EJCRIM
European Journal of Case Reports in Internal Medicine

IATROGENIC HYPERCALCEMIA IN A PATIENT WITH TYPE 2 DIABETES AND CHRONIC KIDNEY DISEASE

Maja Mačković[1], Nikolina Marić[1], Ivan Kralj[2], Miro Bakula[3]

[1] Intensive Care Unit, Department of Internal Medicine, Sveti Duh University Hospital, Zagreb, Croatia
[2] Division of Hematology, Department of Internal Medicine, Sveti Duh University Hospital, Zagreb, Croatia
[3] Division of Endocrinology, Diabetes and Metabolic Diseases, Department of Internal Medicine, Sveti Duh University Hospital, Zagreb, Croatia

Corresponding author's e-mail: majamacko@yahoo.com

Received: 04/08/2026
Accepted: 24/08/2026
Published: 29/09/2026

Conflicts of Interests: The Authors declare no conflict of interest.
Patient Consent: We have obtained written informed consent from the patient for publishing his clinical history.
This article is licensed under a CC Attribution-NonCommercial-NoDerivatives 4.0 License

How to cite this article: Mačković M, Marić N, Kralj I, Bakula M. Iatrogenic hypercalcemia in a patient with type 2 diabetes and chronic kidney disease. EJCRIM 2026;13:doi:10.12890/2026_007398

ABSTRACT

Introduction: The introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RA) and non-steroidal mineralocorticoid receptor antagonists (nsMRA) has significantly improved outcomes in patients with type 2 diabetes, obesity and chronic kidney disease (CKD). However, the increasing use of combination therapies may result in previously unrecognized adverse drug interactions.

Case description: We report the case of a 59-year-old man with obesity, type 2 diabetes, CKD stage 3b, albuminuria and established cardiovascular disease receiving optimized treatment with renin–angiotensin–aldosterone system blockade, sodium-glucose cotransporter-2 inhibition, semaglutide and finerenone. Mild finerenone-associated hyperkalaemia was treated with calcium polystyrene sulfonate. Several weeks later, the patient developed symptomatic severe non-parathyroid hormone-mediated hypercalcemia accompanied by acute kidney injury, fatigue, muscle weakness, constipation, polyuria and polydipsia. Extensive investigations excluded solid and haematological malignancy, granulomatous disease and endocrine disorders. Hypercalcemia was attributed to increased calcium absorption from calcium polystyrene sulfonate, likely facilitated by prolonged gastrointestinal transit secondary to semaglutide-induced constipation. Treatment consisted of withdrawal of the offending medications, aggressive intravenous hydration, loop diuretics and a reduced dose of intravenous zoledronic acid, resulting in normalization of serum calcium and recovery to baseline kidney function. Semaglutide and finerenone were subsequently reintroduced without recurrence of hyperkalaemia or hypercalcemia, eliminating the need for potassium binders.

Conclusion: This case highlights a previously unreported mechanism of iatrogenic hypercalcemia resulting from the interaction between contemporary cardio-renal-metabolic therapies and underscores the importance of careful monitoring for unexpected adverse effects when combining newer agents with established treatments.

KEYWORDS

Iatrogenic hypercalcemia, cardiovascular-kidney-metabolic syndrome

EFIM European Federation of Internal Medicine

Publisher smc media srl

LEARNING POINTS

- Patients treated for cardiovascular-kidney-metabolic syndrome require several lines of pharmacological therapy with potential for developing side-effects.
- The diagnostic algorithm for non-parathyroid hormone-mediated hypercalcemia should always include thorough investigation of medications and their potential for interactions.

INTRODUCTION

The triad of type 2 diabetes (T2D), obesity and chronic kidney disease (CKD) represents a significant public health burden, associated with a high risk of cardiovascular events, progression to end-stage kidney disease (ESRD), and mortality. Until recently therapeutic opportunities were limited, introduction of new drugs such as glucagon like peptide-1 receptor agonists (GLP-1 RA) and non-steroidal mineralocorticoid receptor antagonists (nsMRA) becoming a new standard of care.

GLP-1 RA have transformed the management of T2D and obesity, providing effective glycaemic control, significant weight loss, and cardiovascular benefits. Primary mechanisms involving insulin secretion stimulation, glucagon release suppression, and delayed gastric emptying can sometimes cause serious gastrointestinal side effects.

