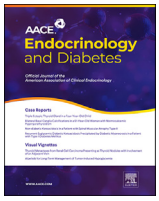
AACE Endocrinology and Diabetes 13 (2026) 107–111

Endocrinology and Diabetes
www.endocrinologydiabetes.org



Case Report

The Hidden Threat of Antacid Overuse: A Case of Severe, Slow-Burning Hypercalcemia (Serum Calcium of 22.8 mg/dl)

Sandhya Shanthosh Kumar, MD [1,*], Sani Yasnain, MD [1], Saira Tanveer, MD [1], Niveditha Manivannan, MD [2]

[1] *Department of Internal Medicine, UPMC Mercy, Pittsburgh, Pennsylvania*
[2] *Department of Endocrinology, UPMC Mercy, Pittsburgh, Pennsylvania*

ARTICLE INFO

Article history:
Received 29 June 2025
Received in revised form
24 August 2025
Accepted 16 September 2025
Available online 22 September 2025

Key words:
calcium carbonate
hypercalcemia
MAS
milk-alkali syndrome

ABSTRACT

Background/Objective: Severe hypercalcemia presents with significant symptoms and life-threatening systemic effects. This case report highlights a rare presentation of severe hypercalcemia due to milk-alkali syndrome (MAS) with surprisingly mild symptoms.
Case Report: A 44-year-old woman presented to the emergency department following a fall that occurred due to losing balance while attempting to pick up her medications that had fallen on the floor, resulting in right fibula fracture. She was incidentally found to have severe hypercalcemia with a serum calcium level of 22.8 mg/dL, despite having only mild symptoms such as brain fog and occasional nausea. Laboratory workup revealed acute kidney injury, metabolic alkalosis and a suppressed parathyroid hormone in the setting of excess intake of calcium carbonate tablets for uncontrolled gastroesophageal reflux disease. This, combined with the clinical and laboratory findings, led to a diagnosis of MAS. The patient was treated with aggressive intravenous fluid hydration and calcitonin, which rapidly improved her severe hypercalcemia.
Discussion: MAS is resurfacing as one of the leading causes of hypercalcemia. This resurgence is particularly relevant given the widespread use of calcium-alkali agents for management of osteoporosis, chronic kidney disease, and gastroesophageal reflux disease. The syndrome can present with mild or nonspecific symptoms which makes diagnosis challenging, especially in patients with complex comorbidities. Awareness of MAS is critical for timely identification and treatment.
Conclusion: MAS should be considered a key differential diagnosis in patients with hypercalcemia. Early detection and intervention are essential to reverse metabolic disturbances and prevent potentially life-threatening outcomes.

Introduction

Severe hypercalcemia, defined by serum calcium levels exceeding 14.0 mg/dL, represents a critical medical condition often accompanied by a spectrum of symptoms affecting multiple organ systems. Patients with calcium levels above 12 mg/dL are commonly symptomatic and can present with a wide range of symptoms including lethargy, confusion, abdominal pain, vomiting, constipation, polyuria, renal colic, and in severe cases, psychosis, arrhythmias and coma. Prompt recognition and management of severe hypercalcemia is essential to prevent potentially fatal complications, including renal failure, life-threatening cardiac arrhythmias, and neurological deterioration.

Milk-alkali syndrome (MAS), once a rare diagnosis, has resurfaced as the third leading cause of severe hypercalcemia, largely attributable to the widespread use of calcium-containing supplements and antacids for conditions like gastroesophageal reflux disease (GERD), chronic kidney disease, and osteoporosis. MAS is characterized by the classic triad of severe hypercalcemia, metabolic alkalosis and acute kidney injury. Its clinical presentation often mimics other common causes of hypercalcemia such as

Abbreviations: CT, computed tomography; GERD, gastroesophageal reflux disease; MAS, milk-alkali syndrome; OTC, over-the-counter; PTH, Parathyroid hormone.

