Open Access https://www.jparathyroid.com

Journal of Parathyroid Disease

Journal of Parathyroid Disease 2023,11, e11225

DOI:10.34172/jpd.2023.11225

Review

Effect of sodium-glucose transporter 2 inhibitors on bone

Mahdi Baradaranfard, Taha Ameli*

Abstract

Diabetes mellitus is a common illness, and the number of people affected by this condition is expected to increase significantly. Complications associated with type 2 diabetes mellitus, such as cataracts, retinopathy, neuropathy, and orthostatic hypotension, can increase the risk of falls and subsequent bone fractures. Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and ipragliflozin are a group of medications known as sodium-glucose cotransporter-2 inhibitors (SGLT-2i), which are oral drugs used to treat type 2 diabetes mellitus. This group of medications is a recent addition to the current treatment options for this condition. There are concerns about the impact of SGLT-2 inhibitors on bone health. Although drugs in this category have similarities in reducing blood glucose and preventing cardiovascular disease, they can have varying effects on bone metabolism. The effect of SGLT-2 inhibitors (SGLT-2is)-induced weight loss on bone mineral density (BMD) and bone turnover is significant and cannot be disregarded. Although SGLT-2 inhibitors were initially predicted to increase the likelihood of bone fractures, clinical evidence contradicts this assumption. It is noteworthy to emphasize that empagliflozin and dapagliflozin did not indicate an increased risk of fractures. It is also interesting to note that SGLT2i drugs positively affect heart function and can reduce the incidence of heart failure, which can lead to a decrease in osteoporosis and bone fractures. Based on clinical trials and real-world evidence, there does not appear to be a link between the administration of SGLT2 inhibitors and the risk of fractures. However, caution should still be exercised when prescribing these drugs to patients with advanced disease or kidney complications who may be at higher risk of bone fractures. It is always important to consider individual patient factors and potential risks before making treatment decisions.

Keywords: Bone mineral density, Osteoporosis, Sodium-glucose cotransporter-2 inhibitors, Bone fracture, Type 2 diabetes mellitus

Please cite this paper as: Baradaranfard M, Ameli T. Effect of sodium-glucose transporter 2 inhibitors on bone. J Parathyr Dis. 2023;11:e11225. doi:10.34172/jpd.2023.11225.

Introduction

Diabetes mellitus (DM) is a widespread illness in the present era, and it is projected that the number of individuals afflicted by this condition will rise significantly in the forthcoming years. Diabetes mellitus is a chronic metabolic disorder characterized by elevated levels of blood glucose and a reduction in bone density and quality, which are the key markers of this condition.

Cardiovascular issues, kidney complications, neuropathy, loss of vision, and amputation are among the potential consequences of diabetes. Continuous deterioration in bone density and quality can lead to significant bone fractures. As a result, individuals with diabetes are more likely to experience bone fractures, such as those in the hip and vertebrae, compared to those who do not have diabetes. Another consequence of this condition is the elevated risk of falls, which can ultimately result in bone fractures.

Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and ipragliflozin are medications that fall under the category of sodium-glucose cotransporter-2 inhibitors (SGLT-2i). The group of medications is a recent addition among the oral drugs utilized for treating type 2 diabetes mellitus, and it aids in lowering blood glucose levels. These drugs act at the distal kidney tubules to decrease glucose reabsorption in the tubules. These medications also efficiently regulate calcium and phosphate levels in the blood. In addition, these medications provide various advantages, such as weight loss, blood pressure reduction, lowering the chances of cardiovascular diseases, minimized hospitalization for heart failure, and slowing down the advancement of diabetes-induced kidney complications.

The United States Food and Drug Administration (FDA) has cautioned about several safety issues, including urinary and genital tract infections, ketoacidosis, acute kidney injury, amputation of the lower limbs, and bone fractures (1). The predominant adverse reactions observed during the treatment with SGLT-2 inhibitors appear to be infections of the urinary and genital tracts and conditions associated with reduced intravascular volume (2).

