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UNMASKING OF NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM AFTER SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITOR INITIATION

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ABSTRACT

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have complex interactions with bone metabolism, including an increase in parathyroid hormone (PTH) levels. Here we report a case of a SGLT2 inhibitor-induced hypercalcemia due to primary hyperparathyroidism. In the subset of patients with normocalcemic primary hyperparathyroidism, SGLT2 inhibitor initiation can unmask the disorder causing overt hypercalcaemic hyperparathyroidism. Although normocalcemic primary hyperparathyroidism is a rare entity, we propose obtaining a baseline PTH level before starting a SGLT2 inhibitor in patients with calcium levels in the upper limit of normal and normal total 25-hydroxyvitamin D levels, especially if they are under vitamin D supplementation. PTH should be rechecked in order to exclude overt primary hyperparathyroidism.

KEYWORDS

SGLT2 inhibitors, hypercalcemia, hyperparathyroidism

LEARNING POINTS

- Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a class of medications that cause secondary hyperparathyroidism.
- In patients with normocalcemic primary hyperparathyroidism, SGLT2 inhibitor' initiation can cause overt hyperparathyroidism and hypercalcemia.
- We propose obtaining a baseline parathyroid hormone level before starting a SGLT2 inhibitor in patients with calcium levels in the upper limit of normal especially if they are under vitamin D supplementation.

INTRODUCTION

Owing to the fact that any new antidiabetic agent must demonstrate its safety regarding cardiovascular outcomes, sodium-glucose cotransporter-2 (SGLT2) inhibitors represent a major paradigm shift in the treatment of patients with chronic renal disease and heart failure. These agents are now considered as first-line therapy in people with diabetes and atherosclerotic cardiovascular disease, heart failure or nephropathy and are also an important pillar of heart failure treatment, irrespective of ejection fraction or presence of

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diabetes. Well known adverse effects of SGLT2 inhibitors are mycotic genital infections and diabetic ketoacidosis. The resulting ever-increasing use of these agents makes real world data an indispensable source of information regarding both their effectiveness and their safety.

CASE DESCRIPTION

A 70-year-old woman presented to our hospital due to worsening fatigue. Her past medical history included hypertension, diabetes, dyslipidaemia and vitamin D deficiency with a total 25-hydroxyvitamin D (25-OH-D) level of 12.2 ng/ml, for which she was started on calcium and cholecalciferol 2 months prior. At that time, her calcium and creatinine levels were 10 mg/dl and 0.8 mg/dl respectively. Four weeks prior to this presentation, she was prescribed dapagliflozin 10 mg od, substituting metformin in her diabetes regimen. After dapagliflozin initiation she reported fatigue and dizziness. One week before admission dapagliflozin was substituted with canagliflozin without symptom improvement. On admission, her medications included amlodipine, valsartan, carvedilol, canagliflozin, rosuvastatin, calcium carbonate and cholecalciferol.

Her physical examination was normal, notably with no pedal oedema. She was afebrile, with a blood pressure 170/97 mmHg, heart rate 100 bpm and oxygen saturation 96% on ambient air. Her electrocardiogram showed sinus tachycardia without findings suggestive of ischemia. Laboratory tests showed a calcium level of 17 mg/dl, creatinine 1.4 mg/dl and total 25-OH-D 19 ng/ml *(Table 1)*. Intravenous fluids and zoledronic acid were initiated for the management of hypercalcemia. Canagliflozin was discontinued and the calcium levels returned to normal.

On admission her parathyroid hormone (PTH) level was 1229 pg/ml while computed tomography revealed a lesion measuring 2.5 cm in diameter inferior to the right thyroid lobe. Technetium (99mTc) sestamibi parathyroid scintigraphy displayed an image compatible with adenoma. The patient was treated with monthly zoledronic acid infusions in order to maintain her calcium levels in the normal range. She underwent parathyroidectomy 4 months after her discharge. Pathological examination excluded parathyroid cancer and confirmed the diagnosis of adenoma. At 12 months following parathyroidectomy her calcium and PTH levels remained normal.

