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non-surgical clinical management of Kidney Stones

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Title: Non-surgical Clinical Management of Recurrent Nephrolithiasis in Primary Hyperoxaluria Type 3: Long-term Stabilization with Phytate Supplementation

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Abstract

We report the clinical course of a patient with recurrent nephrolithiasis due to primary hyperoxaluria type 3 (PH3), successfully stabilized with phytate supplementation. A 31-year-old female with childhood-onset, recurrent bilateral nephrolithiasis underwent metabolic and genetic evaluation. She was initiated on potassium citrate, later complemented with calcium supplementation and phytate (Lit-Control® pH Balance). Following phytate introduction, urinary crystalluria of calcium oxalate monohydrate markedly decreased, stone size remained stable, and renal function was preserved over two years of follow-up. The patient remained asymptomatic, requiring no further surgical interventions. Phytate supplementation, combined with potassium citrate and dietary calcium, provided long-term stabilization of stone disease in PH3. This case highlights the potential of non-surgical, phytate-based therapy to reduce lithogenic risk and preserve renal function in rare hereditary stone disorders.

Introduction

Nephrolithiasis is a common condition with a heterogeneous etiology, ranging from dietary and metabolic factors to genetic predisposition. Recurrent kidney stones, particularly those beginning in childhood or adolescence, often signal underlying metabolic abnormalities and warrant comprehensive evaluation. Early identification of predisposing factors is critical to prevent progressive renal damage, reduce stone recurrence, and guide targeted management. In clinical practice, detailed assessment includes family history, biochemical analysis, and imaging studies, with genetic testing increasingly recognized as an essential tool in patients with early-onset or severe disease. This report describes the clinical course, diagnostic work-up, and management

of a young adult woman presenting with recurrent kidney stones, highlighting the role of urine microscopy monitoring and novel adjunctive therapies.

Clinical case description

a. Patient information / Medical records

A 29-year-old woman was referred to our nephrolithiasis clinic for evaluation of recurrent kidney stones. Her medical history included cesarean section in 2014 and ovarian vein embolization in 2022. Family history was notable for recurrent nephrolithiasis in her father.

The first renal colic episode occurred at age 9 and the patient was treated with shockwave lithotripsy. Recurrent bilateral nephrolithiasis developed at age 15, with no urinary tract infections reported. She underwent left percutaneous nephrolithotomy at the age of 18 for a 3 cm staghorn calculus with no complications. At 28, left flexible ureteroscopy with stenting was performed. Stone analysis in 2021 revealed calcium phosphate (40%), calcium oxalate dihydrate (30%), and calcium oxalate monohydrate (30%). Morphological classification was unavailable.

b. Diagnostic support studies

At her first consultation in our clinic, urine sediment examination demonstrated an abundance of calcium oxalate monohydrate crystals (Figure 1), strongly suggestive of a primary oxalate metabolism disorder. Dietary assessment excluded excessive oxalate intake, while clinical history and investigations ruled out secondary causes of enteric hyperoxaluria such as inflammatory bowel disease or prior intestinal surgery. A genetic etiology was therefore suspected, and a targeted nephrolithiasis gene panel was ordered.