Received: 31 May 2023, Accepted: 20 July 2023, ePublished: 14 August 2023

Clinical Research Development Center, Najafabad Branch, Islamic Azad University, Najafabad, Iran

***Corresponding author:** Taha Ameli, Email: Tahaameli1377@gmail.com, Tahaameli1377@smd.iaun.ac.ir

Implication for health policy/practice/research/ medical education

Sodium-glucose cotransporter-2 inhibitors, including canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and ipragliflozin, are oral drugs used to treat type 2 diabetes. These medications can cause weight loss, which has a significant impact on bone mineral density and turnover. Although initial studies suggested that sodium-glucose cotransporter-2 inhibitors could increase the risk of bone fractures, subsequent clinical trials and real-world evidence have not supported this association. Therefore, there appears to be no link between administering sodium-glucose cotransporter-2 inhibitors and an increased risk of fractures.

Administering canagliflozin to patients with a reduced estimated glomerular filtration rate (eGFR) and a 300 mg dosage resulted in a mild osmotic diuresis and minor alterations in the levels of certain serum electrolytes, including magnesium, phosphate, and potassium (3). Health institutions have issued cautions concerning the occurrence of bone fractures linked to canagliflozin. Studies have indicated that SGLT-2 inhibitors may result in sarcopenia and dyspnea among elderly individuals due to decreased muscle mass (4). There are apprehensions regarding the influence of SGLT-2 inhibitors on bones, which could occur through the following mechanisms: (1) increasing the serum phosphate levels by enhancing the reabsorption of phosphate in the tubules, which stimulates parathyroid hormone (PTH) and 23 Fibroblast growth factors, (2) weight loss, and (3) diminishing the intravascular volume and elevating the chances of orthostatic hypotension and positional vertigo (5).

Research conducted on diabetic patients with moderate renal impairment has revealed that 9.4% of those treated with dapagliflozin (10 mg/d) suffered from bone fractures. Patients who received a placebo treatment did not encounter any fractures. During a 104-week trial involving diabetic patients aged 55-80 years, canagliflozin (300 mg/d) resulted in a decline in total hip bone density as compared to placebo (-2.1% versus -0.9%) (1).

According to the canagliflozin cardiovascular assessment study (CANVAS), bone fractures were considerably greater among individuals who were administered canagliflozin than those who were given a placebo (6). A review of nine clinical trials, which included the CANVAS study and eight smaller trials, found that the administration of canagliflozin was associated with a significant rise in the occurrence of bone fractures (7).

The use of canagliflozin in the CANVAS was associated with a significantly higher incidence of bone fractures compared to the placebo group. Data from nine clinical trials, which included CANVAS and eight other smaller trials, were analyzed and revealed that the incidence of fractures was significantly higher in patients taking canagliflozin (6). However, other large randomized controlled trials (RCTs) of canagliflozin or other SGLT-2 inhibitors did not show an increased risk of fractures. Less than 50% of the individuals who participated in these randomized controlled trials were 65 years old and above, and there needs to be more data on the prevalence of fractures in older individuals receiving SGLT-2i (6,7). Additionally, there have been no indications of an elevated risk of bone fractures in other clinical studies investigating the cardiovascular outcomes of SGLT-2 inhibitors for individuals with type 2 diabetes (5). Different drugs of this category reduce blood glucose and prevent cardiovascular disease, but despite having standard features, they can have different effects on bone metabolism (8).

Method of search

The PubMed database was selected for searching articles related to the topic. In the first stage, about 80 articles were selected. Then, based on the year of publication and the relevance of the topic, about 20 articles were chosen. The text of these articles was studied, and the desired content was selected from each. According to the results of the studies, the primary attention was on the articles published in the last years. To search, we conducted the following keywords: bone mineral density, osteoporosis, sodium-glucose cotransporter-2 inhibitors, bone fracture, and type 2 diabetes mellitus.

Identifying the features of disordered bone metabolism in "diabetic bone disease"

Individuals who have type 2 diabetes mellitus (T2DM) experience a minor rise in bone mineral density (BMD); however, this is linked with an elevated possibility of suffering from bone fractures. The increased BMD could be linked to the anabolic impact of hyperinsulinemia. A disruption in the bone's microscopic architecture, along with a decline in bone quality and strength, can result in a rise in fracture susceptibility (2). An inequity of minerals affecting the durability of spinal bones was detected in women who have undergone postmenopausal and have T2DM.

