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REVIEW

Risk of fracture with dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors in real-world use: systematic review and meta-analysis of observational studies

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Abstract

Summary In the present meta-analysis based on real-world data, the use of dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1ra), or sodium-glucose cotransporter-2 inhibitors (SGLT2i) was not associated with the risk of fracture.

Introduction Cumulative evidence from randomized control trials (RCTs) with limited fracture events showed that the use of DPP-4i, GLP-1ra, or SGLT2i may not affect the risk of fracture. However, additional insights from large population-based studies with routinely collected data on fracture events and an adequate amount of fracture events are necessary to draw firm conclusions. To refine and complement the results from RCTs, a systematic review and meta-analysis of observational studies were performed to investigate the association between the use of DPP-4i, GLP-1ra, or SGLT2i and the risk of fracture in real-world settings.

Methods The PubMed and Web of Science databases were searched to identify relevant observational studies. A random-effect model was used to estimate the summary relative risks (RRs).

Results The use of DPP-4i (RR 0.83, 95% CI [confidence interval] 0.60, 1.14; $n = 11$), GLP-1ra (RR 0.65, 95% CI 0.24, 1.74; $n = 4$), or SGLT2i (RR 1.02, 95% CI 0.91, 1.16; $n = 4$) was not associated with the risk of fracture. In general, there was a consistent lack of association between the use of DPP-4i or GLP-1ra and the risk of fracture across nearly all subgroups, except for a significantly reduced risk of hip fracture with the use of GLP-1ra (RR 0.21, 95% CI 0.04, 0.98).

Conclusions Cumulative real-world evidence does not support an association between the use of DPP-4i, GLP-1ra, or SGLT2i and the risk of fracture. Our findings, together with the cumulative evidence from RCTs, should reassure policy makers and medical practitioners that the use of these medications is unlikely to increase the risk of fracture among type 2 diabetes mellitus patients in general. Further studies need to investigate the long-term impact of these drugs on the fracture risk, particularly in high-risk populations.

Keywords diabetes mellitus · DPP-4 inhibitors · GLP-1 receptor agonists · SGLT2 inhibitors · fracture

K. Hidayat and X. Du contributed equally to this work.

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Introduction

The prevalence and incidence of diabetes mellitus (DM) continues to increase with the number of adults living with DM increasing from 108 million in 1980 to 422 million in 2014 [1]. Given this consideration, DM can present a serious global public health concern due to increased morbidity, mortality, and health care burden among individuals with this condition [2, 3].

It is commonly known that type 2 diabetes mellitus (T2DM) can lead to serious complications, including cardiovascular disease, kidney disease, neuropathy, blindness, and

lower extremity amputation [4]. Apart from these complications, T2DM has also been increasingly recognized to have a detrimental effect on bone health [5]. Indeed, there is emerging epidemiological evidence that individuals with T2DM may have a higher risk of fracture than those without T2DM [6, 7]. Although the exact underlying biological mechanisms for the skeletal effects of T2DM remain unclear, the increased risk of fracture in T2DM patients is possibly explained by a combination of an increased risk of falls, impaired bone quality, and direct or indirect treatment effects of certain glucose-lowering medications [5, 8–10].

There is currently ongoing research evaluating the safety and efficacy of newer classes of glucose-lowering medications such as dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1ra), and sodium-glucose cotransporter-2 inhibitors (SGLT2i). GLP-1ra are postulated to stimulate bone formation by promoting osteoblast differentiation and inhibiting osteoclast activity [11, 12]. In this context, DPP-4i have been suggested to exert beneficial effects on bone health by prolonging the half-life of plasma GLP-1, leading to the enhanced activity of GLP-1 on bone [11, 12]. Conversely, there is suggestion that SGLT2i could adversely affect bone health by activating the fibroblast growth factor 23, 1,25-dihydroxyvitamin D, and parathyroid hormone axis [13]. The effects of DPP-4i [14–19], GLP-1ra [20–22], or SGLT2i [23–27] use on the risk of fracture have been reported by a number of meta-analyses of randomized controlled trials (RCTs) and large multicenter RCTs (Table 1), with most suggesting that the use of DPP-4i, GLP-1ra, or SGLT2i may not affect the risk of fracture. However, firm conclusions could not be drawn owing to several common limitations shared by these studies, such as a small number of fracture events, fracture not being the primary outcome of interest, and the data on fracture events not being routinely collected. Given these considerable concerns, additional insights from large population-based studies with routine collection fracture data and adequate fracture events are necessary to refine and complement the results from RCTs. We aimed to investigate the association between the use of DPP-4i, GLP-1ra, or SGLT2i and the risk of fracture in real-world settings by conducting a systematic review and meta-analysis of observational studies.

Methods

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist was used as the basis in preparing and reporting the present systematic review and meta-analysis of observational studies [28]. Two investigators (K.H. and X.D.) independently performed the literature search, study selection, data extraction, and quality assessment. Any discrepancies between investigators were resolved by consensus.

Search strategy

We searched the PubMed and Web of Science databases to identify relevant original studies that were published from the database inception to February 2019. The relevant published articles were identified using the following search terms: (dipeptidyl peptidase-4 inhibitors or sitagliptin or vildagliptin or saxagliptin or linagliptin or anagliptin or teneligliptin or alogliptin or trelagliptin or gemigliptin or dutogliptin or omarigliptin or exenatide or liraglutide or lixisenatide or albiglutide or dulaglutide or glucagon-like peptide-1 receptor agonists or incretin or sodium-glucose cotransporter-2 inhibitors or canagliflozin or dapagliflozin or empagliflozin) and fracture. No language restriction was imposed in our database searches. The references cited in the relevant articles were also screened to identify relevant articles that were not captured through the database searches.

Study selection

The observational studies with either cohort or case-control designs were eligible for inclusion in the present study if they reported risk estimates (relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs)) with 95% confidence intervals (CIs) for the association between the use of DPP-4i, GLP-1ra, or SGLT2i and the risk of fracture.

Data extraction and quality assessment

A standard form was used to extract the following information from the included studies: the first author's last name, publication year, country, age of the participants, study design, data source, time period by which the data were collected, exposure of interest versus comparators, outcome investigated, fracture classification, number of fracture events in patients exposed to medications, number of overall patients exposed to medications, number of fracture events in patients who were not exposed to medications, number of overall patients who were not exposed to medications, and adjustment for selected confounders. From each study, the risk estimates with 95% CIs from the maximally adjusted model were extracted. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) [29].