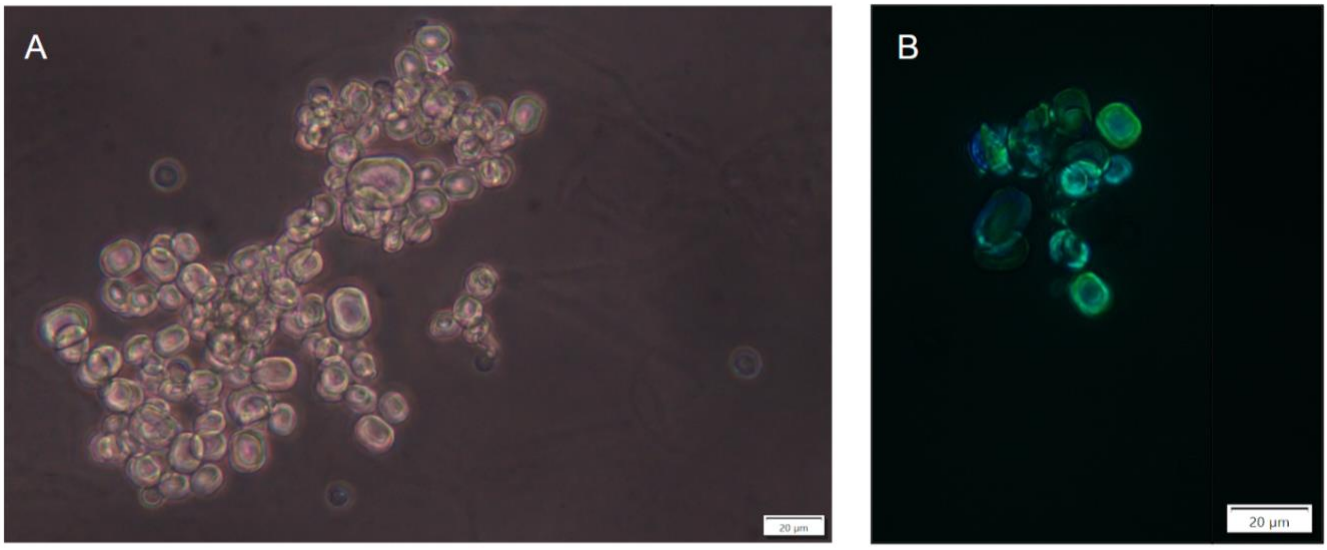

Figure 1 (A) - Agglomerate of large crystals of monohydrate calcium oxalate, oval shaped with depressed center and enlarged extremities (Phase contrast, 400x; urine pH=6). **Figure 1 (B)** - Polychromatic polarization of monohydrate calcium oxalate crystals (Polarzing light, 400x; urine pH=6).

c. Definitive Diagnosis

Genetic testing subsequently identified a guanine-to-thymine substitution at position 700+5 in the intronic region of the HOGA1 gene (c.700+5G>T), found in homozygosity, thereby establishing the diagnosis of primary hyperoxaluria type 3 (PH3). Initially two consecutive 24-hour urine collections showed adequate urine

volumes (>1900 mL/day), absence of significant proteinuria, normocalciuria, normomagnesuria, and normocitraturia, but persistent hyperoxaluria in the range of 45–72 mg/24h (Table 1).

Table 1. Results of 24-hour urine collections of the patient's initial evaluation

Date	Volume mL	Protein mg/24h	Urea mmol /24h	Creatinine mg/24h	Uric acid mmol/24h	Calcium mmol/24h	Magnesium mmol/24h	Citrate mg/24h	Sodium mmol/24h	Oxalate mg/24h	Oxalate mg/L
Nov 2022	2700	108	347	1289	2.87	3.40	55.4	577	97	45	16
Dec 2022	1900	78	290	1294	3.18	4.75	90.4	601	133	72	37.7

d. Treatment

While waiting for genetic results pyridoxine therapy was initially started empirically and then discontinued after genetic confirmation. The patient was counseled to maintain a daily urine output exceeding 2 liters and a calcium intake of approximately 1 g per day, primarily through dairy products (one serving per meal). Potassium citrate therapy was initiated, which successfully increased citrate excretion to ~1000 mg/24h. Despite this improvement, crystalluria persisted, even with adequate diuresis and increased urinary citrate levels. Consequently, phytate supplementation (Lit-Control® pH Balance, one tablet every 12 hours) was initiated as a urinary calcium chelator (Table 2).

e. Evolution and progress

Due to a lack of disease control, phytate supplementation was initiated. During the 7-month follow-up, which included litho control and pH balance monitoring (Table 2), a marked decrease in calcium oxalate monohydrate (COM) crystalluria was observed on microscopic evaluation of the urinary sediment. Notably, the disappearance of the crystals was verified rapidly after the treatment began. Throughout the follow-up period, the patient's stone burden remained stable, and she experienced no symptomatic episodes of renal colic. Renal function was maintained throughout, and no surgical interventions were necessary.

