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The effects of Sodium-glucose cotransporter 2 (SGLT2) inhibitors on fracture risk. A review of the literature

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REVIEW

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ABSTRACT

Background

Diabetes mellitus is now approaching an epidemic and osteoporotic fractures had a high mortality and morbidity, Salt-glucose transporters inhibitors (SGLT-2) are relatively new class of oral hypoglycemic medications with cardio-renal protective effects, the association of SGLT-2 inhibitors with fracture risk is controversial.

Aims

The current review aimed to assess the relationship of SGLT-2 inhibitors with osteoporosis and fracture risk.

Methods

An electronic literature search was carried out in the PubMed, and Google Scholar. The keywords used were SGLT2 inhibitors-canagliflozin, dapagliflozin, empagliflozin, osteoporosis, and fracture risk. Two hundred and twenty-four were found, the number stood at 21 after removing irrelevant article and duplication and applying the inclusion and exclusion criteria.

Results

There were 21 studies, six on canagliflozin, five on dapagliflozin, five on empagliflozin, and another five on drugs combinations. Six of the studies were pooled analysis, four randomized controlled trials, three reviews, two meta-analyses, one case-control study, one comparative cohort, an opinion, and one essay. No association was found between fracture risk, dapagliflozin, and empagliflozin, the results were mixed regarding canagliflozin.

Conclusion

SGLT-2 inhibitors were not associated with fracture risk except canagliflozin when used among patients with cardiovascular disease or at risk and among patients with low baseline glomerular filtration rate. The observed increased fracture risk among patients taking canagliflozin may be due to fall and decreased bone mineral density due to weight loss.

Key Words

SGLT-2i, fracture risk, mineral bone density

What this study adds:

1. What is known about this subject?

There is an existing controversy regarding the use of SGLT-2 inhibitors among patients with osteoporosis.

2. What new information is offered in this study?

Empagliflozin and dapagliflozin are safe medications among patients with osteoporosis.

3. What are the implications for research, policy, or practice?

Patients with type 2 diabetes mellitus and osteoporosis should have the benefits of cardio-renal protection of empagliflozin and dapagliflozin.

Background

Diabetes mellitus induced bone fragility has been recently recognized as diabetes complication, the main cause is the deterioration in bone quality evidenced by decreased bone formation and remodelling. Many factors are to blame including accumulation of advanced glycation end-products, insulin, insulin-like growth factor-I, chronic hyperglycemia, and homocysteine. The increased risk of fracture among patients with type 2 diabetes is independent of body mass index as obesity which is prevalent among patients with

type 2 diabetes mellitus and may be present in patients with type 1 diabetes mellitus leads to a higher bone mineral density[1,2]. However recent literature has suggested that obesity may be as risk for fracture when adjusted for body mass index. The DEXA scan could be misleading in the diagnosis of osteoporosis in patients with diabetes, as T-scores and FRAX scores are likely to under-represent a diabetic patients risk for fracture[3]. High-resolution peripheral quantitative computed tomography that evaluates the microarchitecture separately for cortical and trabecular bone is promising. Trabecular bone score and trabecular bone score-adjusted FRAX can also be used to estimate fracture risk independent of bone mineral density [4,5]. Sodium-glucose co-transporter (SGLT2) inhibitors are relatively new class oral hypoglycemic medications that reduce plasma sugar independent of insulin, they also reduce blood pressure, body mass index, and cardiovascular mortality. The role of these medications in fracture risk is controversial. Some studies reported hypercalciuria among patient treated with SGLT-2 inhibitors 1, other reported a slight increase in phosphate, magnesium, serum collagen type 1 beta-carboxy telopeptide (beta-CTX), a bone resorption marker, and osteocalcin, a bone formation marker and no changes in serum or urinary calcium, vitamin D, or parathyroid hormone[6]. A recent blind randomized crossover study from USA 7 conducted among 25 hospitalized healthy adults for five days showed that canagliflozin 300mg induced a prompt increase in serum phosphorus, which triggers downstream changes in fibroblast growth factor (FGF23), 1,25-dihydroxy vitamin D, and parathyroid hormone. A recent review concluded that SGLT2 inhibitors induce small increases in serum concentrations of magnesium, potassium, and phosphate. The small increase in serum phosphate concentration may result in reduced bone density and increased risk of bone fractures, mainly seen with canagliflozin [7-9]. Paschou and colleagues9 reviewed the literature and recommended that canagliflozin should be avoided in patient with osteoporosis. In contradiction another review showed that canagliflozin was not associated with meaningful changes in serum or urine calcium, parathyroid hormone, or vitamin D, increases in serum magnesium and phosphate were observed without changes in their urinary excretion, Increases in serum collagen type-1 beta-carboxy-telopeptide (beta-CTX), a bone resorption marker, and osteocalcin, a bone formation marker, and increased fracture risk at extremities were reported. The observed decreased bone mineral density at the hip is consistent with weight loss [10]. Another study found increased phosphate reabsorption leading to secondary hyperparathyroidism, furthermore, weight loss in the initial phase of treatment may increase bone turn over leading to decrease bone mineral density, fall, and changes in hydration status may explain the increased fracture risk observed among patients with cardiovascular disease and impaired renal function[11]. Animal studies reported Canagliflozin treated mice demonstrated an increase in urinary calcium loss; FGF23 was also increased[12]. A high PTH, RatLAPs, and urinary calcium were observed among mice with diabetes, Canagliflozin treated mice showed a further increase in RatLAPs possibly suggesting bone resorption. Detrimental metaphyseal changes were also seen[13]. The current review assessed the relationship between SGLT-2 inhibitors and fracture risk.