Finerenone, a selective nsMRA, demonstrates significant benefits in reducing the progression of CKD and cardiovascular events. Its mechanism of action, however, carries the risk of a well-documented side effect - hyperkalaemia, sometimes necessitating the use of potassium binders. Despite the availability of newer potassium lowering agents, sodium- and calcium-containing resins remain widely used.

Although symptomatic iatrogenic hypercalcemia is not expected from the sequential introduction of these three agents, this case report would like to draw attention to previously unrecognized interactions that clinicians should consider.

CASE DESCRIPTION

A 59-year-old male with a long-standing history of hypertension, hyperlipidaemia, T2D, obesity (body mass index 37.1 kg/m2), gout, coronary artery disease, CKD stage 3b A3 albuminuria and mild secondary hyperparathyroidism (parathyroid hormone [PTH] 8.2 pmol/l) attended a routine nephrology follow-up. His renal disease was attributed to biopsy proven nephroangiosclerosis, diabetic kidney disease and secondary focal segmental glomerulosclerosis with initial presentation of nephrotic-range proteinuria. Following initiation of full dose renin-angiotensin-aldosteron system (RAAS) inhibition (valsartan 360 mg), sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy (dapagliflozin 10 mg), GLP-1 RA (semaglutide 1 mg subcutaneously once weekly), statin (atorvastatin 40 mg) alongside diet, optimisation of blood pressure, glycemia and significant reduction of albuminuria were achieved (from an initial urinary albumin excretion of 8 g/day to 1.3 g/day).

Considering increased cardiovascular risk and the potential of slowing CKD progression, finerenone 10 mg was introduced. Renal function remained stable (serum creatinine 235 µmol/l, estimated glomerular filtration rate body surface area adjusted [eGFR BSA adjusted] 35 ml/min/1.73m2) and urinary albumin-to-creatinine ratio (uACR) further decreased to 26.4 mg/mmol. For mild hyperkalaemia of 5.3 mmol/l 1 dose of calcium polystyrene sulfonate (CPS) with biggest meal was prescribed.

On subsequent follow-up patient reported pronounced fatigue, muscle weakness, polydipsia, polyuria, constipation, sleep disturbance and depression. Physical examination was unremarkable. Laboratory data revealed rise in serum creatinine to 314 µmol/l, total calcium 3.11 mmol/l, ionized calcium of 1.66 mmol/l, PTH 0.43 pmol/l, serum albumin 32 g/l, 25-hydroxycholecalciferol 50.6 nmol/l, and he was admitted to the hospital.

Diagnostic assessment of non-PTH-mediated hypercalcemia necessitates primarily exclusion of malignancy, as well as endocrine disorders, granulomatous diseases, and drugs. Since the detection of PTH-related peptide is unavailable in our country, thorough malignancy screen was performed. Contrast-enhanced total-body computed tomography scan excluded solitary neoplasm, osteolysis or pulmonary changes attributable to sarcoidosis. Tumour markers and thyroid-stimulating hormone were within normal range.

Elevated levels of kappa free light chains (k-FLC) 195 mg/l, lambda free light chains (λ-FLC) 248 mg/l, with normal ratio of 0.79, elevated beta-2-microglobulin (β-2M) of 17.4 mg/l, plasmatic immunoglobulin (Ig) G 19.7 g/l, IgA 9.3 g/l, IgM 1 g/l, required additional haematologic evaluation. Serum electrophoresis and immunofixation were without monoclonal protein. Bone marrow aspirate and biopsy showed no monoclonal plasma cells and negative Congo red stain excluded amyloidosis, definitely eliminating the diagnosis of hematologic malignancy.

After comprehensive evaluation, the hypercalcemia was considered to be an iatrogenic, medication-related adverse effect resulting from the combination of therapies (GLP-1 RA and CPS).

Intensive intravenous hydration alongside parenteral furosemide with omission of all interfering drugs was implemented. Due to a slow decline in serum calcium

levels, while awaiting diagnostic results, a single reduced dose of zoledronic acid (2 mg). On day 3 was applied proceeding uneventfully. Serum calcium levels returned to normal on day 5 (total calcium 2.35 mmol/l) with rise in serum PTH subsequently reaching premorbid levels.

