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An Association Between SGLT-2 Inhibitors and Bone Mineral Changes: A Critical Review

Sumedh Gatadi, Mahendra Rathour, Jahngeer Alam

Department of Pharmacology, Jawaharlal Nehru Medical College, Faculty of Medicine, Aligarh Muslim University, Aligarh, Uttar Pradesh, INDIA, Pin 202 002

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KEYWORDS

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ABSTRACT:

The case of diabetes has now become a life-threatening modality in many countries. The treatment options for diabetes have seen a major shift towards sodium glucose co-transporter-2 (SGLT-2) inhibitors. Diabetes has been reported several times to cause changes pathologically in bone mineralization and metabolism while SGLT-2 inhibitors are also believed to have a negative impact on these bone homeostatic processes. In this study, we have particularly focused on the bone mineral changes occurring due to the application of anti-SGLT-2 agents, that will help to answer to the question 'do SGLT-2 inhibitors actually have adverse impact on the bone mineralization and metabolic processes or this pathological deterioration of the bone is solely on account of diabetes?'. To test this hypothesis, we conducted a decisive and critical review of literature by screening several data bases with a number of keywords. We selected 37 appropriate studies to include in this work, where, a total of 20 studies were associated with observational trials, 10 were the case reports, one was a case series, and the rest of the articles concern meta-analysis or review papers. In this analysis, we have observed that the most of the discussed studies reveal SGLT-2 inhibitors to be safe in diabetic patients and there are no significant abnormalities to bone mineralization except the agent canagliflozin. However, the authors still suggest performing large prospective studies to validate a strong association between SGLT-2 inhibitors and the bone mineral changes as the clear temporal relationships are lacking due to a limited number of studies.

1. Introduction

Diabetes mellitus (DM), known as a chronic metabolic disorder, is characterized by elevated levels of plasma glucose (Zimmet et al., 2016; Lovic et al., 2020). The International Diabetes Federation has reported that around 9% of the global population ageing 20 to 79 years is diabetic. In India, the burden of the disease is increasing continuously with 77 million cases and these cases were projected to reach 134 million by 2045 (Polavarapu et al., 2020). As per the research done by Vijayakumar et al (2019), the Asian region has recognized as the epicenter of diabetes which contributes to 60% of the global burden. The above discussed statistics shows that the disease diabetes is day by day becoming one of the major health problems among non-communicable diseases in this 21st Century. There are two well known forms of DM: the type-1 DM, in which deficiency of insulin is seen consequent to pancreatic beta cell destruction; and the type-2 DM (T2DM), in which insulin resistance is seen which leads to hyperglycaemic state in human beings (Schmidt, 2018). The etiological factors of diabetic hyperglycaemia are multifactorial and are generally recognized as macrovascular and microvascular complications (Javeed and Matveyenko, 2018) that can be managed by patient centric approaches including lifestyle modifications and combination therapies of medications (Zheng et al., 2018).

The glucose lowering drug therapies concern improving the sensitivity of tissues to insulin, augmenting the insulin availability, etc (Melmed et al., 2015). Sodium glucose co-transporter 2 (SGLT-2) is a target of great significance in the pathophysiology of DM. The discovered inhibitors of the target SGLT-2 are a

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relatively new family of medications that lowers blood sugar by reducing the reabsorption of glucose in the renal proximal tubules (Shiba et al., 2018). This class of inhibitors acts on the glycated haemoglobin (particularly HbA1c) to reduce it by 0.6-0.8% (or 6-8 mmol/mol) without increasing the risk of hypoglycaemia. These drugs induce weight loss and ameliorate the biological hyperactivities such as high blood pressure, increased lipid profile, and hyperuricemia. The recently reported potential findings by Saisho (2020) on SGLT-2 inhibition with agents, namely empagliflozin, canagliflozin and dapagliflozin show a number of key improvements especially in cardiovascular and renal outcomes.