Statistical analysis

RRs were chosen as the common measurement of the associations. Therefore, the HRs and ORs reported in the included studies were deemed equal to the RRs. A DerSimonian and Laird random-effect model [30] was used to estimate the summary RRs for the association between the use of DPP-4i, GLP-1ra, or SGLT2i and the risk fracture. If possible, subgroup analyses were performed according to predefined criteria. In addition, a sensitivity analysis that excluded one

Table 1 The selected randomized-controlled trials (RCTs) investigating the association between the use of dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors and the risk of fracture

Reference; study type	Variables	Proportion of patients with fracture		Risk estimate (95% CI)
		Exposed group (no. fractures/no. overall)	Non-exposed group (no. fractures/no. overall)	
DPP-4i				
Yang et al., 2017 [14] Meta-analysis of RCTs $n = 75$	Alogliptin vs. placebo	NR	NR	0.54 (0.29, 1.01)
	Linagliptin vs. placebo	NR	NR	1.09 (0.53, 2.27)
	Saxagliptin vs. placebo	NR	NR	1.11 (0.85, 1.47)
	Sitagliptin vs. placebo	NR	NR	0.55 (0.27, 1.13)
	Vildagliptin vs. placebo	NR	NR	1.15 (0.31, 4.25)
	Sitagliptin vs. GLP-1ra	NR	NR	1.21 (0.24, 6.28)
	Sitagliptin vs. thiazolidinediones	NR	NR	2.01 (0,25, 16, 29)
	Alogliptin vs. sulfonylureas	NR	NR	0.92 (0.30, 2.82)
	Saxagliptin vs. sulfonylureas	NR	NR	2.01 (0.60, 6.71)
	Sitagliptin vs. sulfonylureas	NR	NR	1.09 (0.49, 2.43)
	Sitagliptin vs. SGLT2i	NR	NR	0.60 (0.14, 2.59)
	Sitagliptin vs. metformin	NR	NR	0.62 (0.03, 11.83)
Fu et al., 2016 [15] Meta-analysis of RCTs $n = 64$	Overall	364/33,452	358/28,754	0.95 (0.82, 1.10)
	Type			
	Alogliptin	53/6972	61/5113	0.79 (0.55, 1.14)
	Linagliptin	23/4667	10/2971	1.19 (0.60, 2.38)
	Saxagliptin	266/11,662	248/10,215	1.02 (0.86, 1.21)
	Sitagliptin	17/8422	35/9485	0.67 (0.39, 1.15)
	Anagliptin	3/68	0/40	4.16 (0.22, 78.51)
	Vildagliptin	2/1661	4/930	0.50 (0.12, 2.05)
	Duration			
	≥ 52 week	332/21,645	330/19,996	0.97 (0.83, 1.13)
	< 52 weeks	32/11,807	28/8758	0.76 (0.46, 1.27)
	Comparators			
	Active drug	24/7594	35/9179	0.91 (0.54, 1.52)
	Placebo	340/26,235	334/21,718	0.95 (0.81, 1.10)
Mamza et al., 2016 [16] Meta-analysis of RCTs $n = 37$	DPP-4i vs. active comparators	31/6648	16/5733	1.59 (0.91, 2.80)
	DPP-4i vs. placebo	55/13,868	48/10,003	0.82 (0.57, 1.16)

Table 1 (continued)

Reference; study type	Variables	Proportion of patients with fracture		Risk estimate (95% CI)
		Exposed group (no. fractures/no. overall)	Non-exposed group (no. fractures/no. overall)	
Monami et al., 2011 [17] Meta-analysis of RCTs $n = 28$	DPP-4i vs. comparators			
	Overall	26/11,880	37/9175	*0.60 (0.37, 0.99)*
	Duration			
	≥ 52 week	NS	NS	0.70 (0.32, 1.52)
	< 52 weeks	NS	NS	0.54 (0.28, 1.03)
	DPP-4i vs. placebo	11/5877	21/4928	*0.41 (0.21, 0.81)*
SAVOR-TIMI 53, 2015 [18] Multicenter, randomized, double-blind, placebo-controlled trial in 26 countries	Saxagliptin vs. placebo			
	Overall	241/8250	240/8212	1.00 (0.83, 1.19)
	CVD subjects	184/6494	177/6465	1.04 (0.84, 1.28)
	MRF subjects	57/1786	63/1747	0.89 (0.62, 1.27)
	RF, normal-mild	191/6986	185/6930	1.03 (0.84, 1.26)
	RF, moderate	42/1122	48/1118	0.86 (0.57, 1.31)
	RF, severe	8/172	7/164	1.11 (0.40, 3.17)
	Age < 75	184/7111	189/7051	0.97 (0.79, 1.18)
	Age ≥ 75	57/1169	51/1161	1.13 (0.77, 1.65)
	Male	124/5512	121/5525	1.03 (0.80, 1.33)
	Female	117/2768	119/2687	0.95 (0.74, 1.23)
	White	208/6241	199/6166	1.03 (0.85, 1.26)
	Non-white	33/2039	41/2046	0.81 (0.51, 1.28)
	North America	106/2635	106/2631	1.00 (0.76, 1.31)
	Latin America	27/1348	22/1363	1.25 (0.71, 2.21)
	Asia Pacific	17/785	26/768	0.64 (0.34, 1.18)
	Europe	91/3512	86/3450	1.04 (0.78, 1.40)
	Europe Union	59/2350	61/2280	0.94 (0.66, 1.35)
TECOS study, 2017 [19] Multicenter, randomized, double-blind, placebo-controlled trial in 38 countries	Sitagliptin vs. placebo			
	Overall	189/7332	186/7339	1.03 (0.84, 1.27)
	Major osteoporotic fracture	75/7332	71/7339	1.07 (0.77, 1.49)
	Hip fracture	18/7332	16/7339	1.11 (0.57, 2.18)

Table 1 (continued)

Reference; study type	Variables	Proportion of patients with fracture		Risk estimate (95% CI)
		Exposed group (no. fractures/no. overall)	Non-exposed group (no. fractures/no. overall)	
GLP-1ra				
Zhang et al., 2018 [20] Meta-analysis of RCTs $n = 54$	Semaglutide vs. exenatide	NR	NR	2.76 (0.2, 33.31)
	Semaglutide vs. liraglutide	NR	NR	1.95 (0.08, 18.97)
	Semaglutide vs. lixisenatide	NR	NR	1.18 (0.08, 20.52)
	Semaglutide vs. albiglutide	NR	NR	1.49 (0.08, 24.05)
	Semaglutide vs. dulaglutide	NR	NR	1.5 (0.11, 17.7)
	Semaglutide vs. placebo	NR	NR	0.47 (0.04, 3.63)
	Exenatide vs. semaglutide	NR	NR	0.36 (0.03, 4.99)
	Exenatide vs. liraglutide	NR	NR	0.35 (0.07, 1.41)
	Exenatide vs. lixisenatide	NR	NR	0.44 (0.05, 4.24)
	Exenatide vs. albiglutide	NR	NR	0.54 (0.07, 4.51)
	Exenatide vs. dulaglutide	NR	NR	0.54 (0.11, 2.74)
	Exenatide vs. placebo	NR	NR	*0.17 (0.03, 0.67)*
	Liraglutide vs. semaglutide	NR	NR	1.06 (0.11, 12.26)
	Liraglutide vs. exenatide	NR	NR	2.87 (0.71, 13.52)
	Liraglutide vs. lixisenatide	NR	NR	1.24 (0.22, 9.76)
	Liraglutide vs. albiglutide	NR	NR	1.55 (0.26, 10.89)
	Liraglutide vs. dulaglutide	NR	NR	1.56 (0.42, 6.6)
	Liraglutide vs. placebo	NR	NR	0.49 (0.18, 1.13)
	Lixisenatide vs. semaglutide	NR	NR	0.84 (0.05, 12.86)
	Lixisenatide vs. exenatide	NR	NR	2.3 (0.24, 18.9)
	Lixisenatide vs. liraglutide	NR	NR	1.81 (0.1, 14.56)
	Liraglutide vs. albiglutide	NR	NR	1.24 (0.1, 14.41)
	Liraglutide vs. dulaglutide	NR	NR	1.25 (0.13, 9.57)
	Liraglutide vs. placebo	NR	NR	0.39 (0.05, 1.79)
	Albiglutide vs. semaglutide	NR	NR	0.67 (0.04, 11.9)
	Albiglutide vs. exenatide	NR	NR	1.86 (0.22, 14.51)
	Albiglutide vs. liraglutide	NR	NR	0.64 (0.09, 3.79)
	Albiglutide vs. lixisenatide	NR	NR	0.81 (0.07, 10.47)
	Albiglutide vs. dulaglutide	NR	NR	1.01 (0.13, 7.48)
	Albiglutide vs. placebo	NR	NR	0.31 (0.04, 1.77)
	Dulaglutide vs. semaglutide	NR	NR	0.67 (0.06, 8.86)

