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Case Report

The Fluctuation of Serum PTH Level of Type 2 Diabetes mellitus' Patient on Oral Dapagliflozin

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Abstract

Background: Sodium-Glucose co-Transporter 2 (SGLT2) inhibitors, a set of relatively new medicines treating type 2 diabetes showed a great number of merits in control of glycemia and cardiovascular risk factor management, but also attracted attention on bone fracture. One of those major effects on skeleton might be Parathyroid Hormone (PTH).

Case Presentation: We present the case of a 68-year-old female patient with type 2 diabetes on insulin injection and oral acarbose therapy who was admitted with constant hyperglycemia to our hospital. In the beginning, she showed a high level of serum PTH. In the process of oral dapagliflozin treatment, PTH concentration firstly increased and then decreased to the normal range. Diagnostic tests are completed to exclude hyperparathyroidism.

Conclusions: The use of SGLT2 inhibitors among diabetes and non-diabetic populations is increasing, a great deal of undiscovered influence, such as hormone and ion fluctuation needs further investigation.

Keywords: PTH level; SGLT2 inhibitor; Dapagliflozin; Type 2 diabetes mellitus; Calcium and phosphate homeostasis

Background

Sodium-Glucose Co-Transporter-2 (SGLT2) inhibitors, including empagliflozin, canagliflozin, and dapagliflozin, are glucose-lowering drugs that also lower blood pressure, bodyweight, significantly reducing cardiovascular and all-cause mortality [1], and might reduce the risk of dialysis, transplantation, or death due to kidney disease [2], Though promising results in the treatment of diabetes, increasing data from post-marketing studies indicate their adverse effects such as diabetic ketoacidosis, genital and urinary tract infection, cancer, bone fracture and foot and leg amputation [3]. The effect of anti-diabetic medications on bone metabolism has received increasing attention, considering that type 2 diabetes mellitus is a common metabolic disorder with adverse effects on bone metabolism [4].

Parathyroid Hormone (PTH) can exert both anabolic and catabolic effects on the skeleton. While it also plays a central role in regulating extracellular fluid calcium and phosphate homoeostasis. PTH can enhance Calcium reabsorption in the kidney, whereas at the same time inhibiting phosphate reabsorption and producing phosphaturia [5]. Recent studies have shown that SGLT2 inhibitors induce small increases in serum concentrations of magnesium, potassium and phosphate [6].

In this report, we describe a patient with poor control of glucose level treated with dapagliflozin, whose serum balance of calcium, phosphate and the level of PTH were related to the oral administration of SGLT2 inhibitors. Its putative mechanism will be discussed.

Case Presentation

A 68-year-old female with hypertension, atrial fibrillation and coronary heart disease was admitted seven times to our inpatient department due to poor glycemic control. Her history revealed numbness and tingling in her feet and blurry vision, without chest distress nor pain, breath obstruction. The patient had no history of bone disease, hematuria, renal colic, urolithiasis, dyspepsia, or constipation. Her home medications included acarbose 50mg three times daily, 12 Unit of subcutaneous insulin aspart 30 injection before breakfast and dinner due to diabetes, and aspirin 100 mg daily and betaloc 25mg daily and nifedipine 30mg daily for hypertension and coronary heart disease. The patient had not taken calcium and vitamin D supplement. Her fasting blood glucose was maintained at approximately 11mmol/L. On physical examination at admission, her temperature was 36.0°C, with a pulse rate of 68 bpm, blood pressure of 140/90mmHg, and a respiratory rate of 18 bpm. She had an irregular heart rhythm of 78 bpm. She was overweighted and BMI was 30.29Kg/m^2.