DISCUSSION

Ninety percent of renal reabsorption of glucose takes place in the proximal tubules and requires a carrier protein, referred to as SGLT2. SGTL2 inhibitors are hypoglycaemic agents that block this protein resulting in glycosuria. Although their mechanism of action involves glucose, water and sodium manipulation, phase 3 trials have not revealed clinically meaningful electrolyte abnormalities as adverse effects.

SGLT2 inhibition is associated with enhanced renal proximal tubular reabsorption of phosphate by increasing availability of sodium to be reabsorbed with the former at that site. The resulting hyperphosphatemia induces an increase in PTH and fibroblast growth factor 23 (FGF23) levels[1]. This triggers a homeostatic response, restoring serum phosphorus toward baseline levels. A study in healthy hospitalized patients confirmed that canagliflozin increased mean levels of phosphorus, FGF23 and PTH by 16%, 20% and 25% respectively, disproportionally to the concomitant decrease of the glomerular filtration rate (GFR)[2]. Dapagliflozin has similar effects, further indicating that the interference in phosphate metabolism and in FGF23 and PTH levels is a class effect, although with a considerable interindividual variation. These metabolic disturbances are obviously directly related to bone health; an increase in bone fractures was noted with canagliflozin in the CANVAS program but not confirmed in other canagliflozin trials neither in a meta-analysis of all SGTL2 inhibitors[3]. Nevertheless, because of this interference in the PTH axis, SGLT2 inhibitors are considered a class of medications

Variable	2 months before admission	Admission	Discharge	Post parathyroidectomy	Reference range
Haemoglobin (g/dl)	14	14.4	14	13	12-15
Urea (mg/dl)	37	63	30	35	16-48
Creatinine (mg/dl)	0.8	1.4	1.1	0.9	0.5-0.9
Calcium (mg/dl)	10	17	10	9	8.6-10.3
Phosphate (mg/dl)	N/A	1.7	1.2	2	2.5-4.5
Total 25-OH-D (ng/ml)	12,2	19	N/A	N/A	>30
Parathyroid hormone intact (pg/ml)	N/A	1229	N/A	N/A	15-65

Abbreviations: N/A, not available.

Table 1. The patient's laboratory data.

Reference	SGLT2 inhibitor	Ca before (mg/dl)	Ca after (mg/dl)	PTH before-after (pg/ml)	Total 25-OH-D (ng/ml)	Diagnosis
Masri et al., 2021[6]	Canagliflozin	10.1	12.2	59.2-79.6	24 (suppl)	SHP
Masri et al., 2021[6]	Canagliflozin	10.2	10.8	N/A-57	18	SHP
Masri et al., 2021[6]	Empagliflozin	N/A	10.6	N/A-82	21.8	SHP
Awada et al., 2022[7]	Empagliflozin	N/A	10.9	N/A-52	23.8 (suppl)	Adenoma
Akhanli et al., 2020[8]	Dapagliflozin	Normal	11.2	N/A-70.8	33.16	Adenoma
Kaur et al., 2015[9]	Canagliflozin	Normal	17.4	N/A-11	24	Ketoacidosis
Vidas et al., 2018[10]	Dapagliflozin	9.7	11	N/A-40	N/A	SHP

Abbreviations: SGLT2, sodium-glucose cotransporter-2; Ca, calcium; PTH, parathyroid hormone; N/A, not available; SHP, SGLT2 inhibitor-associated secondary hyperparathyroidism; suppl, under vitamin D supplementation.

Table 2. Previous cases of SGLT2 inhibitor-induced hypercalcemia.

causing secondary hyperparathyroidism (i.e. increase in PTH levels) along with thiazide diuretics, lithium, anticonvulsants and bisphosphonates.