Table 1 (continued)

Reference; study type	Variables	Proportion of patients with fracture		Risk estimate (95% CI)
		Exposed group (no. fractures/no. overall)	Non-exposed group (no. fractures/no. overall)	
	Dulaglutide vs. exenatide	NR	NR	1.84 (0.36, 9.48)
	Dulaglutide vs. liraglutide	NR	NR	0.64 (0.15, 2.4)
	Dulaglutide vs. lixisenatide	NR	NR	0.8 (0.18, 7.46)
	Dulaglutide vs. albiglutide	NR	NR	0.99 (0.13, 7.8)
	Dulaglutide vs. placebo	NR	NR	0.31 (0.06, 1.33)
Su et al., 2015 [21] Meta-analysis of RCTs $n = 16$	GLP-1ra vs. comparators	23/5040	15/3410	1.05 (0.59, 1.87)
	Liraglutide vs. comparators	8/3737	13/2175	*0.38 (0.17, 0.87)*
	Exenatide vs. comparators	20/2681	7/2613	*2.09 (1.03, 4.21)*
Mabilleau et al., 2014 [22] Meta-analysis of RCTs $n = 7$	GLP-1ra vs. active comparators	13/2918	6/1337	0.75 (0.28, 2.02)
SGLT2i				
Azharuddin et al., 2018 [23] Meta-analysis of RCTs $n = 40$	SGLT2i vs. comparators			
	Overall	302/20,460	104/11,883	1.01 (0.83, 1.23)
	Mean age ≥ 60 years	230/8611	120/4848	0.99 (0.79, 1.25)
	Mean age < 60 years	72/11,849	44/7035	1.07 (0.73, 1.56)
	Pre-existing CKD	19/940	11/580	1.03 (0.48, 2.19)
	No pre-existing CKD	283/19,520	153/11,303	1.01 (0.83, 1.24)
	Pre-existing CVD	193/6110	97/3274	1.00 (0.78, 1.28)
	No pre-existing CVD	109/14,350	67/8609	1.04 (0.76, 1.42)
	Follow-up ≥ 52 weeks	286/15,507	149/8646	1.03 (0.84, 1.26)
	Follow-up < 52 weeks	16/4953	15/3237	0.78 (0.38, 1.61)
	Canagliflozin vs. placebo	324/3029	14/1564	0.87 (0.44, 1.71)
	Canagliflozin vs. active treatment	22/2377	6/1592	1.98 (0.91, 4.31)
	Dapagliflozin vs. placebo	22/3214	15/2062	1.05 (0.54, 2.06)
	Dapagliflozin vs. active treatment	2/836	4/616	0.45 (0.09, 2.28)
	Empagliflozin vs. placebo	194/7229	107/3717	0.91 (0.72, 1.17)
	Empagliflozin vs. active treatment	38/3775	18/2332	1.46 (0.83, 2.57)
Ruanpeng et al., 2017 [24] Meta-analysis of RCTs $n = 20$	SGLT2i vs. placebo	54/8286	33/4178	0.67 (0.42, 1.07)
	Canagliflozin vs. placebo	30/3884	19/1599	0.66 (0.37, 1.19)
	Dapagliflozin vs. placebo	17/2073	6/1302	0.84 (0.22, 3.18)
	Empagliflozin vs. placebo	7/2329	8/1277	0.57 (0.20, 1.59)

Table 1 (continued)

Reference; study type	Variables	Proportion of patients with fracture		Risk estimate (95% CI)
		Exposed group (no. fractures/no. overall)	Non-exposed group (no. fractures/no. overall)	
Tang et al., 2016 [25] Meta-analysis of RCTs $n = 38$	Overall	323/20,264	176/11,303	1.02 (0.84, 1.23)
	Type of control			
	Placebo	281/14,796	149/7840	0.98 (0.80, 1.20)
	Active treatment	42/5468	27/3463	1.24 (0.76, 2.02)
	Type of SGLT2i			
	Canagliflozin	59/5864	25/2982	1.24 (0.79, 1.95)
	Dapagliflozin	32/4355	23/3041	0.91 (0.52, 1.60)
	Empagliflozin	232/10,045	128/5280	0.99 (0.79, 1.23)
	Mode of therapy			
	Combination therapy	317/18,037	175/10,241	1.00 (0.83, 1.21)
	Monotherapy	6/2227	1/1062	2.56 (0.54, 12.17)
	Length of follow-up			
	≥ 52 weeks	317/16,985	171/9589	0.98 (0.81, 1.19)
	< 52 weeks	20/1933	4/886	2.05 (0.86, 4.87)
	Ethnicity			
	White patients	303/18,331	172/10,417	0.98 (0.81, 1.19)
	Asian patients	20/1933	4/886	2.05 (0.86, 4.87)
	Pre-existing CKD			
	Yes	21/940	14/580	0.92 (0.46, 1.85)
	No	302/19,324	162/10,723	1.02 (0.84, 1.24)
	Pre-existing CVD			
	Yes	188/6115	95/3277	0.99 (0.77, 1.27)
	No	135/14,149	81/8026	1.05 (0.79, 1.39)
	Mean age			
	≥ 60	250/8786	134/5120	0.99 (0.80, 1.22)
	< 60	73/11,478	42/6183	1.12 (0.76, 1.64)
	Source of data			
	Publications	284/9631	157/5745	1.01 (0.83, 1.23)
	Clinical trial registration	39/10,633	19/5558	1.08 (0.62, 1.88)

Table 1 (continued)

Reference; study type	Variables	Proportion of patients with fracture		Risk estimate (95% CI)
		Exposed group (no. fractures/no. overall)	Non-exposed group (no. fractures/no. overall)	
CANVAS Program (CANVAS and CANVAS-R), 2017 [26] Multicenter randomized, single-blind, placebo-controlled trials in 30 countries	Canagliflozin vs. placebo			
	Low-trauma fracture (primary outcome)			
	CANVAS	NR	NR	*1.56 (1.18, 2.06)*
	CANVAS-R	NR	NR	0.76 (0.52, 1.12)
	CANVAS Program	NR/5795	NR/4347	1.23 (0.99, 1.52)
	All fracture (secondary outcome)			
	CANVAS	NR	NR	*1.55 (1.21, 1.97)*
	CANVAS-R	NR	NR	0.86 (0.62, 1.19)
	CANVAS Program	NS/5795	NS/4347	*1.26 (1.04, 1.52)*
CANVAS and 8 non-CANVAS studies, 2016 [27] Pooled analysis of 9 placebo- and active-controlled trials	Canagliflozin vs. placebo/treatment			
	Overall	177/6554	69/3640	*1.32 (1.00, 1.74)*
	Pooled non-CANVAS studies	63/3668	32/2199	1.09 (0.71, 1.66)
	Pooled 2-year non-CANVAS studies	38/1445	17/719	1.06 (0.60, 1.88)
	CANVAS	114/2886	37/1441	*1.51 (1.04, 2.19)*
	Anatomical region (CANVAS)			
	Upper limb	46/2886	16/1441	1.42 (0.80, 2.50)
	Lower limb	48/2886	17/1441	1.44 (0.82, 2.54)
	Pelvis	1/2886	2/1441	0.24 (0.02, 2.68)
	Skull or facial bone	3/2886	0/1441	—
	Spine	6/2886	1/1441	2.95 (0.36, 24.53)
	Thoracic cage	14/2886	3/1441	2.30 (0.66, 7.99)