Lower dose semaglutide (0.5 mg subcutaneously once weekly) and finerenone 10 mg were reintroduced with normal levels of serum potassium excluding the need for potassium binders.

DISCUSSION

The incidence of cardiovascular-renal-metabolic (CRM) overlap is increasingly recognized carrying the burden of myriad of negative endpoint events. The development of new therapeutics that simultaneously impact multiple adjacent conditions has become a new standard of care supported by many different society guidelines. The introduction of SGLT2i, GLP-1 RA and nsMRA on top of standard treatment has shown multiple beneficial effects on metabolic risk factors, kidney function and the cardiovascular system[1].

Our patient had multiple comorbidities requiring comprehensive management – full dose of RAAS blockade alongside SGLT2i managed to reduce risk factors to some extent and there was an opportunity for nsMRA (finerenone 10 mg daily). Hyperkalaemia, a concerning adverse event of MRA particularly in CKD patients, may limit the use of finerenone in this population. To mitigate this risk, a low-potassium diet, furosemide and SGLT2i as a proven method of risk reduction were implemented[2].

Serum potassium levels exceeding 5 mmol/l, allow for additional therapy implementation, especially in patients ineligible for treatment discontinuation of offending drugs due to positive long-term effects. The pharmacological management of nonemergent hyperkalaemia has a number of licensed potassium exchange agents. Although new drugs, such as patiromer and sodium zirconium cyclosilicate, are available, the cation-exchange resins sodium polystyrene sulfonate and CPS are still widely used due to low price and widespread availability[3]. CPS is an ion-exchange resin facilitating removal of excess potassium by exchanging calcium for potassium ions in the gastrointestinal tract, particularly the colon. The content of calcium is 1.6-2.4 mmol/g of CPS, single oral dose including 14.96 g of powder. Side effects are mainly gastrointestinal (obstipation), with hypercalcemia rarely being reported[4,5].

GLP1-RA, available in oral and subcutaneous form, are a powerful tool in treating CRM patients. One of these is semaglutide, characterized by high affinity and specificity for the GLP-1 receptor, coupled with a prolonged half-life due to albumin binding. The most common side effects include gastrointestinal symptoms (nausea, vomiting, diarrhoea or constipation, abdominal cramps) which can abate over time or with dose reduction. According to the summary of product characteristics (SmPC) of the drug no renal dose adjustment is necessary in any degree of renal impairment and the intensity of side effects is similar to patients with preserved renal function[6].

Hypercalcemia (serum level ≥2.6 mmol/l) usually presents with signs and symptoms like polyuria, polydipsia, constipation, weakness, neuropsychiatric effects, nausea, vomiting, fatigue, anorexia, and confusion, in severe cases leading to cardiac arrhythmias, stupor and coma. Diagnostically, it is crucial to differentiate between PTH-mediated (normal–high PTH) from non-PTH-mediated (low PTH) hypercalcemia[7]. Approximately 90% of cases are due to primary hyperparathyroidism or malignancies. Since our patient had severely suppressed PTH levels it was essential to exclude medication-induced hypercalcemia, underlying malignancy, granulomatous disorder, and endocrinopathies. Extensive work-up excluded solid organ and hematologic malignancy, granulomatous disease and endocrine disorders. Detection of hematologic malignancy was of special concern due to elevated levels of k-FLC, λ-FLC and β-2M of 17.4 mg/l. Bone marrow aspiration and biopsy definitely excluded any plasma cell or B-cell clonal disorder, elevated levels attributable to the degree of kidney disfunction. It is known that the main determinant of the serum level of β-2M is the stage of kidney function, ESRD patients having serum β-2M levels up to 60 times of normal value[8]. Moreover, elevated β-2M is strongly associated with cardiovascular morbidity and mortality making our patient even more eligible for all applicable cardioprotective interventions[9].

