

Unveiling *CYP24A1* Mutation in Unexplained Hypercalcemia in an Adult: A Case Report

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Disclosures

Disclosure forms are available with the article online.

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Keywords

Hypercalcemia, Vitamin D, Calcium, Bone, Blood, Sarcoidosis, Renal insufficiency, Renal failure, 24,25(OH)₂-vitamin D, CYP24A1 mutation

Abstract

We present the clinical history of a 60-year-old man with persistent skeletal pain and recurrent renal stones associated to chronic hypercalcemia with fluctuating serum calcium levels. Elevated 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations in the absence of vitamin D supplementation together with a decreased 24,25-dihydroxyvitamin D concentration suggested altered vitamin D metabolism. Genetic testing demonstrated a biallelic loss-of-function mutation in the *CYP24A1* gene, responsible for reduced vitamin D inactivation. This rare condition, usually associated with idiopathic infantile hypercalcemia, may manifest later in life. Early recognition and management are critical to prevent complications such as recurrent nephrolithiasis, nephrocalcinosis, and renal failure.

Background

Hypercalcemia is a potentially life-threatening condition with a broad differential diagnosis that includes parathyroid hormone (PTH)-mediated and non PTH-mediated causes. Among the latter, neoplastic or paraneoplastic disorders, various granulomatous disorders such as sarcoidosis, or vitamin D intoxication are the most frequent causes. In addition, loss of function of *CYP24A1*, which encodes 25-hydroxyvitamin D 24-hydroxylase, the key enzyme in the degradation of 25-hydroxyvitamin D (25-(OH)D) and 1,25-dihydroxyvitamin D (1,25-(OH)₂D), impairs the inactivation of active vitamin D metabolites, leading to hypercalcemia, hypercalciuria, nephrocalcinosis, and—rarely—osteoporosis. It is typically associated with severe idiopathic infantile hypercalcemia (1). Milder forms have been recently reported in adulthood (2–8).

Case Report

A 60-year-old man presented with skeletal pain involving the lower limbs and lower back of more than 10 years' duration. The pain was attributed to osteoarthritis. However, symptoms persisted despite trials of multiple pharmacological therapies and physical therapy. The patient did not report significant weight change, fever, or skin lesions.

His medical history included hypertension, hypercholesterolemia, allergic asthma, hyperuricemia, cholecystectomy, and limited colectomy for diverticulitis. Regarding family history, no kidney or bone disease was known in the patient's deceased parents.

Starting at 55 years old, the patient has had repeated kidney stones, requiring two lithotripsy procedures. Hypercalcemia associated with PTH suppression was noted during previous hospitalizations, but no specific cause could be identified. The patient did not report taking vitamin D supplements.

Table 1. Usual Serum and Urine Variables (2018–2024)

Parameter	Normal range	Mean (SD)	Min–Max	n values*
Total calcium, mmol/L†	2.20–2.55	2.66 (0.28)	2.22–3.40	25
Phosphate, mmol/L	0.81–1.45	1.09 (0.15)	0.67–1.31	22
Creatinine, μmol/L	59–101	120 (10.6)	97–141	33
25-(OH) D, μg/L	>30	65.0 (17.3)	36.7–86	13
PTH, ng/L‡	17.3–74.1	6.97 (5.95)	<0.6–17.9	9
Urinary calcium, mmol/mmol creat§	<0.4	0.63 (0.09)	0.53–0.78	7

25-(OH) D = 25-hydroxyvitamin D; PTH = parathyroid hormone.
*Results are expressed as mean ± standard deviation; n is the number of recorded values for each variable.
†Available usual values for calcium metabolism were collected retrospectively from 2018 to 2024.
‡When PTH levels were undetectable (detection limit 0.6 pg/mL), the value of 0.6 was chosen to calculate mean and SD.
§Urinary calcium excretion is calculated from creatinine excretion from 24-hour urine collections. It is expressed as mmol of calcium per mmol of creatinine.

Overall, the patient presented in good general condition. Physical examination revealed diffuse tenderness over the lower back and legs. Cardiovascular, pulmonary, and abdominal examinations were unremarkable. No lymphadenopathy or skin lesions were noted.

Initial laboratory tests revealed an elevated calcium level (total calcium, 3.02 mmol/L) with normal serum phosphate (1.19 mmol/L). His PTH level was totally suppressed (<6 ng/L); his serum 25-(OH)D and 1,25-(OH)₂D levels were 86 μg/L and 62 ng/L, respectively, with mild renal insufficiency (serum creatinine level, 126 μmol/L).

After an extensive work-up, including blood tests (C-reactive protein, erythrocyte sedimentation rate, complete blood count, angiotensin convertase, immunoelectrophoresis, light chain assay, parathyroid hormone–related protein) and appropriate imaging (positron emission tomography-computed tomography, computed tomography scan, and bone scintigraphy) no malignancy or signs of sarcoidosis or myeloma were detected.