The apoptosis of osteoblasts is triggered by oxidative stress and an inflammatory reaction occurring in the affected area in models of diabetic mice. The incidence of falls and consequent bone fractures may also be influenced by complications related to T2DM, such as cataracts, retinopathy, neuropathy, and orthostatic hypotension. Despite the bone matrix synthesis benefits provided by insulin's anabolic properties, observational studies have revealed that using exogenous insulin increases the risk of hip and vertebral fractures (9).

Impact of SGLT-2 Inhibitors on mineral metabolism

Sodium

About 33% of sodium is stored within the bone matrix, and around 40% is replaced with plasma sodium (10). Persistent hyponatremia enhances osteoclast differentiation and bone resorption by elevating osteoclast sensitivity to extracellular sodium levels, which, in turn,

raises the possibility of hip fractures. Furthermore, SGLT-2 inhibitor-triggered hypovolemia and resulting "hyponatremia" may lead to fatigue, weakness, or psychosomatic and neurological symptoms, which can heighten the likelihood of experiencing falls and fractures (11).

Magnesium

Around 66% of magnesium is stored within bone tissue. The intricate mechanism of SGLT-2 inhibitors in regulating magnesium balance has yet to be clarified. Empirical research has demonstrated that SGLT-2 inhibitors can increase serum magnesium levels in T2 diabetic patients proportionally and dose-dependently. The lowered levels of magnesium in the bloodstream can indirectly affect bone metabolism by amplifying osteoclast activity and the secretion of PTH. This can lead to diminished vitamin D synthesis and activation, ultimately causing bone resorption. Furthermore, SGLT-2i increases aldosterone concentration with natriuretic function, increasing excretion. The magnesium-regulating mechanisms eventually result in a slight rise in the magnesium level within the bloodstream.

Calcium

SGLT-2 inhibitors decrease the reabsorption of calcium in the proximal tubules. SGLT-2 inhibitors boost the excretion of calcium in the urine and increase the reabsorption of phosphate in the kidneys, leading to elevated PTH levels, which ultimately lowers the levels of active vitamin D. PTH can stimulate bone resorption and increase the excretion of phosphorus in urine, thereby increasing serum calcium levels while decreasing phosphorus levels (12).

Phosphorus

SGLT-2 inhibitors obstruct the transport and reabsorption of glucose and sodium. The sodium-phosphate transporters' function relies on sodium, and phosphate reabsorption escalates in the proximal tubules to uphold the sodium concentration gradient in the tubule (13). A study that involved 25 healthy participants conducted a randomized crossover trial under single-anonymized conditions. The study revealed that administering canagliflozin resulted in a slight, albeit meaningful, elevation in serum phosphorus levels. Conversely, the study showed that the administration of canagliflozin increased serum fibroblast growth factor 23 (FGF23) and PTH levels, while the level of 1,25-dihydroxyvitamin D decreased. Continued high levels of PTH can lead to increased breakdown of bone tissue. High levels of phosphate in the blood (hyperphosphatemia) can increase the risk of bone fractures in individuals with type 2 diabetes and chronic kidney disease who also suffer from renal bone disease. Elevated levels of FGF23 hinder the reabsorption of phosphorus in the proximal tubules of the kidneys and also inhibit the secretion of PTH, which decreases the release of phosphate from bones. Furthermore, FGF23 decreases the conversion of 25-hydroxyvitamin D to 1,25-dihydroxy vitamin D, reducing the absorption of calcium and phosphate through the intestine. In summary, the elevation of PTH and FGF23 levels further increases the excretion of phosphorus (14).

The effect of SGLT-2 on bone turnover

The homeostatic regulation between osteoclast-mediated bone resorption and osteoblast-facilitated bone synthesis plays a critical role in determining the quality of bone tissue. Individuals diagnosed with DBD exhibit bone metabolic irregularities with low bone turnover attributes. The impact of SGLT-2i on bone metabolism and turnover could be mediated indirectly. Canagliflozin elevates the concentration of type I collagen carboxyl-terminal peptide b (b-CTX), a distinctive marker of bone resorption. There was a marked increase in osteocalcin levels, a biomarker of bone formation. In contrast to ipragliflozin, dapagliflozin and empagliflozin did not exhibit any considerable impact on type I procollagen amino-terminal propeptide (PINP) or b-CTX, which serve as indicators of bone resorption.

