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REVIEW

Sodium-Glucose Co-Transporter 2 Inhibitors and Fracture Risk

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ABSTRACT

Patients with type 2 diabetes mellitus (T2DM) appear to have increased risk for fractures. In this context, the finding that canagliflozin, a sodium-glucose co-transporter-2 (SGLT) inhibitor, increased the risk for fracture compared with placebo in the Canagliflozin Cardiovascular Assessment Study (CANVAS), a large randomized controlled trial (RCT) in patients with established cardiovascular disease or multiple cardiovascular risk factors, created concern. In the present review, we summarize the data regarding the association between SGLT2 inhibitors and fracture risk in patients with T2DM. In contrast to the findings reported in CANVAS, canagliflozin did not affect the risk of fracture in a more recent, large RCT in patients with diabetic nephropathy. In addition, empagliflozin and dapagliflozin, other members of this class, also do not appear to affect the incidence of fracture. Moreover, there is no clear pathogenetic mechanism through which SGLT2 inhibitors increase the risk for fractures. Therefore, available data are inconclusive to attribute to these drugs a direct responsibility for bone fractures.

Keywords: Canagliflozin; Dapagliflozin; Empagliflozin; Fracture; Sodium-glucose co-transporter-2 inhibitors; Type 2 diabetes mellitus

Key Summary Points

Patients with type 2 diabetes mellitus appear to have increased risk for fractures.

Canagliflozin, a sodium-glucose co-transporter-2 (SGLT) inhibitor, increased the risk for fracture compared with placebo in a large randomized controlled trial (RCT) in patients with established cardiovascular disease or multiple cardiovascular risk factors but not in a more recent, large RCT in patients with diabetic nephropathy.

Empagliflozin and dapagliflozin, other members of this class, also do not appear to affect the incidence of fracture.

There is no clear pathogenetic mechanism through which SGLT2 inhibitors increase the risk for fractures.

Overall, available data are inconclusive to attribute to SGLT2 inhibitors a direct responsibility for bone fractures.

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INTRODUCTION

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the newest class of oral medications for the management of type 2 diabetes mellitus (T2DM) [1]. Canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin have already been approved by the US Food and Drug Administration (FDA) for the management of T2DM [2, 3], whereas luseogliflozin, tofogliflozin, and ipragliflozin have been approved in Japan [4–6]. The SGLT2 inhibitors can be used either as monotherapy or in combination with other antidiabetic agents. In randomized clinical trials, canagliflozin, dapagliflozin, and empagliflozin reduced the risk for hospitalization for heart failure and empagliflozin also reduced cardiovascular and all-cause mortality [7–9]. Accordingly, in patients with T2DM and established cardiovascular disease, SGLT2 inhibitors and glucagon-like peptide 1 receptor agonists with proven reduction of the cardiovascular risk are proposed as the preferred add-on therapy to metformin, when combination treatment is needed [10].

Despite these beneficial effects of SGLT2 inhibitors on cardiovascular events, an increased risk of fractures was observed in the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial in patients treated with canagliflozin [7]. In contrast, the incidence of fractures did not differ between patients treated with placebo and either dapagliflozin or empagliflozin in the Dapagliflozin Effect on Cardiovascular Events trial (DECLARE-TIMI 58) and the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients trial (EMPA-REG OUTCOME), respectively [8, 9]. These findings have potential implications in patients with T2DM, who appear to be at increased risk for fractures [11, 12]. In the present review, we summarize the data regarding the association between SGLT2 inhibitors and fracture risk in patients with T2DM. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

SEARCH STRATEGY

The PubMed database was reviewed for papers using the terms “diabetes”, “sodium-glucose co-transporter 2 inhibitors”, “canagliflozin” “dapagliflozin”, “empagliflozin”, “fracture”, and “bone”. The references of pertinent articles were also hand-searched for relevant papers. Only studies published in English were considered.

