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Review Article

Risk of fracture with sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes: an updated meta-analysis of randomized controlled trials

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Abstract: Background: Type 2 diabetes mellitus (T2DM) increases the risk of fractures. This meta-analysis compared the effects of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i) on fracture risk in patients with T2DM. Method: A systematic search of PubMed, Web of Science, Embase, and Google Scholar was conducted up to August 6, 2023. Seven cohort studies (n = 1,199,267 participants at baseline; n = 357,119 after propensity matching) comparing SGLT-2i use with DPP-4i use and reporting fracture outcomes were included. Data were extracted and analyzed using a random-effects model. Subgroup analyses were performed by age (<70 and ≥70 years) and sex. Results: In general, SGLT-2i therapy was linked to reduced fracture risk when compared to DPP-4i (OR: 0.89, 95% CI: 0.81-0.98). Heterogeneity was high (I^2 = 64.3%). Upon stratified analysis by age, no statistically significant difference was observed between the fracture risk in the <70 years and ≥70 years subgroups upon comparison of SGLT-2i with DPP-4i. No significant difference was also observed in the female subgroup. Conclusion: This meta-analysis indicates SGLT-2i therapy could be linked with reduced overall fracture risk in comparison to DPP-4i in the general population of T2DM. The benefit was not seen in subgroup analysis based on age and sex. Additional research, ideally with increased cases within subgroups, is required to determine the impact of these drugs on fracture risk in patient subgroups.

Keywords: Type 2 diabetes mellitus, fracture risk, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, cohort studies, elderly patients

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders. Its development is caused by a combination of factors: cellular insulin insensitivity (the inability to respond to insulin) and impaired insulin secretion by pancreatic beta-cells [1].

In this metabolic disorder, blood glucose levels elevate, and elevated blood glucose can damage various organs, such as the kidneys, heart, nerves, eyes, and blood vessels. T2DM accounts for 90% of all diabetes cases worldwide [2, 3].

Based on data from the Global Burden of Disease study and World Health Organization (WHO) reports, 8.5% of adults aged 18 and older had diabetes in 2014. Diabetes was the direct cause of 1.5 million deaths, and 48% of all deaths in 2019 occurred in individuals under

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70. Approximately 460,000 deaths from kidney disease were associated with diabetes. Elevated blood glucose levels contributed to about 20% of cardiovascular deaths [4].

Patients with type 2 diabetes mellitus (T2DM) face a higher risk of fractures compared to those without diabetes. Observational studies have documented an increased incidence of fractures in various locations, including the pelvis, femoral neck, spine, and hip, as well as other sites [5-7]. The likelihood of experiencing T2DM and fractures is particularly elevated in older adults. Additionally, T2DM is associated with complications such as delayed fracture healing, including delayed union or non-union, which can significantly impact recovery [8, 9]. However, maintaining proper glycemic control may help reduce fracture risk in the elderly [10]. Previous studies have shown that sodium-glucose cotransporter 2 inhibitors (SGLT2i) can reduce glycated haemoglobin by 0.5-1.5%, depending on the dosage [11].

Inhibiting SGLT2 blocks glucose reabsorption in the proximal renal tubule, decreasing the blood glucose levels. SGLT2 inhibitors also induce moderate weight loss, reduce blood pressure, and lower cardiovascular mortality risk [12, 13]. One of the main adverse effects of SGLT2i is the elevated risk of genitourinary infections. Additionally, these agents have been associated with an increased risk of bone fractures, potentially mediated by altered calcium-phosphate homeostasis, elevated parathyroid hormone (PTH) levels, and reduced bone mineral density. Volume depletion or hypotension has been also proposed as a potential cause of falling related to SGLT2 inhibitors [14-17].

Dipeptidyl peptidase-4 inhibitors (DPP-4is) are second-line agents that decrease the glucose level by enhancing levels of incretin hormones. These incretins increase glucose-dependent insulin release and reduce glucagon secretion [18]. Gastrointestinal intolerance, an increased incidence of pancreatitis and infections are known adverse effects of DPP-4is, while the effect of these antidiabetic agents on cardiac outcomes remains controversial [19, 20]. Reducing the risk of bone fracture has been reported as a beneficial effect of DPP4is. These medications can potentially enhance osteoblast differentiation and bone formation, leading to improvement of bone quality and density. Additionally, they may reduce osteoclast differentiation and bone resorption through suppression of inflammatory cytokines [21].

Several studies have reported varying results regarding the effect of SGLT2 inhibitors on the risk of bone fractures. The incidence rate of bone fractures induced by canagliflozin in the CANVAS study was significantly higher than that of the placebo group (15.4 versus 11.9 fractures per 1000 person-years) [22]. In the CANVAS study, canagliflozin was associated with a higher incidence of fractures compared with placebo (15.4% vs. 11.9% per year, P = 0.02) [23]. Another study investigating canagliflozin examined the relationship between reduced bone mineral density in the canagliflozin group and fracture risk [15]. Furthermore, a study with a 104-week follow-up period demonstrated an elevated risk of fractures associated with SGLT2 inhibitors (SGLT2i) (7.7% vs. 0%) [24]. The DECLARE study, which compared dapagliflozin with placebo in patients with T2DM, concluded that the risk of fracture in the dapagliflozin group was comparable to that in the placebo group [25]. Similarly, the EMPA-REG OUTCOME study, which compared empagliflozin (10 mg/day or 25 mg/day) with placebo, showed a comparable fracture risk with empagliflozin [26]. In the VERTIS CV study, the risk of fracture was not increased by ertugliflozin [27]. However, some other studies have concluded that SGLT2 inhibitors may decrease the incidence of fractures [28, 29].

Previous studies have assessed the fracture risk associated with SGLT2i. However, the absolute fracture risk of SGLT2i remains undefined. This systematic review and meta-analysis aims to determine this absolute risk. Furthermore, given the limited and sometimes conflicting data regarding SGLT2 inhibitor-associated fracture risk, this updated meta-analysis was conducted to evaluate and define the absolute risk of fractures induced by SGLT2 inhibitors compared to DPP4 inhibitors.

Method

The Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses (PRISMA-NMA) guidelines (31) were followed to ensure a systematic approach to the search process and reporting of the findings. It was registered with the International Prospective Register of

Systematic Reviews (PROSPERO) under the registration number CRD420251066125. Available from (https://www.crd.york.ac.uk/PROSPERO/view/CRD420251066125).

First, comprehensive searches were performed in diverse databases in PubMed, Web of Science, Embase, and Google Scholar. Second, the titles and abstracts of the distinguished studies were screened. Second, the titles and abstracts of the identified studies were screened. Furthermore, a manual search of the reference lists of the included studies was conducted to identify any additional relevant articles. Then, the full texts of the screened studies were evaluated based on pre-established inclusion and exclusion criteria. The whole disagreements and discrepancies have been resolved through discussions, and the concluding judgment was made by the first author. Afterwards, the included studies were assessed for their quality. In the end, the results were integrated, and network meta-analyses were guided to analyze and explain the collective data.

Search strategy

A literature search was done using a concept-based approach, focusing on keywords related to "Sodium-glucose cotransporter-2 inhibitors", "type 2 diabetes", "fracture risk", "bone health", "SGLT2 inhibitors", and "osteoporotic fracture". Comprehensive exploration was performed electronically on four different databases, namely PubMed, Web of Science, Embase, and Google Scholar, including the period from their commencement until the 6th of August 2023. To ensure inclusiveness, a search strategy was prepared employing a combination of keywords and medical subject heading terms (MeSH). The search terms, along with accurate keywords demonstrated in **Table 1**.