Diagnostic Assessment

All available data for this patient related to calcium metabolism were collected retrospectively from 2018 to 2024 (Table 1). The patient’s mean serum calcium level was abnormally high (2.66 ± 0.28 mmol/L) but fluctuated over time between 2.22 mmol/L and 3.40 mmol/L. His 25-(OH)D level fluctuated between 36.7 and 86 μg/L. His serum PTH level was consistently below normal, indicating PTH-independent hypercalcemia, while calciuria was consistently abnormally high. Moderate renal insufficiency has been observed in this patient since 2018, without having worsened in the last 5 years.

Blood samples taken during the sunniest months were arbitrarily defined as summer (May to September) and the least sunny months (October to April) as winter. As shown in Figure 1, his mean blood calcium levels were significantly higher in summer than in winter (2.79 ± 0.33 vs. 2.53 ± 0.13 mmol/L; P < 0.02),

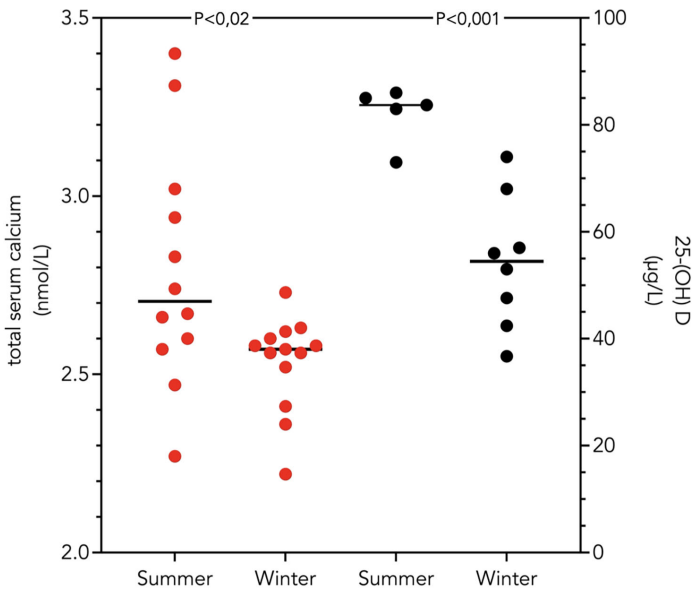


Figure 1. Seasonal variations in calcium and vitamin D. All data available between 2018 and 2024 are shown here. Summer: blood samples taken during the months of May to September. Winter: blood samples taken during the months of October to April.

as were his 25-(OH)D levels (82.1 ± 5.2 vs. 54.3 ± 12.4 μg/L; P < 0.002).

Parameters involved in calcium homeostasis determined in November 2024 are summarized in Table 2. The results confirmed PTH-independent hypercalcemia associated with elevated levels of 25-(OH)D and 1,25-(OH)₂D. His intact fibroblast growth factor 23 (iFGF23) level was 2 times higher than normal.

The concentration of 24,25-dihydroxyvitamin D (24,25-(OH)₂D), measured as previously reported (9), was abnormally low according to 25-(OH)D concentration (10), and the ratio of 24,25-(OH)₂D to 25-(OH)D (metabolite vitamin D ratio

Table 2. Biochemical Indices of Bone Status

Parameter	Normal range	November 2024*
Total calcium, mmol/L	2.20–2.55	2.52
Phosphate, mmol/L	0.81–1.45	1.00
PTH, ng/L	17.3–74.1	9.9
iFGF 23, ng/L	23.2–95.3	197.3
25-(OH) D, μg/L	>30†	58.1
24,25-(OH) ₂ D, μg/L	1.5–5.5	2.02
VMR (24,25/25), %‡	5–25	3.48
1,25-(OH) ₂ D, ng/L	29–83.6	110

1,25-(OH)₂D = 1,25-dihydroxyvitamin D; 24,25-(OH)₂D = 24,25-dihydroxyvitamin D; 25-(OH)D = 25-hydroxyvitamin D; iFGF 23 = intact fibroblast growth factor 23; PTH = parathyroid hormone.
*Data represent serum variable values during vitamin D metabolite evaluation in November 2024.
†Normal vitamin D values are still the subject of debate. A value above 30 μg/L is considered optimal. Values below 20 μg/L are considered deficient, and values above 80 μg/L are considered potentially toxic.
‡VMR represents vitamin D metabolism ratio: ratio of 24,25-(OH)₂D to 25-(OH)D × 100.

[VMR]) was below normal, suggestive of a defect in 25-(OH)D catabolism.

