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Case Report

Sodium-Glucose Co-Transporter Protein 2 Inhibitors Induced Hypercalcemia: A Case Series and Literature Review

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ABSTRACT

Background: Sodium-glucose co-transporter protein 2 (SGLT2) inhibitors are the newest class of oral antihyperglycemic agents. To our knowledge, hypercalcemia has not been labeled as a side effect of this class; nevertheless, 2 cases have been reported over the last few years.
Case Report: We present a case series of 3 patients with type 2 diabetes mellitus (T2DM) in whom hypercalcemia developed when they were started on canagliflozin and dapagliflozin treatment. In cases 1 and 2, hypercalcemia developed shortly after increasing the canagliflozin dose. In both cases, calcium levels returned to the normal range 1 week after discontinuing canagliflozin treatment. In case 3, laboratory workup revealed an elevated serum calcium level shortly after switching the therapy to dapagliflozin.
Discussion: The first reported case of hypercalcemia related to SGLT2 inhibitor use was described in relation to canagliflozin. High calcium level was also reported in a patient after introducing dapagliflozin. In our cases, hypercalcemia was first noted after increasing the dose of canagliflozin and after introducing dapagliflozin. Although the exact causes are unknown, we propose a comprehensive multifactorial mechanism.
Conclusion: This is the first reported case series of hypercalcemia associated with SGLT2 inhibitors. Although the exact mechanisms remain uncertain, these drugs may predispose individuals to hypercalcemia. Monitoring for signs and symptoms of hypercalcemia or better switching to more selective SGLT2 inhibitors in at-risk patients could potentially prevent this complication.

Introduction

Sodium-glucose co-transporter protein 2 (SGLT2) inhibitors are the newest class of oral antihyperglycemic agents that have been approved for the treatment of diabetes mellitus. They act by inhibiting SGLT2 in the proximal tubule of the kidney, preventing the reabsorption of glucose and thereby promoting low blood glucose levels. For many years, there have been significant developments in both the safety and efficacy of this class of medication. Labeled adverse effects include euglycemic diabetic ketoacidosis, genital and urinary tract infection, bone fractures, cancer, hypotension, hyperkalemia, and foot and leg amputation.[1-8]

To our knowledge, hypercalcemia has not been labeled as a side effect of this class; nevertheless, 2 cases have been reported over the last few years after starting the use of this class of medication when it was initially approved by the U.S. Food and Drug Administration 7 years ago.[9,10]

We present a case series of 3 patients with type 2 diabetes mellitus (T2DM) in whom hypercalcemia developed when they were started on SGLT2 inhibitor treatment. We performed a literature review of this topic, discussing the possible pathophysiology, and we have proposed a preventive strategy for SGLT2 inhibitor–induced hypercalcemia.

Case Report

Case 1

A 66-year-old woman with a history of T2DM maintained on metformin, sitagliptin, and canagliflozin presented to our clinic for a regular follow-up visit shortly after increasing canagliflozin dose

Abbreviations: CSA, corrected for serum albumin; PTH, parathyroid hormone; SGLT1, sodium-glucose transport protein 1; SGLT1s, SGLT1 symporters; SGLT2, sodium-glucose transport protein 2; T2DM, type 2 diabetes mellitus.

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to 300 mg/d. She was found to have an elevated serum calcium level. The patient was asymptomatic, and past medical records revealed normal to high-normal calcium levels. She was maintained on cholecalciferol-D_3 for the history of vitamin D deficiency but not on any calcium supplementation. Her daily calcium intake was estimated to be 450 mg/d. Past medical history included hypertension treated with telmisartan and atenolol, Hashimoto thyroiditis treated with levothyroxine replacement therapy, and dyslipidemia treated with rosuvastatin.

On presentation, her calcium level corrected for serum albumin (CSA) was 12.2 mg/dL (reference range, 8.3-10.2 mg/dL), confirmed on repeated reading, markedly higher than her baseline at 10.1 mg/dL before initiating canagliflozin treatment. Further workup revealed an elevated plasma creatinine level of 1.15 (reference range, 0.51-0.95), with a normal thyroid-stimulating hormone level of 3.4 (reference range, 0.24-4) and 25-hydroxy vitamin D level of 98 nmol/L (reference range, >75 nmol/L). However, an inappropriately high parathyroid hormone (PTH) level of 79.6 (reference range, 15-65) was found, which was 59.2 1 year earlier.