Participants and inclusion criteria

Stringent criteria, aligned with the PICOS (population, intervention, comparator, outcome, and study design) framework, were used to screen papers for inclusion in this study. Only population-based cohort studies (S) examining SGLT-2i utilization (I) in patients with T2DM (P), compared with control groups or other anti-diabetic agents (C), and reporting overall fractures as an outcome (O) were included. Furthermore, only full-text articles published in English were considered. All other study designs were excluded.

Outcome measures

The primary focus of our research is to inspect the connection between SGLT-2i utilization in patients with T2DM, and the risk of bone fracture.

Data extraction

The data extraction procedure was done using a preplanned template, which covered details from the trials, such as the primary investigator's name, year of publication, sample size, duration of the trial, types of interventions employed, and control measures. In addition, we looked at patients' baseline characteristics, including sample size, age, sex, baseline comorbidities (such as a history of fractures, osteopenia, osteoporosis), and duration of diabetes. In addition, we investigated the consequences of bone fractures, which affected both general fractures and, if present, specific fractures of the limbs and hips. Two researchers independently extracted duplicate copies of data, and all differences and disagreements were resolved as part of a discussion.

Assessment of risk of bias

To precisely evaluate the studies implied in our research, we engaged the Newcastle-Ottawa Scale (NOS) [30]. It was used to assess the risk of bias in cohort studies. This tool evaluated the quality of observational studies established on three essential aspects: the selection of subject, the equivalence of individuals about demographics and critical potential confounders, and the ascertainment of the prearranged outcome. The final collective score which could be gained by each study ranged from 0 to 9, where a score ≥7 was classified as a good-quality trial.

Data analysis

A meta-analysis was performed using R version 4.2.2 ("Innocent and Trusting") to investigate the risk of fracture associated with SGLT2 inhibitors in patients with T2DM. Heterogeneity was assessed using the I^2 statistic [31], and sensitivity analyses were performed to assess the robustness of the findings. The odds ratio

Table 1. Search strategy for selected databases

Search engine	Search strategy	Date & nember
Pubmed	((“fracture”[Title/Abstract]) OR (torsion[Title/Abstract]) OR (broken[Title/Abstract]) OR (break[Title/Abstract])) AND ((diabetes[Title/Abstract]) OR (diabetes mellitus[Title/Abstract]) OR (diabetes[Title/Abstract]) OR (diabetes type 2[Title/Abstract])) AND ((sodium-glucose cotransporter-2 inhibitors[Title/Abstract]) OR (sodium-glucose cotransporter-2 inhibitor[Title/Abstract]) OR (dapagliflozin[Title/Abstract]) OR (empagliflozin[Title/Abstract]) OR (canagliflozin[Title/Abstract]) OR (ertugliflozin[Title/Abstract]))	English, august 4th, 2023 95
Scopus	(TITLE-ABS-KEY(sodium-glucose cotransporter-2 inhibitors) OR TITLE-ABS-KEY(sglt2 inhibitors) OR TITLE-ABS-KEY(empagliflozin) OR TITLE-ABS-KEY(dapagliflozin) OR TITLE-ABS-KEY(canagliflozin)) AND (TITLE-ABS-KEY(fractures) OR TITLE-ABS-KEY(bone break) OR TITLE-ABS-KEY(torsion)) AND (TITLE-ABS-KEY(diabetes) OR TITLE-ABS-KEY(diabetes mellitus) OR TITLE-ABS-KEY(diabetes type 2))	English, august 6th, 2023 784
Google Scholar	allintitle: fracture sodium OR glucose OR cotransporter OR 2 OR inhibitor OR empagliflozin OR linagliptin OR sitagliptin OR dapagliflozin “diabetes mellitus”	English, august 4th, 2023 173
	allintitle: sglt2 fracture OR broken OR torsion OR spiral “diabetes mellitus”	English, august 4th, 2023 4
	allintitle: metformin fracture OR broken OR torsion OR spiral “diabetes mellitus”	English, august 4th, 2023 5
	allintitle: canagliflozin fracture OR broken OR torsion OR spiral “diabetes mellitus”	English, august 4th, 2023 2
	allintitle: diabetes fracture OR broken OR torsion OR spiral “sodium-glucose cotransporter-2 inhibitors”	English, august 4th, 2023 23
	allintitle: fracture diabetes OR mellitus OR type OR 2 “sodium-glucose cotransporter-2 inhibitors”	English, august 4th, 2023 31

(OR) and 95% confidence interval (CI) were summarized for the overall analysis and for each pairwise direct and indirect comparison. A full design-by-treatment interaction random-effects model was used to assess consistency and ensure the suitability of the MA. A node-splitting model was performed to evaluate the inconsistency of direct and indirect effect sizes, which were visualized using a forest plot. The surface under the cumulative ranking curve (SUCRA) and P-scores were calculated for each treatment in the meta-analysis to determine their respective probabilities of reducing the risk of total fractures.

The statistical significance level was set at $P<0.05$.

Publication bias

By using the comparison-adjusted funnel plot, the risk of publication bias was checked. Also, linear regression and rank correlation tests were used to check the funnel plot asymmetry.

Results

Selection process

Figure 1 presents the PRISMA flow diagram of the study selection process for this review. Our comprehensive keyword search across multiple databases yielded 155 potentially relevant records. After removing 21 duplicates, 134 articles remained. Subsequent screening of titles and abstracts based on pre-defined inclusion and exclusion criteria resulted in 68 articles. Full-text review of these articles led to the final inclusion of 7 references in our meta-analysis.

Characteristics of eligible studies

The present investigation was performed as an updated review of previous articles [32-35]. In this review, we assessed seven cohort studies conducted in China [36], Taiwan [37], Italy [38], Denmark [39], South Korea [39, 40], and Canada [41]. A total of 1,199,267 participants were enrolled in the eligible studies, including 149,727 in the SGLT2i group and 1,049,540 in the Dipeptidyl peptidase-4 inhibitor (DPP4i) group. Following propensity score matching, except in one study [38]. Baseline patient characteristics were adequately comparable between the groups. Therefore, a total of 357,119 patients remained, with 221,862 in the SGLT2i group and 135,257 in the DPP4i group. Overall, 38.9% (n = 92,267) of participants were female and 61.05% (n = 144,840) were male. Specifically, across the six studies, 42.14% (n = 46,376) of the SGLT2i group and 36.11% (n = 48,881) of the DPP4i group were female. Sample sizes ranged from 362 to 332,004 patients. The mean age of participants across these studies was approximately 63.22 years (63.09 years in the SGLT2i groups and 63.45 years in the DPP4i groups), based on the mean age reported in six of the seven studies. The study by Mascolo et al. reported the range of participant ages (**Table 2**) [38]. Data from four studies focusing on patient age were included in the subgroup analysis [36, 37, 39]. In two cohort studies, results from two different datasets were reported; we excluded the dataset comparing patients in the SGLT2 versus Glucagon-like peptide-1 receptor agonist group [39].