Methodology

Eligibility criteria according to PICOS

Studies are eligible if they were conducted on humans in the English language published during the period from 2012-September 2019. No limitations for the study type. Animal studies were not included.

Information sources and search methods

An electronic literature search was carried out in PubMed, and Google Scholar databases. The keywords used were SGLT2 inhibitors-canagliflozin, dapagliflozin, empagliflozin, fracture risk, and osteoporosis. To be included for review, the following criteria were considered: the patient or with of type 2diabetes and with fracture risk and osteoporosis associated with SGLT2 inhibitors.

Titles and abstracts were screened independently by two authors and full article retrieved for the manuscripts found relevant for the topic. Additional articles were searched and identified through hand searching of the bibliography. The retrieved full-text articles were assessed for eligibility for inclusion and data were extracted by the authors using proforma. Any disagreement in the selection of articles and data was discussed and solved between the researchers.

Results and Discussion

In the literature search, a total of 224 articles were identified. After removal of duplication, irrelevant articles, nineteen full articles were approached Figure :1 for analysis and review. (Tables 1-5) illustrated studies on canagliflozin, dapagliflozin, empagliflozin, and combinations of SGLT-2 inhibitors respectively.

Results

There were 21 articles with a total of 1186939 participants, the mean duration of follow-up was , Six (28.5 %) were from the USA, 9 from Europe (42.8 %), and four (19 %) from Asia, one from Australia (4.7 %), and one from Canada (4.7%).

Studies on canagliflozin

(six studies including 96317 patients): one pooled analysis of 9 controlled trials, two randomized controlled trials (RCTs),

Two analysis of four randomized controlled studies, a population-based study, and a review of clinical studies. Four were the USA, one published in Australia, and one from Canada.

Studies on dapagliflozin

(five studies including 36303 patients): Two controlled trials, a case-control study, an opinion, and one pooled analysis of 30 randomized controlled trials. Four were from Europe and one from the USA.

Studies on empagliflozin

(Five studies, 738848 patients were included): four pooled data from 62 randomized controlled trials and a review. Three from Europe and two from Asia.

Study on Salt-glucose co-transporters inhibitors (SGLT-2)

(Five studies among 614571 participants): Two meta-analyses of 60 randomized controlled trials, a nested case-control study, a review of 38 randomized controlled trials, and a comparative cohort. Two were from Europe, two from Asia, and one from the USA.