CI confidence interval, *CANVAS* the CANagliflozin cardioVascular Assessment Study, *CANVAS-R* the CANagliflozin cardioVascular Assessment Study-Renal, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *DPP-4i* dipeptidyl peptidase-4 inhibitors, *GLP-1ra* glucagon-like peptide-1 receptor agonists, *MRF* multiple risk factors, *NR* not reported, *RF* renal function, *SAVOR-TIMI 53* the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53, *SGLT2i* sodium-glucose cotransporter-2 inhibitors, *TECOS* the Trial Evaluating Cardiovascular Outcomes with Sitagliptin

Italic numbers indicate a statistically significant association ($P < 0.05$)

study in each run was performed to ensure the robustness of the overall findings. The statistical heterogeneity across studies was assessed using Q and I^2 statistics. For the Q statistic, $P < 0.1$ was considered statistically significant; for the I^2 statistic, the following cut-off points were used to define the degree of heterogeneity: < 25% (low heterogeneity), 25–50% (moderate heterogeneity), > 50–75% (high heterogeneity), and > 75% (severe heterogeneity) [31]. Publication bias was evaluated using Begg's rank correlation test and Egger's linear regression test [32]. If publication bias was evident, the trim and fill method was performed to correct the bias [33]. All statistical analyses were performed using STATA software version 11.0 (STATA Corp., College Station, TX, USA). All P values were two-sided, and the level of significance was set at < 0.05.

Results

Literature review and study characteristics

A flow chart of the study selection process is shown in Fig. S1. Initial database searches yielded a total of 358 entries (157 from PubMed and 201 from Web of Science). Ninety-nine articles were available for full-text review following the removal of duplicates and an abstract/title review. After full-text review, 81 articles were further excluded for the following reasons: RCTs investigating the effects of DPP-4i, GLP-1ra, or SGLT2i on the risk of fracture ($n = 70$); RCTs investigating the effects of DPP-4i, GLP-1ra, or SGLT2i on bone mineral density (BMD) or bone markers ($n = 10$) [34–43]; observational study investigating the association between other diabetes medications and the risk of fracture ($n = 1$) [44]. Finally, 18 articles [45–62] were included in the present meta-analysis. Of these, 14 were cohort studies [45, 47–55, 57, 60–62], and four were case-control studies [46, 56, 58, 59]. The characteristics of the included studies are presented in Table 2. The included studies were mostly conducted in high-income Western countries. All data regarding participant characteristics, medications, and medical diagnoses were identified through databases or registries. The 10th revision of the International Classification of Diseases was used to classify fracture in nearly all studies. All of the included studies were considered good in quality (NOS ≥ 7). Age and sex were the most frequently adjusted variables among the included studies.

Meta-analyses

Twelve studies were included in the meta-analysis of DPP-4i [45–56]. For GLP-1ra [51, 57–59] and SGLT2i [59–62], four studies were included in each meta-analysis. The rates of fracture in users were generally comparable to those in comparators, with the exception of two studies [49, 51] that reported higher rates of fractures in users than in comparators (Table 2). Notably, both studies showed that DPP-4i [49, 51] or GLP-1ra [51] use was associated with a lower risk of fracture. Primary analyses revealed that the use of DPP-4i (RR 0.83, 95% CI 0.60, 1.14; Fig. 1), GLP-1ra (RR 0.65, 95% CI 0.24, 1.74; Fig. 1), or SGLT2i (RR 1.02, 95% CI 0.91, 1.16; Fig. 1) was not associated with the risk of fracture. Severe heterogeneity was observed in the analyses of DPP-4i ($I^2 = 98\%$, $P < 0.01$) and GLP-1ra ($I^2 = 99\%$, $P < 0.01$), whereas no heterogeneity was observed in the analysis of SGLT2i ($I^2 = 0\%$, $P = 0.62$). The test for publication bias indicated no evidence of publication bias (P Begg's > 0.50, P Egger's > 0.13).

In general, the lack of association between the use of DPP-4i or GLP-1ra and the risk of fracture persisted across nearly all subgroups (Table 3), except for a significantly reduced risk of hip fracture with GLP-1ra use (RR 0.21, 95% CI 0.04, 0.98). However, the association between the use of GLP-1ra and a significantly lower risk of hip fracture appeared to be driven by a strong inverse association in a study by Starup-Linde et al. [51], as the association became statistically non-significant after the exclusion of this study (RR 0.43, 95% CI 0.15, 1.19). A sensitivity analysis that excluded one study in each run revealed that the observed overall findings were not dominated by a single study (data not shown).

Discussion

It has been postulated that DPP-4i and GLP-1ra may have beneficial effects on bone health, whereas SGLT2i may have adverse effects on bone health [11–13]. In the present meta-analysis based on real-world data, the use of DPP-4i or GLP-1ra was not associated with a reduced risk of fracture. Likewise, there was no elevated risk of fracture associated with SGLT2i use. The lack of association between fracture risk with DPP-4i or GLP-1ra use remained consistent when stratified by the sex, fracture site, and age of the participants. In brief, the principal findings from the present meta-analysis do not support an association between the use of DPP-4i, GLP-1ra, or SGLT2i and the risk of fracture, which is in agreement with the results from several meta-analyses of RCTs (Table 1). The cumulative evidence from RCTs and observational studies confirm that the use of DPP-4i, GLP-1ra, and SGLT2i may have overall neutral effects on the risk of fracture among homogenous groups of patients in the strictly controlled environment of RCTs and among heterogeneous groups of patients in the real-world settings of observational studies. The continuous long-term use of DPP-4i was not associated with the risk of any fracture (> 4.0–8.5 years of use), osteoporotic fracture (> 3.0–8.5 years of use), or hip fracture (> 2.0–8.5 years of use) [50]. Furthermore, no cumulative dose-dependent risk was observed with the use of DPP-4i or