The follow-up interval ranged from six months [36, 41] to two years [37]. The mean duration of diabetes, reported in five studies, ranged from 3.4 [39] to 12.4 years [41]. Mean Hemoglobin A1c (HbA1c) (%) and mean estimated glomerular filtration rate (eGFR) (mL/min per 1.73 m^2) were reported in the studies by Lui et al. (8.4 ± 1.6 and 81.9 ± 20.3, respectively) [36] and Cowan et al. (8.04 ± 1.2 and 73 ± 13.5, respectively) [41]. Lui et al. also reported a mean body mass index (BMI) of 27.6 ± 5.5 kg/m^2 and a mean fasting plasma glucose level of 8.9 ± 3.1 mmol/L [36]. In the study by Hulten et al., HbA1c and BMI levels were categorized. The following ranges were observed in the SGLT2i and DPP4i groups within the Aurum & GOLD cohorts: For BMI, ≥35 kg/m^2 (42.5-46.5%), 30-34.9 kg/m^2 (30.6-32.3%), 25-29.9 kg/m^2 (18.1-20.0%), and <25 kg/m^2 (2.9-3.6%). For HbA1c, ≥9.0% (38.2-40.8%), 8.0-8.9% (28.6-31.5%), 7.0-7.9% (22.6-23.8%), and <7.0% (4.4-5.8%) [39].

Regarding prescription characteristics, the most frequently administered medications of SGLT2i type were empagliflozin (34.7%-69%), dapagliflozin (28.2%-30.3%), and canagliflozin (0.3%-37.08%). Besides, in some references, the effects of ertugliflozin [36, 39] or/and ipragliflozin [39, 40] were examined. The most pre-

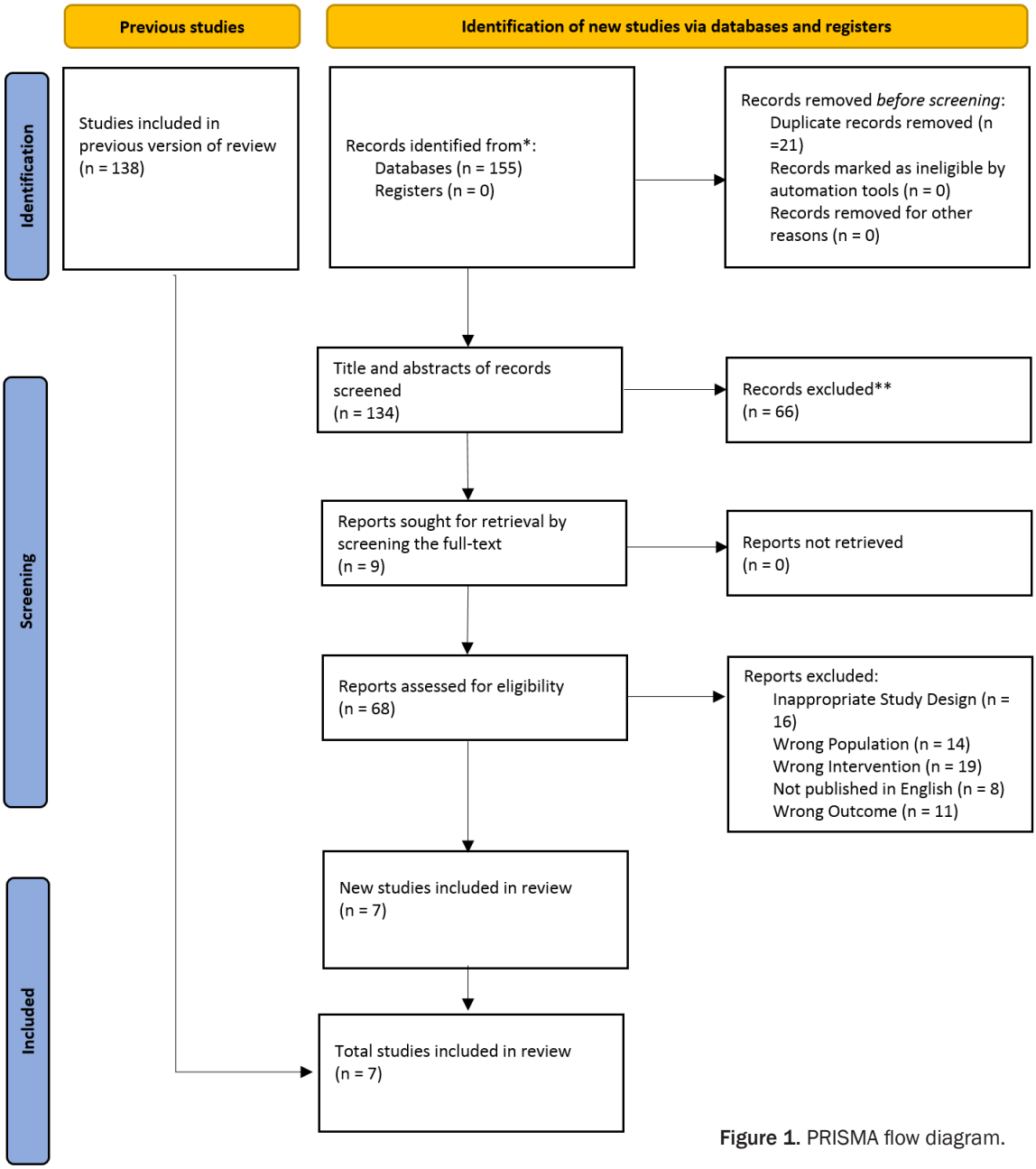

Figure 1. PRISMA flow diagram.

scribed DPP4 inhibitors were sitagliptin (33.6%-74.39%), linagliptin (20.7%-21.2%), vildagliptin (16.6%), alogliptin (14.4%), and saxagliptin (4.4%) [36, 38-41]. Furthermore, some studies evaluated the outcomes of anagliptin, teneligliptin, gemigliptin, and evogliptin [39, 40].

Regarding other active antidiabetic agents, metformin (55.36%-87.9%), followed by sulfonylureas (46.17%-56.6%), insulins (14.1%-32.2%), and thiazolidinediones (13.1%-20.4%), were commonly used in combination with either SGLT2 inhibitors or DPP4 inhibitors.

Additionally, some patients used anti-osteoporotic medications. For example, calcium and vitamin D3 supplements (2.5%-8.4%), bisphosphonates (0.3%-5%), denosumab (0.35%-1%), and SERMs (0.19%-1.2%) were frequently prescribed.

The prevalence of some diabetes-related comorbidities, including cardiovascular and osteoporotic diseases, was significantly higher than that of other underlying conditions. These less prevalent conditions included severe hypoglycemia (18.6%) [36, 40], congestive heart fail-