Canagliflozin and fracture risk

Canagliflozin 100, and 300mg was assessed in nine placebo and active-controlled studies (10194 patients), Canagliflozin Cardio-Vascular Assessment Study (CANVAS) (4327 participants with a prior history/risk of cardiovascular disease, and a pooled population of 8 non-CANVAS studies (5867 patients). Fracture increased in upper and lower extremities in CANVAS studies but was similar in other studies. The increased fracture risk among the CANVAS population who had prior history/risk of cardiovascular disease, a lower baseline glomerular filtration rate (GFR) and a higher diuretic use may be mediated by falls 14. A 26-week, double-blind, placebo-controlled trial with a 78-week extension. 55-80 years (N=716) patient with uncontrolled type 2 diabetes mellitus were enrolled. Canagliflozin showed significant reductions in total hip BMD and increases in bone formation and resorption biomarkers, due at least in part to weight loss [13-15]. Showed that Fractures tended to occur as early as 12 weeks after initiating treatment with canagliflozin 100mg and 300mg among patients at high risk of cardiovascular diseases but not among others, and were primarily located in the distal parts of the upper and lower extremities, the postulated mechanisms were increases in serum collagen type 1 beta-carboxy telopeptide (beta-CTX), a bone resorption marker, and osteocalcin, a bone formation marker. A recent analysis 15 of the CANVAS and CANVAS-renal study showed that the association of fracture risk observed in the CANVAS trial cannot be explained. Furthermore, there is a null observation between the drug and fracture risk in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial suggesting that the association of fracture could be due to chance or fall-related mechanisms. Further recent studies of RCTs showed no association of canagliflozin with fracture risk [16-18].

Dapagliflozin and fracture risk

A randomized, double-blind, placebo-controlled study from Sweden 18 included 182 patients with type 2 diabetes not controlled with metformin, patients were given dapagliflozin 10mg for 24 weeks followed for 78 weeks. No change in bone markers or bone mineral density was observed at 102 weeks. A case-control study 19 among 22618 patients with type 2 diabetes mellitus matched for age, sex, body mass index, and duration of diabetes (4548 received dapagliflozin) showed no significant increase in fracture risk. Mannucci et al. concluded that the increased fracture risk with canagliflozin is not seen with dapagliflozin. A low vitamin D and high parathyroid hormone are postulated mechanisms for the increased ratio among canagliflozin users. A pooled analysis of phase 1-111 studies 22 (nine) on general safety showed no increased risk of fracture with dapagliflozin. An international, multi-center, randomized, parallel-group, double-blind, placebo-controlled study 23 enrolled patients with T2DM (women 55-75 years and men 30-75 years). Patients received dapagliflozin 10mg added to metformin or placebo followed for 78 weeks. serum markers of bone formation (procollagen type 1 N-terminal propeptide; P1NP) and resorption (C-terminal cross-linking telopeptides of type I collagen; CTX), Bone Mineral Density (BMD) as assessed by standardized Dual-Energy X-ray Absorptiometry (DXA) were not affected by dapagliflozin [19-21].

Empagliflozin and fracture risk

Pooled data were analyzed from 17 phases 1-111 trials with six extensions including 12283 patients assigned to empagliflozin 10mg, empagliflozin 25mg, and placebo concluded a low rate of bone fracture which was similar across treatment group[22-24]. Another pooled data from phase 1-111 randomized plus extension studies (patients 12620 assigned to empagliflozin 10mg, empagliflozin 25 mg, and placebo). The rates of bone fracture were similar across treatment groups[25,26]. A recent review concluded that empagliflozin is not associated with an increased risk of bone fracture. Yabe et al. [27] analyzed data from 15 trials including 708 East Asian found no link between empagliflozin and fracture, more data analyzed from phase 1-111 trials including EMPA-REG H2H-SU trial 28 in which patients received empagliflozin 25 mg or glimepiride as an add-on to metformin for 104 weeks with a 104-week extension and another phase 1-111 trials. No increased fracture risk was observed in empagliflozin treated patients compared to placebo or glimepiride.