The impact of SGLT-2 inhibitors (SGLT-2is)-induced weight reduction on BMD and bone turnover cannot be ignored. An RCT study reported reduced hip BMD in elderly obese patients following weight loss. Conversely, there was a simultaneous rise in osteocalcin, a marker of bone formation, and b-CTX, a marker of bone resorption, implying that loss of body weight could stimulate bone metabolism and trigger bone resorption. Adiponectin, an anti-inflammatory cytokine, is induced after an increase in adiposity and acts as a regulator of osteoclast function. Expressing adiponectin receptors in osteoblasts amplifies osteoblast differentiation and maturation (12).

In theory, SGLT2 inhibitors (SGLT2is) are predicted to elevate the probability of bone fractures. However, clinical evidence contradicts this assumption. External factors, such as accidents and falls, significantly impact bone fractures. Although SGLT2is do not alter bone durability, bone fractures can occur due to some external forces (2).

Bone fractures were more significant among individuals with moderate renal impairment than those with mild or no renal impairment. Additionally, patients with retinopathy or neuropathy exhibited higher rates of bone fractures in both the medication and placebo-treated groups. The duration of diabetes for ten years is regarded as a risk factor for bone fractures due to the elevated likelihood of falling (9).

The percentage of BMD changes from baseline to twelve months after taking the drug has been evaluated. The reduction of lumbar spine BMD was the highest in the group that had simultaneous use of SGLT2i (empagliflozin) and metformin or sulfonylurea combination (8).

A recent meta-analysis of clinical trials revealed that weight loss induced by dietary interventions (with an average weight reduction of 7 to 11 kg) was significantly

related to a reduction in hip BMD and early alterations in bone markers (PINP, osteocalcin, CTX, NTX). Treatment with canagliflozin increased BMD and CTX, as well as weight loss, in patients. In canagliflozin users, weight loss was found to be responsible for almost 40% of the total reduction in hip BMD.

In the CANVAS study, it was observed that the occurrence of fractures in patients who were treated with canagliflozin was significantly higher (3.9% for a dose of 100 mg and 4% for a dose of 300 mg) compared to those who received a placebo (2.6%). Fractures are most commonly observed in the upper and lower body during the initial weeks of canagliflozin treatment, and their incidence increases gradually over time, as reported in a study. The cause of the elevated fractures with canagliflozin is yet to be determined.

Watts et al. found that there was a dose-related rise in adverse events associated with volume depletion (such as orthostatic hypotension, postural dizziness, and syncope) in their study, which could result in fractures related to falls during the initial stages of canagliflozin treatment.

Another study investigated the impact of dapagliflozin on the risk of bone fractures in 252 patients with uncontrolled type 2 diabetes and mild renal failure. The findings suggested that volume depletion may also contribute to an increased likelihood of fractures. Seven out of thirteen individuals who experienced a fracture had a medical history of diabetic neuropathy or orthostatic hypotension, as indicated by the findings of this study (15).

Patients with diabetes who receive insulin treatment may have an increased risk of fractures, possibly due to the higher likelihood of experiencing chronic complications of the disease over time. This study suggests that using empagliflozin does not lead to an increased risk of fractures resulting from falls in patients. The percentage of individuals experiencing adverse bone fracture events was more significant among patients with retinopathy or neuropathy in the empagliflozin and placebo groups. Patients with type 2 diabetes are more prone to bone fractures compared to individuals who do not have this condition (9).

The VERTIS CV study (evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial) did not find a significant increase in fracture risk associated with using ertugliflozin. Some reports suggest that among the SGLT2 inhibitors available, canagliflozin may be linked to a higher risk of fractures (12).

The CANVAS found a significant increase in bone fractures and total hip BMD reduction among those taking canagliflozin compared to the placebo group. However, no increased risk was observed in the CANVAS-RENAL study.

