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BONE AND DIABETES (A SCHWARTZ AND P VESTERGAARD, SECTION EDITORS)

Glucose-Lowering Drugs and Fracture Risk—a Systematic Review

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Abstract

Purpose of Review Diabetes mellitus (DM) is associated with increased fracture risk. The aim of this systematic review was to examine the effects of different classes of glucose-lowering drugs on fracture risk in patients with type 2 DM. The heterogeneity of the included studies did not allow formal statistical analyses.

Recent Findings Sixty studies were included in the review. Metformin, dipeptidylpeptidase-IV inhibitors, glucagon-like peptide-1 receptor agonists, and sodium–glucose cotransporter 2-inhibitors do not appear to increase fracture risk. Results for insulin and sulphonylureas were more disparate, although there may be an increased fracture risk related to hypoglycemia and falls with these treatments. Glitazones were consistently associated with increased fracture risk in women, although the evidence was sparser in men.

Summary New glucose-lowering drugs are continuously being developed and better understanding of these is leading to changes in prescription patterns. Our findings warrant continued research on the effects of glucose-lowering drugs on fracture risk, elucidating the class-specific effects of these drugs.

Keywords Type 2 diabetes · Fracture · Glucose-lowering drugs · Antidiabetics · Glitazones · Insulin · Systematic review

Introduction

Diabetes mellitus (DM) is associated with an increased risk of fracture [1••]. In patients with type 1 DM (T1D), the fracture risk may be increased as much as sevenfold compared to subjects without DM [1••], whereas the risk in patients with type 2 DM (T2D) is 1.3-fold increased [1••]. In T2D, the increased risk of fracture is not explained by a lower bone mineral density (BMD); on the contrary, BMD is often reported to be higher in T2D compared to controls [1••].

Although the mechanisms behind increased fracture rates in DM are not fully uncovered, ongoing research has suggested that bone deteriorates in DM due to structural changes in bone with increased cortical porosity [2] and alterations in

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the bone collagen as a result of the accumulation of advanced glycation end-products [3], or due to low bone turnover causing micro-fractures which may lead to fractures despite relatively high BMD [4]. Furthermore, characteristics and severity of diabetes have been investigated. Although diabetes-related complications are associated with fractures, patients without complications also have an increased fracture risk [5]. The duration of diabetes is associated with fracture risk in some studies [6]; however, in the studies aiming to investigate T2D exclusively, some patients with T1D may have been included [7]. Falls and hypoglycemia are less well investigated in DM due to underreporting and information bias [8]. Both falls and hypoglycemia are associated with fractures; however, they do not fully explain the fracture rates in T1D and T2D [9].

Thus, the increased fracture risk may be increased due to several factors. New glucose-lowering treatments for T2D are being developed at a rapid pace, with some of these showing beneficial effects on renal and cardiovascular outcomes. However, glucose-lowering therapies may also influence fracture risk. Metformin is recognized as the first-line treatment of T2D, and second-line treatment consist of insulin, dipeptidylpeptidase-IV inhibitors (DPP-IVis), sodium-glucose cotransporter 2 inhibitors (SGLT2-is), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), glitazones, and sulphonylureas. Recently, SGLT2-is and GLP-1 RAs have become recommended treatments in individuals with T2D and cardiovascular disease, and SGLT2-is are also recommended to prevent progression of chronic kidney disease (estimated glomerular filtration rate 30 to ≤ 60 ml/min) [10]. This systematic review aims to examine the evidence on the effects of glucose-lowering drugs on fracture risk in patients with T2D.

Methods

The PRISMA guidelines were followed [11]. A systematic literature search was conducted using Medline at PubMed (1966–2020) in January 2020 and last updated on February 27, 2020. Studies were deemed eligible for inclusion if they investigated associations between use of glucose-lowering drugs and fracture risk in patients with T2D. The following types of studies were included in the review: observational studies, randomized controlled trials (RCTs), meta-analyses containing at least one RCT that was not included in the literature search. Studies were not excluded on the basis of language or publication date. The glucose-lowering drugs that were investigated were insulins, metformin, sulphonylureass, glitazones, DPP-IVis, GLP-1 RAs, and SGLT2-is.

Free-text search terms were used. The search terms were "diabetes and fracture" in combination with "insulin," "thiazolidinediones," "glitazones," "sglt-2," "sodium glucose cotransporter 2," "sglt2," "dpp-4," "dipeptidyl peptidase-4 inhibitors," "glucagon-like peptide-1," "glp-1," "glucagon-like peptide 1 receptor agonist," "sulfonylurea," "sulphonylurea," or "metformin." In total, 1583 papers were identified. After excluding duplicates and evaluating title and abstract, 106 publications were assessed in full text. Of these, 60 publications were included in this review. Figure 1 provides a flow-chart for in-/exclusion of studies. Studies were excluded if the population was without diabetes, there was no investigation of glucose-lowering drugs, or fracture was not the outcome. Data were extracted by two reviewers, JSL and ZAM, and included publication year, data source, study design, investigated glucose-lowering drug, comparator (if applicable), population mean/median age, duration of follow-up, adjustment, and result of the study. The outcome measures included were as follows: number of fractures (prevalence), odds ratios (OR), relative risks, hazard ratios (HR), and incidence rates. The quality of each included study was evaluated by the level of evidence using levels of evidence (March 2009) by the Oxford Centre for Evidence-Based Medicine [12]. Furthermore, possible sources of bias in the various studies were evaluated to identify potential difficulties in the interpretation of their findings. In drawing up the conclusions, weight was given to the results of studies of higher order evidence and with limited bias. In this systematic review, we did not perform any statistical analysis due to differences in study design, drug of use, use of comparator, outcome, and duration of follow-up.

Results

In total, 60 studies were included. Table 1 presents the included studies and extracted data. Study designs were mainly cohorts ($N = 33$), but also case-control studies ($N = 10$), cross-sectional studies ($N = 2$), RCTs ($N = 6$), and meta-analyses of RCTs were included ($N = 8$). Fourteen studies investigated multiple glucose-lowering drugs, two studies investigated sulphonylureas, six studies investigated insulins, eight studies investigated SGLT2-is, five studies investigated GLP-1 RAs, 11 studies investigated DPP-IVis, and 14 studies investigated glitazones. Metformin was examined in 15 studies, although primarily as a comparator for other drugs. The study sizes ranged between 223 [61] and 499,526 [60•] participants, and the mean ages of the investigated populations ranged from 43 years [9] to 81 years [25]. The follow-up of the studies ranged between 12 weeks [47] and 20 years [22]. Thus, the studies were heterogenous in design, study size, age of participants, and follow-up.

