10,501 (21.01)	0.035
2010	6924 (13.74)	157,247 (14.64)	0.026	6862 (13.73)	7138 (14.28)	0.016
2011	11,932 (23.67)	228,535 (21.28)	−0.057	11,853 (23.71)	11,682 (23.37)	−0.008
2012	7377 (14.63)	134,933 (12.56)	−0.060	7314 (14.63)	6446 (12.90)	−0.050
2013	5439 (10.79)	122,520 (11.41)	0.012	5379 (10.76)	5375 (10.75)	−0.000
2014	3454 (6.85)	85,097 (7.92)	0.041	3402 (6.81)	3439 (6.88)	0.003
Geographic region, n(%)						
Northeast	13,955 (27.93)	230,576 (21.78)	−0.145*	13,953 (27.93)	13,813 (27.64)	−0.006
Midwest	8916 (17.84)	225,789 (21.33)	0.085	8916 (17.84)	8714 (17.44)	−0.011
South	21,483 (42.99)	450,285 (42.54)	−0.014	21,483 (43.00)	21,989 (44.01)	0.020
West	5613 (11.23)	151,812 (14.34)	0.090	5613 (11.23)	5450 (10.91)	−0.010
Comorbidities						
Hypertension, n(%)	35,805 (71.03)	659,453 (61.40)	−0.205*	35,518 (71.05)	35,459 (70.94)	−0.003
Lipid metabolism disorder, n(%)	32,557 (64.59)	589,420 (54.88)	−0.199*	32,317 (64.65)	32,614 (65.24)	0.012
Obesity, n(%)	6621 (13.13)	151,925 (14.14)	0.029	6558 (13.12)	6007 (12.02)	−0.033
Smoking, n(%)	4077 (8.09)	100,989 (9.40)	0.047	4033 (8.07)	3361 (6.72)	−0.051
Charlson comorbidity score[e], mean ± SD	2.36 ± 2.06	1.68 ± 1.75	−0.354*	2.36 ± 2.06	2.26 ± 2.06	0.047
Indicators of diabetes severity						
Diabetes complications severity index[f], mean ± SD	2.97 ± 2.47	2.27 ± 2.29	−0.291*	2.97 ± 2.47	2.87 ± 2.45	0.042
Medication use, n(%)[g]						
Antihypertensive	24,542 (48.69)	536,228 (49.93)	0.025	24,354 (48.72)	23,711 (47.43)	−0.026
Antihyperlipidemic	15,120 (29.99)	316,572 (29.47)	−0.011	15,018 (30.04)	14,407 (28.82)	−0.027
Steroids	6916 (13.72)	166,253 (15.48)	0.050	6863 (13.73)	6100 (12.20)	−0.045
Anti-inflammatory	8471 (16.80)	232,006 (21.60)	0.122*	8389 (16.78)	7405 (14.81)	−0.054

* Indicates an imbalance of covariates between the DPP4I's group and the non-DPP4I's group (i.e., standardized difference ≥ 0.1).

[a] This group includes initiators of metformin (n = 763,091, 71.05%); sulfonylureas (n = 244,390, 22.75%); thiazolidinediones (n = 51,500, 4.79%); meglitinides (n = 9814, 0.91%); and GLP-1 RAs (n = 5267, 0.49%).

[b] In this group, a total of 4161 individuals developed MSk conditions: arthralgia (n = 3389, 81.45%), arthropathy (n = 611, 14.68%), and RA or other inflammatory polyarthritis (n = 161, 3.87%).

[c] This group includes initiators of metformin (n = 32,239, 64.49%); sulfonylureas (n = 13,978, 27.96%); thiazolidinediones (n = 2878, 5.76%); meglitinides (n = 643, 1.29%); and GLP-1 RAs (n = 250, 0.50%).

[d] In this group, a total of 5165 individuals developed MSk conditions: arthralgia (n = 4200, 81.32%), arthropathy (n = 783, 15.16%), and RA or other inflammatory polyarthritis (n = 182, 3.52%).

[e] Charlson comorbidity score was a continuous variable.[20]

[f] Diabetes complications severity index was a continuous variable.[21]

[g] Medication use was categorized as *yes* or *no*. The selection of the medications was based on the previous studies[14,22] and the authors' discussion.