However, this anti-diabetics category has also reported for the adverse and deleterious effects on the bone mineralization and metabolic processes. Moreover, a long-term exposure of diabetic environment leads to various characteristic changes in bone metabolic pathways as well as in bone architecture. The bone mineral abnormalities include the changes related to bone mineral density (BMD), the bone micro-architecture (BMA), and the bone mineral turnover (BMT). BMD is a measure of the inorganic mineral content in the bone while BMA is a determinant of bone strength and bone mechanical properties (Carbonare and Giannini, 2004; Boskey, 2013; Kranioti et al., 2019). These changes in bone mineralization are brought through a variety of mechanisms on molecular and structural levels (Murray and Coleman, 2019). We know that there are not solely the diabetes-induced abnormalities in bone mineralization and metabolism, but various researchers have also identified the bone mineral changes against SGLT-2-targeting therapy (Nauck, 2014; Reddy and Inzucchi, 2016).

2. Objectives

The authors of this manuscript have tried to explore the molecular mechanisms of the abnormal consequences that are either associated with bone metabolism, bone mineral homeostasis, or hormonal biomarkers particularly in the population treated with SGLT-2 inhibitors. We believe that this comprehensive analysis of human studies would lead readers and researchers to identify the treatment value of anti-diabetic SGLT-2 inhibitors and their impact on bone strength and fragility

3. Methods

In this work, we have done an extensive review of literature by reviewing the scholarly data bases such as PubMed, Google scholar, Scopus, Cochrane library, Nature, X-Mol, EBSCO, Loop, etc. We made a colossal search for randomized controlled trials, observational studies, meta-analysis studies and review articles by utilizing the keywords; diabetes, diabetes mellitus, sodium glucose co-transporter, SGLT-2, SGLT-2 inhibitors, bone metabolism, bone mineralization, bone micro-architecture, and bone turnover markers. Upon searching of the selected keywords, we had found a match of 163 articles, out of which, we included only the appropriate 37 articles in this work. Out of these 37 articles, a total of 20 were found to be the observational studies. There were 10 case reports and one was a case series. The rest of the articles were meta-analysis or review papers. All the articles were evaluated for the subtle changes occurring due to anti-diabetic therapy of SGLT-2 inhibitors in bone remodeling, a life cyclic process of the aged bone-resorption osteoclast cells and the new bone-formation osteoblast cells.

4. Results

The outcomes from the analyzed studies were found not to be very clear and transparent; however, we have tried to make specific conclusions after reviewing and discussing the collected data more comprehensively. We report that the SGLT-2 inhibitor canagliflozin lead to a completely loss of bone by affecting all three markers viz. BMD, BMA, and BMT. In addition, the drug ipragliflozin also show to impact the bone integrity by disturbing bone microarchitecture that mostly favors old bone-resorption. Reversely, dapagliflozin and empagliflozin have been proven to be very safe as far as bone mineral changes are concerned. Thus, studies of these anti-SGLT-2 drug molecules, alone or in combinations, found to vary from each other in a broad range. The present available findings are complex and make us unable to reach a conclusion. In a nutshell, we suggest researchers and healthcare providers that SGLT-2 inhibitors (except canagliflozin) are quite safe to treat T2DM patients and the bone mineral changes in patients could only be the cause of a long-term diabetic exposure.

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SGLT-2 Inhibitors	Effects on Bone Integrity & Strength		
	Bone mineral density	**Bone micro-architecture**	**Bone mineral turnover**
Canagliflozin	Deleterious	Deleterious	Deleterious
Dapagliflozin	Not Significant	No Effect	Not Significant
Empagliflozin	Not Significant	No Effect	No Effect
Ipragliflozin	Not Significant	Not Known	Deleterious

Table: SGLT-2 Inhibitors and their effects on bone integrity and strength

5. Discussion

Bone is a heterogeneous composite consisting of an analogue of geologic hydroxyapatite, an organic matrix, cells, and water (Boskey, 2013). There are several regulatory hormones such as parathyroid hormone, calcitonin, 1,25-dihydroxyvitamin D (calcitriol), and fibroblast growth factor-23 that also involved in bone mineralization homeostasis (Melmed et al., 2015). Extracellular bone matrix is composed of two materials, the inorganic mineral component consisting mainly of hydroxyapatite and which provides stiffness, the quality that is measured by a conventional bone mineral density scan. Another material is the organic part, composed predominantly of interconnecting collagen fibres and which provides tensile strength and counteracts shear stresses. These material properties of bone tissue are regulated by cellular activity, bone tissue turnover rate, and collagen cross-link formation (Murray and Coleman, 2019).