A 24-hour urinary collection revealed low calcium excretion of 56 mg/24 h (less than 100 mg/24 h) with a calculated calcium-to-creatinine clearance ratio estimated at 0.007 (less than 0.01), suggestive of a possible underlying familial hypocalciuric hypercalcemia; however, the patient was not tested for this condition.

The rise in calcium level noted after introducing and increasing the dose of canagliflozin leads to the hypothesis that canagliflozin intake may cause severe hypercalcemia in the presence of occult underlying pathology.

Canagliflozin treatment was stopped, and the patient was advised to increase her water intake. On a follow-up visit 1 week after discontinuing canagliflozin treatment, her calcium levels returned to the normal range at 9.9 mg/dL (reference range, 8.3-10.2 mg/dL).

Case 2

A 75-year-old man with a history of T2DM maintained on glucagon-like peptide-1 receptor agonist, metformin, and canagliflozin (100 mg daily) presented for a follow-up visit a few months after increasing canagliflozin dose to 300 mg per day; he was found to have an elevated serum calcium level. The patient reported no symptoms, and previous laboratory investigations revealed high-normal calcium levels through the period when he was maintained on treatment with 100 mg canagliflozin per day. His estimated daily calcium intake was 300 mg/d. His past medical history included hypertension maintained on angiotensin II receptor blocker (300 mg) and hydrochlorothiazide (12.5 mg) and coronary artery disease.

On presentation, his calcium level CSA was 10.8 mg/dL (reference range, 8.3-10.2 mg/dL), with a baseline of 10.2 mg/dL before escalating canagliflozin dose to 300 mg/d.

Further workup revealed a plasma creatinine level of 1.15 (reference range, 0.51-0.95), thyroid-stimulating hormone level of 3.4 (reference range, 0.24-4), and PTH level of 57 (reference range, 15-65) with low 25-hydroxy vitamin D level of 45 nmol/L (reference range, >75 nmol/L).

Canagliflozin treatment was stopped, and sulfonylurea (gliclazide) was added to the previous treatment. On follow-up, the patient's calcium level CSA dropped back to 9.8 mg/dL (8.3-10.2 mg/dL).

Case 3

A 64-year-old woman with a known history of T2DM maintained on glimepiride, metformin, vildaglipitin, and empagliflozin (25 mg daily) presented to our clinic after she lost follow-up for more than 1 year. In the meantime, she was shifted from empagliflozin to dapagliflozin treatment. Laboratory workup revealed an elevated serum calcium level CSA of 10.6 mg/dL (reference range, 8.3-10.4 mg/dL). Her past medical history included hypertension treated with angiotensin-converting enzyme inhibitors (captopril 25 mg twice daily). Her estimated daily calcium intake was 600 mg/d, and none of her medications could affect her calcium levels.

Additional workup revealed a plasma creatinine level of 0.57 (reference range, 0.7-1.2), thyroid-stimulating hormone level of 1.87 (reference range, 0.24-4), low 25-hydroxy vitamin D level of 54.6 nmol/L (reference range, >75 nmol/L), and elevated PTH level of 82 (reference range, 15-65). The 24-hour urinary calcium excretion was normal (205 mg/24 h) with a calculated calcium-to-creatinine clearance ratio estimated at 0.01.

The patient's chart review revealed an elevated calcium level CSA of 10.4 mg/dL (reference range, 8.8-10.2 mg/dL) while she was maintained on empagliflozin treatment. Since the patient was symptom-free, she was maintained on canagliflozin with close monitoring of her calcium levels.

Discussion

The first reported case of hypercalcemia related to SGLT2 inhibitor use was described in relation to canagliflozin use in a patient with high oral calcium intake, severe volume depletion, and diabetic ketoacidosis.[9] High calcium level was also reported in a patient after introducing dapagliflozin in the presence of other risk factors for hypercalcemia, including thiazides and high calcium intake.[11] In our case, hypercalcemia was first noted after increasing the dose of canagliflozin. Although the exact cause is unknown, we propose a comprehensive multifactorial mechanism.