* Address correspondence to Dr Sandhya Shanthosh Kumar, Department of Internal medicine, UPMC Mercy, 1400 Locust St, Pittsburgh, PA 15219.
E-mail address: shanthoshkumars@upmc.edu (S. Shanthosh Kumar).

https://doi.org/10.1016/j.aed.2025.09.008

malignancy or primary hyperparathyroidism, which can lead to unnecessary and costly diagnostic evaluations. Therefore, heightened awareness of MAS among healthcare providers is vital to ensure early diagnosis and timely intervention, preventing severe complications and ultimately end organ failure.

Case Description

A 44-year-old female presented to the emergency department following a fall that occurred due to losing balance while attempting to pick up her medications that had fallen on the floor and was found to have a right fibula fracture. Her past medical history was significant for hypertension, type 2 diabetes mellitus, peripheral neuropathy with chronic left foot neuropathic ulcer, uterine fibroids and GERD. She was also diagnosed with stage IA right breast carcinoma 7 months ago for which she underwent mastectomy followed by radiation and thereafter continued on treatment with tamoxifen and leuprolide.

Incidentally, routine blood work revealed a profoundly elevated serum calcium level of 22.8 mg/dL (normal range 8.4 to 10.4 mg/dL) with an ionized calcium of 2.38 mmol/L (normal range 1.12 to 1.32 mmol/L). Repeat testing confirmed persistent severe hypercalcemia with a serum calcium of 22.5 mg/dL and ionized calcium of 2.36 mmol/L. Historical lab values from 5 months prior showed normal hematology and biochemistry including serum calcium of 8.9 mg/dL. On review, the patient reported experiencing brain fog, occasional nausea and vomiting over the preceding 2 to 3 weeks, which she attributed to a recent increase in gabapentin dosage from 300 mg to 900 mg 3 times daily for her neuropathy. She denied headaches, palpitations, abdominal or flank pain, constipation, polyuria, polydipsia, or bone pain. The patient was hemodynamically stable, alert and oriented, without acute distress and physical examination was unremarkable aside from baseline peripheral neuropathy and tenderness over the right leg consistent with recent trauma. Her medications included hydrochlorothiazide, tamoxifen, leuprolide, semaglutide, and vitamin D 4000 IU daily. She also admitted to consuming approximately 8 to 10 tablets of over-the-counter (OTC) calcium carbonate daily for uncontrolled GERD.

Laboratory studies revealed acute kidney injury with a creatinine of 2.5 mg/dL (baseline 0.6 mg/dL), metabolic alkalosis with pH 7.54 and bicarbonate 39 mmol/L, hypokalemia (2.9 mmol/L) and hypomagnesemia (1.5 mg/dL). Electrocardiogram demonstrated a prolonged QTc interval of 528 ms (normal <460 ms), which normalized following electrolyte repletion. PTH was suppressed at 14 pg/mL. Levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and thyroid-stimulating hormone were within normal limits (Refer to Table 1). Chest x-ray and computed tomography (CT) scan of the abdomen and pelvis showed no abnormalities.

In the context of the classic triad of severe hypercalcemia, metabolic alkalosis, and acute kidney injury with suppressed PTH, along with a history of excessive calcium carbonate ingestion, a diagnosis of MAS was established. Treatment consisted of cessation of exogenous calcium intake, aggressive intravenous fluid hydration and administration of calcitonin. Within 48 h, serum calcium and creatinine levels improved significantly to 16.2 mg/dL and 1.93 mg/dL. The patient was discharged on hospital day 7 with a serum calcium of 10.7 mg/dL, ionized calcium of 1.4 mmol/L and creatinine 1.41 mg/dL. She was transitioned to a proton pump inhibitor for management of GERD. Follow-up labs at 3 months postdischarge showed serum calcium of 8.4 mg/dL and serum creatinine of 0.6 mg/dL (baseline). (Refer to Table 2).