Table 2. Baseline characteristics of patients in included studies

Authors (reference), pubication year	Lui et al [36], 2023	Peng et al [37], 2023	Mascolo et al [38], 2023	Hulten et al [39], 2023	Han et al [40], 2021	Ko et al [39], 2023	Cowan et al [41], 2022
Country	China	Taiwan	Italy	Denmark	South Korea	South Korea	Canada
Study design	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort
All Participants	28696	42310	869	57391	31398	369534	144694
Sample size of SGLT2i group	14348	21155	507	19324	15699	37530	38994
Sample size of DPP4i group	14348	21155	362	38067	15699	332004	105700
Duration of diabetes (year)	10.7 ± 8.4	8.35		3.4			12.4
Follow-up duration	180 days-365 days	2	7	1.4 & 1.6 years	384.7 ± 246.3 days	1.45 ± 1.42 years	180 days -365 days
Mean age (year) SGLT2i group	60.6 ± 11.2	58.28 ± 10.80	18-64 Years (32.0%) 65-85 Years (44.0%) More than 85 Years (3.9%)	Aurum: 55.4 ± 10.6 GOLD: 56.8 ± 10.4	71.9 ± 5.5	60.6 ± 9.7	72 ± 5
Mean age (year) DPP4i group	60.5 ± 11.7	58.07 ± 11.56	18-64 Years (17.7%) 65-85 Years (45.0%) More than 85 Years (11.9%)	Aurum: 55.4 ± 8.0 GOLD: 56.8 ± 8.4	71.8 ± 5.5	60.6 ± 9.9	73 ± 3
Male/Female (%) in SGLT2i group	63.5/36.5	56.65/43.35	39.0/57.4	Aurum: 63.3/36.7 GOLD: 61.5/38.5	42.5/57.5	-	59.26/40.74
Male/Female (%) in DPP4i group	63.7/36.3	57.14/42.86	38.4/59.7	Aurum: 63.6/36.4 GOLD: 62.0/38.0	42.5/57.5	-	60.37/39.63
SGLT2i agents	Empagliflozi, Dapagliflozin, Canagliflozin, Ertugliflozin		Empagliflozi, Dapagliflozin, Canagliflozin	Empagliflozi, Dapagliflozin, Canagliflozin, Ertugliflozin	Empagliflozi, Dapagliflozin, Ipragliflozin	Empagliflozi, Dapagliflozin, Ertugliflozin, Ipragliflozin	Empagliflozi, Dapagliflozin, Canagliflozin
DPP4i agents	Sitagliptin, Linagliptin, Alogliptin, Vildagliptin		Sitagliptin, Saxagliptin, Vildagliptin, Alogliptin, And Linagliptin		Sitagliptin, Saxagliptin, Linagliptin, Vildagliptin, Alogliptin, Anagliptin, Tenegliptin, Gemigliptin, Evogliptin	Alogliptin, Evogliptin, Gemigliptin, Linagliptin, Saxagliptin, Sitagliptin, Teneligliptin, Vildagliptin	Linagliptin, Saxagliptin, Sitagliptin

Other active glucose-lowering medications	Metformin, Sulfonylureas, Insulin, Thiazolidinediones, Glucagon-like peptide-1 receptor agonist, alpha-glucosidase inhibitors	Metformin, Sulfonylureas, Insulin, Thiazolidinediones, Glucagon-like peptide-1 receptor agonist, Meglitinides, Acarbose	Metformin	Metformin	Metformin, Sulfonylureas, Insulin, Thiazolidinediones, Glucagon-like peptide-1 receptor agonist, Alpha-glucosidase, Meglitinides	Metformin, Sulfonylureas, Insulin, Thiazolidinediones, Glucagon-like peptide-1 receptor agonist, Alpha-glucosidase, Meglitinides	Metformin
Anti-osteoporotic medications	Calcium and Vitamin D3 supplements, Bisphosphonates, Hormone replacement therapy	Bisphosphonates, Denosumab, SERMs, Teriparatide	-	Patients using anti-osteoporotic drugs (defined as the use of bisphosphonates, strontium ranelate, bazedoxifene, raloxifene, vitamin D3 [cholecalciferol], calcium or parathyroid hormone [PTH]/calcitonin) in the 12 months prior to the index date were excluded from the analysis	-	Calcium and Vitamin D3 supplements, Bisphosphonates, SERMs, RANKL inhibitors, Parathyroid hormone [PTH]/ Calcitonin	Denosumab, Bisphosphonates, Oral steroid
Comorbidities	Congestive Heart Failure, Ischemic Stroke, Transient Ischaemic Attack, Chronic Obstructive Pulmonary Disease, Liver Disease, Osteoporosis, History of Fractures, Rheumatoid Arthritis and other Inflammatory Polyarthritis, History of Falls, Severe Hypoglycemia, Diabetic Retinopathy, Hyperparathyroidism, Dementia	Hip Fracture, Vertebra Fracture, Shoulder Fracture, And Forearm Fracture, Non-major osteoporotic fracture, Fall, Osteoporosis	Glucose metabolism disorders (incldiabetes mellitus), Appetite and general nutritional disorders, Heart failures, Urinary tract signs and, Renal disorders (excl nephropathies), General system disorders NEC, Nervous system, skull and spine therapeutic procedures, Vascular hypertensive disorders	Alzheimer's disease/dementia, Arrhythmia, Osteoporosis, Osteoarthritis, Paralysis	Cardiovascular disease, Myocardial infarction, PCI with stent, Unstable angina, Angina pectoris, Heart failure, Atrial fibrillation, Stroke, Peripheral artery Disease, Chronic kidney disease, [Diabetic neuropathy, Diabetic retinopathy, Diabetic nephropathy, Severe hypoglycaemia, Keto-/lactate acidosis], Cancer, Frailty	Asthma, Chronic kidney disease, Congestive heart failure, COPD, Dementia, Epilepsy, Gout, Hyperlipidemia, Hypertension, Ischemic heart disease, Liver cirrhosis, Osteoarthritis, Osteoporosis, Parkinson disease, Rheumatoid arthritis, Stroke, Thyroid disease	Fragility fracture Previous fall Dementia Rheumatoid arthritis Osteoporosis Coronary artery disease Diabetic retinopathy Diabetic neuropathy

Abbreviations: SGLT2i, Sodium-glucose cotransporter-2 inhibitor; DPP4i, Dipeptidyl peptidase-4 inhibitor; eGFR, Estimated glomerular filtration rate; CVD, Cardiovascular disease; PCI, Percutaneous coronary intervention; COPD, Chronic obstructive pulmonary disease; SERMs, Selective estrogen receptor modulators; RANKL, Receptor activator of nuclear factor kappa-B ligand.

ure (9.4%) [36, 40], diabetic retinopathy (12.2% and 33.6%) [36, 40], hip fracture (1.08%) [37], vertebral fracture (1.60%) [37], glucose metabolism disorders (e.g., diabetes mellitus) (64.1%) [38], cancer (32.7%) [39], history of fracture (28.1%) [39], cardiovascular disease (45.9%) [40], hypertension (53.9%) (31), osteoarthritis (34.4%) [39], coronary artery disease (31%) [39], and previous fall (15%) [41]. **Table 2** provides an overview of the detailed characteristics of eligible studies.