3.1.Bone Mineral Density (BMD)

A randomized control trial performed by Bilezikian et al (2016) has shown to impact BMD after canagliflozin treatment. The diabetic patients those aged 55-80 were randomly selected to treat with canagliflozin or placebo. The treatment with canagliflozin 300 mg per day over 104 weeks resulted in accelerated loss of total hip BMD in comparison to placebo (2.1% vs 0.9%). In another study, the treatment was randomized to dapagliflozin in 182 T2DM patients and placebo groups for 102 weeks. However, the changes of a little significance were found from this baseline study particularly in BMD of lumbar spine, femoral neck, or total hip BMD (Bolinder et al., 2014). Furthermore, no significant differences between empagliflozin and glimepiride groups in the BMD were noted by Kohler et al (2018). Moreover, in another study, one hundred and three T2DM patients who had been on sitagliptin treatment were enrolled and divided into ipragliflozin (51 patients) or metformin (52 patients) groups randomly, however, here also no significant differences were reported by Koshizaka and his colleagues (2021) between these two groups in BMD of the fourth lumbar vertebra (1.58% vs 3.09%, P= 0.504). In the case of SGLT-2 targeting, there are not much literature can support the hypothesis of SGLT-2 inhibitory therapy that induce adverse effects on the BMD. The reported results are seemed to be very mixed findings as many studies reporting no significant changes upon SGLT-2 inhibitory therapy in the BMD rather than a few. Here, we have found that no SGLT-2 inhibitor affects the BMD rather than canagliflozin. Therefore, the authors' assessment predicts that the SGLT-2 inhibition may, however, reverse the diabetes-caused changes in the BMD. In this sense, the authors suggest researchers and scientists to find a separate narration of diabetes and SGLT-2 inhibitors on the BMD to make it clear whether these inhibitors are more prone to produce serious

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changes in the BMD or they are undoing the diabetes-enhanced adverse consequences on BMD.

3.2.Bone Micro-Architecture (BMA)

Patients with T2DM who were taking canagliflozin appeared to be at an increased risk of fracture in the CANVAS trial compared to placebo, and further the data analysis revealed an increased risk of fracture over the course of the 188-week study period for those taking canagliflozin 100 or 300 mg compared to placebo (15.4% vs 11.9% participants with fracture per 1000 patient years; Hazard ratio (HR)- 1.26; 95% Confidence interval (CI)- 1.04 to 1.52 (Neal et al., 2017). In the CREDENCE trial, canagliflozin could not show an increase in fracture cases (HR- 0.98; 95% CI- 0.70 to 1.37). However, the statistical analysis of this outcome was limited due to the trial's premature termination after 2.6 years (Mahaffey et al., 2019), and hence, no specific conclusion from this trial can be made. A meta-analysis using nine placebo and active controlled trials was found with a higher rate of fractures among canagliflozin users versus those not taking the drug as 2.7% for drug vs 1.9% for placebo (Watts et al., 2016). Further, in other studies, on comparing canagliflozin to a placebo, the risk of bone fracture was not found to be increased (Tang et al., 2016; Ruanpeng et al., 2017; Li et al., 2019; Cheng et al., 2019).