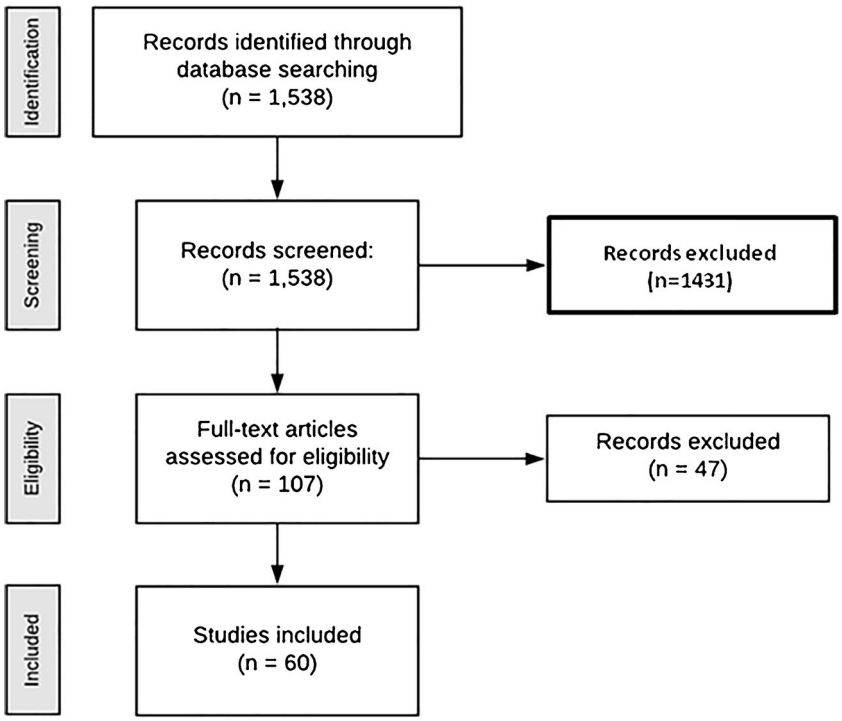

Fig. 1 Flow-chart for in-/exclusion of studies

Bias and Limitations

The meta-analyses of RCTs were limited by short durations of follow-up [36, 42, 47]. Some included studies with a follow-up period as short as 12 weeks, and only one meta-analysis contained studies with follow-up periods up to 4 years [46, 67]. Due to these short follow-up periods, the numbers of fractures are relatively limited, making the interpretation of results difficult. An increased fracture risk with a short time to follow-up would suggest an increased risk of falls or hypoglycemia, whereas fractures due to bone fragility may require years to be detected. Furthermore, fractures were not the primary outcome in the analyses in these studies. In comparison to the cohort studies, the RCTs have limited study population sizes. The study by Kohler et al., which is a pooled analysis of 14 RCTs and a post hoc analysis of an additional RCT, included more than 14,000 subjects with T2D; however, the large pooled analysis ($n = 12{,}620$) had follow-up durations which varied between 8 days and 78 weeks (apart from one study with a duration of 2.6 years), whereas the relatively small post hoc analysis of participants from the EMPA-REG study ($n = 1545$) had the longest duration of follow-up of 208 weeks [37]. Thus, the RCTs and meta-analyses of RCTs have certain flaws in interpretations of fracture risk as a long-term consequence of glucose-lowering treatment. The observational studies are in general biased by confounding by (contra)-indication. Thus, one drug might have been chosen based on certain traits of patients. Furthermore, the comparator in both RCTs and observational studies is variable; non-diabetes subjects, T2D patients without pharmacological treatment, and T2D patients using different combinations of glucose-lowering drugs. A general concern regarding cohort studies utilizing registries is whether the comparator constitutes a different group of T2D patients. The T2D population is comprised of participants with very different characteristics, from patients with normal body mass index (BMI) to very obese individuals, from patients with several comorbidities to patients with few, and the treatment may differ in regard to the severity of diabetes. Also, many patients are treated with three or four glucose-lowering drugs. Thus, the cohort studies may compare patients with less severe diabetes (first- or second-line therapy) with more severe diabetes (three or more drugs). Another possible bias of cohort studies is that some studies may include patients with T1D among the insulin users; this bias would overestimate the risk of fracture in insulin users as the relative fracture risk is higher in T1D compared to T2D. Some cohort studies follow patients before the introduction of treatment and thus the patients need to have survived a period before treatment to be included in the study. This can introduce immortal time bias, which is recognized in one of the studies included in this systematic review [48, 72]. In addition, if drug effects on fracture are expected to arise from alterations in bone tissue, a lag time after drug initiation would be expected [73]. Although this lag time is ill-defined, short follow-up durations would not be sufficient to explore bone-related effects but perhaps instead only fall-related effects on fracture risk.

Finally, several included studies have drawn on data from the same data sources, permitting some level of reporting bias. However, since these studies were performed at different

Table 1 Studies investigating antidiabetic drugs and fracture risk in patients with type 2 diabetes

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
Glucose-lowering drug unspecified or multiple GLDs examined								
Chen 2015 Taiwan, National Health Insurance Database (2000–2010) [13]	Case control (selects on outcome)	3427 with T2D and fracture; 3427 with T2D and no fracture; 53% women	Glitazone users or repaglinide users vs. non-users: other GLDs in fracture vs. non-fracture group	62.3 non--fracture group; 62.6 fracture group	N/A	Age, sex, stroke, osteoporosis, end stage renal disease	Glitazones increased risk of fracture (OR 1.19, CI 1.03–1.37) although non-significantly in men. Repaglinide increased risk (OR 1.20, CI 1.01–1.41) of fracture. No association with other SU, insulin or metformin.	III
Choi 2016 South Korea, Health Insurance Review and Assessment service of South Korea (2007–2011) [14]	Cohort	207,558 subjects with GLD prescriptions; 44–58% women	Different GLDs vs. non-users	All aged 50 or more	1.9	Age, sex, comorbidity score, osteoporosis, antiosteoporotic treatment, osteoporosis-related diseases	Compared to Non-users: SU (HR 1.53, CI 1.42–1.64), Metformin (HR 1.12, CI 1.04–1.21), metformin+glitazone (HR 1.50, CI 1.22–1.84), and SU + glitazone (HR 1.91, CI 1.57–2.33) were associated with increased risk of fracture. Conversely, the combinations of metformin and SU and metformin and DPP-IVi were not associated with fracture.	II
Hung 2017 Taiwan, Taiwan National Health Insurance (2001–2011) [15]	Cohort	5173 controls and 2588 with hypoglycemia; 57% women	Different GLDs vs. non-users	70	3.9	Age, sex, comorbidity, drug use	Use of SU (HR 1.44, CI 1.07–1.92), Insulin (HR 1.89, CI 1.25–2.83) and use of SU and insulin (HR 2.03, CI 1.33–3.10) were all associated with increased risk of hip fracture compared to non-users.	II
Kanazawa 2010 Japan, Shimane University Hospital [16]	Cross-sectional	494 men with T2D; 344 postmenopausal women with T2D	GLDs users vs. non-users	58–72	N/A	Age, BMI, HbA1c, serum creatinine, serum C-peptide, lumbar BMD, diabetes duration	In men, no GLD was associated with VF. In women, insulin (OR 2.20, CI 1.13–4.27), glitazone (OR 3.51, CI 1.09–11.38) and SU (OR 0.51, CI 0.27–0.93) were associated with fracture, whereas metformin was not (OR 0.75, CI 0.37–1.52).	III–IV
Lee 2019 US, Veterans Health Administration (2000–2010) [17]	Cohort	662,628 male veterans with T2D	GLDs	74–76	3.4	Baseline HbA1c, fracture risk–related factors and diabetes-associated complications	Insulin was associated with fracture (HR 1.10, CI 1.07–1.12), particularly in those with HbA1c < 6.5%. Glitazones were associated with	II

Table 1 (continued)