T2DM AND FRACTURES

In the Rotterdam study, patients with T2DM had 1.33 times higher risk for nonvertebral fractures than nondiabetic subjects [11]. Paradoxically, diabetic patients have higher bone mineral density (BMD) [11]. In another study, patients with T2DM also had greater risk for vertebral fractures than nondiabetic individuals [12]. Interestingly, this increase in risk was independent of BMD (Table 1) [12].

Several mechanisms have been proposed to explain the association between T2DM and fractures. Advanced glycation end products (AGEs) are accumulated in the bones and contribute to the low bone quality in diabetic patients [13]. Indeed, serum levels of pentosidine appear to be associated with the risk of fracture in patients with T2DM [14]. Moreover, insulin and insulin-like growth factor 1 (IGF1) have an important anabolic effect on bone metabolism. Low levels of IGF1 are associated with increased risk for fractures [15]. Osteocalcin, which is mainly produced by osteoblasts, is a bone formation marker [16]. Serum osteocalcin levels in women with T2DM are lower compared with nondiabetic women [17, 18]. Moreover, there is an inverse association between serum osteocalcin levels and both fasting glucose levels and insulin resistance [19]. Incretins have also been implicated in the pathogenesis of increased fracture risk in patients with T2DM. The gastric inhibitory polypeptide (GIP) contributes to the promotion of bone formation and to the reduction of bone absorption and is reduced in patients with T2DM [20]. Sclerostin, a protein that is expressed in osteocytes, is increased in T2DM and might also play a role in the poor bone quality

Table 1 Major observational studies that showed an association between type 2 diabetes mellitus (T2DM) and risk of fractures

References	*n*	Major findings	Comments
[11]	6655	Patients with T2DM had increased nonvertebral fracture risk than subjects without T2DM (hazard ratio 1.33, 95% confidence interval 1.00–1.77)	Patients with T2DM had higher bone mineral density than subjects without T2DM The increased fracture risk was present only in treated patients with T2DM and not in newly diagnosed patients
[12]	996	T2DM was an independent risk factor for prevalent vertebral fracture	Bone mineral density was not associated with the presence of vertebral fracture in patients with T2DM

of these patients [21, 22]. More specifically, sclerostin binds to its low-density lipoprotein receptor-related proteins 5 and 6, which are found in osteoblasts. This leads to the inhibition of the Wnt-β–catenin pathway, which results in inhibition of osteoblastogenesis and bone formation [23]. Finally, the levels of vitamin D were also shown to be lower in patients with T2DM [24, 25].

SGLT2 INHIBITORS AND FRACTURE RISK

In the CANVAS trial (n = 10,142 patients with T2DM who were either at least 30 years old with established cardiovascular disease or at least 50 years old with two or more of the following cardiovascular risk factors: T2DM duration at least 10 years, systolic blood pressure greater than 140 mmHg despite treatment with at least one antihypertensive agent, current smoking, micro- or macroalbuminuria, or high-density lipoprotein cholesterol level below 39 mg/dl), the incidence of all fractures was higher with canagliflozin than with placebo [15.4 vs. 11.9 participants with fractures per 1000 patient-years; hazard ratio (HR) 1.26, 95% confidence interval (CI) 1.04–1.52] [7]. In contrast, in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial [n = 4401 patients with T2DM and chronic kidney disease (estimated glomerular filtration rate 30–90 ml/min/1.73 m^2 and urinary albumin-to-creatinine ratio greater than 300 mg/g) followed up for a median of 2.6 years], the incidence of fractures did not differ between patients who were randomized to receive canagliflozin and those who were randomized to receive placebo (11.8 and 12.1 fractures/1000 patient-years; HR 0.98, 95% CI 0.70–1.37) [26]. On the other hand, in the EMPA-REG OUTCOME trial (n = 7020 patients with T2DM and established cardiovascular disease) and in the DECLARE-TIMI 58 trial (n = 17,160 patients with T2DM and either established cardiovascular disease or multiple cardiovascular risk factors), empagliflozin and dapagliflozin did not increase the risk for fractures compared with placebo during a median follow-up of 3.1 and 4.2 years, respectively [8, 9]. More recently, in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, which included 1983 patients with T2DM, New York Heart Association class II, III, or IV heart failure and an ejection fraction no greater than 40%, dapagliflozin did not increase the risk of fractures during a median follow-up of 1.8 years [27]. Notably, the mean age of patients was similar in all these studies (Table 2) but the CANVAS trial enrolled a higher proportion of female and obese patients than the EMPA-REG OUTCOME trial [7–9, 26, 27]. Moreover, T2DM duration was longer in the CANVAS trial than in the DECLARE-TIMI 58 trial [7, 8]. Given that female gender, obesity, and longer duration of T2DM are risk factors for fracture, these differences

