A rare metabolic complication: Hypercalcemic crisis in a patient using a GLP-1 agonist

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Abstract

Hypercalcemic crisis is a rare complication of markedly elevated serum calcium levels and most commonly occurs in patients with paraneoplastic syndrome or primary hyperparathyroidism.[1] We present the case of a hypercalcemic crisis in a 54-year-old woman who was recently started on semaglutide while also taking a thiazide diuretic. After ruling out other potential causes by measuring parathyroid hormone (PTH), parathyroid hormone–related protein (PTHrP), 1,25-dihydroxy vitamin D, and 25-hydroxy vitamin D levels, it was determined that dehydration from inadequate fluid intake in the setting of semaglutide therapy, combined with increased serum calcium levels associated with thiazide diuretic use, precipitated a hypercalcemic crisis in this patient.

Keywords: Hypercalcemic crisis, GLP-1 agonists, paraneoplastic syndrome, primary hyperparathyroidism

Introduction

Hypercalcemic crisis is a rare endocrine emergency associated with increased mortality.[1] Rapid diagnosis and treatment can improve outcomes; however, there is no standardized definition for the condition.[1] An arbitrary definition suggested by Ahmad et al. is "an albumin-corrected serum calcium level >14 mg/dL, associated with the presence of multiorgan dysfunction."[1]

Acute exacerbation of calcium levels and subsequent decompensation typically occur in individuals who already have mild hypercalcemia.[1] The most common etiology of hypercalcemic crisis is primary hyperparathyroidism.[1] Accordingly, it is essential to determine whether a patient presenting with hypercalcemic crisis has primary hyperparathyroidism by evaluating serum parathyroid hormone (PTH) levels.

Additional potential causes of hypercalcemic crisis listed by Ahmad et al. include humoral hypercalcemia of malignancy involving parathyroid hormone–related protein (PTHrP), ectopic formation of 1,25-dihydroxyvitamin D by a tumor or in sarcoidosis, bone destruction associated with malignancy, medications such as estrogens and thiazide diuretics, excessive ingestion of vitamins D or A, immobilization, and familial hypocalciuric hypercalcemia.[1] Treatment of hypercalcemic crisis depends on the underlying cause.[1]

In this report, we present a case of hypercalcemic crisis in a patient who recently started semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, as a new complication associated with these medications[4,5] and a new potential etiology of the condition. Furthermore, given the rising popularity of GLP-1 receptor agonists, we highlight important clinical considerations regarding their use alongside thiazide diuretics to prevent dehydration and reduce the risk of precipitating hypercalcemic crisis.

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Case Report

A 54-year-old woman with a past medical history of obesity, essential hypertension treated with hydrochlorothiazide, losartan, and amlodipine, and

well-controlled Type 2 diabetes managed with semaglutide presented to the hospital with syncope and hypercalcemia. Prior to the hypercalcemic episode, she had been taking semaglutide for 2.5 months and had been on hydrochlorothiazide without complications for 4 years.

At presentation, the patient reported taking one calcium supplement daily but was uncertain whether the dose was 0.5 g or 1 g. She also noted inadequate fluid intake in the context of a recent semaglutide dose increase from 0.5 mg to 1 mg. The patient did report severe gastritis symptoms after increasing the dose of semaglutide for which she was taking TUMS™ every 3–4 hours. As part of the hypercalcemia work-up, serum calcium, parathyroid hormone (PTH), parathyroid hormone–related protein (PTHrP), and 25-hydroxyvitamin D levels were obtained during her hospitalization. Her peak calcium level was 16.5 mg/dL, indicating significant hypercalcemia. Parathyroid hormone and PTHrP were suppressed at 5 pg/mL and 9 pg/mL, respectively. Her 25-hydroxyvitamin D level was elevated at 108 ng/mL despite no vitamin D supplementation.

The patient was referred to the Endocrinology Clinic, where primary hyperparathyroidism and malignancy-related PTHrP elevation were ruled out, as both PTH and PTHrP levels were low (Table 1).[1] In addition, the mildly elevated 25-hydroxyvitamin D level made vitamin D–mediated hypercalcemia less likely.[2] To evaluate for possible sarcoidosis-related overproduction of 1,25-dihydroxyvitamin D, the patient's 1,25-dihydroxyvitamin D level was measured and found to be low at 20 pg/mL.[1] She was instructed to continue her medications, discontinue calcium supplements, avoid vitamin D supplementation, ensure adequate hydration, and return for follow-up in 3 months.

At the 3-month follow-up visit, she was asymptomatic with normalized laboratory values: calcium 9.7 mg/dL, PTH 18 pg/mL, and 25-hydroxyvitamin D 70 ng/mL. She had continued hydrochlorothiazide but avoided calcium and vitamin D supplements as instructed. During this visit, she was advised to discontinue hydrochlorothiazide, refrain from calcium and vitamin D supplementation, maintain adequate hydration, use alternative medication for reflux symptoms and undergo repeat laboratory testing in 3 months, with a planned follow-up visit in 1 year.

Discussion

Hypercalcemic crisis is a rare but serious complication of elevated serum calcium levels and is associated with significant mortality.[1] Treatment depends on the underlying cause, which in this case was dehydration and medication-induced hypercalcemia.[1] Management involved discontinuing the patient's calcium supplement and thiazide diuretic use to reduce serum calcium levels, along with education on the importance of maintaining adequate hydration, particularly in the context of semaglutide therapy.

Semaglutide, a GLP-1 receptor agonist used to treat diabetes, has also gained popularity as a

Table 1. Patient Laboratory Values

	Calcium (Normal Range: 8.8–10.5 mg/dL)	PTH (normal Range: 15–65 pg/mL)	PTHrP (Normal Range: 11–20 pg/mL)	Vitamin D 1,25 (pg/mL)	Vitamin D 25 (ng/mL)	Comments
At hospitalization	16.5*	5	9	–	108	Patient presented in hypercalcemic crisis
3-month follow-up (Endo Clinic)	9.7	18	–	–	70	Patient was asymptomatic with normalized laboratory values

*Peak calcium level during hospitalization

weight-loss aid.[4,5] It can affect kidney function, especially in the setting of dehydration.[4,5] Thiazide diuretics act on the distal convoluted tubule of the nephron to promote diuresis; however, they also increase calcium reabsorption, which can elevate serum calcium levels.[1,6] Dehydration can further impact glomerular filtration rate and reduce renal calcium excretion.[1] Therefore, ensuring adequate fluid intake is essential to prevent hypercalcemic crisis, as illustrated in this patient.

Clinicians should be aware of the signs of hypercalcemic crisis and maintain a high index of suspicion in patients presenting with related symptoms, as rapid diagnosis and treatment can improve outcomes.[1] Clinical features may include nephrolithiasis, nausea, vomiting, bone pain, impaired memory, impaired concentration, and hypertension.[2]

Conclusion

In conclusion, hypercalcemic crisis is a rare condition that is usually caused by primary hyperparathyroidism.[1] In this case report, we present a 54-year-old female patient who was recently placed on semaglutide in the setting of previous, long-term thiazide diuretic use. After ruling out other potential causes of hypercalcemic crisis by measuring levels of parathyroid hormone, parathyroid hormone-related protein, vitamin D 1,25-Dihydroxy level, and vitamin D 25 hydroxy total, it was determined that dehydration from inadequate fluid intake in the setting of semaglutide utilization and increased serum calcium levels from thiazide diuretic use led to hypercalcemic crisis in this patient.

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