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
							fracture (HR 1.16, CI 1.13–1.19). Metformin was associated with decreased risk of fracture (HR 0.88, CI 0.87–0.90). SU was associated with fracture in those with HbA1c < 6.5%.	
Losada 2018 Spain,Information System for Research Development in Primary Care database, Catalonia Spain (2006–2012) [18]	Case control	2049 T2D patients with fracture; 10,228 T2D patients without fracture. 0.7% women	GLDs vs. metformin monotherapy	73	N/A	GLD, age, sex, socio-economic status, BMI, eGFR, HbA1c, smoking, alcohol use, conditions/medications affecting fracture risk. Age- and sex-matched	Insulin use (OR 1.63, CI 1.30–2.04) and SU and metformin (OR 1.29, CI 1. 07–1.56), were associated with fracture. DPP-IVi users and non-users did not have increased risk of fracture.	III
Melton 2008, Rochester Epidemiology project (1970–1994) [19]	Cohort	1964 patients with DM. 49% women	GLDs	62	12	Multivariate model. Variables not specified	Insulin (HR 1.3, CI 1.1–1.5) and metformin use (HR 0.7, CI 0.6–0.96) were associated with fracture. No association between SU or glitazones and fracture risk.	II
Monami 2008 Italy, Diabetes Outpatient Clinics of The University of Florence [20]	Case control	83 T2D patients with fracture; 249 T2D patients without fracture. 64% women	GLDs	68–70	N/A	Concomitant hypoglycemic treatments. Matched for age, sex, diabetes duration, HbA1c, BMI, CCI score, smoking status, and alcohol abuse.	SU (OR 0.77, CI 0.44–1.37) and metformin (OR 0.94, CI 0.54–1.65) were not associated with fracture, whereas current insulin use was (OR 1.77, CI 1.05–2.97).	III
Nicodemus 2001 US, Iowa Womens Health Study [21]	Cohort	47 T1D; 1682 T2D; 30,377 controls. All postmenopausal women.	GLDs vs. no DM	61–62	9.5	Age, smoking, estrogen use, BMI	Insulin treatment (HR 2.66, CI 1.52–4.64) and OGLD (HR 1.80, CI 1.03–3.16) were associated with increased hip fracture, whereas T2D with no treatment was not.	II
Schneider 2013 US, ARIC study [22]	Cohort	1605 with DM. 48–58% women	GLDs	56	20	Not specified	OGLD was not associated with fracture (HR 0.97, CI 0.60–1.55), whereas insulin was associated with fracture (HR 1.87, CI 1.15–3.05).	II
Starup-Linde 2017 Denmark, DNH (1996–2011) [23]	Cohort	180,073 with incident T2D. 46–63% women	GLDs	59–73	5.5	Adjusted by propensity score, age sex, previous MOPF, CCI, diabetic complications, previous	Current use of SU (HR 1.44, CI 1.39–1.49) and glitazones (HR 3.01, CI 2.65–3.43) increased fracture	II

Table 1 (continued)

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
						hypoglycemia/falls, alcohol use, medication	risk. Metformin (HR 0.73, CI 0.71–0.76), insulin (HR 0.80, CI 0.77–0.84), DPP-IVis (HR 0.28, CI 0.25–0.32), and GLP-1 RAs (HR 0.19, CI 0.16–0.22) decreased fracture risk.	
Starup-Linde 2016 Denmark, DNH [24]	Case control	2627 with diabetes. 46–51% women	GLDs	63–66	N/A	Comorbidities, age, sex, drug use, biochemical markers	Insulin (HR 1.03, CI 0.66–1.61), glitazones (HR 1.94, CI 0.38–9.86), metformin (HR 0.74, CI 0.49–1.10), SU (HR 1.06, CI 0.69–1.61), and GLP-1 RA (HR 0.36, CI 0.13–1.03) were not significantly associated with fracture.	III
Vestergaard 2005 Denmark, DNH (2000) [9]	Case control	124,655 cases (fracture) and 373,962 controls (non-fracture), of whom 2.6% and 1.7% had T2D, respectively. 52% women	GLDs	43	N/A	Drug use, prior fracture, hypoglycemia, comorbidity, number of contacts to GP or specialist, socio-economic status	SU (HR 0.85, CI 0.76–0.95) and Metformin (HR 0.81, CI 0.70–0.93) were associated with a reduced risk of fracture. Insulin (HR 0.88, CI 0.76–1.02) was not associated with fracture.	III
Wallander 2017 Sweden, FRAILCO (2008–2014) [25]	Cohort	79,159 T2D; 343,603 controls. 48–59% women	Insulin users, OGLDs, and T2D non-users vs. non-diabetics	78–81	1.3	Age, sex, weight, height, previous fracture, comorbidity, drug use, self-reported falls	Insulin use (HR 1.19, CI 1.14–1.24) was associated with fracture, whereas non-users (HR 0.95, CI 0.89–1.02) and OGLD users (HR 1.02, CI 0.98–1.06) were not at increased risk.	II
Sulphonylureas								
Lapane 2015 US, Medicare Beneficiary Summary Files (Nursing home residents) [26•]	Cohort	12,327 new users. 67–69.5% women	SUs vs. metformin	67–70	683 days	Propensity score-matched. Adjustment variables not specified.	No increased fracture risk of SU compared to metformin (HR 1.14, CI 0.83–1.56).	II
Rajpathak 2015 US, OptumInsight (2002–2005) [27]	Cohort	13,195 SU users; 13,195 non-SU users (all OGLD treated). 47–48% women	SUs vs. non-users	72.5	4	Propensity score-matched, adjusted for region, osteoporosis, drug use	SU associated with increased risk of hip fracture (HR 1.46, CI 1.17–1.82).	II

Table 1 (continued)

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
Insulin								
Ahmed et al. 2005 Norway, Tromsø (1994–2001) [28]	Cohort	373 patients with T2D. 53% women	Insulin users vs. non-users	64.0–68.2	Not specified, but states followed for 6 years	Age, BMI, smoking	No effect of insulin on all non-vertebral fractures or hip fractures.	II
Corrao 2019 Italy, National Health Service in Lombardy (2005–2012) [29••]	Cohort	136,307 subjects switched from OGLD to another GLD. 44% women	Switch to insulin vs. switch to other GLD	67.6	3.2	Matched by age, index date, status of GLD, follow-up duration	Switch to insulin was associated with an increased risk of fracture HR 1.5 (CI 1.3–1.6).	II
Losada-Grande 2017 Spain, Information System for Research Development in Primary Care database, Catalonia Spain (2006–2013) [30•]	Cohort	2979 insulin users with T2D; 14,895 non-insulin users with T2D. 43.5% women	Insulin users vs. non-users	62	1.4 for insulin users and 4.6 for non-insulin users	Propensity score-matched. Adjusted for BMI and drug use	Insulin use was associated with fracture (HR 1.38, CI 1.06–1.80).	II
Ottenbacher 2002 US, Hispanic Established Population for the Epidemiological Study of the Elderly [31]	Cohort	690 with DM; 2194 controls. 585 women	Insulin users vs. controls	72 years	7	Age, gender, BMI, ever smoked, previous stroke, lower extremity functional ability, distance vision	Insulin use was associated with fracture (HR 2.57, CI 1.30–5.10).	II
Pscherer 2016 Germany, Disease Analyzer database (2000–2013) [32]	Cohort	105,960 patients with T2D. 46–48% women	Insulin users vs. OGLDs	63–66	2.0 for insulin, 2.5 for OGLD	Age, gender, drug use, comorbidity, HbA1c	No difference between insulin and OGLD in fracture risk (OR for OGLD: 0.87, CI 0.72–1.06). SU use was associated with fracture compared to no SU (OR 1.86, CI 1.06–3.29).	II
Schwartz 2000 US, Study of Osteoporotic Fractures [33]	Cohort	657 women with T2D; 8997 controls	Insulin users vs. non-users	71–72	9.4	Age, BMI, BMD	Compared to non-diabetics, insulin users and non-insulin users had an increased risk of non-vertebral fractures (RR 1.68, CI 1.19–2.35, and RR 1.30, CI 1.10–1.52, respectively).	II

Table 1 (continued)