The entity of normocalcemic primary hyperparathyroidism (i.e. autonomous hypersecretion of PTH with calcium levels consistently within normal range) is recognized since 2009 but its natural history and associated risks are incompletely defined and understood[4]. It seems that calcium and vitamin D homeostasis is disturbed years before a diagnosis of primary hyperparathyroidism is made and a normocalcemic state of autonomous PTH secretion precedes the overt hypercalcaemic form in some patients.

In our case, the chronological sequence of the laboratory findings and symptoms suggests that dapagliflozin unmasked a previous normocalcemic primary hyperparathyroidism due to parathyroid adenoma resulting in severe hypercalcemia and hypophosphatemia. Although we do not know our patient's baseline value of PTH, we can assume the diagnosis of normocalcemic primary hyperparathyroidism taking into account her calcium level in the upper limit of normal before dapagliflozin initiation, the presence of a parathyroid adenoma and the extremely high levels of PTH at admission.

A Danish population study[5] showed significantly lower levels of total 25-OH-D in patients with normocalcemic primary hyperparathyroidism compared with controls, as is the case for hypercalcaemic primary hyperparathyroidism. Vitamin D controls the function of the parathyroid glands by suppressing the gene encoding PTH synthesis so it is speculated that either deficiency or increased metabolism of vitamin D can cause parathyroid proliferation and adenoma formation. In theory, coexisting vitamin D deficiency can mask the hypercalcemia in patients with primary hyperparathyroidism who will become hypercalcaemic once vitamin D is corrected after supplementation. Nevertheless, it has been shown that vitamin D supplementation in patients with primary hyperparathyroidism who are deficient lowers PTH without change in calcium levels and, in fact, some experts recommend vitamin D supplementation in patients with primary hyperparathyroidism and coexisting vitamin D deficiency in order to ameliorate PTH levels. Our patient was still vitamin D deficient at admission even after cholecalciferol supplementation, so vitamin D did not contribute to the unmasking of primary hyperparathyroidism.

Our review of the literature revealed seven cases of SGLT2 inhibitor induced hypercalcemia[6-10] in which the three most widely used SGLT2 inhibitors - dapagliflozin, empagliflozin and canagliflozin - are implicated. Two of these cases were due to previous undiagnosed normocalcemic primary hyperparathyroidism related to parathyroid adenoma *(Table 2)*. Of note, a search for primary hyperparathyroidism was not performed in all cases with elevated PTH levels.

Our case suggests that SGLT2 inhibitors not only increase PTH levels causing secondary hyperparathyroidism but can also unmask primary hyperparathyroidism in a subset of patients with undiagnosed normocalcemic primary hyperparathyroidism, especially in the presence of hypovolemia and renal injury. SGLT2 inhibitor-induced volume depletion and a decrease in the GFR are known effects of these medications that may be detrimental in elderly patients. The ensuing hypovolemia coupled with the stimulation of PTH production by SGLT2 and the ongoing calcium supplementation destabilized the delicate balance of normocalcemic hyperparathyroidism resulting in severe hypercalcemia in our patient.

As normocalcemic primary hyperparathyroidism is a diagnosis of exclusion, with secondary hyperparathyroidism due to vitamin D deficiency, chronic renal disease or medications being much more common, it is difficult to recognize the patients at risk for hypercalcemia after SGLT2 inhibitor initiation. Taking into account the data provided from the aforementioned Danish study[5], patients with normocalcemic hyperparathyroidism tend to have mild vitamin D deficiency and calcium levels in the upper limit of normal. This mild deficiency usually leads to the

prescription of vitamin D supplementation. So, although cost-effectiveness is a serious concern, we propose obtaining a baseline PTH level in patients under vitamin D supplementation and normal 25-OH-D level, who have a calcium level at the upper limit of normal (i.e. greater than 10 mg/dl) before starting a SGLT2 inhibitor. If increased, PTH and calcium levels should be re-checked in 2-4 weeks to exclude an unmasked primary hyperparathyroidism.

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