Table 2 Characteristics of the included studies

References	Age	Design	Data source (inclusion years); follow-up	Exposure
DPP-4i				
Driessen et al., 2014 [45][a]; UK	61 years	Cohort	The Clinical Practice Research Datalink (June 2007 to August 2012); median 3.7 years	Current users of DPP-4i vs. current users of NIDM
Driessen et al., 2015 [46]; Denmark	55 years	Case-control	The Danish National Health Service (2007–2011); median 2.1 years	Current users of DPP-4i vs. current users of NIDM (excluding incretin users)
Choi et al., 2016 [47]; South Korea	≥ 50 years	Cohort	The Health Insurance Review and Assessment Service of South Korea (January 2008 to June 2011); mean 1.9 years	Metformin + DPP-4i initiators vs. non-users of glucose lowering medications
Majumdar et al., 2016 [48]; USA	52 years	Cohort	The Clinformatics Data Mart Database (OptumInsight) (January 2004 to December 2009); median 2 years	New users of sitagliptin vs. non-users of sitagliptin
Dombrowski et al., 2017 [49]; Germany	61.6 years	Cohort	The Disease Analyzer database (IMS HEALTH) (January 2008 to December 2014); mean 1.5 years	Ever users of DPP-4i vs. never users of DPP-4i
Driessen et al., 2017 [50]; UK	61 years	Cohort	The Clinical Practice Research Datalink (June 2007 to August 2015); mean 6.3 (DPP-4i) and 5.6 (NIDM) years	Current users of DPP-4i vs. current users of NIDM (excluding GLP-1ra users)
Starup-Linde et al., 2017 [51]; Denmark	66 years	Cohort	The Danish National Patient Register and the Register of Medicinal Product Statistics (January 1996 to December 2011); mean 5.5 years	Current users of DPP-4i vs. non-users of glucose-lowering medications
Wallander et al., 2017 [52]; Sweden	80.8 years	Cohort	The Swedish registry "Senior Alert" (2008–2014); mean 1.3 years	Sitagliptin vs. non-users of sitagliptin
Gamble et al., 2018 [53]; UK	58.8 years	Cohort	The Clinical Practice Research Datalink GOLD (January 2001 to January 2016); mean 1.2 years	New users of DPP-4i vs. new users of sulfonylureas
Hou et al., 2018 [54]; Taiwan	54 years	Cohort	Medical claims data of the Longitudinal Cohort of Diabetes Patients (1999–2013); maximum 5 years	Metformin + DPP-4i vs. metformin + other second line diabetes medications
Lin et al., 2018 [55]; Taiwan	63 years	Cohort	The Longitudinal Health Insurance Database 2000 (2009–2012); mean 3.3 years	Sitagliptin vs. non-users of sitagliptin
Losada et al., 2018 [56]; Spain	73 years	Case-control	The Information System for Research Development in Primary Care (SIDIAP) (2006–2012); not specified	DPP-4i vs. metformin
GLP-1ra				
Driessen et al., 2015 [57]; UK	57 years	Cohort	The Clinical Practice Research Datalink (June 2007 to August 2012); median 5.1 (GLP-1ra) and 3.6 (NIDM) years	Current users of GLP-1ra vs. current users of NIDM (excluding DPP-4i users)
Driessen et al., 2015 [58]; Denmark	55 years	Case-control	The Danish National Health Service Register (2007–2011); not specified	Current users of GLP-1ra vs. current users of NIDM (excluding incretin users)
Starup-Linde et al., 2017 [51]; Denmark	66 years	Cohort	The Danish National Patient Register and the Register of Medicinal Product (January 1996 to December 2011); 5.5 years	Current users of GLP-1ra vs. non-users of glucose-lowering medications
Schmedt et al., 2019 [59]; Germany	63.9 years	Case-control	The InGef database (November 2011 to December 2016); not specified	Current users of metformin + GLP-1ra vs. current users of metformin + DPP4-i
SGLT2i				
Toulis et al., 2018 [60] UK	59.4 years	Cohort	The Health Improvement Network (THIN) (January 2013 to January 2016); mean 1 year	Dapagliflozin initiators vs. non-users of SGLT2i
Ueda et al., 2018 [61] Sweden and Denmark	61 years	Cohort	Nationwide health and administrative registers in Sweden and Denmark (July 2013 to December 2016); median 270 to 274 days	New users of SGLT2i users vs. new users of GLP-1ra
Fralick et al., 2019 [62] US	55 years	Cohort	Two US commercial health care databases (Optum Clinformatics Data Mart and IBM MarketScan) (March 2013 to October 2015); mean 34 weeks	New users of canagliflozin vs. new users of GLP-1ra
Schmedt et al., 2019 [59]; Germany	63.9 years	Case-control	The InGef database (November 2011 to December 2016); not specified	Current users of metformin + SGLT2i vs. current users of metformin + DPP4-i

Table 2 (continued)

References	Outcomes investigated	Fracture classification	No. events/No. overall in the exposed group (%)	No. events/No. overall in the non-exposed group (%)	Adjustment					
					Age	Sex	OP/OT	Falls	PF	G
DPP-4i										
Driessen et al., 2014 [45][a]; UK	All fracture, hip fracture, radius/ulna fracture, vertebral fracture, and major osteoporotic fracture	Read codes and World Health Organization classification	454/22,510 (2)	8886/216,816 (4)	–	–	√	–	–	–
Driessen et al., 2015 [46]; Denmark	All fracture, hip fracture, radius/ulna fracture, vertebral fracture, and major osteoporotic fracture	ICD-10 codes	219/451 (5)	6993/14,202 (5)	–	–	√	–	√	√
Choi et al., 2016 [47]; South Korea	Composite fracture, vertebral fracture, and non-vertebral fracture	ICD-10 codes	146/8717 (1.7)	1269/83,404 (1.5)	√	√	√	–	–	–
Majumdar et al., 2016 [48]; USA	Major osteoporotic fracture	ICD-9 codes	53/8894 (0.6)	688/63,834 (1.1)	√	√	√	–	–	√
Dombrowski et al., 2017 [49]; Germany	All fracture and hip fracture	ICD-10 codes	266/4160 (6.3)	345/4160 (8.3)	–	–	–	–	–	–
Driessen et al., 2017 [50]; UK	Major osteoporotic fracture and hip fracture	Read codes and World Health Organization classification	1700/46,355 (3.7)	12,575/281,899 (4.4)	√	√	√	√	√	√
Starup-Linde et al., 2017 [51]; Denmark	All fracture, vertebral fracture, forearm fracture, and major osteoporotic fracture	ICD-10 codes	68/15,559 (0.4)	5171/155,074 (3.3)	√	√	–	√	√	–
Wallander et al., 2017 [52]; Sweden	Hip fracture	ICD-10 codes	Not reported	Not reported	√	√	–	–	√	√
Gamble et al., 2018 [53]; UK	Fragility fractures (upper extremity, hip, and spine)	Read codes and ICD-10 codes	27/7993 (0.3)	162/26,636 (0.6)	√	√	–	–	–	√
Hou et al., 2018 [54]; Taiwan	All fracture, hip fracture, upper extremity fracture, and lower extremity fracture	ICD-9 codes	340/3996 (8.5)	419/3996 (10)	√	√	√	√	√	√
Lin et al., 2018 [55]; Taiwan	All fracture	ICD-9-CM codes	221/1463 (15)	215/1463 (14)	√	√	√	–	–	√
Losada et al., 2018 [56]; Spain	All fracture	ICD-10 codes	14/77 (18)	625/4079 (15)	√	√	√	√	–	–
GLP-1ra										
Driessen et al., 2015 [57]; UK	All fracture, hip fracture, radius/ulna fracture, vertebral fracture, and major osteoporotic fracture	Read codes and World Health Organization classification	180/8354 (2)	8449/208,462 (4)	√	√	√	–	–	√
Driessen et al., 2015 [58]; Denmark	All fracture, hip fracture, radius/ulna fracture, vertebral fracture, and major osteoporotic fracture	ICD-10 codes	80/151 (5.3)	6993/14,202 (5)	–	–	√	–	√	√
Starup-Linde et al., 2017 [51]; Denmark	All fracture, vertebral fracture, forearm fracture, and major osteoporotic fracture	ICD-10 codes	5/9440 (0.05)	5171/155,074 (3.3)	√	√	–	√	√	–
Schmedt et al., 2019 [59]; Germany	Fracture of upper or lower limbs	ICD-10 GM codes	47/2286 (2)	865/39,169 (2)	–	–	√	–	–	√
SGLT2i										
Toulis et al., 2018 [60] UK	All fracture and fragility fracture	ICD-10 codes	58/4548 (1.2)	231/18,070 (1.2)	√	√	–	–	–	–
Ueda et al., 2018 [61] Sweden and Denmark	All fracture	ICD-10 codes	228/17,213 (1.3)	263/17,213 (1.5)	√	√	–	–	–	–
Fralick et al., 2019 [62] US	All fracture	ICD-9 codes	247/79,964 (3)	224/79,964 (3)	√	√	√	√	–	√
Schmedt et al., 2019 [59]; Germany	Fracture of upper or lower limbs	ICD-10 GM codes	38/1711 (2.2)	865/39,169 (2.2)	–	–	√	–	–	√