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
SGLT-2 inhibitors								
Adimadhayam et al. 2019, US, Truven Health Market Scan (2009–2015) [34]	Cohort	61,098 patients with diabetes. 47% women	Newly initiated SGLT-2is vs. newly initiated DPP-IVis	54.7	219 days	Propensity score-matched	In the initial 14 days of SGLT-2i treatment, women had an increased fracture risk (HR 2.49, CI 2.02–6.05) as did men and women combined (HR 1.82, CI 0.99–3.32). No later effect of SGLT2i on fractures.	II
Fralick 2019 US, Two US health care databases OPTUM and MarketScan [35]	Cohort	79,964 users initiating canagliflozin; 79,964 users initiating GLP-1 RA. 45–49% women	Canagliflozin vs. GLP-1RAs	54.5–56.3	203–264 days	Propensity score-matched	No increased risk of fracture by canagliflozin treatment (HR 0.98. CI 0.75–1.26).	II
Jabbour 2018 multinational [36]	Pooled analysis of data from 13 RCTs	2295 placebo and 2360 dapagliflozin	Dapagliflozin vs. placebo or other GLD	58–59	Up to 24 weeks	N/A	No difference in fractures (0.3% in dapagliflozine group and 0.7% in placebo group).	II
Kohler 2018 Multinational, Phase I–III clinical trials and EMPA-REG H2H-SU trial [37]	Post hoc analysis of one RCT, and pooled analysis of RCTs	In EMPA-REG 1545 with T2D; in clinical trials 12,620	Empagliflozin vs. placebo or SU	N/A	Clinical trials with follow-up of 8 days to 78 weeks and one trial of 2.6 years and a 52-week extension and EMPA-REG with 208 weeks	N/A	No increased fracture risk for empagliflozin compared to SU or compared to placebo.	I–II
Schmedt 2018 Germany, InGef database (2011–2016) [38]	Case control	7522 T2D with fracture; 296,845 T2D controls. 59% women	DPP-IVis on top of metformin vs. other NIGLD on top of metformin	68	N/A	Matched by age, sex, data of entry, follow-up duration. Comorbidities, drug use.	Met+GLP-1 RA, met+SU, met + insulin and met + SGLT2-i were not associated with fracture compared to metformin+DPP-IVi	III
Tang 2016 Multinational [39••]	Meta-analysis of RCTs	38 RCTs (30,384 patients)	SGLT-2is vs. placebo or other GLDs	52–69	24–160 weeks	N/A	SGLT2-i was not associated with fracture risk when compared to active treatment (OR 1.24, CI 0.76–2.02) or placebo (OR 0.98, CI 0.80–1.20).	I–II
Ueda 2018 Sweden and Denmark, Nationwide Danish and	Cohort	17,213 new SGLT2-i users; 17,213 new GLP-1RA users. 58–62% women	SGLT-2is vs. GLP-1 RAs	60–62	270–274 days	Propensity score-matched	SGLT2-i was not associated with fracture compared to GLP-1RA (HR 1.11, CI 0.93–1.33).	II

Table 1 (continued)

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
Swedish registries (2013–2016) [40]								
Watts 2015 US [41••]	Pooled analysis of RCTs	10,194 T2D. 34–48% women	Canagliflozin vs. vs. placebo or other GLDs	58–62	52 weeks to 2.4 years	N/A	Canagliflozin was associated with an increased risk of fracture (HR 1.32, CI 1.00–1.74).	I–II
GLP-1 receptor agonists								
Cheng 2019 China [42]	Meta-analysis of 38 RCTs	39,795 with T2D	GLP-1 RAs vs. placebo or other GLDs	45.9–74.0	26 weeks to 42 months	N/A	GLP-1 RA was associated with a decreased risk of fracture (OR 0.71, CI 0.56–0.91).	I–II
Driessen 2015 UK, CPRD (2007–2012) [43]	Cohort	216,816 NIGLD users with T2D. 47% women	GLP-1 RAs vs. NIGLD	53.5 GLP-1 RA, 61 other NIGLD	5.1	Age, sex, BMI, smoking status, comorbidity, drug use, HbA1c, retinopathy, neuropathy	GLP-1RA was not associated with fracture compared to other NIGLD (HR 0.99, 0.82–1.19).	II
Driessen 2015 Denmark, DNH [44]	Case control	229,145 T2D cases (fracture); 229,145 controls. (14,353 NIGLD users in total). 56% women	GLP-1 RAs vs. non-incretin NIGLD	55	N/A	Life-style, comorbidity, drug use	GLP-1RA was not associated with fracture compared to non-incretin NIGLD (OR 1.16, CI 0.83–1.63).	III
Mabilleau 2014 France [45]	Meta-analysis of RCTs	7 RCTs (2913 GLP-1 RA-treated patients; 1337 controls)	GLP-1 RAs vs. placebo or other GLDs	53–59	26–104 weeks	N/A	GLP-1 RA was not associated with fracture (OR 0.75, CI 0.28–2.02).	I–II
Su 2015 [46]	Meta-analysis of RCTs	16 RCTs (11,206 patients)	GLP-1 RAs vs. placebo or other GLDs	46–60	12–104 weeks	N/A	Liraglutide was associated with a decreased risk of fracture (OR 0.38, CI 0.17–0.87), whereas exenatide was associated with an increased risk of fracture (OR 2.09, CI 1.03–4.21).	I–II
DPP4-inhibitors								
Chen 2019 China [47]	Meta-analysis of 87 RCTs	93,772 participants.	DPP-IVis vs. placebo or other GLDs	49.7–78.3	12 weeks to 43 months	N/A	DPP-IVi was not associated with fracture risk compared to placebo or active comparators (OR 1.01, CI 0.90–1.12).	I–II
Dombrowski 2017 Germany, IMS HEALTH (2008–2014) [48]	Cohort	4160 users of DPP-IVi and 4160 non-users. All users of metformin and T2D diagnosis.	DPP-IVis vs. non-user	61.6	Not specified	Matched by age, sex, diabetes duration, BMI, index year, physicianAdjusted for daily	DPP-IVi was associated with a reduced risk of fractures HR 0.67 (CI 0.54–0.84).	II

Table 1 (continued)

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
		40% women				metformin dose, HbA1c, complications, comorbidities		
Driessen 2014 UK, CPRD (2007–2012) [49]	Cohort	216,816 with prescription of NIGLD matched to 216,816 control. 43–47% women	DPP-IVis vs. controls or NIGLDs	59–61	5.0	Age, sex, BMI, smoking, complications, comorbidity, drug use	No increase in fracture risk with DPP-IVi (HR 0.89, CI 0.71–1.13) nor with DPP-IVi+insulin use (HR 1.36, CI 0.97–1.90). Increased risk with DPP-IVi+glitazone use (HR 1.77, CI 1.42–2.20). No increased fracture risk in DPP-IVi users compared with other NIGLD users.	II
Driessen 2015 Denmark, DNH [50]	Case control	229,145 cases (fracture); 229,145 controls. (14,653 NIGLD users in total). 55.6% women	DPP-IVis vs. other (non-GLP-1 RA) NIGLDs	55	N/A	Age, sex, life-style, comorbidity, drug use	DPP-IVi use was not associated with fracture (OR 0.97, CI 0.79–1.18).	III
Driessen 2017 UK, CPRD (2007–2015) [51]	Cohort	328,254 NIGLD users, of these 46,355 DPP-IVi users. 42–49% women	DPP-IVis vs. NIGLDs	59.7–61.5	6.3 DPP-IVi, 5.6 other NIGLDs	Age, sex, BMI, HbA1c, previous fractures and falls, life-style, comorbidity, drug use	DPP-IVi use was not associated with fracture (HR 0.99, CI 0.93–1.06). No increased fracture risk in users of DPP-IVi for any duration of use (up to 8.5 years), except 2.0–2.9 years (HR 1.23, CI 1.03–1.48).	II
Gamble 2017 UK, CPRD (2007–2016) [52]	Cohort	7993 new users of DPP-IVi and 26,636 new users of SU. 40% women	DPP-IVis vs. SUs	58.8	1.2	Propensity score-adjusted, number of GLDs used	No increased risk of fracture by DPP-IVi use compared to SU (HR 0.80, CI 0.51–1.24) or compared to insulin. However, lower risk when compared to glitazones (HR 0.47, CI 0.26–0.83).	II
Hou 2018 Taiwan, Longitudinal Cohort of Diabetes Patients (2009–2013) [53]	Cohort	3996 metformin and DDP-IVi users; 3996 non-DPP-IVi users. 46% women	DPP-IVi vs. other second-line GLDs	54	Not specified. Maximum 5 years	Propensity score-matched	DPP-IVi use was associated with a reduced risk of fractures (HR 0.86, CI 0.74–0.99).	II
Josse 2017 multinational [54••]	Post hoc analysis of TECOS study RCT	7332 sitagliptin and 7339 placebo. 29% women	Sitagliptin vs. placebo or other GLDs	65.5	3.0	N/A	No difference in fractures (HR 1.01, CI 0.82–1.23) between groups. Metformin use associated with lower risk of fracture (HR 0.76, CI 0.59–0.98) and Insulin use associated with increased risk of	I–II