Nevertheless, another clinical trial involving patients with chronic kidney disease and using a placebo as a control group showed a tendency towards higher bone fractures with dapagliflozin. On the other hand, data from clinical trials of FDA-approved drugs suggest that empagliflozin and dapagliflozin did not indicate an increased risk of fractures. In contrast, dapagliflozin was found to be a risk factor for bone fractures in people with impaired kidney function. Canagliflozin showed a higher incidence of bone fractures than other drugs and was associated with decreased total hip BMD. In contrast, ertugliflozin and dapagliflozin did not impact mineral density or show no association with bone fractures, unlike other SGLT2 inhibitors (789).

In contrast, a clinical trial that involved 716 individuals with T2DM who received canagliflozin treatment for 52 weeks did not reveal any notable discrepancy in vertebrae and femur BMD or bone strength compared to the placebo group. SGLT2i drugs have been found to positively affect heart function and reduce the incidence of heart failure. These effects can lead to a decrease in the occurrence of osteoporosis and bone fractures that can result from heart failure (16).

The occurrence of fractures in upper and lower limbs, including hip fractures, was investigated based on data from a pooled analysis of a clinical trial of 12 000 patients with type 2 diabetes who were given a placebo. The findings indicate no significant differences in the statistics between the patients who received the medication and those who were given the placebo.

Combination therapies containing empagliflozin did not result in a significant reduction in BMD. In contrast, hip BMD was found to decrease dose-dependently with the administration of canagliflozin (15). No changes were observed in BMD measurements in other areas, such as the femoral neck (8).

This study found that there was no significant alteration in calcium and phosphate homeostasis after 52 weeks of treatment with canagliflozin (300 mg/d), as determined by serum markers of bone resorption (CTX) (15).

Thirty-eight RCTs with 30 384 participants were reviewed from the beginning of the study until January 2016. However, the evidence from these studies did not show any adverse effect of SGLT2 inhibitors on fractures. Kohler et al conducted a study in 2018 to assess the fracture risk in diabetic patients treated with empagliflozin. The data showed that 2.8%, 2.5%, and 2.9% of patients in the empagliflozin 10 mg, empagliflozin 25 mg, and placebo groups experienced bone fractures (2).

Conclusion

The impact of SGLT2 inhibitors on bone fractures appears not influenced by the drug class's direct effects on bones. Instead, it is likely associated with falls and hydration status alterations resulting from osmotic diuresis. Conversely, the patient population in cardiovascular outcome trials differs from other studies. Factors such as age, duration of diabetes, number of co-existing medical conditions, concurrent medication usage, and the frequency of

cardiovascular diseases and microvascular complications may contribute to the potential inaccuracies in studies investigating the impact of SGLT-2 inhibitors on bone metabolism. In summary, real-world evidence does not show any connection between using SGLT2 inhibitors and the risk of fractures. The findings of this research, along with RCT data, should alleviate concerns of health policymakers and clinicians about the potential for increased fracture risk in T2DM patients who use these medications. Nonetheless, it is advisable to exercise caution when prescribing SGLT2i to patients with advanced disease or kidney complications who are susceptible to bone fractures. Further research involving larger cohorts is required to assess the prolonged impact of these medications on fracture risk, particularly in high-risk groups.

Authors' contribution

Conceptualization: MB and TA
Data curation: MB
Funding acquisition: TA.
Formal analysis: MB.
Investigation: MB.
Methodology: TA.
Resources: MB , TA.
Project Administration: MB, TA.
Supervision: MB, TA.
Validation: TA.
Visualization: MB.
Writing–original draft: MB , TA.
Writing–review and editing: MB , TA.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely
observed by the authors.

Funding/Support

None.