Studies on canagliflozin, dapagliflozin, and empagliflozin
A meta-analysis conducted in the year 2016 29 included 38 RCTs (10 canagliflozin, 15 dapagliflozin, and 13 empagliflozin) involving 30 384 patients, with follow-ups ranging from 24 to 160 weeks. No increased fracture risk was observed. A more recent meta-analysis of 20 studies 30 (8286 patients) found no association of canagliflozin, dapagliflozin, and empagliflozin with an increased fracture but the results were limited with short duration and follow-up, and low incidence of the event of interest. A recent nested case-control study 31 including 210042 patients (7522 vs. 296845 control subjects). The addition of SGLT-2 inhibitors to metformin was not associated with increased fracture risk. Similarly, studies published by Udeh et al. 32 and Azharuddin and colleagues 33 reported no association of empagliflozin and fracture risk[28-30].

Conclusion

Canagliflozin showed an increased fracture risk and decreased bone mineral density among patients with prior history/at risk of cardiovascular disease, on a high dose of diuretic, and lower baseline GFR and may be explained by falls and weight reduction. , the postulated mechanisms were increases in serum collagen type 1 beta-carboxy telopeptide (beta-CTX), a bone resorption marker, and osteocalcin, a bone formation marker. No association of dapagliflozin and empagliflozin with fracture risk was reported. In people with or at risk of osteoporosis, it may be prudent to use empagliflozin or dapagliflozin rather than canagliflozin, due to the documented cardio-renal protection of SGLT-2 inhibitors. Based on the current controversy of the increased risk for bone fractures observed with canagliflozin, it is better to be more vigilant waiting for a piece of solid evidence.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

The ethical committee of the Medical College, University of Tabuk approved the research (Ref. Number, READ, 0050)

Figures and Tables

Figure 1:

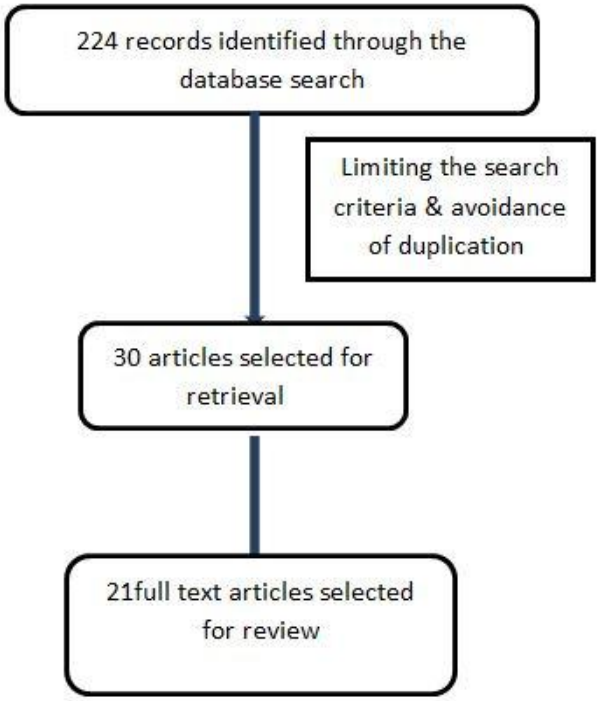

Table 1: Country of reviewed articles and the duration of the studies

Character	No %
Study country	
Europe	9 (42.8%)
USA	6 (28.5%)
Asia	4 (19.0%)
Australia	1 (4.7%)
Canada	1 (4.7%)
Duration of follow-up	
Range	1.5-5 years
Mean± SD	2.54±1.07

Table 2: Studies on canagliflozin.

Author	year	country	Type of study	Drug	dose	Duration	No of patients	Result
Watts, et al.	2016	USA	CANVAS placebo-controlled trial and pooled data from other 8 studies	Canagliflozin	100&300mg	2.2 years	10194	Fracture increased in upper and lower extremities in CANVAS studies but was similar in other studies
Bilezikian, et al.	2016	USA	a double-blind, placebo-controlled trial	Canagliflozin	100&300mg	1.5 years	716	significant reductions in total hip BMD and increases in bone formation and resorption biomarkers, due at least in part to weight loss
Blevins	2017	USA	A review of	Canagliflozin	100&300mg	Two		Increased