Table 1 (continued)

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
							fracture (HR 1.40, CI 1.02–1.91). No associations between SU or Glitazone use and fracture.	
Majumdar 2016 US, Clinformatics Data Mart Database; OptumInsight (2004–2010) [55]	Cohort	72,738 patients with T2D. 44–46% women	Sitagliptin vs. non-users	52	2	Age, sex, socio-economic, comorbidity, drug use, propensity score	Sitagliptin (HR 1.1, CI 0.8–1.4), metformin (HR 1.0, CI 0.8–1.2) were not associated with fracture. SU (HR 1.3, CI 1.1–1.5), glitazones (HR 1.2, CI 1.0–1.5) and insulin (HR 2.1, CI 1.6–2.8) were associated with fracture.	II
Mosenzon 2015 US, SAVOT-TIMI 53 Trial [56]	Post hoc analysis of RCT	8280 treated with saxagliptin and 8212 treated with placebo. 33–49% women	Saxagliptin vs. placebo	65	2.1	Treatment and clinically meaningful baseline variables: not specified.	Saxagliptin was not associated with fracture (HR 1.0, CI 0.83–1.19). Insulin use at baseline was associated with fracture (HR 1.45, CI 1.21–1.73), although nonsignifiant after adjustment for diabetes duration.	I–II
Ustulin 2019 Korea, National Health Insurance Service (2009–2014) [57]	Cohort	1410 DPP-IVi users; 4172 non-DPP-IVi users; 5582 controls. 33–45% women	DPP-IVis vs. non-users	Not specified	3.11–4.09	Age, gender, drug use, diabetes severity, comorbidities	DPP-IVi use was not associated with fracture compared to non-users or controls.	II
Glitazones								
Bazelier 2012, Denmark, DNH (1996–2007) [58]	Cohort	180,409 OGLD users; 490,147 controls. 47% women	Glitazones vs. other GLD	62.6	5.3	Age, gender, drug use, cerebrovascular disease, history of fracture	Compared to other GLDs, users of glitazones had a significantly increased risk of fractures at foot/ankle HR 1.54 (CI 1.17–2.04), tibia/fibula HR 1.70 (CI 1.22–2.37), and decreased risk of hip fractures HR 0.61 (CI 0.39–0.96). The risk of any osteoporotic fracture was also increased in those with 30 or more prescriptions of glitazones (OR 3.03, CI 2.03–4.52).	II
Bazelier 2012, the Netherlands, PHARMO RLS [59]	Cohort	123,452 patients with T2D; 451,388 controls; 53% women.	GLD users, divided by stage vs. controls	64	4.5	Age, sex, use of statins	Users of glitazones (regardless of co-medication) had an HR of 1.49 (CI 1.28–1.73), although this was only significant in females (HR 1.64, CI 1.41–1.92)	II

Table 1 (continued)

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
							but not in males (HR 1.22, CI 0.94–1.56). Users of metformin or SU had an HR of 1.11 (CI 1.06–1.17), users of metformin and SU an HR of 1.03 (CI 0.96–1.11), and users of insulin (regardless of co-medication) an HR of 1.24 (CI 1.14–1.36).	
Bazelier 2013 Netherlands, UK, and Denmark, GPRD, RLS, DNH [60•]	Meta-analysis of cohorts	196,025 patients with diabetes and 196,024 controls (GPRD); 123,452 patients with diabetes and 451,388 controls (RLS); 180,049 patients with diabetes and 490,147 controls (DNH). 45.1–52.9% women	Glitazone users vs. other GLDs	61.6–64.3	3.8–5.5	Matched on age and sex. Adjusted by age, sex, use of other GLDs	Current glitazone treatment increased any fracture risk (HR 1.27, CI 1.21.1.34); however, this was not present in a sensitivity analysis for men.	I–II
Bilezikian, 2013, Multicenter [61]	Double blinded RCT	225 postmenopausal with T2D	Rosiglitazone vs. metformin	63.8	52 weeks	N/A	5 fractures in glitazone group, 1 in metformin group.	II
Habib 2017 US, Health maintenance organization in Michigan (2000–2007) [62]	Cohort	19,070 patients with diabetes. 50.5% women	Glitazone users vs. non-users	58.3	3.0 for non-glitazone and 4.99 for glitazone	Age, sex, race, life-style, comorbidity, drug use, HbA1c	Glitazones increased fracture risk (HR 1.34, CI 1.05–1.71), this was only present in women but not men in sensitivity analyses.	II
Home 2009 Multinational, RECORD study [63]	RCT	4447 patients with T2D on metformin or SU monotherapy. 49–54% women	Rosiglitazone + metformin/SU vs. metformin and SU	57.0–59.8	5.5	N/A	Rosiglitazone increased fracture risk (RR 1.57, CI 1.26–1.97); only significant in women in sensitivity analysis.	I–II
Hsiao 2010 Taiwan, Taiwan National Health Insurance (2000–2005) [64]	Case control	18,003 with fracture; 90,015 matched controls. 54.2–60.6% women	Glitazone vs. non-users	62.4	N/A	Diabetes severity, drug use, comorbidities	Cumulative glitazone use more than 180 days was associated with hospitalization for fracture (OR 1.54, CI 1.37–1.74). This was significant in both men and women (OR 1.23, CI 1.02–1.50, and OR 1.76, CI 1.52–2.04, respectively). For 30–180 days of cumulative use, the effect was similar but not significant in men.	III

Table 1 (continued)