Table 2 Characteristics of the major trials that evaluated sodium-glucose co-transporter 2 inhibitors in patients with type 2 diabetes mellitus (T2DM)

References	Trial	*n*	Inclusion criteria	Age (years)	Female (%)	BMI (kg/m^2)	T2DM duration (years	Follow-up (years)	Fracture risk
[7]	CANVAS	10,142	Established CVD or age $\geq$ 50 years with $\geq$ 2 cardiovascular risk factors	63	36	32.0	13.5	2.4	HR 1.26, 95% CI 1.04–1.52
[26]	CREDENCE	4401	Chronic kidney disease	63	34	31.3	15.8	2.6	HR 0.98, 95% CI 0.70–1.37
[8]	DECLARE-TIMI 58	17,160	Established CVD or multiple cardiovascular risk factors	64	37	32.0	10.5	4.2	HR 1.04, 95% CI 0.91–1.18
[27]	DAPA-HF	1983	New York Heart Association class II, III, or IV heart failure and ejection fraction $\leq$ 40%	66	23	28.2	NR	1.8	2.1% in both placebo and dapagliflozin group
[9]	EMPA-REG OUTCOME	7020	Established CVD	63	29	30.6	NR	3.1	3.9% and 3.8% in the placebo and empagliflozin group, respectively

BMI body mass index, *CANVAS* Canagliflozin Cardiovascular Assessment Study, *CVD* cardiovascular disease, *HR* hazard ratio, *CI* confidence interval, *CREDENCE* Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, *DECLARE-TIMI 58* Dapagliflozin Effect on Cardiovascular Events trial, *DAPA-HF* Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure, *NR* not reported, *EMPA-REG OUTCOME* Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients trial

Table 3 Meta-analyses of randomized controlled trials that evaluated the association between sodium-glucose co-transporter 2 (SGLT2) inhibitors and the risk of fracture

References	Number of studies	Number of patients	Major findings	Comments
[28]	30	23,372	Similar incidence of bone fractures in patients receiving SGLT2 inhibitors and placebo	When the effects of canagliflozin, dapagliflozin, and empagliflozin on fractures were analyzed separately, none was associated with increased risk for fracture
[29]	27	20,895	Similar incidence of bone fractures in patients receiving SGLT2 inhibitors and placebo	In groups at higher risk for fracture, including women and the elderly, no increase in the incidence of fracture was noted in patients treated with SGLT2 inhibitors

might have played a role in the higher risk of fracture observed in the CANVAS trial.

In a recent meta-analysis of 30 randomized controlled trials (n = 23,372 patients with T2DM), the incidence of bone fractures did not differ between the groups receiving SGLT2 inhibitors and placebo (odds ratio 0.86, 95% CI 0.70–1.06) [28]. When the effects of canagliflozin, dapagliflozin, and empagliflozin on fractures were analyzed separately, none was associated with increased risk for fracture [28]. Interestingly, studies with follow-up of 52 weeks or less showed that SGLT2 inhibitors reduce the risk for fracture by 45%, whereas studies with longer follow-up showed no association between treatment with these agents and the incidence of fracture (Table 3) [28].