Clinical outcomes

SGLT2 inhibitors and risk of bone fracture compared to DPP4 inhibitors: Generally, SGLT2 inhibitor use was not statistically associated with an increased risk of fracture compared with DPP4 inhibitors in the included studies. However, patients using canagliflozin showed a slightly increased fracture risk in two cohorts. Nevertheless, a sensitivity analysis in the study by Mascolo et al. did not confirm this finding (RR, 1.14; 95% CI, 0.90-1.43) [38, 40]. Overall, in the study by Lui et al., after examining the risk of hip, vertebral, and upper limb fractures, the fracture risk in the two groups was comparable at both 180 days (HR = 1.13, 95% CI: 0.65-1.98, P = 0.671) and 365 days (HR = 1.15, 95% CI: 0.75-1.75, P = 0.519) of follow-up. The incidence rate of upper limb fractures was higher than that of other fracture types [36]. Another cohort study indicated a neutral effect of SGLT2i versus DPP4i therapies on both major osteoporotic fractures (MOF) (HR: 0.89, 95% CI: 0.80-1.00) and non-MOF (HR: 0.89, 95% CI: 0.81-0.98), specifically for fractures of the hip, vertebra, shoulder, and forearm. However, Peng et al. reported a higher incidence of potential adverse effects associated with SGLT2i use in some subgroups at increased fracture risk. These adverse effects were more common in female participants who had had diabetes for more than 8 years and had a history of fracture and osteoporosis. This study also reported a higher estimated event rate of vertebral fracture (events per 100 person-years) [37]. Mascolo et al. identified foot, femur, ankle, and lower limb fractures as the most frequent side effects associated with SGLT2 inhibitor use, although no significant association was found between these medications and fracture risk. Canagliflozin was associated with the highest proportion of these events. Subgroup analysis by age and sex revealed significant differences, indicating a higher probability of fracture in females (RR: 2.36, 95% CI: 1.86-2.98, P<0.001) and individuals older than 65 years (RR: 1.88, 95% CI: 1.47-2.40, P<0.001) [38]. In their comparison of two cohorts (Aurum and GOLD), Hulten et al. found no statistically significant difference in overall MOFs (adjusted Hazard Ratio (aHR): 0.89, 95% CI: 0.64-1.22), nor in MOFs at specific sites, including hip (aHR: 0.16, 95% CI: 0.02-1.19), vertebral (aHR: 0.59, 95% CI: 0.24-1.47), humerus (aHR: 1.00, 95% CI: 0.59-1.68), and radius/ulna (aHR: 1.15, 95% CI: 0.72-1.85). Subgroup analyses by age and sex also revealed no significant differences: for males (aHR: 1.16, 95% CI: 0.91-1.48) and females (aHR: 0.96, 95% CI: 0.73-1.26). Similarly, age-based analyses showed no significant differences: for participants older than 70 years (aHR: 0.93, 95% CI: 0.60-1.44), those between 60 and 69 years (aHR: 0.93, 95% CI: 0.65-1.34), those between 50 and 59 years (aHR: 1.30, 95% CI: 0.94-1.80), and adults aged 18 to 49 years (aHR: 1.00, 95% CI: 0.68-1.49) [39]. The results of on-treatment analysis by Han et al. confirmed the association between administration of SGLT2i and higher risk of genital infection, in addition to a reduced risk of bone fractures (HR: 0.88, 95% CI: 0.81-0.97, P_{value} = 0.007) as well as lower severe hypoglycemia [40]. The evaluation of bone fracture incidence rates showed an approximate 22% variance between the two groups in the Ko et al. study (HR: 0.78, 95% CI: 0.72-0.84). Medication use was not statistically associated with fracture risk in subgroup analyses stratified by age and covariates known to increase fracture risk. However, a protective effect against fractures was observed in patients using SGLT2i who had a prior history of osteoarthritis, compared with DPP4i users (HR: 0.70, 95% CI: 0.63-0.79). Dapagliflozin was associated with the highest reported frequency of fracture events [39]. At 180 days, fracture outcomes were comparable between groups, both in terms of overall risk and fracture site (aHR: 0.95, 95% CI: 0.79-1.13). However, at 365 days, evaluation showed a significantly lower fracture risk in SGLT2i users compared with DPP4i users (HR: 0.88, 95% CI: 0.77-1.00). These associations were not substantially altered by subgroup analysis based on eGFR [41].

Quality of evidence

Table 3 demonstrates the low risk of bias in the included cohort studies, as assessed by the Newcastle-Ottawa criteria. The scoring system was as follows: 1. One point was awarded if exposure data were derived from a prescription registry or medical records. 2. One point was awarded if the study employed a prospective design. 3. One point was awarded if adjustments were made for age. 4. One point was awarded whether adjustments were made for medications (such as antihypertensives, antidiabetics, etc.) or other relevant factors. 5. One point was awarded if the follow-up rate was 80% or higher.

Results of meta-analysis

In the 6 studies examining the association between SGLT2I and DPP4i administration and the risk of bone fracture, the overall pooled effect (ES) was 0.89 (95% CI: 0.81-0.98). In general, SGLT2 inhibitors were shown to have a lower effect on the increased risk of fractures compared to DPP4 inhibitors. The analysis revealed significant heterogeneity (I^2 = 64.3%, *P*-value = 0.016). Due to the high heterogeneity, we carried out a subgroup analysis, the results of which are as follows. **Figure 2** shows the forest plot of the overall analysis.

Based on the results of the Egger test (P<0.001) and the Begg test (P = 0.009) as well as the asymmetric funnel diagram, a significant publication bias was shown in the included studies (**Figure 3**).

Subgroup analysis of patients older than 70 years: A comparison of the results of studies with volunteers over 70 years of age shows that taking SGLT2 inhibitors did not statistically correlate with a higher risk of fracture compared to DPP4 inhibitors (ES: 0.88; 95% CI: 0.76-1.00, P = 0.004). **Figure 4** shows the forest diagram of this subgroup analysis.

Based on the results of the Egger test (P = 0.001) and the Begg test (P = 0.308) as well as the asymmetric funnel diagram (**Figure 5**), a significant publication bias was shown in the included studies.

Subgroup analysis of patients younger than 70 years: Comparing the results of studies with volunteers aged <70 years, it is found that the use of SGLT2 inhibitors did not correlate with a higher risk of fracture compared to DPP4 inhibitors (ES: 0.97; 95% CI: 0.81-1.14, P = 0.004). **Figure 6** shows the forest diagram of this subgroup analysis.

Based on the results of the Egger test (P<0.001) and the Begg test (P = 0.016) as well as the asymmetric funnel diagram (**Figure 7**), a significant publication bias was shown in the included studies.

Subgroup analysis of female patients: Comparing the results of studies with female participants, it is found that, statistically speaking, the use of SGLT2 inhibitors was not associated with a higher risk of fracture compared to DPP4 inhibitors (ES: 1.12, 95% CI: 0.92-1.31, P = 0.290). **Figure 8** shows the forest diagram of this subgroup analysis.

Based on the results of the Egger test (P = 0.125) and the Begg test (P = 0.296), and the symmetrical funnel diagram (**Figure 9**), no significant publication bias was identified in included studies with female patients.

Sensitivity analyses: Sensitivity Analyses: Sensitivity analyses were conducted to assess the robustness of the findings. For the overall analysis, no studies were excluded, confirming the stability of the results. For patients ≥70 years, sensitivity analysis included all studies, reinforcing the reliability of the findings. Similarly, for patients <70 years, no studies were excluded, supporting the consistency of the results. In the female subgroup, sensitivity analysis confirmed the robustness of the findings, with no studies excluded. These analyses underscore the reliability of the meta-analysis conclusions across all evaluated groups.

Discussion

This systematic review and meta-analysis compares the fracture risk between SGLT2 inhibitors and DPP4 inhibitors, two antihyperglycemic classes with different mechanisms of action. SGLT-2 inhibitors induce glycosuria by inhibiting glucose reabsorption in the renal proximal tubule [42], whereas DPP-4 inhibitors enhance incretin secretion from intestinal epithelial cells, thereby stimulating insulin release [43]. SGLT2 inhibitors may adversely affect

Table 3. Results of quality assessment based on Newcastle-Ottawa criteria

First author, year	Selection				Comparability	Outcome			Total Score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure[1]	Outcome was not present at start of study[2]	Control for 2 important factors[3,4]	Assessment of outcome	Follow-up long enough	Adequacy of follow-up of cohort[5]	
Hulten, 2023 [39]	*	*	*	*	**	*	*	*	9
Mascolo, 2023 [38]	*	*	*		**	*	*		7
Ko, 2023 [39]	*	*	*	*	**	*	*	*	9
Peng, 2023 [37]	*	*	*		**	*	*	*	8
Cowan, 2022 [41]	*	*	*	*	*	*	*	*	8
Lui, 2023 [36]	*	*	*	*	*	*	*	*	8
Han, 2021 [40]	*	*	*	*	**	*	*	*	9

[1]A point was given if the exposure data came from a prescription registry or a medical file. [2]A point was given if the study was prospective in design. [3]If age adjustments were made, a point was given. [4]If medicines (such as anti-hypertensives, anti-diabetics, etc.) or any other extra considerations were taken into account, a point was given. [5]A point was given if the follow-up was completed with 80% accuracy or more.