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
Kahn 2008 multinational [65]	Post hoc analysis of the ADOPT RCT	1840 women and 2511 men all with T2D	Rosiglitazone vs. metformin or glyburide	56–57	4.0	Weight, serum creatinine, hematocrit, calcium, HbA1c, waist circumference	In men, fracture rates did not differ between groups. In women, rosiglitazone increased fracture risk compared to metformin and glyburide (HR 1.81, CI 1.17–2.80, and HR 2.13, CI 1.30–3.51, respectively).	I–II
Lin 2017 Taiwan, Taiwan National Health Insurance (2000–2013) [66]	Case control	603 T2D with hip fracture and 603 controls. 66% women	Glitazones vs. other GLDs	77	N/A	Matched on age, comorbidities, index year. Adjusted for DM duration and unspecified covariates	Glitazone use was associated with hip fracture (OR 1.64, CI 1.01–2.67).	III
Loke 2009 [67••]	Meta-analysis of 10 RCTs	13,715 T2D. 38.6% women in studies analyzing by sex	Glitazones vs placebo or GLD	Not specified	1–4	N/A	Fracture risk was higher in the glitazone-treated group (HR 1.45, CI 1.18–1.79); in sex-specific analyses, this was significant in women (HR 2.23, CI 1.65–3.01) but not in men (HR 1.00, CI 0.73–1.39).	I
Mancini 2009 Italy, consecutively recruited [68]	Cross-sectional	43 men with T2D and 22 controls	Rosiglitazone + metformin vs. metformin only	66	N/A	Age, BMI	Rosiglitazone was associated with vertebral fracture risk (OR 6.5, CI 1.3–38.1). Multiple VF were more common in metformin monotherapy than controls ($p < 0.05$).	III
Schwartz 2015 US, ACCORD post hoc analysis [69••]	Cohort	6865 T2D 35% women	Glitazone discontinuation	62.4	4.8	Age, race, BMI, smoking, diabetes duration, HbA1c, insulin use, comorbidities	Glitazone use was associated with non-vertebral fractures in women; however, effects were attenuated when glitazones were discontinued (HR 0.42, CI 0.24–0.74 when comparing discontinuation > 2 years with current users).	II
Solomon 2009 US, Medicare beneficiaries from one US state (1997–2005) [70]	Cohort	2347 glitazone monotherapy; 13,709 SU monotherapy; 4235 metformin monotherapy. Although patients were categorized as being in monotherapy,	Glitazone vs. SU or metformin	76–78	10 months	Age, sex, race, diabetes severity, insulin use, comorbidities, drug use	With metformin or SU as a reference, glitazone was not significantly associated with fractures (RR 1.31, CI 0.98–1.77, and RR 1.21, CI 0.94–1.55, respectively).	II

Table 1 (continued)

Study (author, year, country, and source)	Design	Population	Glucose-lowering drug investigated vs. comparator	Mean/ median age (years)	Mean/median follow-up (years unless otherwise specified)	Adjustment	Results	CEBM Evidence level
		some used insulin. 75–79% women						
Tzoulaki 2009 UK, GPRD (1990–2005) [71]	Cohort	91,521 T2D, patients using insulin were excluded. 46–51% women	Glitazones or SU vs. metformin	65	7.1	Age, sex, duration of DM. Additional variables unspecified.	Rosiglitazone combination therapy increased fracture risk compared to metformin monotherapy (HR 1.53, CI 1.25–1.88). SU was not associated with hip fracture.	II

95% confidence interval (CI), body mass index (BMI), Charlson Comorbidity Index (CCI), Clinical Practice Research Datalink (CPRD), diabetes mellitus (DM), Danish National Health Registers (DNH), dipeptidylpeptidase-IV inhibitors (DDP-IVi), Dutch PHARMO Record Linkage System (RLS), General Practice Research Database (GPRD), glycated hemoglobin A1c (HbA1c), glucagon-like peptide-1 receptor agonists (GLP-1 RA), glucose-lowering drug (GLD), hazard ratio (HR), non-insulin glucose-lowering drug (NIGLD), not applicable (n/a), odds ratio (OR), oral glucose-lowering drug (OGLD), randomized controlled trial (RCT), relative risk (RR), sodium–glucose co transporter-2 inhibitors (SGLT-2i), sulphonylureas (SU), T2D (type 2 diabetes)

Non-user refers to non-users of the specific GLD; for instance, the comparators could use different combinations of other GLD or receive no pharmaceutical treatment

times, included patients by different criteria, and performed different comparisons and analyses, they were considered to be unique and eligible for inclusion. Two studies by Driessen and colleagues both used the Clinical Practice Research Datalink for the years 2007–2020 and 2007 with comparable populations investigating DPP-IVis and fracture. However, the study with the shortest follow-up duration presented additional analyses for insulin and glitazones and was thus included [49, 51].

In the following, the findings for each drug group are presented and discussed.

Metformin

Studies examining the effects of metformin were mainly observational studies. However, one RCT with a 4-year follow-up time reported a reduced risk of fractures in metformin users compared to rosiglitazone users [65]. Metformin monotherapy was associated with an increased fracture risk when compared to a non-diabetes population and a T2D population not using glucose-lowering drugs [14, 59]. However, metformin was mainly associated with neutral outcomes [13, 15, 20, 24, 55, 59] or decreased fracture risk [9, 17, 19, 23, 54••] in comparison to treatment with other glucose-lowering drugs. The interpretation of metformin in terms of fracture risk appears to depend on the comparator used. Based on the current evidence, metformin appears to be neutral in terms of fracture risk, although no final conclusions can be drawn.

Sulphonylureas

An RCT with a median treatment time of 4 years reported a reduced risk in glyburide users compared to rosiglitazone [65]. This RCT also compared rosiglitazone with metformin, and the fracture rates among metformin and glyburide users were similar, although not formally compared [65]. These findings seem to highlight the importance of the comparator used. Observational studies, however, have reported disparate effects of sulphonylureas. Some studies found sulphonylureas—as monotherapy or in combinations—to be associated with an increased fracture risk in comparison to other glucose-lowering drugs [14, 15, 18, 23, 32, 59], whereas other studies reported neutral effects on fracture outcomes [13, 18, 20, 24, 59, 60•, 71]. In two studies, sulphonylurea treatment was associated with a reduced risk of fracture [9, 16]. Compared to non-sulphonylurea users, sulphonylurea use was associated with increased fracture risk in men with HbA1c < 6.5% [17]. To illustrate the divergence of findings between studies examining sulphonylureas: one propensity-matched study with new users of sulphonylureas and with metformin as the comparator reported no difference in fracture risk in T2D [26•], whereas another propensity-matched study where sulphonylureas were compared with other oral glucose-lowering drugs reported an increased hip fracture risk in patients using sulphonylureas [27]. These differences may reflect differences in the cohorts; the study by Lapane et al. included very mild diabetes (monotherapy) with a low risk of hypoglycemia, whereas the other study also included patients that were treated with multiple drugs [27]. A recent meta-analysis reported a 14% increased fracture risk in sulphonylurea users compared to T2D treated with different comparators [74]. Thus, the evidence on sulphonylureas is inconclusive.

Glitazones

A meta-analysis of ten RCTs reports increased fracture risk in female glitazone users compared to placebo or an active comparison [67••]. In addition, two RCTs showed that rosiglitazone was associated with a 57–81% increased fracture risk compared to metformin or sulphonylureas, the finding being significant only in women and not in men [63, 65]. In observational studies, glitazones users had an increased fracture risk compared to non-glitazone users, users of metformin in monotherapy, users of other glucose-lowering drugs, or non-diabetics [13, 14, 16, 23, 55, 59, 60•, 62, 64, 66, 68, 71]; however, in some studies which differentiated between men and women, the increased fracture risk was only present in women [13, 60•, 62, 64]. Furthermore, a study investigating discontinuation of glitazones reported that discontinuation significantly attenuates the fracture risk [69••]. However, glitazones were also associated with neutral outcomes in some studies compared to metformin monotherapy, sulphonylurea monotherapy, or other glucose-lowering drugs [18, 24, 70]; one such study reported a confidence interval from 0.98 to 1.77 [70], another study had only 32 (0.2%) glitazone users [18], and a study had 0.1% glitazone users [24]. Although the RCTs have not been conducted with fracture as the primary outcome, the evidence is compelling that glitazones increase fracture risk in women, whereas it is more uncertain in men.