According to the DECLARE-TIMI trial of 58 cardiovascular outcomes of the Wiviott et al (2019), dapagliflozin does not appear to be associated with an increased fracture risk (HR- 1.04; 95% CI- 0.91 to 1.18; P = 0.59) while the same drug dapagliflozin was observed with a higher number of fractures than a placebo in a small randomized, placebo-controlled trial including 252 patients with T2DM and also moderate renal impairment (Kohan et al., 2015). Furthermore, individual analysis of the meta-analyses by Cheng, Li, Ruanpeng, and Tang, has not found dapagliflozin treatment to be associated with an increased fracture risk. Additionally, the EMPA-REG post-hoc analysis has also concluded that empagliflozin did not cause any increase (3.8%) in fractures at any site as compared to control, 3.9% (Zinman et al., 2015). A meta-analysis showed that 7296 participants who received empagliflozin did not experience a difference 9 Odds ratio- 0.88; 95% CI- 0.70 to 1.12) in bone fracture risk between empagliflozin and placebo (Cheng et al., 2019). Furthermore, no increase in fracture risk was found when empagliflozin was studied in subsequent meta-analyses by Li, Ruanpeng and Kohler. The obtained data from 12,000 participants who were randomized 1:1:1 to empagliflozin 10 mg, 25 mg, or placebo as part of a large phase 1 to 3 clinical trials. According to this study, non-adjudicated bone fracture adverse events were low, and similar between groups comprising 2.8% in the 10 mg dose group, 2.5% in the 25 mg dose group, and 2.9% in the placebo group (Kohler et al., 2018). The study by Kohler and his team has also analyzed the data from EMPA-REG H2H-SU trial in which either empagliflozin 25 mg or glimepiride was added to metformin. Over a period of four years, bone fracture adverse events were similar between empagliflozin (4%) and glimepiride (4%) groups. Recently, anti-SGLT-2 drugs have also shown no risks of fractures as compared to starting DPP-4 inhibitors, according to a statewide cohort trial in Korea comprising 85000 people with type-2 diabetes in both as treated (AT) and intention to treat (ITT) analyses (AT:HR- 0.98, 95% CI- 0.92 to 1.04; ITT:HR- 0.94, 95% CI- 0.89 to 1.00) (Ha et al., 2022). Overall, the results of discussed studies are again not leading us to suggest particular inferences for the SGLT-2 inhibitors-produced abnormalities of BMA as only canagliflozin was found to induce BMA-related changes in diabetes patients. However, we advise researchers to perform prospective open-ended observational studies at a large scale for getting specific outcomes regarding the adverse impact of SGLT-2 inhibitory therapy on the bone architecture and remodeling.

3.3.Bone Mineral Turnover (BMT)

The studies in mice (Thrailkill et al., 2016) and humans (Thrailkill et al., 2017) have demonstrated that canagliflozin increases levels of BMT indicators, specifically the C-terminal telo-peptides of collagen type-I (Rosenstock et al., 2012). However, in a study involving 182 patients, dapagliflozin did significantly not affect markers of the bone formation or resorption when compared with placebo (Bolinder et al., 2012; Ljunggren et al., 2012). Furthermore, empagliflozin treatment also did not increase BMT in non-diabetic rats evaluated for markers of the bone resorption (Yurista et al., 2019). Additionally, in the EMPA-REG H2H-SU trial, the BMT indicators did not alter between baseline and either empagliflozin or glimepiride (Kohler et al., 2018). The effects of SGLT-2 inhibitor, ipragliflozin, versus metformin on bone and muscle in Japanese

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patients with T2DM were studied in a sub analysis of a study of patients with those T2DM patients who were already taking sitagliptin, the baseline body mass index was 22 kg/m2, and the haemoglobin (A1C) was 7-10%. Whereas, patients treated with ipragliflozin had shown the higher levels of TRACP-5b (a resorption marker) than the patients treated with metformin (median 11.94% vs 0.30%, P=0.0001). In case of BMA, this critical discussion about the drug ipragliflozin shows that it can cause bone defects such as bone loss (Koshizaka et al., 2021).

6. Conclusion

We report that canagliflozin and ipragliflozin in actuality have unwanted and kneeling effects on BMT while others show a little or no significant contagious effects on patients' bone architecture. Thus, it would be a key strategy to design follow up studies of SGLT-2 inhibitors for a better understanding of biochemical markers of BMT and further, to report the significant changes of bone mineralization upon anti-SGLT-2 treatment.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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