Highlights

- Life-threatening hypercalcemia may occur silently in milk-alkali syndrome (MAS), delaying timely diagnosis
- Unregulated use of over-the-counter calcium carbonate use is driving a resurgence of MAS
- Prompt identification of the classic triad of hypercalcemia, metabolic alkalosis, and acute kidney injury is essential to avoid costly and unnecessary diagnostic work up
- Thiazide diuretics can worsen hypercalcemia by facilitating hypovolemia, contraction alkalosis, and renal calcium reabsorption
- Tamoxifen-induced hypercalcemia is uncommon without metastatic bone disease

Clinical Relevance

This case underscores the critical need to recognize milk-alkali syndrome as a potentially life-threatening yet reversible cause of severe hypercalcemia, particularly in patients with high calcium-alkali intake and minimal symptoms, to prevent misdiagnosis and avoid unnecessary invasive investigations.

Case Discussion

Historically, MAS was first described in the 1920s when patients were treated with the “Sippy regimen,” a combination of milk and bicarbonate powders, for peptic ulcer disease. Originally, this regimen consisted of hourly administration of milk along with heavily calcinated magnesia and sodium bicarbonate, alternating

Table 1
Summary of Laboratory results and Notable Findings

Laboratory Test	Patient's value	Normal reference range	Interpretation
Total serum calcium	22.8 → 22.5 mg/dL	8.4 – 10.4 mg/dL	Severely elevated
Ionized calcium	2.38 → 2.36 mmol/L	1.12 – 1.32 mmol/L	Severely elevated
Serum creatinine	2.5 mg/dL	0.6 – 1.3 mg/dL	Acute kidney injury
Venous blood gas	pH 7.54 HCO_3^- 39 mmol/L pCO2 46 mmHg	pH 7.32 – 7.42 HCO_3^- 22 – 28 mmol/L pCO2 41 – 51 mmHg	Metabolic alkalosis
Parathyroid hormone	14 pg/mL	15 – 65 pg/mL	Suppressed
25-hydroxyvitamin D	32 ng/mL	20 – 50 ng/mL	Normal
1,25-dihydroxyvitamin D	60 pg/mL	18 – 72 pg/mL	Normal
Parathyroid hormone-related peptide	11 pg/mL	11 – 20 pg/mL	Normal
Serum potassium	2.9 mEq/L	3.5 – 5.0 mEq/L	Hypokalemia
Serum magnesium	1.5 mg/dL	1.7 – 2.2 mg/dL	Hypomagnesemia
Serum chloride	92 mmol/L	98 – 112 mmol/L	Low

Table 2
Summary of Laboratory Trends With Inpatient Treatment

Hospital day	Serum calcium (mg/dL)	Ionized calcium (mmol/L)	Interventions
Day 1	22.8 → 22.5	2.38 → 2.36	Normal saline 1L bolus + NS @ 150 cc/h Calcitonin 345IU x 2 doses
Day 2	17.4 → 17.9 → 16.8	2.05 → 2.09 → 1.93	Normal saline @ 150 cc/h Calcitonin 345IU x 2 doses
Day 3	16.2 → 14.3	1.84 → 1.72	Normal saline @ 150 cc/h
Day 4	13.3	1.70	Normal saline @ 75 cc/h
Day 5	11.7	1.55	Normal saline @ 75 cc/h
Day 6	11.1	1.51	Normal saline @ 75 cc/h
Day 7	10.7	1.40	Discharged
3 mo follow up	8.4	-	-

with bismuth subcarbonate and sodium bicarbonate. Over time, this treatment evolved into several diverse regimens leading to increased incidence of toxicity presenting with hypercalcemia, metabolic alkalosis, and acute kidney injury, which together became known as the classic triad of MAS.[1,2]

With the advancement of safer, more effective alternative treatments such as non-absorbable antacids, H2-receptor antagonists and proton pump inhibitors, which offered superior acid suppression with fewer side effects, there was a notable decline in the use of the Sippy regimen. Additionally, the discovery of Helicobacter pylori as a primary cause of peptic ulcers led to targeted antibiotic treatments, further reducing the need for calcium-based therapies.[3]

