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Do Sodium-Glucose Cotransporters Type 2 Inhibitors Cause Hypercalcemia?

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Abstract

Background: Few data suggest that the use of sodium-glucose cotransporter's type 2 inhibitors (SGLT2is) might be associated with hypercalcemia.

Objective: To review investigations of calcium status in subjects using SGLT2is.

Methods: Pubmed search until November 10, 2022. Search terms included SGLT2is, calcium, hypercalcemia, adverse effects. Pertinent case reports, clinical trials, reviews and meta-analyses were included.

Results: Seven case reports described hypercalcemia (serum calcium 10.6-17.4 mg/dl) among patients using 3 SGLT2is (canagliflozin n=3), dapagliflozin (n=2), and empagliflozin (n=2). The highest calcium level recorded of 17.4 mg/dl was likely due to calcium toxicity in a man who was taking 1600-4000 mg of calcium carbonate daily. In 5 of the 6 remaining cases, there were other factors causing hypercalcemia, namely intake of hydrochlorothiazide (2 patients), undiagnosed primary hyperparathyroidism (2 patients) and possible familial hypocalciuric hypercalcemia (1 patient). Four investigations designed to examine electrolyte abnormalities in patients using SGLT2is did not found any significant changes in serum calcium levels after 5 days to 3 months of follow-up. Large clinical trials of SGLT2is including thousands of patients with different pathologies did not report hypercalcemia as adverse effect of SGLT2is. One meta-analysis showed that SGLT2is might be associated with minimal increase in mean serum calcium levels of 0.04 mg/dl.

Conclusions: The balance of evidence suggests that use of SGLT2is does not cause clinically meaningful hypercalcemia. Therefore, for users of SGLT2is, monitoring of serum calcium values more frequently than in standard care is not indicated. Yet, close follow-up of circulating calcium levels may be required among SGLT2is users having other risk factors for hypercalcemia such as thiazide use or untreated primary hyperparathyroidism.

Keywords: *Sodium-glucose cotransporters type 2 inhibitors; Calcium; Hypercalcemia; Parathyroid hormone; Diabetes*

Introduction

SGLT2is are widely used drugs for multiple indications: treatment of type 2 diabetes, heart failure and chronic kidney disease (CKD) due to their favorable impact on cardiorenal outcomes and mortality [1-5]. Several studies have shown that use of SGLT2is was associated with mild increase in serum magnesium and phosphates [6]. Meanwhile, few data are available regarding the effects of SGLT2is on calcium homeostasis. The first reported case of hypercalcemia related to SGLT2i was published in 2015 by Kaur and Winters [7]. They described a patient with high oral calcium intake, severe volume depletion, and diabetic ketoacidosis. Since then, few case reports described patients with mild hypercalcemia possibly related to different SGLT2is [8-11]. However, elevation in serum calcium concentrations is not listed among adverse effects of SGLT2is approved by the Federal Drug Administration (FDA) [12-15].The purpose of this review is to clarify the effects of SGLT2is on serum calcium concentrations based on case reports, short-term mechanistic studies, and large clinical trials.

Case Reports

Review of literature revealed 7 patients (49 to 75-year-old, 3 women) presenting with hypercalcemia in relation to intake of SGLT2is, 3 cases with canagliflozin, 2 with empagliflozin and 2 with dapagliflozin (Table 1).