DPP-4i dipeptidyl peptidase-4 inhibitors, *G* glucocorticoids, *GLP-1ra* glucagon-like peptide-1 receptor agonists, *NIDM* non-insulin diabetes medications, *OP/OT* osteoporosis/osteoporosis treatments, *PF* previous fracture, *SGLT2i* sodium-glucose cotransporter-2 inhibitors, *ICD-9* the 9th revision of the International Classification of Diseases, *ICD-10* the 10th revision of the International Classification of Diseases, *CM* clinical modification, *GM* German modification

[a] We used the updated findings from this study (see Driessen et al. 2017) in the main analysis. However, the risk estimates for sex and several fracture sites from this study were included in subgroup analyses because sex-specific and site-specific risk estimates were not reported in the updated study

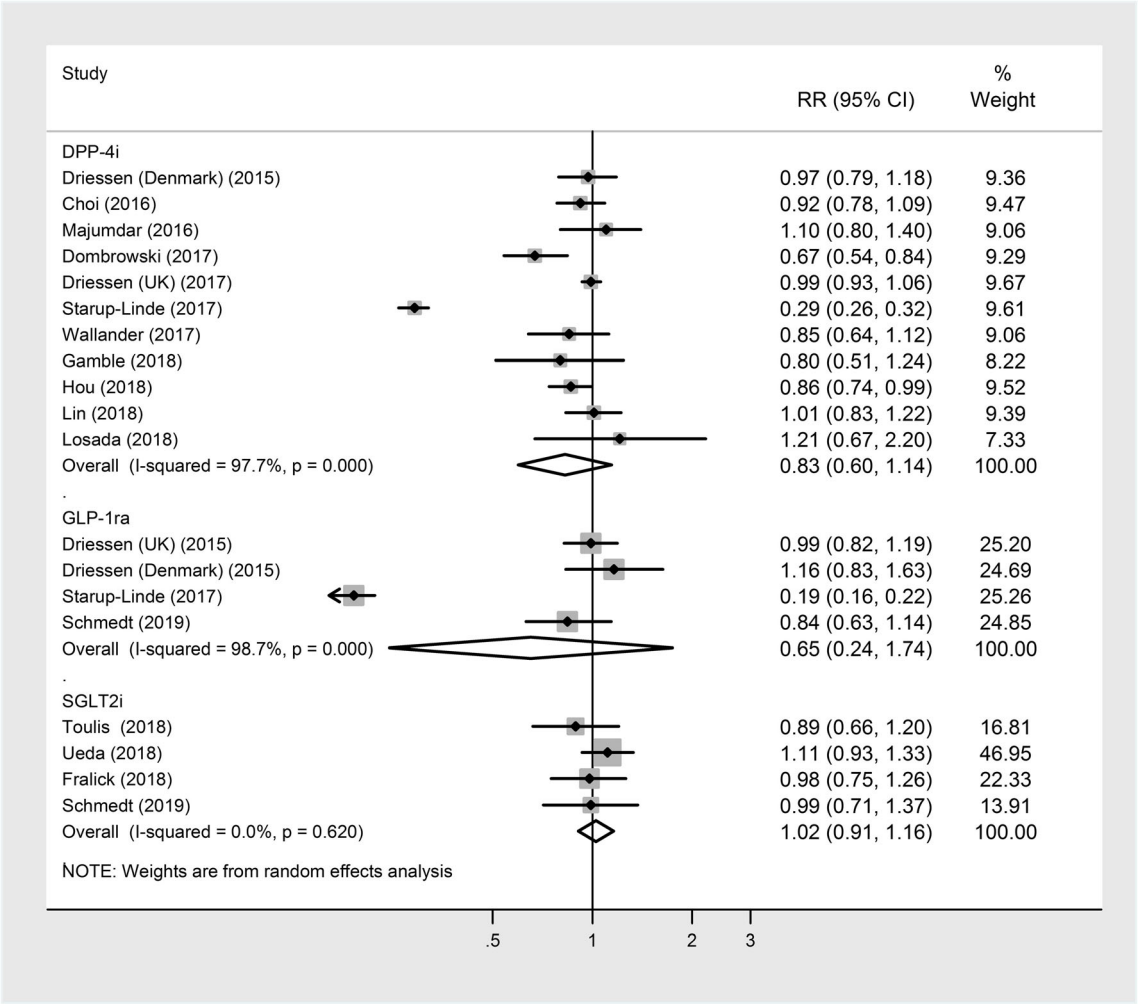

Fig. 1 Forest plot for the association between the use of dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors and the risk of fracture in real-world settings

GLP-1ra [45, 46, 57, 58]. The lack of association between the use of DPP-4i, GLP-1ra, or SGLT2i and the risk of fracture in RCTs and observational studies was further strengthened by the evidence that these glucose-lowering medications have a minimal impact on BMD or bone metabolism markers in humans (Table 4) [34–43]. Since the use of DPP-4i, GLP-1ra, or SGLT2i did not significantly affect the risk of fracture, these findings may have significant clinical implications because some commonly prescribed second- and third-line glucose-lowering medications (i.e., sulfonylureas, thiazolidinediones, and insulin) have been directly or indirectly linked with a higher risk of fracture [8, 9, 18, 19, 44, 48]. Therefore, DPP-4i, GLP-1ra, or SGLT2i could be considered as an alternative to those medications.

Although the association between the use of DPP-4i or GLP-1ra and the risk of fracture in real-world settings has been previously reported in a meta-analysis of observational studies [63], which also showed no association between both medications and the risk of fracture (DPP-4i: RR 1.02, 95% CI 0.91, 1.13; GLP-1ra: RR 1.03, 95% CI 0.87, 1.22), the present meta-analysis is superior to the prior meta-analysis in several aspects. First, more studies were included in the present meta-analysis, particularly in the analysis of DPP-4i, granting more power to perform meaningful subgroup analyses by potential effect modifiers, such as the fracture site and the sex of the participants. Moreover, we also reported an association between SGLT2i use and fracture risk. Altogether, the present meta-analysis is the first to report the association between the risk of fracture and the use of DPP-4i, GLP-1ra, or SGLT2i in the real world.