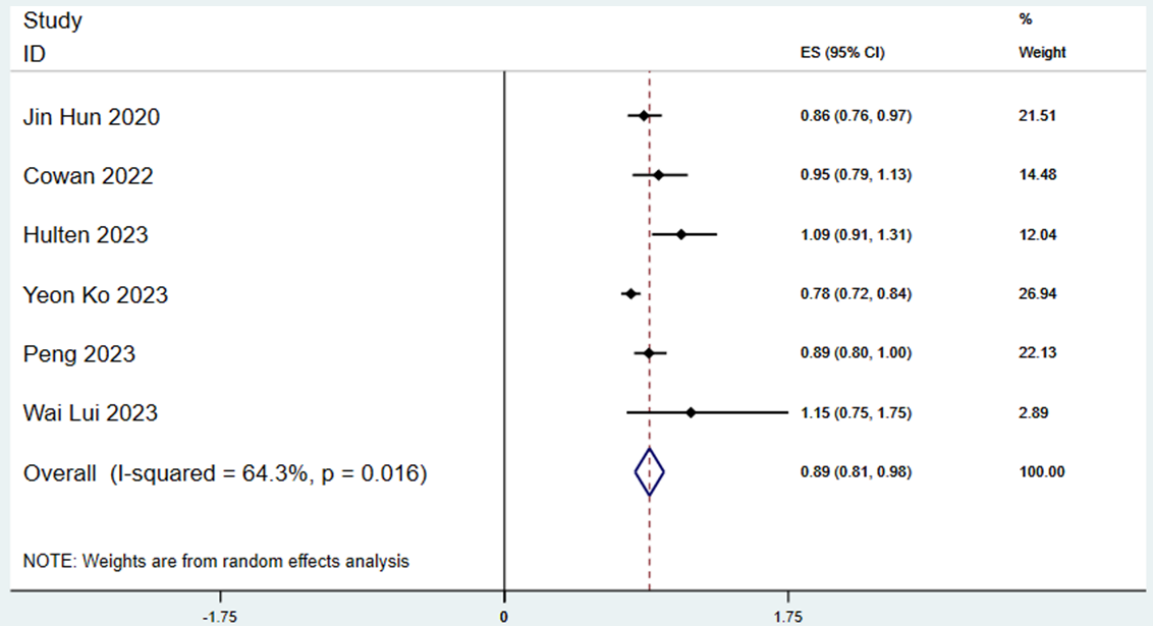

Figure 2. Forest plot of the overall association between SGLT2i versus DPP4i administration and risk of bone fracture.

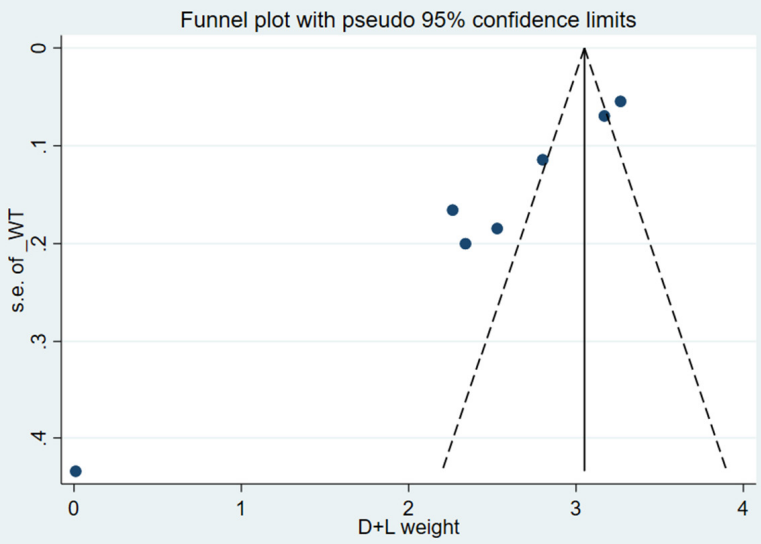

Figure 3. Funnel plot of studies investigating association between SGLT2i versus DPP4i administration and risk of bone fracture.

bone health by increasing phosphate reabsorption, disrupting calcium-phosphate homeostasis, and elevating parathyroid hormone (PTH) levels, potentially contributing to skeletal fragility [14, 44]. In contrast, DPP4 inhibitors are associated with enhanced osteoblast differentiation and reduced osteoclast differentiation, leading to improvement of bone quality and bone density [45-47]. Despite multiple studies, the relationship between these medications and fracture outcomes remains inconclusive.

This meta-analysis aimed to evaluate and compare the fracture risk associated with SGLT2 inhibitors and DPP-4 inhibitors. It also aimed to assess new studies and update previous meta-analyses. We analyzed the results in four categories: 1) the general population, 2) patients aged 70 years or older, 3) patients older than 70 years, and 4) female patients. Based on data from 731,879 patients who received SGLT2 inhibitors or DPP-4 inhibitors, SGLT2 inhibitors were associated with a lower fracture risk than DPP-4 inhibitors. However, this difference was not observed among women or patients younger than 70 years or 70 years and older. This meta-analysis showed a lower risk of fracture among the general population receiving SGLT2 inhibitors compared with those receiving DPP4 inhibitors. However, in other subgroups, including females, patients older

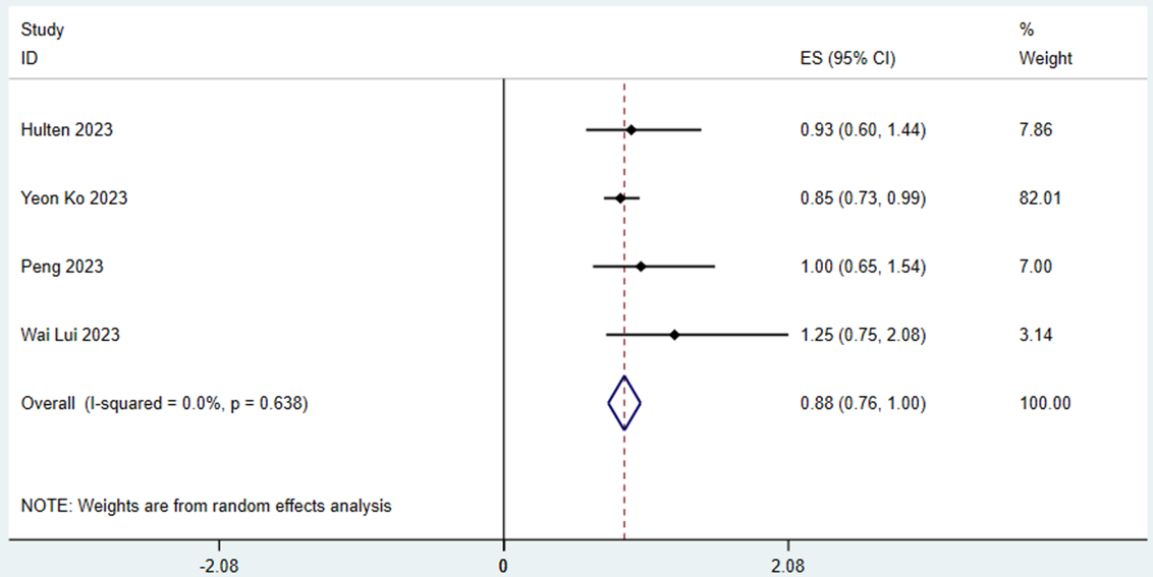

Figure 4. Forest plot of subgroup analysis for studies investigating association between SGLT2i versus DPP4i administration and risk of bone fracture in patients older than 70 years.