,et al.			clinical studies			years		fracture among patients at high risk of cardiovascular diseases but not among others, and were primarily located in the distal parts of the upper and lower extremities
Zhou, et al.	2019	Australia	An analysis of two RCTs	canagliflozin			10,142 individuals with type 2 diabetes	The fracture risk observed in CANVAS could be related to the propensity to fall
Perkovic, et al.	2019	USA	RCT (CREDENCE updates)	Canagliflozin	100mg	2.26 years	4401 renal impaired patients	No increased fracture risk
Fralick, et al.	2019	Canada	A population-based study	Comparing canagliflozin and GLP-1like peptide		2.5 years	79 964	No increased fracture risk compared to GLP-1 like peptides

Table 3: Studies on Dapagliflozin

Author	year	country	Type of study	Drug	dose	Duration	No of patients	Result
Bolinder ,et al.	2014	Sweden	A randomized, double-blind, placebo-controlled study	Dapagliflozin	10mg	1.5 years	182	No change in bone markers or bone mineral density was observed at 102 week
Touilis, et al	2018	UK	A case-control study	Dapagliflozin	10mg	3 years	22618	No significant increase in fracture risk
Mannucci, et al.	2017	Italy	Opinion					increased fracture risk is not seen with dapagliflozin
Fioretto, et al.	2016	USA	A pooled analysis of 30 phases 11b-111 placebo-controlled trials	Dapagliflozin	2.5, 10, and15mg	Up-to nearly 4 years	13321	No fracture risk in the dapagliflozin
Ljunggren ,et al.	2012	Sweden	International, multi-center, randomized, parallel-group, double-blind, placebo-controlled study	Dapagliflozin	10mg	1.5 years	182	serum markers of bone formation and resorption and bone mineral density were not affected by dapagliflozin

Table 4: Studies on Empagliflozin.

Author	year	country	Type of study	Drug	dose	Duration	No of patients	Result
Kohler, et al.	2016	Germany	Pooled data were analyzed from 15	Empagliflozin	10&25mg		12283	a low rate of bone fracture which was similar across

			randomized phases I-III trials					the treatment group
Kohler, et al.	2017	Germany	Pooled data were analyzed from 17 randomized phases I-III trials	Empagliflozin	10&25mg		12620	The rates of bone fracture were similar across treatment groups
Frampton, et al.	2018	New Zeland	Review	Empagliflozin				empagliflozin is not associated with an increased risk of bone fracture.
Yabe, et al.	2018	Japan	A pooled analysis of 15 phases 11b-111 placebo-controlled trials	Empagliflozin	10&25mg		709, 724 and 708 East Asian	Fractures rate were similar.
Kohler, et al.	2018	Germany	A pooled analysis of 15 phases 11b-111 placebo-controlled trials including EMPA-REG H2H-SU trial	Empagliflozin	10mg&25mg	Nearly two years	4221	No increased fracture risk was observed in empagliflozin treated patients compared to placebo or glimepiride.

Table 5: The relationship of Canagliflozin, Dapagliflozin, and Empagliflozin to fracture risk

Author	year	country	Type of study	Drug	Duration	No of patients	Result
Tang, et al.	2016	China	A review of 38 randomized control trials	Canagliflozin, Dapagliflozin, and Empagliflozin	3.1 years	30 384	No risk of fracture
Ruanpeng, et al	2017	USA	A meta-analysis of 20 RCTs	Canagliflozin, Dapagliflozin, and Empagliflozin		8286	No significant increase in fracture risk
Schmidt, et al.	2018	Germany	A nested case-control study	Canagliflozin, Dapagliflozin, and Empagliflozin	5 years	210042	Not associated with an increased risk of fractures of the upper or lower limbs compared to the use of DPP-4 inhibitors

Udeh, et al.	2018	Sweden	Comparative cohort comparing patients on SGLT-2inhibitors and glucagon-like peptide 1 (GLP1) receptor agonists	Canagliflozin, Dapagliflozin, and Empagliflozin		34416	No association with amputation or fracture risk
Azharuddin, et al.	2018	India	A meta-analysis of 40 randomized controlled trials	Canagliflozin, Dapagliflozin, and Empagliflozin		32,343	No detrimental effects on fracture risk

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