Table 2. Patient's follow up and treatment

	24h urine CItrate mg/24h	24h urine Oxalate mg/24	Potassium citrate	Lit Control pH Balance	Urine Sediment Crystalluria
2022					
Nov	577	45			+
2023					
Jan					+
May	546	46			+
Jul	1066	74			+
Dec	1063	69			+
2024					
Jul	586	50			-
Dec	968	69			-
2025					
Jan					-

f. Clinical results

Following the introduction of phytate supplementation, the patient's urinary calcium oxalate monohydrate crystalluria resolved completely. Stone burden remained stable throughout the follow-up period, and the patient experienced no symptomatic episodes. Renal function was preserved, and no surgical interventions were required. These findings indicate sustained disease stabilization and therapeutic effectiveness of phytate in conjunction with potassium citrate and dietary calcium.

Discussion

Primary hyperoxaluria (PH) is a rare autosomal recessive disorder of glyoxylate metabolism characterized by excessive endogenous oxalate production, recurrent nephrolithiasis, and progressive risk of renal impairment. Three genetically distinct forms are recognized: PH1, PH2, and PH3. PH1 is the most common and carries the poorest prognosis, whereas PH2 and PH3 are less frequent and typically follow a milder course. PH3 results from biallelic mutations in HOGA1, which encodes 4-hydroxy-2-oxoglutarate aldolase, a mitochondrial enzyme expressed in the liver and kidney. Loss-of-function mutations in HOGA1 lead to glyoxylate accumulation and subsequent oxalate overproduction. Our patient presented with childhood-onset, recurrent bilateral nephrolithiasis and was ultimately diagnosed with PH3 after genetic confirmation of the splice-site mutation

c.700+5G>T in homozygosity, one of the most frequently reported HOGA1 variants in Europe.[1] Although stone analysis revealed a mixed calcium oxalate and calcium phosphate composition, such findings are nonspecific and cannot differentiate PH3 from idiopathic stone disease.[1] Instead, the combination of early onset, persistent hyperoxaluria, and marked crystalluria raised strong suspicion for an inherited disorder. The predominance of calcium oxalate monohydrate crystals is metabolically suggestive of hyperoxaluria, particularly when crystal counts exceed 200 per mm³ and when few or no calcium oxalate dihydrate crystals are present. This striking abundance of calcium oxalate monohydrate typically indicates severe oxalate overproduction, as seen in massive hyperoxaluria, most characteristically in hereditary hyperoxalurias.[2] Conventional PH management focuses on hyperhydration, urinary alkalinization, and dietary strategies to lower lithogenic risk.[3,4] Pyridoxine, effective in some PH1 patients through its cofactor role for alanine-glyoxylate aminotransferase, is ineffective in PH3.[5] In this case, potassium citrate was prescribed to enhance urinary citrate excretion, and dietary calcium was recommended to bind intestinal oxalate. Despite these measures, crystalluria persisted, underscoring the need for additional interventions.