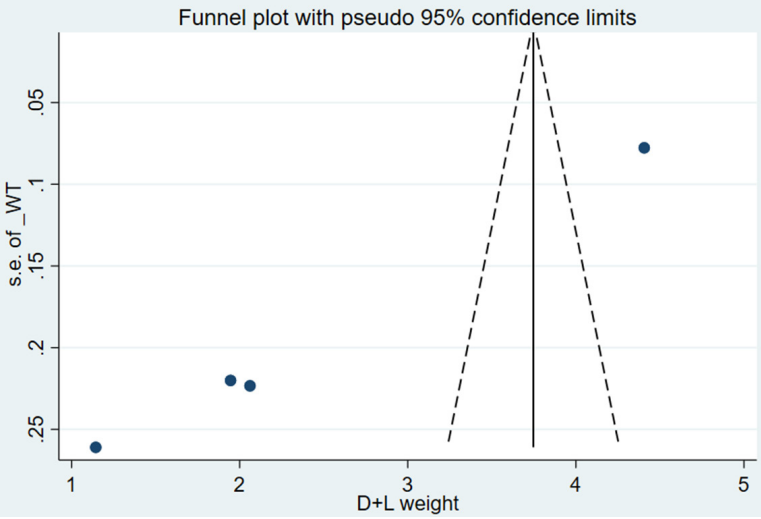

Figure 5. Funnel plot of studies investigating association between SGLT2i versus DPP4i administration and risk of bone fracture in patients people older than 70 years.

than 70 years, and patients younger than 70 years, there were no statistically significant differences between the two groups.

A study conducted in Hong Kong found no significant association between SGLT2 inhibitors and fracture risk [48]. While that study also found no link between proteinuria and increased fracture risk (8), another Korean study reported an association between proteinuria and increased hip fracture risk [49]. Furthermore, a separate real-world, population-based Korean study found no significant difference in bone fracture risk between patients using SGLT2 inhibitors and those who were not [50]. According to the DAPA-CKD trial, dapagliflozin did not increase fracture risk among patients with chronic kidney disease [51]. The CANVAS study and a meta-analysis reported an increased fracture risk associated with canagliflozin [34, 52]. These results from the CANVAS study were primarily observed in older adults with a history of lower baseline eGFR, higher diuretic use, and a history of cardiovascular disease [52]. CANVAS-R did not show an increased fracture risk with canagliflozin [53].

SGLT2 inhibitors were associated with an increased risk of MOFs compared with DPP-4 inhibitors among female patients with a diabetes duration of less than 8 years, a history of osteoporosis, and a history of fracture. In these patients, SGLT2 inhibitors may increase the

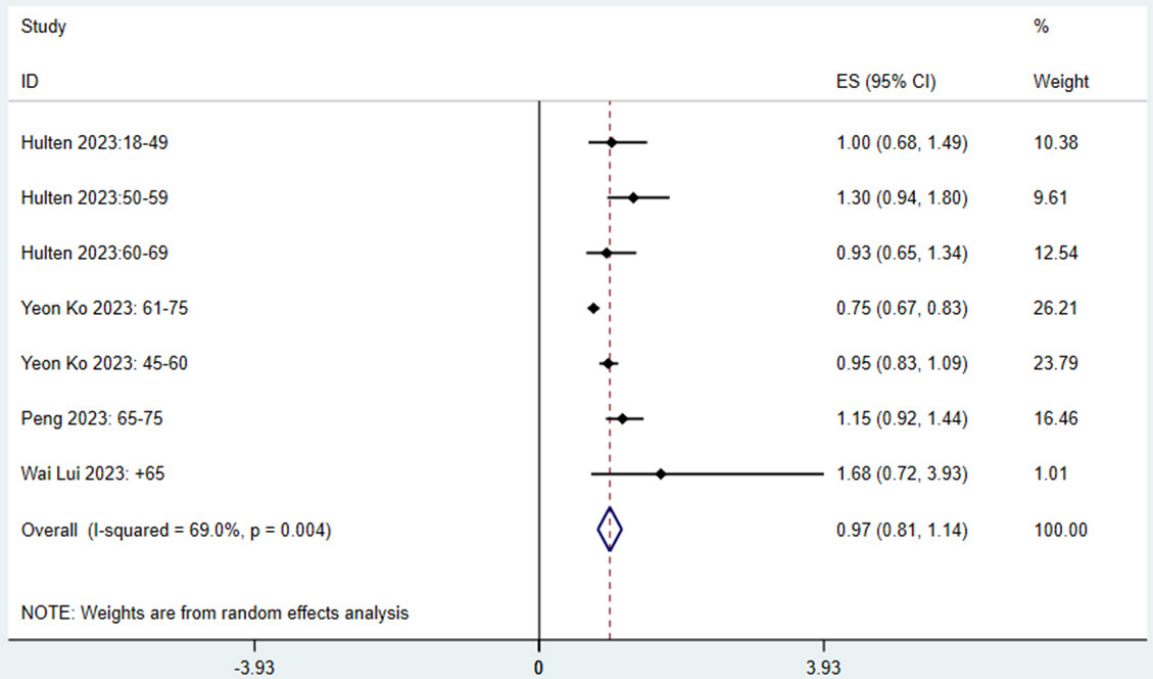

Figure 6. Forest plot of subgroup analysis for studies investigating association between SGLT2i versus DPP4i administration and risk of bone fracture in patients younger than 70 years.

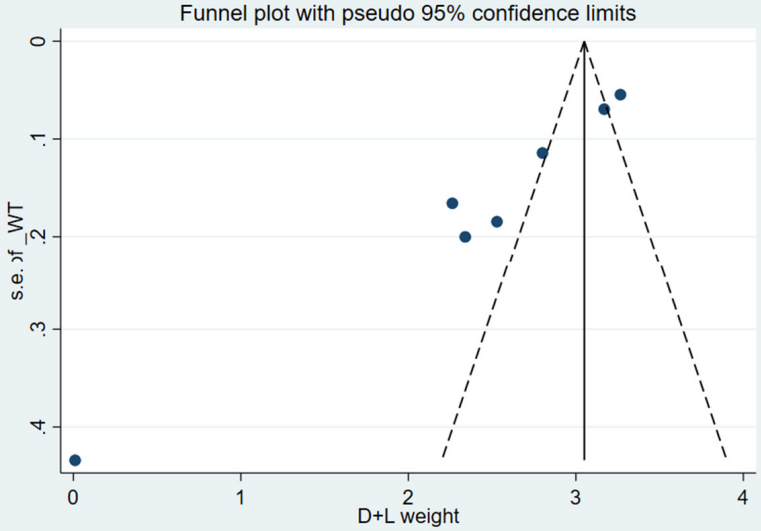

Figure 7. Funnel plot of studies investigating association between SGLT2i versus DPP4i administration and risk of bone fracture in patients younger than 70 years.

risk of fracture by 21%, 34%, 92%, and 49%, respectively [37]. A large Canadian cohort study of older adults found no increased fracture risk associated with SGLT2 inhibitors compared with DPP-4 inhibitors at 180 and 365 days after discontinuation. However, this cohort study observed a higher overall fracture rate than previous studies. Additionally, among patients with an eGFR between 30 and 45 mL/min/1.73 m^2, new SGLT2 inhibitor users had a lower fracture risk at 365 days compared with DPP-4 inhibitor users (weighted hazard ratio with 95% CI 0.64 [0.43-0.95]) [41]. However, another retrospective cohort study in Korean patients aged 65 and older with type 2 diabetes found a similar fracture risk between SGLT2 inhibitors and DPP4 inhibitors [40]. Another cohort study showed no significant difference in fracture risk compared with DPP4 inhibitors, even when the analysis was limited to patients with treatment durations exceeding 811 days [39]. A large, nationwide cohort study of postmenopausal patients with type 2 diabetes found that SGLT2 inhibitors did not increase the risk of overall fracture, and that SGLT2 inhibitors were associated with a 22% lower rate of incident overall survival compared with DPP4 inhibitors [54].