Insulin

In regard to fracture risk, several studies report that insulin use was associated with an increased fracture risk compared to other glucose-lowering drugs, non-insulin use, metformin monotherapy, or non-diabetics [15–22, 25, 31, 54••, 55, 59], but insulin use was also associated with neutral outcomes in other studies using similar comparators [9, 13, 24, 28, 32]. A study comparing women with T2D with non-diabetics reported that insulin users had an increased fracture risk, but so did non-insulin users [33]. A study investigating switch from oral glucose-lowering drugs to insulin found that this was associated with an increased fracture risk [29••], and in a propensity score-matched study insulin users displayed an increased fracture risk compared to non-insulin users [30•]. The evidence on

insulin use and fracture risk is difficult to decipher, as insulin therapy in T2D may be related to longer diabetes duration and severity, and epidemiologic studies may include T1D incorrectly classified as insulin using T2D, thereby overestimating fracture risk. Furthermore, some studies compare to a non-diabetic reference [28, 31, 33], whereas others compare to other patients with diabetes [18, 29••, 32]. Similarly to sulphonylureas, insulin use is associated with a risk of hypoglycemia. Insulin-treated patients with DM have a higher risk of low-impact falls [75], and under the assumption of frail bones this may lead to fractures. The combination of insulin and sulphonylureas was associated with a twofold increased risk of hip fracture [15], and insulin use was associated with increased fracture risk in men with HbA1c < 6.5% [17]. Insulin use was associated with a reduced risk of fracture in one study [23]. Thus, physicians should be aware that the risk of hypoglycemia associated with insulin may lead to fractures.

DPP-IV Inhibitors

Most population-based observational studies reported no association between DPP-IVis and fracture, even in those with a treatment duration of 4 years or more compared to non-insulin glucose-lowering drugs or non-DDP-IVi use [49–52, 55, 57]. Neither in combination with metformin [14, 18] nor with insulin and metformin [18] could an association be found between DPP-IVi treatment and fracture when compared to metformin monotherapy or non-DPP-IVi use. However, DPP-IVis were associated with a reduced risk of fracture in one study where they were compared to glitazones [52] and in two population-based studies compared to non-DPP-IVi use [48, 53], although one of these studies may be subject to immortal time bias [48]. In post hoc analyses of RCTs, DPP-IVi treatment was not associated with fracture compared to placebo [54••, 56]. In a meta-analysis of RCTs, DPP-IVi treatment was not associated with fractures compared to placebo or other glucose-lowering drugs [47]. However, the meta-analysis is limited by short follow-up durations (12 weeks to 43 months). In terms of fracture risk, treatment with DPP-IVi appears to be safe.

GLP-1 Receptor Agonists

GLP-1 RA treatment was associated with neutral fracture related outcomes in cohort studies [24, 43, 44]. In a meta-analysis of RCTs with follow-up durations between 26 weeks and 42 months, GLP-1 RA treatment was associated with a reduced fracture risk [42], whereas other meta-analyses of RCTs reported neutral results [45, 46]. These meta-analyses are limited by short durations of follow-up (12 to 104 weeks). The current evidence, thus, points to neutral effects on fracture risk in patients with T2D.

Sodium-Glucose Cotransporter 2 Inhibitors

The current evidence from observational studies and RCTs is sparse and limited by short durations of follow-up. No difference in fracture risk was observed in two propensity score–matched cohort studies comparing new users of SGLT2-is with new users of GLP-1 RA [35, 40]. In a propensity score–matched cohort study comparing new users of SGLT2-is with new users of DPP-IVi, an initial increase in fracture risk was observed in SGLT2-i users; however, this attenuated with longer treatment duration [34]. The finding is supported by a case-control study where combination treatment of metformin and SGLT2-is was not associated with fracture when compared to metformin and DPP-IVi in combination [38]. The initial fractures might be due to initial episodes of hypoglycemia in this study sample. However, users of insulin were excluded from the study, and SGLT2-is are in general considered safe in terms of hypoglycemia, wherefore we speculate this to be a chance finding. A meta-analysis of RCTs limited by short study durations (24–160 weeks) and a pooled analysis of 13 RCTs (of 12 or 24 weeks' duration) reported no increased fracture rate in SGLT2-i users compared to placebo or active treatment [36, 39••]. Another meta-analysis of RCTs with at least 52 weeks of follow-up reported a 32% increased fracture risk compared to placebo or active treatment [41••]. A post hoc analysis collating data from RCTs reported no increased fracture risk in SGLT2-i users compared to users of sulphonylureas or placebo [37]. Although the evidence in general supports no effect of SGLT2-is on fracture risk, the pooled analysis of data from RCTs reported an increased fracture risk in canagliflozine treated subjects [41••]. However, this study was compromised by short duration of treatment and of follow-up [41••].

Discussion

This systematic overview has presented data on the associations between glucose-lowering drugs and fracture risk. As highlighted, short study durations presented major limitations in both RCTs and meta-analyses, making assessment of fracture risk difficult. Fracture outcomes in studies with short durations (less than 1 year) would expectedly be due to falls and hypoglycemia, whereas long-term alterations of bone quality and structure expectedly evolve after a longer exposure. Although this review assesses several levels of evidence, the RCTs had limited study size in comparison to cohort studies. Observational studies, although examining larger population sizes, are subject to inherent bias, such as confounding by indication and comparison of dissimilar T2D populations. In addition, individuals with T1D may have been misclassified as having T2D in some studies, and registry data on medication are similarly subject to flaw.

Metformin is the backbone of T2D treatment. In vitro studies suggest that metformin is bone anabolic by increasing osteoblastogenesis via increased Runx2 secretion [76]. However, in humans treatment with metformin for 12 months, treatment did not change C-terminal cross-linked telopeptide of type-I collagen (CTX) levels, but bone specific alkaline phosphatase and pro-collagen type I N-terminal propeptide (P1NP) levels were reduced [77], and circulating metformin levels were not associated with CTX or P1NP levels [78].

The studies included in this review examining metformin were observational studies, and various comparators were used. Overall, the evidence points towards a neutral effect of metformin on fracture risk.

Sulphonylureas were found in an animal study to increase bone formation and inhibit changes caused by estrogen deficiency [79]. In humans, 12 months of glyburide treatment did not change CTX levels, and P1NP was slightly reduced, although to a lesser extent compared to metformin use [77]. Sulphonylureas are associated with hypoglycemic episodes [15], although a systematic review concluded that the evidence was too sparse to conclude that sulphonylureas increase risk of falls [80]. However, falls represent a plausible mechanism by which sulphonylurea-induced hypoglycemia may increase fracture risk. The findings regarding sulphonylureas in this review were more disparate, however, as some studies reported neutral outcomes, while others reported either increased or decreased fracture risk. These seemingly contrasting findings may be due to differences between studies, as there appears to be a difference between individuals in monotherapy and individuals treated with multiple glucose-lowering drugs. However, it is worth considering whether the increased risk of hypoglycemia is associated with an increased fracture risk mediated by falls in individuals with strict glycemic control or concomitant use of insulin.

Glitazones are the glucose-lowering drugs with the most evidence on bone health and fracture risk. Glitazones cause differentiation of mesenchymal stem cells into an adipocytic lineage instead of an osteoblastic lineage [81]. Humans treated with glitazones have demonstrated increased CTX levels, reduced P1NP levels [77], and lower BMD [67••].

Glitazones were well-examined compared to the other glucose-lowering drugs, and the evidence points more clearly towards an increased fracture risk in women, whereas the evidence is less definitive in men. Thus, caution should be taken when prescribing glitazones to women.

Insulin is suggested to be bone anabolic [82]. In a murine model of type 1 diabetes, treatment with insulin led to significantly less bone loss [83]. Thus, insulin and addition of exogenous insulin may improve bone mass. However, a study reported no acute changes in bone turnover markers at different insulin levels in both non-diabetic subjects and patients with T2D [84]. The type of insulin seems to be of no consequence, as CTX and P1NP increased similarly in both groups after randomization to 2 years of treatment with short-acting insulin (aspart) or long-acting insulin (NPH, neutral protamine Hagedorn) [78]. With regard to fracture risk, insulin treatment was associated with varying findings, although several studies reported increased fracture risk. This may be related to misclassification of T1D as T2D and may also be related to more severe diabetes in individuals receiving insulin than in non-insulin users. However, the risk of hypoglycemia associated with insulin use may be a cause of falls and fractures.