Table 1: *Case reports of hypercalcemia related to use of SGLT2is.*

Reference	Patient	SGLT2i	Serum calcium (albumin-corrected)	PTH (pg/ml)	urine calcium (mg/24 h)	Contributing factors
1.Kaur and Winters [7]	60-year-old man	Canagliflozin, dose NR	17.4 mg/dl (8.9-10.3)	11 (12-88)	NR	Calcium toxicity 8-10 *tums tablets/day
2.Marques Vidas et al [8]	63-year-old woman	Dapagliflozin 5 mg q12h	11.0 mg/d dropped to 10.4 mg/dl after stopping hydrochlorothiazide	40	NR	Hydrochlorothiazide 12.5 mg/d
3.Akhanli et al, [9]	49-year-old man	Dapagliflozin 10 mg/d for 6 months	11.28 mg/dl (8.8-10.6)	70.8 (15-65)	492 (100-300)	Underlying hyperparathyroidism
4.El Masri et al [10] Lebanon	66- year-old woman	Canagliflozin 300 mg/d	12.2 mg/dl (N 8.3-10.2)	79.6 pg/ml	56 mg (100-300)	Possible familial hypocalciuric hypercalcemia
5.El Masri et al [10]	75-year-old man	Canagliflozin 300 mg/d	10.8 mg/dl	57 pg/ml	NR	Hydrochlorothiazide 12.5 mg/d
6.El Masri et al [10]	64-year-old woman	Empagliflozin 25 mg/d	10.6 mg/dl (8.3-10.4)	82	205 mg	None
7.Awada et al [11]	57-year old man	Empagliflozin for 2 years	10.9 (8.8-10.6)	21 (9-39), repeat PTH 13.8 (15-76)	415 (100-300) done 4 weeks after stopping empagliflozin	Underlying primary hyperparathyroidism

Number between brackets represent the normal reference range
In many patients, reference range was not reported.
*Each tums tablet contains 200-400 mg of calcium carbonate.
Abbreviations: SGLT2is: sodium-glucose co-transporter 2 inhibitors, PTH: parathyroid hormone, NR: not reported

Serum calcium on presentation ranged from 10.6 to 17.4 mg/dl. Circulating calcium values before starting SGLT2is were not reported except in one case [8]. In 6 of the 7 cases, there were other factors causing hypercalcemia. The most obvious example was the first reported patient by Kaur and Winters who presented with hypercalcemic emergency (serum Ca 17.4 mg/dl (normal reference 8.9-10.3 mg/dl) and diabetic ketoacidosis (DKA). This 60-year-old man was taking large amounts of calcium carbonate in the form of 8-10 tums tablets daily for 1 week for treatment of heart burn. Since each tablet of tums contains 200-400 mg of calcium carbonate, his daily intake ranged from 1600 to 4000 mg of calcium carbonate daily, i.e. his hypercalcemia was largely attributed to calcium toxicity. In addition, severe dehydration as result of DKA exacerbated hypercalcemia. Thus, the contribution of canagliflozin in inducing hypercalcemia in this case is minimal if any. Two other patients had underlying primary hyperparathyroidism, 2 patients were taking hydrochlorothiazide, and 1 patient had possible undiagnosed familial hypocalciuric hypercalcemia (Table 1). Another observation arguing against a major role of SGLT2is in causing hypercalcemia was the fact that in 2 patients, the SGLT2i was not discontinued without recurrence of hypercalcemia . Thus, in general, the evidence derived from the above case reports is considered weak and does not support a direct causative role of SGLT2is in the development of hypercalcemia.

Mechanistic Studies

To the best of the author's knowledge, there are 4 clinical studies that examined electrolyte status, including calcium, and pertinent hormones in subjects starting 3 different SGLT2is (Table 2). As depicted in table 2, these studies had different designs, follow-up durations, and included healthy subjects as well as patients with type 2 diabetes with and without various degrees of kidney function.

Table 2: *Mechanistic studies to examine serum calcium and pertinent markers in subjects using SGLT-2is.*