^{99m}Tc-Pyrophosphate bone scintigraphy was reevaluated for metabolic bone disease using the Fogelman index, a semiquantitative bone scintigraphy tool based on 7 criteria for diagnosing metabolic bone disease. In the present case, the Fogelman Metabolic Score was scored between 1 and 2. This score is generally higher than 2 in metabolic bone diseases with high bone turnover (11). Bone alkaline phosphatase, measured at 7.5 µg/L ($n = 5.5$ to 24.6), was also not consistent with accelerated metabolic bone turnover. Dual-energy x-ray absorptiometry showed normal bone density.

Analysis of the *CYP24A1* gene identified heterozygous variants c.428_430delAAGp. (Glu143del) and c.1226T>C p. (Leu409Ser). Various functional studies have demonstrated that these variants lead to a loss of function and, therefore, can be considered pathogenic (class V) (1, 12).

No supplementary genetic testing could be performed in family members because the patient had no offspring and the patient's parents were deceased.

Discussion

In the case of hypercalcemia, the first step is to determine whether the hypercalcemia is PTH mediated or associated with inhibition of PTH secretion, as in the present case. An increased parathyroid hormone-related protein level would suggest a paraneoplastic cause, and CT and PET scans might point to a cancerous cause or granulomatosis, especially sarcoidosis. In the absence of vitamin D intake or vitamin D-rich supplements, the possibility of defective catabolism of vitamin D metabolites due to a loss-of-function mutation in the *CYP24A1* gene encoding 24-hydroxylase can be hypothesized.

This is a rare cause of hypercalcemia and is not usually included in recommended algorithms (13). In the present case, the combination of elevated levels of 25-(OH)D and 1,25-(OH)₂D and a decreased level of 24,25-(OH)₂D, together with a below-normal VMR, is characteristic of insufficient activity of the 24-hydroxylase enzyme, which is responsible for metabolizing both 25-(OH)D and 1,25-(OH)₂D. This also explains why 1,25-(OH)₂D levels were particularly high despite mild renal insufficiency. An increase in the active metabolites of the vitamin leads to hypercalcemia with hypercalciuria. The analysis of the *CYP24A1* gene identified compound heterozygous variants c.428_430delAAG p. (Glu143del) and c.1226T>C p. (Leu409Ser), which are well-known pathogenic variants shown to induce loss of 25-hydroxyvitamin D 24-hydroxylase catabolic activity (1, 12).

Mutations in the *CYP24A1* gene were initially described in children with often severe hypercalcemia. In recent years, clinical pictures dominated by hypercalciuria-induced lithiasis and renal disease with possible nephrocalcinosis have been reported in adults (2–8).

Bi-allelic *CYP24A1* mutations can cause idiopathic infantile hypercalcemia, adult-onset nephrocalcinosis, and possibly bone metabolism disorders. Of interest, most heterozygous *CYP24A1* mutation carriers have a normal VMR and are usually asymptomatic without bone manifestations. However, they may have an increased risk for nephrocalcinosis (14).

An elevated iFGF23 has been previously demonstrated in 1 of 5 adult patients with *CYP24A1* mutations reported by Meusburger and colleagues (6). The increase in iFGF23 level is secondary to renal failure, PTH collapse, and increased 1,25-(OH)₂D. Retrocontrol of 1,25-(OH)₂D synthesis by iFGF23 via *CYP24A1* stimulation is ineffective in the presence of the *CYP24A1* mutation, which also contributes to the increase in 1,25-(OH)₂D. High levels of iFGF23 and 1,25-(OH)₂D are expected to inhibit osteoblastic function, which may lead to bone demineralization. However, bone demineralization has rarely been reported in patients with loss of 24-hydroxylase function (5).

Our patient exhibited no signs of metabolic bone disease, suggesting that the skeletal pain was likely independent of the calcium metabolism disorders associated with 24-hydroxylation deficiency of active vitamin D metabolites.

Seasonal fluctuations in blood calcium levels can be explained by the increased production of vitamin D secondary to ultraviolet light exposure, even in northern countries with relatively little sun exposure. The influence of sunlight exposure in patients with impaired 24-hydroxylation of vitamin D due to *CYP24A1* mutations has been previously reported (5).

Thus, potential strategies to reduce the risk for hypercalcemia in patients with a *CYP24A1* loss-of-function mutation include not only limiting vitamin D supplementation but also minimizing excessive exposure to sunlight.

The reported case is exemplary in several respects. Follow-up over several years has emphasized the seasonal variability of hypercalcemia associated with fluctuations in vitamin D. In addition, the absence of bone involvement despite prolonged elevation of 1,25-(OH)₂D and iFGF23, which should have led to decreased osteoblast function, bone resorption, and demineralization, shows that not all *CYP24A1* mutations have the same clinical phenotypic impact.

In summary, it is proposed that monogenic 24-hydroxylase loss of function should be given greater emphasis in diagnostic algorithms as the cause of nephrolithiasis with hypercalcemia and low PTH, not only in pediatric populations but also in adults.

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