Hypoglycemia is an unwanted side effect of both insulin and SUs. If these drugs can be administered without causing hypoglycemia and fall risk, it may be possible to avoid an increased risk of fractures.

In vitro studies have suggested that DPP-IVis influence bone metabolism by prolonging the effects of gastric inhibitory peptide (GIP) [85], and in T1D patients GIP infusion decreased CTX levels independently of glycemia [86]. Also, sitagliptin inhibited bone resorption in vitro [87].

In almost all studies, DDP-IVis were not associated with fracture risk, suggesting that DPP-IVi treatment is probably safe with regard to fracture, although most studies were observational and intervention studies were limited by short follow-up.

Thus, the evidence suggests that DPP-IVis are safe in terms of fracture risk, albeit with no protective effect.

GLP-1 RA constitutes a relatively new glucose-lowering drug group which has cardioprotective effects [88]. Osteoblastic cell lines express GLP-1 receptors, and GLP-1 increases osteoblastic differentiation and proliferation [89] and GLP-1 receptor knockout mice had an increased number of osteoblasts and reduced bone mass [90]. In an RCT on patients with T2D, liraglutide treatment for 26 weeks did not alter CTX or P1NP despite weight loss and preserved hip BMD compared to the placebo group [91]. Additionally, in obese subjects undergoing weight loss by caloric restriction liraglutide prevented bone loss and increased P1NP compared to controls [92]. Although the preclinical and clinical evidence points to potential beneficial effects of GLP-1 RAs on bone, GLP-1 RAs were not associated with fracture risk in the presented studies. However, it is worth considering whether GLP-1 RAs may protect bones during weight loss, which is associated with frailty fractures in T2D [93]. It is expected that the numbers treated with GLP-1 RAs will increase due to the cardioprotective effect. Thus, it is important to observe potential side effects such as fracture in the coming years.

SGLT2-is are also a relatively new group of glucose-lowering drugs with both cardioprotective and renoprotective effects [94, 95]. In terms of bone health, it was hypothesized that the glucosuria seen in SGLT2-i treatment would cause an osmotic loss of minerals and thereby bone loss. Diabetic mice treated with SGLT2-is had impaired cortical and trabecular bone microarchitecture and increased CTX levels compared with non-treated animals [96]; however, not all animal studies

found detrimental effects of SGLT2-is [97]. In older patients with T2D, levels of CTX and P1NP increased and a small yet significant bone loss was observed in canagliflozin-treated patients with T2D compared with placebo-treated patients with T2D [98]. Thus, it is unclear whether SGLT2-is have a negative effect on bone health. However, it is also worth considering whether SGLT2-is has an indirect effect on fracture risk by inducing weight loss [99].

SGLT2-is was not associated with fracture risk in most of the included studies, although a pooled analysis of data from RCTs with 1–2 years of follow-up did report an increased fracture risk. There may be differential effects among SGLT2-is as Watts et al. found canagliflozine to be associated with an increased risk of adjudicated fractures with a HR of 1.32 (95% CI 1.00–1.74) [41••] and the meta-analysis by Tang et al. reported a pooled OR of 1.24 (95% CI 0.79–1.95) [39••]. Although non-significant, the meta-analysis by Tang et al. is suggestive of an increased fracture risk in canagliflozine users. In contrast, neither dapagliflozine nor empagliflozine were associated with fracture risk in the pooled analyses [36, 37, 39••]. Thus, future studies should examine possible differential effects of SGLT2-is. As more patients will be treated with these drugs and current studies have relatively short follow-up periods, it is important to follow potential fractures in SGLT2-i and GLP-1 RA-treated individuals and patients undergoing intended weight loss.

Metformin is an insulin sensitizer, and SGLT2-i and GLP-1 RA both cause a mild to moderate weight loss; thus, these drugs are commonly used in obese T2D subjects. Metformin, SGLT2-is, and GLP-1 RAs all appear to be neutral in terms of fracture risk; however, this may be partly due to confounding by indication in observational studies; as increasing BMI is associated with increased BMD and obesity itself is associated with reduced fracture risk [100], although debated as abdominal obesity has been associated with fractures [101]. In addition, obese individuals may be less prone to hypoglycemia due to insulin resistance.

The uncertainty in interpreting the results of studies on fracture risk and glucose-lowering drug use is emphasized by the fact that while studies have found increased fracture risk in individuals with T2D [1••], some studies have found the effect to be fully attenuated after adjusting for insulin use [25, 102]. Fracture risk may, for instance, be elevated in certain diabetic populations due to a variety of factors influencing fall risk in addition to hypoglycemia. Apart from age being a risk factor for falls [103], diabetes itself is associated with an increased risk of falls [104] at least in part due to polypharmacy, poor walking function (including affected posture and gait), and reduced cognitive function [105, 106]. Gait performance may be affected by complications to diabetes, such as diabetic sensory neuropathy [107], diabetic retinopathy [108], or reduced muscle strength [109]. In addition, concomitant drug use (e.g., antihypertensive drugs) and comorbidities (e.g., dizziness and cardiovascular disease) increase fall risk [110].

Finally, a general concern with registry studies is underreporting; both fracture rates and T2DM prevalence may be subject to error, leading to underestimation of associations.

Conclusion

Metformin, dipeptidylpeptidase-IV inhibitors, glucagon-like peptide-1 receptor agonists, and sodium–glucose cotransporter 2-inhibitors appear to be safe with regard to fracture risk. Results for insulin and sulphonylureas were more disparate, although there may be an increased fracture risk related to hypoglycemia and falls with these treatments. Glitazones were consistently associated with increased fracture risk in women, although the evidence was sparser in men.

When prescribing glucose-lowering drugs, particularly to the elderly osteoporosis-prone population, care must be given in determining the right drug to prescribe, and fracture risk should be considered in this assessment. In particular, it is worth noting the introduction of new glucose-lowering drugs and changes in possible prescription patterns.

It is important to gain a better understanding of the effects of different glucose-lowering drugs on fracture risk, as fractures lead to higher morbidity and mortality, and evidently more so in the diabetic population [111]. Therefore, our findings warrant continued research on the effects of glucose-lowering drugs on fracture risk, elucidating the class-specific effects of these drugs.

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Compliance with Ethical Standards

Zheer Al-Mashhadi and Jakob Starup-Linde drafted the manuscript, conducted the systematic literature search contributed to the interpretation of data, critical editing of written text, and approved the final version of the manuscript. Rikke Viggers, Rasmus Fuglsang-Nielsen, Frank de Vries, Joop van den Bergh, Torben Harsløf, Bente Langdahl, and Søren Gregersen contributed to the interpretation of data, critical editing of written text, and approved the final version of the manuscript.

Conflict of Interest Z Al-Mashhadi, R Viggers, R Fuglsang-Nielsen, JP van den Bergh, T Harsløf and S Gregersen declare no conflict of interest.

J. Starup-Linde reports personal fees from GSK Pharma A/S and Gilead Sciences Denmark, outside the submitted work.

F. de Vries supervises three PhD students who are currently employed with F. Hoffmann La Roche Ltd. (Welwyn Garden City UK and Basel, Switzerland). The topics of their PhDs do not relate to the current study. Dr. de Vries has not received any fees or reimbursements for this.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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PRISMA flow diagram adapted from *From* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:https://doi.org/10.1371/journal.pmed1000097