Crystalluria monitoring is an important tool in the management of hereditary stone disorders. Urine sediment microscopy provides rapid feedback on lithogenic activity, allowing clinicians to assess the impact of therapeutic adjustments far earlier than imaging can detect new stones. Positive crystalluria reflects ongoing lithogenic processes, whereas its resolution indicates successful suppression of stone formation. In this case, monitoring crystalluria effectively guided therapy, preventing further stone growth before it occurred. **Phytate (inositol hexakisphosphate, InsP6)** is a naturally occurring polyphosphate with strong inhibitory effects on the nucleation, growth, and aggregation of calcium oxalate and calcium phosphate crystals. It is the principal storage form of phosphorus in plants, accounting for up to 75% of total seed phosphate, and is particularly abundant in whole grains, legumes, nuts, and seeds.[6] Daily intake ranges from 0.3 to 2.6 g/day in Western diets and up to 4–5 g/day in predominantly vegetarian populations.[2] Early animal studies raised concerns about mineral deficiencies when sodium phytate was administered at pharmacological doses, but subsequent research has shown that moderate intake of calcium–magnesium phytate is safe and associated with systemic health benefits.[7] Its crystallization-inhibiting properties stem from multiple phosphate groups that bind calcium-rich surfaces of crystal nuclei, a mechanism shared with pyrophosphate and bisphosphonates. Both experimental and clinical studies confirm that phytate prevents calcium oxalate stone formation as well as other pathological calcifications, including vascular and skeletal deposits.[8] In our patient, phytate supplementation (Lit-Control® pH Balance) resulted in complete resolution of calcium oxalate monohydrate crystalluria, stabilization of stone burden, and absence of symptomatic episodes over more than two years, with preserved renal function. These outcomes are consistent with experimental evidence and highlight the translational potential of phytate as a safe and effective adjunctive therapy. In PH3, where conventional measures may be insufficient and disease-specific treatments such as RNAi therapies—currently available only for PH1—are not established, phytate supplementation could represent a valuable therapeutic option. **RNAi therapies** such as lumasiran and nedosiran represent a major advancement for patients with PH1. Lumasiran, targeting hepatic glycolate oxidase, has demonstrated a mean 65% reduction in urinary oxalate and normalization in 52% of patients older than 6 years in the Illuminate A trial.[9] Nedosiran, inhibiting LDHA, theoretically targets all PH types, but data suggest limited efficacy in PH2, likely due to the systemic nature of GRHPR deficiency.[10] Even when RNAi therapies significantly reduce oxalate excretion, residual lithogenic risk may persist, underscoring the potential benefit of adjunctive interventions such as phytate supplementation. This case illustrates that patients with ongoing crystalluria or elevated stone-forming activity could benefit from phytate, particularly in PH2 and PH3, where RNAi therapies are not yet established or fully effective. This case underscores several important points: first, crystalluria assessment offers valuable diagnostic and monitoring information in hereditary stone disorders, complementing biochemical and genetic analyses. Second, in the absence of targeted pharmacological options for PH3, integration of crystallization inhibitors such as phytate into standard care may mitigate lithogenic risk, stabilize disease progression, and preserve renal function.

Conclusions and Recommendations

This case illustrates the effective long-term management of recurrent nephrolithiasis in a patient with primary hyperoxaluria type 3 through a combination of potassium citrate, dietary calcium, and phytate supplementation. Key conclusions include: **(1)** Crystalluria monitoring is essential. Urine sediment microscopy allows rapid evaluation of lithogenic activity and therapeutic efficacy, providing actionable information well before stones are detectable on imaging. Persistent crystalluria reflects ongoing stone-forming risk, while its resolution serves as an early indicator of successful intervention. **(2)** Phytate supplementation is a promising adjunct therapy. In this patient, phytate effectively suppressed calcium oxalate crystallization, stabilized stone burden, prevented symptomatic episodes, and preserved renal function over two years. Its use may be particularly valuable in patients with elevated lithogenic activity or incomplete response to emerging RNAi therapies. **(3)** Finally, optimal management requires a multidisciplinary approach that combines genetic diagnosis, metabolic evaluation, individualized dietary guidance, urological expertise, and emerging adjunctive therapies such as phytate can complement standard measures and improve outcomes. We recommend routine assessment of crystalluria in patients with PH or other high-risk stone disorders and consideration of phytate supplementation in cases where conventional measures and/or RNAi therapies do not fully normalize lithogenic risk.

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