References

1. Blau JE, Taylor SI. Adverse effects of SGLT2 inhibitors on bone health. Nat Rev Nephrol. 2018;14:473-4. doi: 10.1038/s41581-018-0028-0.
2. Li X, Li T, Cheng Y, Lu Y, Xue M, Xu L, et al. Effects of SGLT2 inhibitors on fractures and bone mineral density in type 2 diabetes: An updated meta-analysis. Diabetes Metab Res Rev. 2019;35:e3170. doi: 10.1002/dmrr.3170.
3. Weir MR, Kline I, Xie J, Edwards R, Usiskin K. Effect of canagliflozin on serum electrolytes in patients with type 2 diabetes in relation to estimated glomerular filtration rate (eGFR). Curr Med Res Opin. 2014;30:1759-68. doi: 10.1185/03007995.2014.919907.
4. Koshizaka M, Ishikawa K, Ishibashi R, Maezawa Y, Sakamoto K, Uchida D, et al. Effects of ipragliflozin versus metformin in combination with sitagliptin on bone and muscle in Japanese patients with type 2 diabetes mellitus: Subanalysis of a prospective, randomized, controlled study (PRIME-V study). J Diabetes Investig. 2021;12:200-6. doi: 10.1111/jdi.13340.
5. Haraguchi A, Shigeno R, Horie I, Morimoto S, Ito A, Chiba K, et al. The effect of luseogliflozin on bone microarchitecture in older patients with type 2 diabetes: study protocol for a randomized controlled pilot trial using second-generation, high-resolution, peripheral quantitative computed tomography (HR-pQCT). Trials. 2020;21:379. doi: 10.1186/s13063-020-04276-4.
6. Zhuo M, Hawley CE, Paik JM, Bessette LG, Wexler DJ, Kim DH, et al. Association of Sodium-Glucose Cotransporter–2 Inhibitors With Fracture Risk in Older Adults With Type 2 Diabetes. JAMA Network Open. 2021;4:e2130762-e. doi: 10.1001/jamanetworkopen.2021.30762.
7. Mannucci E, Monami M. Bone Fractures with Sodium-Glucose Co-transporter-2 Inhibitors: How Real is the Risk? Drug Safety. 2017;40:115-9. doi: 10.1007/s40264-016-0470-5.
8. Ha J, Lim Y, Kim MK, Kwon HS, Song KH, Ko SH, et al. Comparison of the Effects of Various Antidiabetic Medication on Bone Mineral Density in Patients with Type 2 Diabetes Mellitus. Endocrinol Metab (Seoul). 2021;36:895-903. doi: 10.3803/EnM.2021.1026.
9. Kohler S, Kaspers S, Salsali A, Zeller C, Woerle HJ. Analysis of Fractures in Patients With Type 2 Diabetes Treated With Empagliflozin in Pooled Data From Placebo-Controlled Trials and a Head-to-Head Study Versus Glimepiride. Diabetes Care. 2018;41:1809-16. doi: 10.2337/dc17-1525.
10. Hannon MJ, Verbalis JG. Sodium homeostasis and bone. Curr Opin Nephrol Hypertens. 2014;23:370-6. doi: 10.1097/01.mnh.0000447022.51722.f4.
11. Verbalis JG, Barsony J, Sugimura Y, Tian Y, Adams DJ, Carter EA, et al. Hyponatremia-induced osteoporosis. J Bone Miner Res. 2010;25:554-63. doi: 10.1359/jbmr.090827.
12. Dong B, Lv R, Wang J, Che L, Wang Z, Huai Z, et al. The Extraglycemic Effect of SGLT-2is on Mineral and Bone Metabolism and Bone Fracture. Front Endocrinol (Lausanne). 2022;13:918350. doi: 10.3389/fendo.2022.918350.
13. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. Lancet Diabetes Endocrinol. 2015;3:8-10. doi: 10.1016/s2213-8587(14)70227-x.
14. Burnett SM, Gunawardene SC, Bringhurst FR, Jüppner H, Lee H, Finkelstein JS. Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women. J Bone Miner Res. 2006;21:1187-96. doi: 10.1359/jbmr.060507.
15. Egger A ,Kraenzlin ME, Meier C. Effects of Incretin-Based Therapies and SGLT2 Inhibitors on Skeletal Health. Curr Osteoporos Rep. 2016;14:345-50. doi: 10.1007/s11914-016-0337-9.
16. Ha KH, Kim DJ, Choi YJ. Sodium–glucose cotransporter 2 inhibitors do not increase the risk of fractures in real-world clinical practice in Korea: A national observational cohort study. Journal of Diabetes Investigation. 2022;13:986-96. doi: 10.1111/jdi.13768.