Pre-existing Risk Factors

Hypercalcemia is a relatively common clinical problem. This occurs when there is accelerated bone resorption, excessive gastrointestinal absorption, or decreased renal excretion of calcium. Among all causes, hyperparathyroidism, malignancy, and medications are the most common. However, the presence of more than 1 cause at a time may be involved in condition exacerbation.

In both previously reported cases of SGLT2 inhibitor–induced hypercalcemia, pre-existing risks for hypercalcemia were evident, including dehydration, acidosis, thiazides, and calcium intake, and the presence of asymptomatic hyperparathyroidism, in our case, was exacerbated after introducing SGLT2 inhibitors.[8,11] In view of this prospect, SGLT2 inhibitors use in the population at risk should always be kept a prime concern.

Osmotic Diuresis

A common cause of mild or transient hypercalcemia is dehydration. SGLT2 inhibitors induce glycosuria that promotes natriuresis and osmotic diuresis, leading to plasma volume contraction. Increased calcium levels could be consequently related to the volume depletion associated with SGLT2 inhibitors use, especially in patients with pre-existing risk factors mentioned above.

Dose-Dependent Increment

In a preclinical study, although no significant differences were found in serum calcium levels, hypercalcemia or a >10% increase in serum calcium was seen in 0.7%, 1.0%, and 1.5% of patients treated with placebo, 100 mg canagliflozin, or 300 mg

canagliflozin, respectively, and 2%, 0.9%, and 0.9% of those with low glomerular filtration rate, respectively, although none revealed association with any changes in serum calcium levels in humans.[12]

The Role of Sodium-Glucose Transport Protein 1 Transporters Inhibition

SGLT2 inhibitors act by inhibiting both sodium-glucose transport protein 1 (SGLT1) and SGLT2. Under normal conditions, SGLT2 symporters located in the early S1 segment of the proximal tubule are responsible for the reabsorption of 80% to 90% of filtered glucose, whereas SGLT1 symporters (SGLT1s) located in the S2/S3 segment of proximal tubule reabsorb the remaining 10% to 20%.[13] Apart from the proximal tubule epithelium, SGLT1s are also located in the luminal brush border of enterocytes and are responsible for glucose absorption in the small intestine.[14] Intestinal inhibition of SGLT1s may potentially cause carbohydrate malabsorption and improve glycemic control. In preclinical studies, carbohydrate malabsorption related to the inhibition of intestinal SGLT1s led to decreased intestinal pH. The acidic medium will eventually enhance calcium solubility and increase vitamin D–independent calcium absorption with subsequent hypercalciuria (Fig. 1).[15,16] Based on mechanistic studies, the removal of glucose from the diet in the presence of canagliflozin can prevent these effects. In clinical studies, however, no significant effects on serum calcium were detected.[17]

The specificity of gliflozins to SGLT2 symporters over its affinity for SGLT1s can vary greatly among different agents of the same class. It is more than 2500-fold for empaglifozin, 2235-fold for ertugliflozin, 1200-fold for dapagliflozin, 200-fold for canagliflozin, and 20-fold for sotagliflozin (Fig. 2).[18] In light of a lower SGLT2 symporters selectivity for canagliflozin and dapagliflozin, more SGLT1s will be inhibited, justifying the reported hypercalcemia with their use, and not with the more selective gliflozins such as empagliflozin and ertugliflozin.[9]

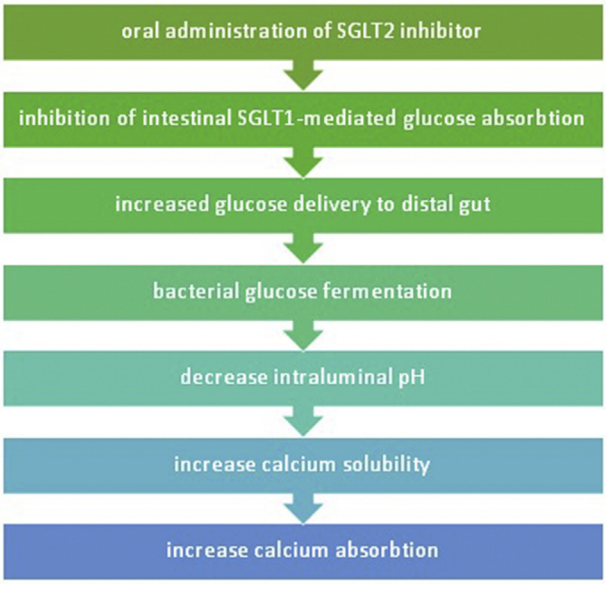

Fig. 1. Proposed hypothesis for increased calcium absorption in patients treated with SGLT2 inhibitors. *SGLT1* = sodium-glucose transport protein 1; *SGLT2* = sodium-glucose transport protein 2.