	Blau et al [16]	**Rau et al [17]**	**de Jong et al [18]**	**Masajtis-Zagajewska et al [19]**
Design	Randomized, placebo-controlled, single-blind, crossover in hospital	Randomized, double-blind, placebo-controlled	Post-hoc analysis of a randomized double-blind, cross-over trial	Prospective, uncontrolled
SGLT2i	Canagliflozin 300 mg/d	Empagliflozin 10 mg/d	Dapagliflozin 10 mg/d	Empagliflozin 10 mg/d
Subjects	25 healthy volunteers, age 38, 36% women	42 patients with type 2 diabetes, age 62, 19% women	31 patients with type 2 diabetes, age 62, 22% women, with early CKD (eGFR 72 ml/min/1.73 m^2)	42 patients with CKD (eGFR 38.6 m/min/1.73 m^2), age 56, 40% women
Follow-up	5 days, with ≥1week wash-out	At day 3, and at 3 months	6 weeks and 6 weeks wash-out	7 days
Serum Ca	No change	No change	No change	No change
Urine Ca	Decreased vs placebo at day 4	No change	NR	No change
Serum P	16% increase vs placebo	Transient increase vs baseline by 11% at day 3	Increase 11% vs baseline	Increased in subgroup of patients with diabetes
PTH	25% increase vs placebo	Transient increase by 22% vs baseline at day 3	Increase 15% vs baseline	No change
FGF-23	20% increase vs placebo	Transient increase vs baseline by 40% at day 3	Increase 20% vs baseline	Increased in subgroup of patients with diabetes
1,25 di-OH vitamin D	9.4% decrease vs placebo	Transient decrease vs baseline by 37% at day 3	Decrease 19% vs baseline	No change

Age is expressed as means in years

Abbreviations: SGLT2is: sodium-glucose co-transporter 2 inhibitors, Ca: calcium, P: phosphorus or phosphate, F; females, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate

Despite these differences, the 4 studies did not demonstrate any significant changes in serum calcium levels. It is noteworthy that in one study of healthy subjects,found significant decrease in urinary calcium excretion on day 4 of canagliflozin therapy versus placebo (1.44 versus 1.66 mmol/creatinine, P = 0.04). Yet, in 2 other studies, urinary calcium excretion was unchanged at day 3, day 7 and 3 months after treatment with empagliflozin 10 mg/d [16-19]. Parathyroid hormone (PTH) and 1,25 di-hydroxy Vitamin D are the 2 main regulators of circulating calcium levels that may lead to hypercalcemia if their levels are increased [20]. Interestingly, 3 of the 4 studies recorded an increase in PTH concentrations by 15-25% and a decline by 9-37% in 1,25 di-hydroxy vitamin D few days after starting SGLT2is The increase in PTH did not result in hypercalcemia presumably due to the concomitant decrease in 1,25 di-hydroxy vitamin D levels. The most consistent finding in the 4 studies was the increase in serum

fibroblast growth factor-23 (FGF-23), the main regulator of serum phosphorus [21]. This increase in FGF-23 is likely a compensatory response to the rise in serum phosphorus.

Serum calcium levels in large clinical trials of SGLT2is

Randomized trials of several years of follow-up and including thousands of patients with or without type 2 diabetes, heart failure, and CKD did not show any evidence of hypercalcemia among adverse effects of various SGLT2is [1-5]. Recently, Zhang et al [6] conducted a meta-analysis of 19 clinical trials that reported calcium data in patients with type 2 diabetes using SGLT2is. Overall, they found that SGLT2is were associated with significant elevation of serum calcium levels by 0.04 mg/dl (0.01 mmol/L) [95% CI 0.0 to 0.04 mg/dl (0.0-0.01 mmol/L)]. However, this minimal increase although statistically significant is unlikely to be clinically meaningful.

Conclusions

Available data derived from mechanistic studies and large clinical trials do not support the concept that SGLT2is cause hypercalcemia. Despite the widespread use of SGLT2is, only 7 cases of hypercalcemia were reported. In the majority of cases, baseline calcium levels were not reported, and patients proved to have other causes of hypercalcemia. Accordingly, in patients starting SGLT2is, monitoring of serum calcium levels more frequently than in routine practice is not required. However, until further data become available, it may be wise to get a baseline serum calcium value before starting SGLT2i to rule out underlying primary hyperparathyroidism or other calcium disorders. In addition, more frequent monitoring of serum calcium concentrations (e.g. every 3-4 months) is recommended in SGLT2is users taking thiazides and those with known untreated primary hyperparathyroidism.

Conflict of Interest

The author has no conflict of interest to declare.

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