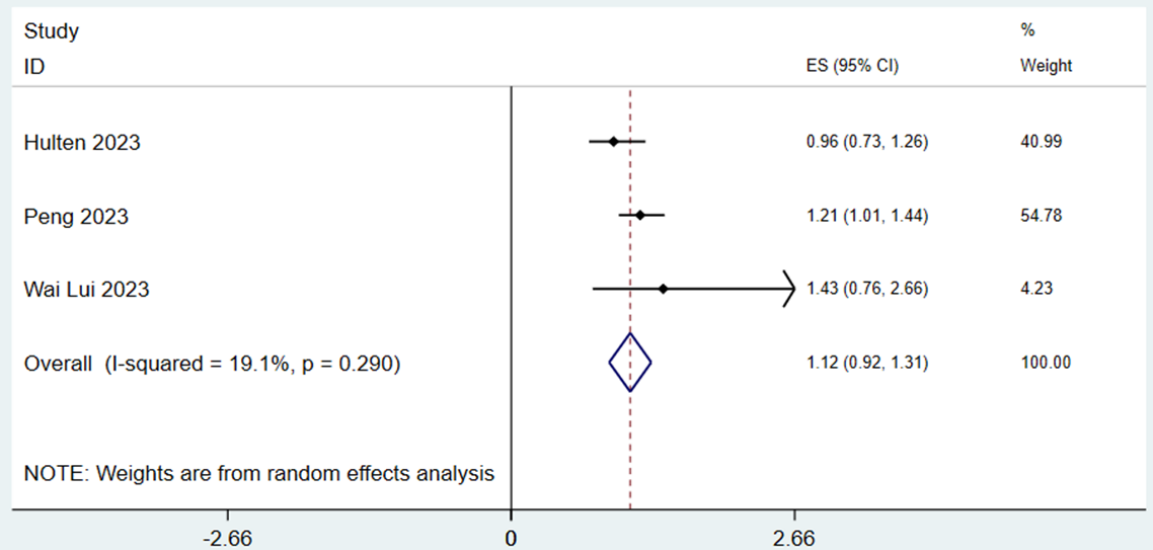

Figure 8. Forest plot of subgroup analysis for studies investigating association between SGLT2i versus DPP4i administration and risk of bone fracture in female patients.

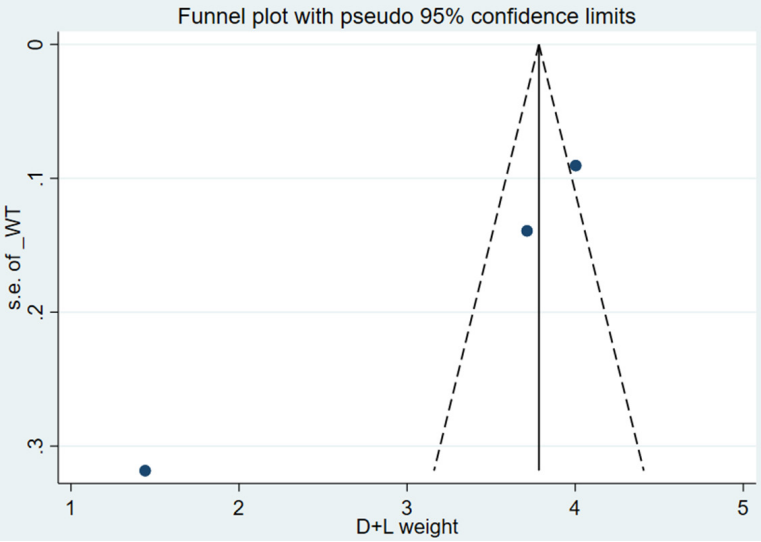

Figure 9. Funnel plot of studies investigating association between SGLT2i versus DPP4i administration and risk of bone fracture in female patients.

This meta-analysis has several strengths: the comprehensive search strategy and compliance with PRISMA guidelines, as well as the large sample size, increased the significance of possible differences in fracture risk. Of course, there are significant restrictions. The estimated heterogeneity of 64.3% is quite strong, indicating differences between papers included, which could be due to differences between studies in SGLT2i classes used and patient populations or other confounding factors. Subgroup analyses were performed, and even so, the limited number of studies reporting data stratified by age and sex may have strongly limited the ability to detect statistically significant differences within those subgroups. Besides, being observational cohort studies creates a possibility of residual confounding even after propensity score matching. Future studies should comprise plans for high-powered, well-designed studies adopting standardized protocols for fracture assessment and reporting to include comprehensive subgroup analyses such as age, sex, and other important clinical characteristics. Further, a longer duration of Follow-up is needed to completely understand the long-term effects of SGLT2i and DPP4i on fracture risk. Indeed, mechanistic studies would also be justified to explore possible mechanisms by which these drugs may affect bone health.

From our perspective, the reduction in fracture risk associated with SGLT2 inhibitors in general population may be due to two mechanisms.

1-the direct pharmacological effect of the drug, 2-the indirect effect of clinical factors such as improved glycemic control, weight loss, and cardiovascular benefits that support bone quality. However, the absence of significant benefits in our subgroup analysis suggests that these advantages may be offset by age-related bone loss or post-menopausal hormonal changes. Therefore, clinicians should adopt a patient-centered strategy and evaluate individual patient risk factors, including bone mineral density and history of fractures, before initiating SGLT2 inhibitor therapy in these populations.

Conclusion

In conclusion, SGLT2 inhibitors were associated with a lower fracture risk compared to DPP4 inhibitors in the general population. However, this difference was not observed in subgroup analyses of females, patients over 70, or patients under 70.

This systematic review and meta-analysis has some limitations, including an insufficient number of articles to analyze males as a separate subgroup. Further studies are needed to determine the precise effect of these medications on fracture risk in males.

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Disclosure of conflict of interest

None.

Abbreviations

T2DM, Type 2 diabetes mellitus; WHO, World Health Organization; SGLT2, Sodium-glucose cotransporter-2; SGLT2i, Sodium-glucose cotransporter-2 inhibitor; PRISMA-NMA, Preferred Reporting Items for Systematic Reviews and Network Meta-Analyses; PICOS, Population Intervention Comparator Outcome Study design; NOS, Newcastle-Ottawa Scale; OR, Odds ratio; CI, Confidence interval; SUCRA, Surface under the cumulative ranking curve; DPP4i, Dipeptidyl peptidase-4 inhibitor; HbA1c, Hemoglobin A1c; eGFR, Estimated glomerular filtration rate; BMI, Body mass index; MOF, Major osteoporotic fracture; aHR, adjusted Hazard Ratio; RR, Relative Risk; HR, Hazard Ratio.

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