PTH-Dependent Hypercalcemia

The increased risk of bone loss and incidence of fractures noted in patients treated with SGLT2 inhibitors, specifically canagliflozin, was partly attributed to the enhanced renal proximal tubular reabsorption of phosphate.[19] This would trigger the secretion of fibroblast growth factor 23 with subsequent inhibition of 1,25-dihydroxy vitamin D production. This would decrease intestinal absorption of calcium with a compensatory increase in PTH production to maintain eucalcemia. This was estimated using a mean reaching up to 25% from baseline.[19] We hypothesized that patients with underlying parathyroid pathology would have altered homeostatic compensation and develop an exaggerated response, leading to hypercalcemia instead, as seen in case 1, where a serum PTH level of 59.2 increased to 79.6 after SGLT2 inhibitor initiation, representing a 34.4% increase from the baseline. The serum calcium level CAS increased from 10.1 to 12.2 as well. Many other factors that we previously mentioned would affect these results and could be implicated in the pathophysiology of hypercalcemia as well. This hypothesis could not be assessed in both cases 2 and 3 as there was no baseline PTH level before starting SGLT2 inhibitor treatment.

Preventive Strategy

Based on the potential of hypercalcemia with less selective SGLT2 inhibitor use, close monitoring of serum calcium levels is recommended in treated patients who have an established or are at risk of hypercalcemia, are taking oral calcium supplements, or are taking any medication with hypercalcemic potential.

Periodic calcium level monitoring, increasing oral hydration, avoiding carbohydrate malabsorption by substituting dietary fructose transported by glucose transporter 5 and not by SGLT1 for glucose, and moving toward the use of more selective SGLT2 inhibitors in at-risk patients are suggested to prevent SGLT2 inhibitor–induced hypercalcemia.[20]

Conclusion

This is the first case series of hypercalcemia associated with less selective SGLT2 inhibitors. Although the exact mechanisms remain uncertain, these drugs may predispose individuals to

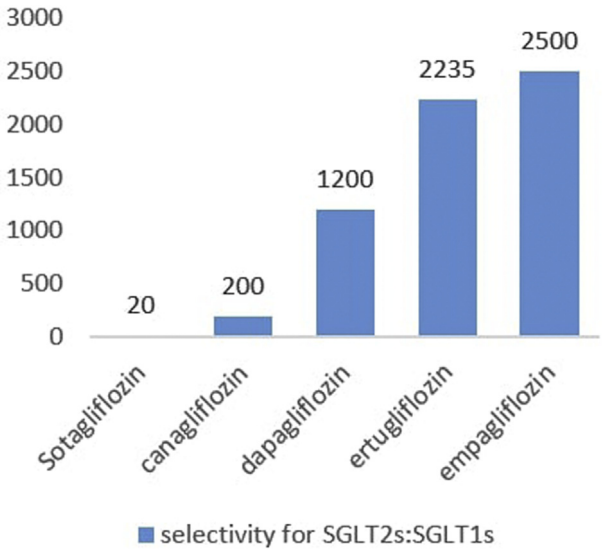

Fig. 2. Gliflozin's affinity to SGLT2 over SGLT1 receptors. *SGLT1* = sodium-glucose transport protein 1; *SGLT2* = sodium-glucose transport protein 2.

hypercalcemia. In view of the data published in the literature, this should be a rare side effect that clinicians should be aware of when used in patients at risk. Monitoring for signs and symptoms of hypercalcemia or better switching to more selective SGLT2 inhibitors in at-risk patients could potentially prevent this outcome.

Disclosure

The authors have no multiplicity of interest to disclose.

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