Following extensive evaluation, the hypercalcemia was considered to be iatrogenic: maintaining finerenone necessitated initiation of potassium lowering agent, and CPS was introduced each gram containing approximately 1.6 to 2.4 mmol of calcium. With normal gut motility, a significant portion of this calcium would not have been absorbed. But in obstipated patients, this could lead to the prolonged residence time in the colon allowing greater dissociation of calcium from the resin and subsequent enhanced absorption into the systemic circulation. Drug-induced hypercalcemia is the third most common cause of non-PTH mediated hypercalcemia, usual culprit drugs being thiazides, lithium, vitamin D and calcium containing supplements.

As for the treatment, since the standard measures did not provide significant calcium reduction, intravenous bisphosphonate was applied subsequently normalising calcium levels accompanied by rise in PTH. Bisphosphonates usage in advanced CKD has been a matter of debate since the majority of clinical trials excluded this patient category. Today bisphosphonates remain a case-by-case therapy beyond the SmPC for this class of medications although adverse effects in CKD patients compared to the general population do not appear to be greatly increased[10]. After 2 weeks mild hypocalcaemia was observed and in 4 weeks all monitored parameters returned to premorbid values.

This case highlights the potential for unexpected interactions between established and newly introduced therapies. To our knowledge, this is the first reported case of iatrogenic hypercalcemia associated with combination of semaglutide and CPS. Close interdisciplinary collaboration and careful monitoring are of paramount importance to ensure safe and effective use of new and old remedies.

REFERENCES

1. Singh A, Kesani H, Verma S, Saleh TM, Rai M. Cardio-Renal Metabolic Syndrome: An Integrated Approach to Prevention and Management. Cureus. 2025;17(10):e94134. doi: 10.7759/cureus.94134.
2. Morales J, Palmer BF. Non-steroidal mineralocorticoid antagonists and hyperkalemia monitoring in chronic kidney disease patients associated with type II diabetes: a narrative review. Postgrad Med. 2024;136(2):111-119. doi: 10.1080/00325481.2024.2316572.
3. Rastogi A, Chertow GM, Collins A, Kelepouris E, Kotzker W, Middleton JP, et al. Utilization of Potassium Binders for the Management of Hyperkalemia in Chronic Kidney Disease: A Position Statement by US Nephrologists. Adv Kidney Dis Health. 2024;31(6):514-522. doi: 10.1053/j.akdh.2024.08.003.
4. Arroyo D, Panizo N, García de Vinuesa S, Goicoechea M, Verdalles U, Luño J. Hypercalcemia as a side effect of potassium binding agents. Nefrologia. 2012;32(5):655-8. English, Spanish. doi: 10.3265/Nefrologia.pre2012.Jun.11500.
5. Wang X, Chen D, Song X, Wang J, Zhang H. Efficacy and safety of calcium polystyrene sulfonate in patients with hyperkalemia and stage 3-5 non-dialysis chronic kidney disease: a single-center randomized controlled trial. J Int Med Res. 2023;51(4):3000605231167516. doi: 10.1177/03000605231167516.
6. Long JJ, Sahi SS, Lemke AI, Na J, Garcia Valencia OA, Budhiraja P, et al. The Use of Semaglutide in Patients With Renal Failure-A Retrospective Cohort Study. Endocr Pract. 2024;30(10):963-969. doi: 10.1016/j.eprac.2024.07.008.
7. Calabrese V, Messina RM, Cernaro V, Farina A, Di Pietro Y, Gembillo G, et al. Hypercalcemia: a practice overview of its diagnosis and causes. Kidney Dial. 2025;5(1):7. doi:10.3390/kidneydial5010007.
8. Asogan H, Al Salmi I, Jha DK, Al Rahbi F, Hannawi S. Beta-2-microglobulin level increases with advanced CKD stages: the implications and significance. World J Med Oncol. 2020;1(1). doi:10.52338/wjoncgy.2020.1003.
9. Argyropoulos CP, Chen SS, Ng YH, Roumelioti ME, Shaffi K, Singh PP, et al. Rediscovering Beta-2 Microglobulin As a Biomarker across the Spectrum of Kidney Diseases. Front Med (Lausanne). 2017;4:73. doi: 10.3389/fmed.2017.00073.
10. Henry N, Hildebrand S, Cunningham J. Management of osteoporosis in chronic kidney disease. Clin Kidney J. 2025;18(10):sfaf228. doi: 10.1093/ckj/sfaf228.