Table 2

Risk of musculoskeletal conditions associated with DPP4Is against non-DPP4Is among propensity-score matched cohorts.

Analysis	Group	No. events	Person-years	IR[a]	HR [95% CI]
Primary analysis	DPP4I initiators (N = 49,988)	5165	44,835	11.52	1.012 [0.971, 1.054]
	vs. Non-DPP4I initiators[b] (N = 49,988)	4161	36,116	11.52	
Stratified analyses	(a) DPP4I initiators (N = 49,980)	4160	36,109	11.52	1.005 [0.965, 1.047]
	vs. Metformin initiators (N = 49,980)	5263	46,077	11.42	
	(b) DPP4I initiators (N = 49,987)	4161	36,112	11.52	0.987 [0.947, 1.029]
	vs. Sulfonylurea initiators (N = 49,987)	5100	44,828	11.38	
	(c) DPP4I initiators (N = 47,201)	3912	34,277	11.41	1.048 [1.002, 1.096]***, ***
	vs. Thiazolidinedione initiators (N = 47,201)	4303	34,981	12.30	
	(d) DPP4I initiators (N = 9741)	840	7052	11.91	0.992 [0.894, 1.101]
	vs. Meglitinide initiators (N = 9741)	678	5516	12.29	
	(e) DPP4I initiators (N = 5200)	406	3751	10.82	0.907 [0.752, 1.094]
	vs. GLP-1 RA initiators (N = 5200)	200	1902	10.52	

* *p* < 0.05.

** *p* < 0.01.

*** *p* < 0.001.

[a] Per 100 person-years.

[b] Initiators of non-DPP4Is (metformin, sulfonylureas, thiazolidinediones, meglitinides, or GLP-1 receptor agonists (GLP-1 RAs)).

5. Conclusions

In conclusion, this study provides estimates of comparative MSk risk among DPP4I initiators compared with non-DPP4I initiators. The study did not find significant evidence to show an increased risk of musculoskeletal conditions among DPP4I initiators. Specifically, among PS-matched cohorts, DPP4I initiators had a similar risk of these conditions compared with initiators of metformin, sulfonylureas, meglitinides, and GLP-1 RAs. Thiazolidinedione initiators had a higher risk of musculoskeletal conditions than DPP4I initiators. These findings may suggest that practitioners can consider initiating DPP4Is for treating T2DM without big concern about the incidence of MSk conditions. Notably, after starting DPP4Is, patients need to be monitored carefully for adverse drug reactions including MSk conditions just as they need to after taking other antidiabetic agents.

Appendix A. Diagnostic codes for conditions included in the study

Conditions	ICD-9-CM codes
Type 2 diabetes	250.x0, 250.x2[22]
Musculoskeletal conditions	
Arthralgia	719.4, 719.5[23]
Arthropathy	713.0, 713.7, 713.8, 716.4, 716.5, 716.6, 716.8, 716.9, 719.8, 719.9[24]
Rheumatoid arthritis or other inflammatory polyarthritis	714.x[14]
Comorbidities	
Hypertension	401–405[25]
Lipid metabolism disorder	272.0–272.4[25]
Obesity	278.0[25]
Smoking	305.1, V1582[25]

ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification.

Appendix B. Risk of musculoskeletal conditions associated with DPP4Is against non-DPP4Is among propensity-score matched cohorts (Sensitivity analyses results)

Maximum follow-up period	Group	No. Events	Person-Years	IR[a]	HR [95% CI]
6 months	DPP4I initiators (N = 49,988)	2159	16,754	12.89	1.018 [0.957, 1.083]
	vs. Non-DPP4I initiators[b] (N = 49,988)	1906	14,936	12.76	
1 year	DPP4I initiators (N = 49,988)	3194	25,892	12.34	1.022 [0.971, 1.075]
	vs. Non-DPP4I initiators[b] (N = 49,988)	2728	22,408	12.17	
2 years	DPP4I initiators (N = 49,988)	4286	35,975	11.91	1.028 [0.983, 1.075]
	vs. Non-DPP4I initiators[b] (N = 49,988)	3235	30,231	11.69	

[a] Per 100 person-years.
[b] Initiators of non-DPP4Is (metformin, sulfonylureas, thiazolidinediones, meglitinides, or GLP-1 receptor agonists (GLP-1 RAs)).

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