A clear tendency towards a lower risk of fracture with the use of DPP-4i or GLP-1ra was observed, although the association did not reach statistical significance. A nonsignificant association between the use of DPP-4i or GLP-1ra and the risk of fracture was observed in all but two studies [49, 51]. In T2DM patients treated in German primary care practices, the use of DPP-4i was associated with a 33% and 57% reduced risk of developing any fractures and hip fractures,

Table 3 Subgroup analyses of the association between dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 receptor agonists use and the risk of fracture

	DPP-4i				GLP-1ra			
	Studies (*n*)	RR (95% CI)	I^2 (%)	*P heterogeneity*	Studies (*n*)	RR (95% CI)	I^2 (%)	*P heterogeneity*
Overall	11	0.83 (0.60, 1.14)	98	< 0.01	4	0.65 (0.24, 1.74)	99	< 0.01
Design								
Cohort	9	0.78 (0.54, 1.14)	98	< 0.01	2	0.43 (0.09, 2.18)	99	< 0.01
Case-control	2	0.99 (0.82, 1.20)	0	0.49	2	0.98 (0.71, 1.34)	50	0.16
Mean age								
≥ 60	6[a]	0.75 (0.43, 1.32)	99	< 0.01	3	0.54 (0.17, 1.74)	99	< 0.01
< 60	4[a]	0.92 (0.82, 1.02)	1	0.55	1	1.16 (0.83, 1.63)	NA	NA
Sex								
Men	6	0.77 (0.49, 1.21)	96	< 0.01	3	0.58 (0.17, 1.91)	98	< 0.01
Women	7	0.76 (0.47, 1.25)	97	< 0.01	3	0.61 (0.17, 2.24)	98	< 0.01
Fracture site								
Vertebral	5	0.79 (0.41, 1.53)	85	< 0.01	3	0.82 (0.17, 3.92)	84	< 0.01
Hip	7	0.65 (0.38, 1.09)	93	< 0.01	3	**0.21 (0.04, 0.98)**	79	< 0.01
Upper extremity	5	0.78 (0.40, 1.55)	94	< 0.01	4	0.55 (0.24, 1.29)	92	< 0.01
Lower extremity (including hip)	6	0.69 (0.41, 1.16)	94	< 0.01	4	0.31 (0.07, 1.44)	92	< 0.01
Major osteoporotic site	4	0.71 (0.33, 1.51)	99	< 0.01	3	0.46 (0,11, 1.93)	98	< 0.01

CI confidence interval, *DPP-4i* dipeptidyl peptidase-4 inhibitors, *GLP-1ra* glucagon-like peptide-1 receptor agonists, *RR* relative risk, *NA* not available

[a] The study by Choi et al. was not included because mean age of the participant was not reported. Bold numbers indicate a statistically significant association ($P < 0.05$)

respectively [49]. A Danish registry-based study by Starup-Linde et al. [51] found that the current use of DPP-4i or GLP-1ra was associated with a significantly lower risk of all fractures, hip fractures, vertebral fractures, and forearm fractures. Despite encouraging findings from both studies, there was concern that the observed association between the use of DPP-4i or GLP-1ra and a significantly lower fracture risk in both studies could have been affected by immortal time bias [64, 65]. Immortal time bias typically results in an artificial overestimation of the outcome rate in the nonexposed group and, at the same time, an underestimation of the outcome rate in the group exposed to the medication, creating the misconception that the medication is highly safe and effective in preventing the outcome of interest [66]. Notably, we did observe a significant inverse association between GLP-1ra use and hip fracture risk that was largely driven by the strong inverse association observed in the study by Starup-Linde et al. [51], as the association became statistically nonsignificant after exclusion of this study.

The effects of GLP-1ra, but not DPP-4i, appeared to be influenced by the specific type of medication used (Table 1). The first meta-analysis of RCTs to report the association between the use of GLP-1ra and fracture risk according to the type of GLP-1ra used showed that exenatide was associated with a higher fracture risk, whereas liraglutide was associated with a lower fracture risk [21]. Conversely, the latest meta-analysis of the same topic found that exenatide was associated with a reduced risk of fracture, whereas semaglutide, liraglutide, lixisenatide, albiglutide, and dulaglutide were not associated with a risk of fracture [20]. In a population-based cohort study using the data from the Clinical Practice Research Datalink database, exenatide and liraglutide did not significantly affect the fracture risk [57]. Concordantly, evidence from RCTs indicated that exenatide and liraglutide did not significantly affect BMD (Table 4) [36–38].

Among the three currently available SGLT2i (canagliflozin, dapagliflozin, and empagliflozin) in the market, canagliflozin is the only SGLT2i that has been linked with an increased risk of fracture (Table 1). Combined data from the CANagliflozin cardioVascular Assessment Study (CANVAS) and the CANVAS-Renal (CANVAS-R) involving a total of 10,142 patients with T2DM and a high cardiovascular risk showed that canagliflozin was associated with an increased risk of all fractures. When the results from the two trials were assessed separately, the positive association between canagliflozin and fracture risk was only evident in CANVAS but not in CANVAS-R [26]. These contradictory findings are perplexing because CANVAS and CANVAS-R have identical inclusion and exclusion criteria. A similar phenomenon was also observed in the pooled analysis of nine studies (CANVAS and eight non-CANVAS studies) showing that canagliflozin was associated with a significantly

Table 4 Summary of the selected studies investigating the effects of dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors on bone mineral density and bone metabolism markers in humans

Reference	Design	Duration	Participants' descriptions	Treatment	Comparator	Endpoints	Findings
DPP-4i							
Bunck et al., 2012 [34]	Double-blind, RCT	1 year	Well-controlled T2DM patients Age: 57 years BMI: 29.2 kg/m^2 HbA1c: 6%	Vildagliptin 100 mg/day ($n = 29$)	Placebo ($n = 30$)	CTX	=
						Serum calcium	=
						Serum alkaline phosphatase	=
						Serum phosphate	=
Vianna et al., 2017 [35]	Double-blind, RCT	1 year	Postmenopausal women with uncontrolled T2DM Age: 62 years BMI: 33 kg/m^2 HbA1c: 7.3%	Vildagliptin 100 mg/day ($n = 21$)	Gliclazide 60-120 mg/day ($n = 21$)	Femoral neck BMD	=
						Lumbar spine BMD	=
						Total hip BMD	=
						CTX	=
						Osteocalcin	=
						P1NP	=
						U-NTX	=
GLP-1ra							
Bunck et al., 2011 [36]	Double-blind, RCT	44 weeks	Metformin-treated T2DM patients Age: 59 years BMI: 31 kg/m^2 HbA1c: 7.5%	Exenatide 10 μg/day (initial dose) to 60 μg/day (maximum dose) ($n = 36$)	Titrated insulin glargine 10 IU/day (initial dose) ($n = 33$)	Total body BMD	=
						Serum calcium	=
						Serum alkaline phosphatase	=
						Serum phosphate	=
Li et al., 2015 [37]	RCT	24 weeks	Newly diagnosed T2DM patients Age: 50 years BMI: 26 kg/m^2 HbA1c: 8.7%	Exenatide 10 μg/day (initial dose) to 20 μg/day (after 4 weeks) ($n = 20$)	Insulin lispro (0.4 IU/kg/day; initial dose) ($n = 21$) or pioglitazone 30 mg/day (initial dose) to 45 mg/day (after 4 weeks) ($n = 21$)	Hip BMD	=
						Lumbar BMD	=
						CTX	=
						Osteocalcin	=
						TRAcP5b	=
Gilbert et al., 2016 [38]	Double-blind, RCT	104 weeks	T2DM patients Age: 54.2 years BMI: 33 kg/m^2 HbA1c: 8%	Liraglutide 1.2 mg/day ($n = 23$) or 1.8 mg/day ($n = 20$)	Glimepiride 8 mg/day ($n = 18$)	Total body BMD	=
						Serum calcium	=
						Serum phosphate	=
SGLT2i							=
Ljunggren et al., 2012 [39] and Bolinder et al., 2014 (update) [40]	Double-blind, RCT	102 weeks	Postmenopausal women whose T2DM was inadequately controlled on metformin Age: 60.7 years BMI: 31.9 kg/m^2 HbA1c: 7.2%	Dapagliflozin 10 mg/day + metformin ($n = 182$)	Placebo + metformin ($n = 182$)	Femoral neck BMD	=
						Lumbar spine BMD	=
						Total hip BMD	=
						CTX	=
						P1NP	=
Bode et al., 2015 [41] and Bilezikian et al.,	Double-blind, RCT	104 weeks			Placebo ($n = 237$)	Distal forearm BMD	=
						Femoral neck BMD	=