In another recent meta-analysis of 27 randomized controlled trials (n = 20,895), SGLT2 inhibitors did not increase the risk of fracture compared with placebo (relative risk 1.02, 95% CI 0.81–1.28) [29]. In groups at higher risk for fracture, including women and the elderly, no increase in the incidence of fracture was noted either [29]. Moreover, three trials (n = 1303) evaluated the effects of SGLT2 inhibitors on BMD and did not show any change in the evaluated skeletal sites (lumbar spine, femoral neck, total hip, and distal forearm) (Table 3) [29].

EFFECTS OF SGLT2 INHIBITORS ON BONE METABOLISM

The exact mechanisms by which the SGLT2 inhibitors might increase fracture risk are unclear. SGLT2 are not expressed in the bone [30]. However, SGLT2 inhibitors might have an impact on the homeostasis of phosphate and calcium, which are essential for the maintenance of bone structure (Fig. 1). SGLT2 inhibitors reduce sodium reabsorption in the apical membrane of the proximal tube cells. As a result, the activity of sodium/phosphate co-transporter, which is located at the apical membrane, is increased, because of the increased electrochemical sodium gradient, leading to increased reabsorption of phosphate in the proximal tube [31, 32]. The ensuing increase in serum phosphate levels induces the secretion of parathormone (PTH) and the production of fibroblast growth factor 23 (FGF23) from osteocytes and osteoblasts [33]. In turn, PTH leads to bone resorption, whereas both PTH and FGF23 reduce renal tubular reabsorption of phosphate and promote the excretion of phosphate in the urine [33, 34]. In addition, FGF23 suppresses the 1-alpha-hydroxylation of vitamin D and the formation of its active form, whereas PTH promotes 1-alpha-hydroxylation [33]. It has been reported that treatment with canagliflozin results in increased serum levels of phosphate, FGF23, and PTH and decreased levels of 1,25(OH)2D [35]. These changes play

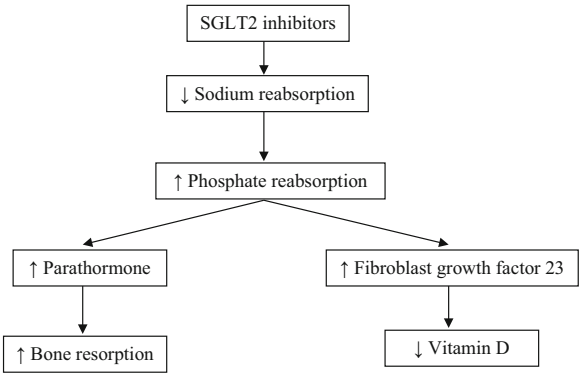

Fig. 1 Effects of sodium-glucose co-transporter 2 inhibitors on modulators of bone metabolism

an important role on bone metabolism and might explain the increased risk for fracture in patients treated with canagliflozin. Treatment with dapagliflozin was also related with increased serum levels of phosphate, PTH, and FGF23 but did not affect 1,25(OH)2D levels [36]. In contrast, empagliflozin does not appear to affect serum levels of phosphate, PTH, and 25(OH)2D [37]. In addition to the effects of SGLT2 inhibitors on bone metabolism, osmotic diuresis and volume depletion, which are related to the use of these agents, might also increase the risk of falls and fracture [7].

CONCLUSIONS

Canagliflozin increased the risk for fracture in the CANVAS trial but not in the CREDENCE trial. In addition, empagliflozin and dapagliflozin do not appear to affect the incidence of fracture. Moreover, there is no clear pathogenetic mechanism through which SGLT2 inhibitors will result in increased risk for fractures. Therefore, available data are inconclusive to attribute to these drugs a direct responsibility for bone fractures.

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