These advancements rendered the Sippy regimen obsolete and significantly reduced the incidence of MAS, until its resurgence in recent years, due to widespread and often excessive use of calcium carbonate supplements, both prescribed and available OTC, for managing conditions such as osteoporosis, GERD and chronic kidney disease. Unlike its historical association with the Sippy regimen, modern MAS is frequently seen in individuals who self-administer high doses of calcium and absorbable alkali without medical supervision, often unaware of the associated risks. Public health campaigns promoting calcium for bone health, particularly targeting postmenopausal women and the elderly, have contributed to unsupervised daily intakes that frequently surpass recommended thresholds. This change in the pattern of calcium consumption has led to a significant resurgence of MAS, now recognized as the third leading cause of hypercalcemia, only next to primary hyperparathyroidism and malignancy-related hypercalcemia.[4]

The pathogenesis of MAS involves a complex interplay between the gastrointestinal tract and the kidneys, typically seen in individuals consuming approximately 3 to 4 g of elemental calcium daily combined with an absorbable alkali. Excessive calcium intake enhances intestinal calcium absorption, a process potentiated by vitamin D and calcitriol, leading to hypercalcemia. This elevated serum calcium causes renal vasoconstriction, a decline in glomerular filtration rate, and diminished urinary calcium excretion. Hypercalcemia also suppresses PTH secretion and stimulates bicarbonate reabsorption in the proximal convoluted tubules in the kidneys, contributing to metabolic alkalosis. Furthermore, hypercalcemia interferes with Na-K-2Cl channels at the thick ascending limb of the Loop of Henle and the antidiuretic hormone activity by inhibiting V2 receptors in the renal collecting ducts through the activation of calcium sensing receptor, leading to natriuresis, impaired water reabsorption and polyuria due to nephrogenic diabetes insipidus. Subsequent hypovolemia leads to activation of the renin-angiotensin-aldosterone system which results in increased renal reabsorption of bicarbonate at the proximal convoluted tubules and the collecting ducts. This, compounded by vomiting and associated gastric acid loss further aggravates hypovolemia and metabolic alkalosis. The resultant alkaline pH favors renal reabsorption of calcium, thereby facilitating a self-perpetuating cycle of hypercalcemia and renal dysfunction[5] (Refer to Fig.).

Hypercalcemia can present with a wide range of symptoms depending on the severity and the organ system affected. Common neurological manifestations include confusion, psychosis, stupor and coma; gastrointestinal manifestations include abdominal pain, vomiting and constipation; renal manifestations include acute kidney injury, polyuria, polydipsia, nephrolithiasis and renal colic; cardiovascular manifestations include short QT interval and arrhythmias; musculoskeletal manifestations include muscle weakness and bone pain.[3]

This article highlights a case of severe hypercalcemia due to MAS with minimal non-specific symptoms relative to the degree of hypercalcemia. The patient was consuming 8 to 10 tablets of OTC calcium carbonate for uncontrolled GERD, often exceeding 4 g of elemental calcium per day. Blood work was notable for a serum calcium level of 22.8 mg/dl, metabolic alkalosis and acute kidney injury, which meets the criteria for the classic triad of MAS.[2] There has been one other case report documented in literature reporting severe hypercalcemia with serum calcium of 22.8 mg/dl secondary to MAS but associated with severe symptoms, unlike in this patient.[6] There were several potential contributing risk factors in this case which were also individually explored and eliminated based on objective information.