Table 4 (continued)

Reference	Design	Duration	Participants' descriptions	Treatment	Comparator	Endpoints	Findings
2016 (update) [42]			Inadequately controlled T2DM patients with a stable antihyperglycemic regimen Age: 60.7 years BMI: 31.9 kg/m^2 HbA1c: 7.2%	Canagliflozin 100 mg/day ($n = 241$) or 300 mg/day ($n = 246$)		Hip BMD Lumbar spine BMD Bone strength CTX Osteocalcin Distal forearm BMD	↓ (at week 104) = = ↑ (at week 52) ↑ (at week 52) =
Rosenstock et al., 2018 [43]	Double-blind, RCT	26 weeks	T2DM that cannot be controlled by metformin alone Age: 60.7 years BMI: 31.9 kg/m^2 HbA1c: 7.2%	Ertugliflozin 5 mg/day ($n = 207$) or 15 mg/day ($n = 205$)	Placebo ($n = 209$)	Femoral neck BMD Hip BMD Lumbar spine BMD Bone strength CTX P1NP Parathyroid hormone	= = = = ↑ = =

=, unchanged; ↑, increased; ↓, reduced

BMD bone mineral density, *BMI* body mass index, *CTX* carboxy-terminal telopeptide of type 1 collagen, *DPP-4i* dipeptidyl peptidase-4 inhibitors, *GLP-1ra* glucagon-like peptide-1 receptor agonists, *HbA1c* Hemoglobin A1c, *P1NP* amino-terminal propeptide of procollagen type 1, *RCT* randomized controlled trial, *TRAcP5b* tartrate-resistant alkaline phosphatase, *SGLT2i* sodium-glucose cotransporter-2 inhibitors, *T2DM* type 2 diabetes mellitus, *U-NTX* urinary amino-terminal

increased risk of fracture among the participants of CANVAS but not among the participants of the non-CANVAS studies [27]. One possible explanation for the elevated fracture risk in CANVAS might be due to a higher proportion of Asian patients in CANVAS (18%) than in CANVAS-R (8%) or in the eight non-CANVAS studies (16%). It has been shown that the risk of fracture is two-fold higher in diabetes patients of Asian origin than in those of non-Asian origin, although it did not reach statistical significance (Table 1: Tang et al. [25]). A double-blind, placebo-controlled trial of patients aged 55–80 years (mean age was 63.6 years) with inadequately controlled T2DM showed that canagliflozin was indeed associated with a small reduction in the total BMD at the hip but not at other skeletal sites. However, the authors noted that the reduced BMD with canagliflozin treatment was unlikely due to its direct effect on bone via the inhibition of SGLT2 but rather due to an increased bone turnover as a consequence of weight loss among the participants (Table 4) [42]. Furthermore, several meta-analyses of RCTs showed that canagliflozin was not significantly associated with the risk of fracture [23–25]. Concordantly, a recent large population-based cohort study involving 79,964 T2DM patients who were newly prescribed canagliflozin users and 79,964 T2DM patients who were newly prescribed GLP-1ra users indicated that canagliflozin was not associated with an increased risk of fracture compared with GLP-1ra [62]. Considering that the controversial findings from CANVAS have not yet been replicated by other studies, the pooled results from the present meta-analysis add further evidence that SGLT2i use may not increase the risk of fracture. Altogether, the evidence from existing literature suggests that canagliflozin has minimal, if any, impact on the risk of fracture among T2DM patients in general. Further studies should investigate whether canagliflozin is associated with an increased risk of fracture among T2DM patients who have a high fracture risk (i.e., patients with old age, a low BMD, a history of fracture or osteoporosis, and those who are frail).

The present study was subject to several limitations that should be considered accordingly. First, considering the nature of observational studies, the findings from the present meta-analysis could have been affected by immortal time bias, lag time bias, or residual and unmeasured confounders. Notably, nearly all of the included studies lacked information on potentially important covariates, such as the severity and duration of DM, date of first use, type of DPP-4i, GLP-1ra, or SGLT2i used, dose regimen prescribed, history of falls, frailty, osteoporosis, and fracture, modifiable lifestyle factors (e.g., smoking, alcohol, body mass index), and biochemical parameters or markers (e.g., BMD, bone turnover markers, bone formation markers, bone resorption markers). Second, it was not feasible for us to perform more meaningful subgroup analyses to identify the potential effect modifiers and the potential source of heterogeneity owing to the limited number of the included studies, particularly in the analyses of GLP-1ra and SGLT2i. For example, we were unable to investigate the association between DPP-4i, GLP-1ra, or SGLT2i and the risk of fracture according to several potential effect modifiers, such as the type of medications used, mode of therapy (combination or monotherapy), or comparators. Third, the present meta-analysis was based only on a comparison between exposed and unexposed medications rather than more informative objective measures (e.g., adherence to the medications, cumulative dose exposure, average daily dose, and continuous duration of use). Given that the majority of the studies utilized prescription data as a proxy for the exposure to medications, the results could have been biased towards a null association due to primary or secondary non-adherence. Fourth, fracture events were rarely confirmed by radiographic imaging. Therefore, the potential underestimation or overestimation of the fracture incidence should also be acknowledged. Fifth, a high degree of heterogeneity was observed across the studies investigating DPP-4i and GLP-1ra, suggesting that the results of these analyses should be interpreted with great caution. Finally, most of the included studies used data from high-income Western countries, which may limit the generalization of our findings to other populations.

Conclusions

In summary, cumulative real-world evidence does not support an association between the use of DPP-4i, GLP-1ra, or SGLT2i and the risk of fracture. Our findings, together with the cumulative evidence from RCTs, should reassure policy makers and medical practitioners that the use of these medications is unlikely to increase the risk of fracture among T2DM patients in general. However, caution is still advised when prescribing SGLT2i to T2DM patients who are at risk of fracture. Further studies need to investigate the long-term impact of these drugs on the fracture risk, particularly in high-risk populations.

Authors' contribution K.H. designed the research. K.H. and X.D. performed the literature search, data extraction, and quality assessment. K.H. performed the data analyses and wrote the paper. B.-M.S. took primary responsibility for the final content. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflicts of interest Khemayanto Hidayat, Xuan Du, and Bi-Min Shi declare that they have no conflicts of interest.

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