During the period of hospitalization, because of the patient's overweight and poorly controlled serum glucose levels, she has administrated dapagliflozin5 mg daily and less insulin dose on Hospital Day (HD)2. After that treatment, laboratory testing revealed BNP 432.00pg/mL, 25-hydroxyvitamin D 69.41nmol/L (reference range 75.0-150.0nmol/L), HbA1c 9.9% and an elevated PTH 110.3pg/mL (reference range 3.6-11.0mmol/L), albumin 43.99g/L, total calcium 2.45mmol/L. The history was reviewed that she used to have a normal level of PTH (70.42pg/ml) three years ago. Later, we increased the oral dose of dapagliflozin (10 mg daily) to control the patient's serum glucose level on HD5. During past trials of dapagliflozin therapy, the patient experienced a fluctuation in serum calcium, phosphate, and PTH level (Table 1). Urinary calcium and urinary phosphorus were also tested at the same time as showed in

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Table 1: Laboratory examination of patients before and after administration of dapagliflozin.

	PTH (reference range 15.0-65.0pg/mL)	Serum calcium (reference range 2.11-2.52 mmol/L)	Serum phosphorus (reference range 0.75-1.02mmol/L)	Urinary calcium (reference range 2.5-7.5mmol/24h)	Urinary phosphorus (reference range 24-48mmol/24h)
HD2	110.3	2.45	1.01		
HD5	173.9	2.39	1.12	7.43	27.7
HD7	74.06	2.27	0.99	7.66	25.2
HD8	61.38	2.48	1.13	11.93	36.4

Table 1. Other potential reasons for high PTH levels are assessed. No enlarged parathyroid glands were examined through ultrasound, and radionuclide imaging of the parathyroid glands showed there was no abnormal radioactive focal localization near the thyroid glands. BNP was rechecked before discharge, decreasing to 211.00pg/mL.

Discussion

This case suggests that SGLT2 inhibitors may alter the dynamics of PTH level, which ties well with previous studies by Blau et al. Who have confirmed that after canagliflozin administration, phosphate, FGF23, and PTH levels increase within the first few hours/day after administration [7]. How these brand-new oral antidiabetic agents make a difference to PTH. The existing evidence cannot yet establish a direct connection between the two. Then which is the "go-betweens"?

Extracellular fluid ionized calcium appears to be the predominant regulator of the production of PTH [8]. By inhibiting reabsorption of glucose at the proximal tubule, SGLT2 inhibitors lead to disruption of calcium, phosphate, and vitamin D homeostasis when considering the drugs' mechanism of action [9]. As a result of SGLT2 inhibition, both glycosuria and urinary calcium excretion are increased [10]. Increased urinary calcium losses contribute to a reduction in serum calcium which then triggers the development of secondary hyperparathyroidism [11].

But neither experiments in diabetic rats treated with dapagliflozin [12] nor meta-analysis of canagliflozin, dapagliflozin, empagliflozin, and ipragliflozin [13] showed significant serum calcium disorder according to recent researches.

Dapagliflozin reduces glucose reabsorption by inhibiting SCLT2 in the proximal tubules of the kidney, thereby promoting urinary glucose excretion and reducing glucose concentration in the blood. The co-transport of phosphate and natrium is enhanced by increasing the electrochemical gradient of sodium ions. High levels of phosphorus in the serum will break the balance of calcium and phosphorus in the blood [14]. At the same time, the increase of serum phosphate may trigger the secretion of Fibroblast Growth Factor 23 (FGF23) [15] that which is also related to the occurrence of PTH increasing.

Recent clinical trials have shown that SGLT2 inhibitors have dramatic beneficial cardiovascular outcomes, including a reduced incidence of cardiovascular death and heart failure hospitalization [16]. The recently DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial demonstrated a marked reduction in worsening heart failure [17]. While, higher serum intact Parathyroid Hormone (PTH) concentrations are known to be associated with coronary artery disease, increased left ventricular mass, and heart failure [18-20].

We speculated the underlying mechanisms of this case may be explained as below: chronic heart failure contributes to the initial high level of PTH. The PTH is further increasing due to dapagliflozin administration. As time extended, improved heart function, which is testified by decreasing BNP, induced declining PTH, and maintained dynamic balance.

Conclusion

The use of SGLT2 inhibitors among diabetes and non-diabetic populations is increasing, and despite cardiovascular benefits, there is a great deal of undiscovered influence. This case highlights these hormone and ion fluctuation occurring concurrently. Given the potentially catastrophic consequences, physicians must maintain appropriate clinical suspicion for inpatients on SGLT2 inhibitors.

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