Thiazide diuretics such as hydrochlorothiazide are used in the management of hypertension. They reduce urinary calcium excretion by facilitating increased reabsorption of calcium at the distal convoluted tubules of the kidneys, which commonly leads to mild hypercalcemia.[7] Severe hypercalcemia with thiazide diuretic is rare, and a case report had previously reported a case of thiazide diuretic induced severe hypercalcemia with a serum calcium of 19.8 mg/dl.[8] This patient was on hydrochlorothiazide 50 mg for hypertension and blood work was notable for hypokalemia, hypomagnesemia and contraction alkalosis, which could reflect the role of hydrochlorothiazide as a potential contributor. Hydrochlorothiazide was discontinued on discharge.

The patient was on tamoxifen for her recent history of breast cancer. Tamoxifen is an estrogen receptor modulator which can alter calcium homeostasis by either modifying osteoclast function or parathyroid hormone-related protein secretion, especially in breast cancer with osteolytic metastasis, which was not the case here.[9] Hypercalcemia is more likely to occur after 1 to 2 weeks and is generally short-lived.[10] The patient had been on tamoxifen for almost 3 months and it was unlikely to have contributed to her presentation. Tamoxifen was ultimately continued on discharge by oncology.

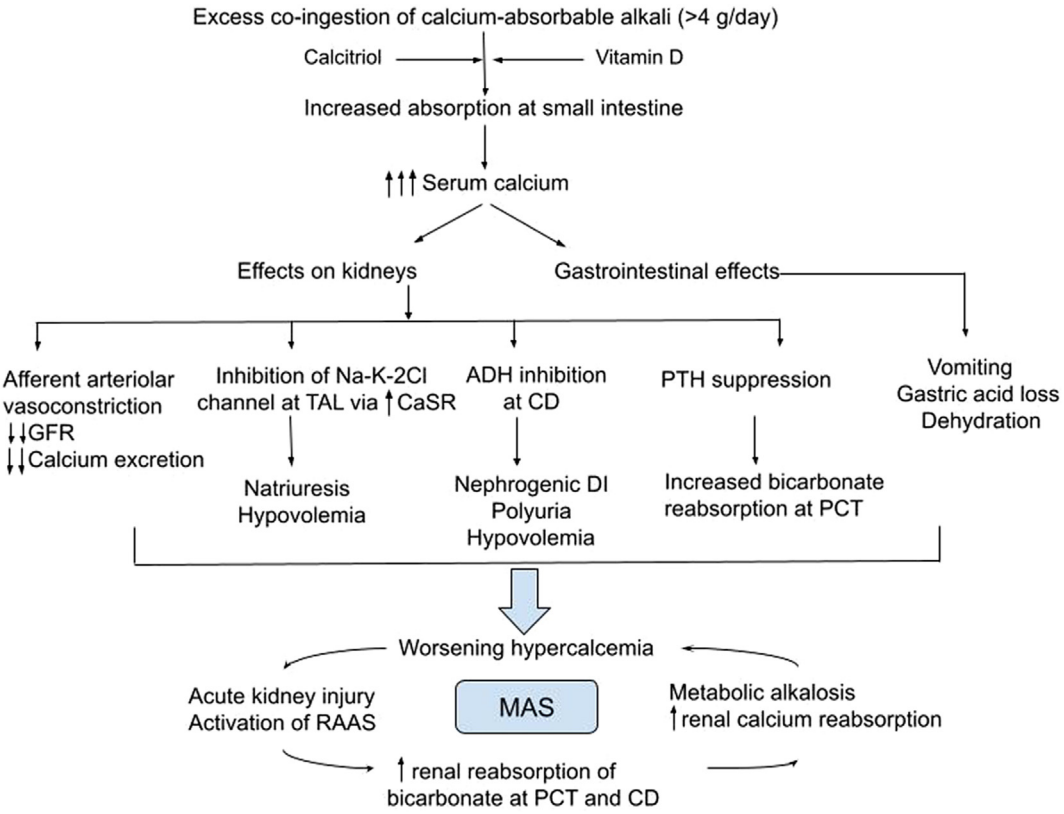


Fig. Self-perpetuating cycle of milk-alkali syndrome (MAS). MAS results from excessive exogenous ingestion of calcium-absorbable alkali, leading to hypercalcemia through increased intestinal calcium absorption (enhanced by vitamin D/calcitriol) and impaired renal excretion. Hypercalcemia causes afferent arteriolar vasoconstriction, reducing GFR and contributing to acute kidney injury. Activation of CaSR in the thick ascending limb inhibits Na-K-2Cl transporters, leading to natriuresis and hypovolemia. Inhibition of ADH receptors in collecting ducts causes nephrogenic DI. Additionally, suppressed PTH enhances bicarbonate reabsorption contributing to metabolic alkalosis, which is further exacerbated by vomiting and dehydration, leading to alkaline pH and increased renal reabsorption of calcium. *ADH* = antidiuretic hormone; *CaSR* = calcium sensing receptor; *CD* = collecting duct; *DI* = diabetes insipidus; *GFR* = glomerular filtration rate; *MAS* = milk-alkali syndrome; *Na-K-2Cl* = sodium-potassium-chloride; *PCT* = proximal convoluted tubule; *PTH* = parathyroid hormone; *RAAS* = renin-angiotensin-aldosterone system; *TAL* = thick ascending loop of Henle.

Hypercalcemia of malignancy was also considered[11] as the patient had been diagnosed with Stage IA right breast cancer 7 months prior. The oncology team had low concerns for recurrence given early treatment with segmental mastectomy, radiation therapy, followed by subsequent hormonal therapy with Tamoxifen and unremarkable surveillance PET CT for metastasis. PTHrP and 1,25-dihydroxyvitamin D were normal. Additionally, inpatient CT imaging was unremarkable for metastatic disease or evidence of a new primary malignancy.

Hyperthyroidism is another well-studied cause of PTH-independent hypercalcemia and is usually mild to moderate and mostly asymptomatic. Severe hypercalcemia is rare.[12] The patient's thyroid-stimulating hormone level was normal. Hypervitaminosis D is another known cause of PTH-independent hypercalcemia and is usually seen in the setting of intake of large doses of vitamin, usually higher than 10 000 IU daily in adults. Lab values show suppressed PTH and elevated phosphorus levels from increased intestinal and renal absorption.[13,14] Our patient reported a daily intake of 4000 IU of Vitamin D; her vitamin D level was 32 ng/ml and had normal phosphorus values, thus making this an unlikely contributor.

Given the severity of hypercalcemia disproportionate to her clinical picture, a paraproteinemia workup was pursued as high serum calcium can be seen in the setting of increased calcium binding to elevated serum globulins, thereby raising total serum calcium.[15] As the biologically active form of calcium, represented by the ionized calcium, is normal in such cases, patients typically present with asymptomatic mild to moderate hypercalcemia. In this patient, relevant investigations including immunoglobulin assays were negative and paraproteinemia was ruled out.

Conclusion

This case highlights an atypical presentation of severe hypercalcemia due to MAS, with minimal clinical symptoms despite life-threatening calcium levels. The patient's excessive calcium carbonate intake underscores the importance of a detailed medication history. Clinicians should maintain a high index of suspicion, especially in patients with nonspecific symptoms and OTC supplement use. Prompt recognition of the MAS triad—hypercalcemia, metabolic alkalosis, and acute kidney injury are critical to enable timely interventions and avoid serious, potentially fatal complications. Importantly, MAS differs from other causes of hypercalcemia, and management essentially focuses on discontinuing exogenous calcium-alkali intake, along with aggressive intravenous fluid hydration and use of calcitonin in severe cases, as compared to hypercalcemia due to other leading causes such as hyperparathyroidism or malignancy-associated hypercalcemia where bisphosphonates or denosumab may be indicated.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT in order to improve language and readability. After using this tool/

service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Statement of Patient Consent

Patient consent was obtained for publication of this case report. All efforts were made to protect patient confidentiality and anonymity, in compliance with institutional and journal guidelines.

Disclosure

The authors have no conflicts of interest to disclose.

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