

Case — Orlistat-induced calcium oxalate crystalluria

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Cite as: Handing G, Pathak UI, Balasubramanian A, et al. Case — Orlistat-induced calcium oxalate crystalluria. *Can Urol Assoc J* 2022;16(10):371-3. <http://dx.doi.org/10.5489/cuaj.7900>

Published online May 20, 2022

Introduction

Hyperoxaluria is a condition defined by abnormally high urinary oxalate excretion that commonly leads to the development of calcium oxalate kidney stones. If hyperoxaluria is not addressed early, recurrent nephrolithiasis and oxalate nephropathy can cause significant morbidity and mortality and can even result in end-stage renal disease (ESRD).¹ Hoppe et al reported 30% of hyperoxaluria patients were first diagnosed after progressing to ESRD.² Although there are many well-recognized causes of hyperoxaluria, there are many others that are lesser known.

Orlistat is an over-the-counter (OTC) lipase inhibitor commonly used for weight loss or prevention of weight gain. It is most often used in patients with diabetes and has been associated with the development of secondary hyperoxaluria.³ Emerging reports suggest that the use of orlistat can be associated with nephrolithiasis and kidney failure.^{4,5} This case report details the clinical course and presentation of a patient with recurrent calcium oxalate nephrolithiasis who was found to have underlying hyperoxaluria secondary to orlistat usage. Herein, we discuss why urologists should be vigilant of the genitourinary complications of orlistat, an OTC weight-loss supplement that may be under-reported by patients.

Case report

A 72-year-old male with hyperlipidemia, chronic constipation, and no prior history of nephrolithiasis presented to an outside hospital with gross hematuria. Computerized tomography (CT) studies showed more than 20 bilateral renal calculi, with the largest being 1.5 cm in the lower pole of the left kidney. An office cystoscopy was unremark-

KEY MESSAGES

- Hyperoxaluria is a condition defined by abnormally high urinary oxalate excretion that commonly leads to the development of calcium oxalate kidney stones.
- Orlistat is an over-the-counter (OTC) lipase inhibitor commonly used for weight loss that has been associated with the insidious development of secondary hyperoxaluria and nephrolithiasis.
- Diagnosis and management of orlistat-induced nephrolithiasis, an uncommon etiology, is not frequently considered by urologists.
- Better awareness of orlistat's common use as a potentially under-reported OTC supplement, and the malabsorptive pathophysiology associated with it, are required.

able. An outside urologist performed shockwave lithotripsy on the dominant stone in the left kidney and the patient subsequently passed significant debris. A stone analysis demonstrated the stone composition to be 95% calcium oxalate and 5% calcium phosphate. At one-year followup, a renal ultrasound showed a progressive increase in right renal stone burden and mild residual left renal stone burden. The patient was referred to our stone clinic both for further surgical management and metabolic evaluation.

An initial CT in our stone clinic demonstrated multiple intrarenal calculi scattered throughout both kidneys, with the largest being a right lower pole partial staghorn calculus measuring 1.5 cm. A right percutaneous nephrolithotomy (PCNL) and stent placement was performed. Endoscopic evaluation revealed several Randall's plaques, which were laser-treated intraoperatively. A renal ultrasound done one month after surgery showed no stones on the right and no stones larger than 3 mm on the left.

Initial metabolic evaluation at our clinic with a 24-hour urine study showed hyperoxaluria (oxalate 106 mg/day),

hypocitraturia (citrate 188 mg/day), and hyperuricosuria (uric acid 1.061 g/day) (Table 1, line 1). No meaningful improvement was evident six months later (Table 1, line 2). He was advised to follow a normal calcium, low-oxalate diet and started on potassium citrate. In the face of persistent hypocitraturia and hyperoxaluria, potassium citrate was gradually titrated up. Calcium citrate and vitamin B6 were also eventually added. As seen in Table 1, abnormalities persisted despite aggressive attempts at metabolic management, and a repeat ultrasound and CT demonstrated increased bilateral stone burden, with the largest stone measuring 5 mm.

A gastroenterology (GI) specialist was consulted to investigate potential gastrointestinal malabsorptive etiologies. During that encounter, it was uncovered that the patient was taking orlistat for weight loss. He had not reported use of this medication to our team previously, as he considered this a natural supplement for weight loss. The GI specialist attributed the nephrolithiasis to fat malabsorption secondary to orlistat and stopped the medication. Six months after orlistat cessation, a followup 24-hour urine study showed resolution of the hyperoxaluria (oxalate 35 mg/day) (Table 1, line 7). At this time, the patient denied any dysuria, hematuria, flank pain, or other symptoms. At 10 months after stopping orlistat, a 24-hour urine study continued to show improvement of hyperoxaluria and mild hypocitraturia and hyperuricosuria.

He continued vitamin B6 and calcium citrate, but allopurinol was added for hyperuricosuria treatment.

An X-ray at his most recent appointment, just over two years after orlistat cessation, revealed stable residual left kidney stones and improvement of right kidney stone burden. His 24-hour urine study had also normalized and prompted discontinuation of all metabolic medications except potassium citrate 20 mEq twice a day (Table 1, line 9).

Discussion

Under normal physiological conditions, free calcium in the intestines binds dietary oxalate. This calcium oxalate complex is poorly absorbed, resulting in fecal excretion; however, when excess fat is present, it preferentially binds calcium. Less free calcium leads to more soluble oxalate absorption by the gut.⁶ High blood levels of oxalate cause accumulation of oxalate in the kidney, as the compound is excreted renally.

Orlistat promotes hyperoxaluria by decreasing fat absorption from the gut. Although the association between orlistat use and calcium oxalate nephropathy is described in nephrology literature, this uncommon etiology is not frequently considered by urologists. Due to the strong link between obesity and nephrolithiasis, orlistat usage in stone formation can be missed, making this a difficult diagnosis.

Table 1. 24-hour urine screen for risk factors of stone formation prior to (lines 1–5) and after (lines 6–9) orlistat cessation on April 4, 2019

Line	Date	Vol 24 ¹ (L/day)	SS CaOX ^{2*}	Ca 24 ³ (mg/day)	Ox 24 ⁴ (mg/day)	Cit 24 ⁵ (mg/day)	SS CaP ^{6*}	pH ⁷	SS UA ^{8*}	UA 24 ⁹ (g/day)	Intervention
1	2017-12-12	3.20	7.94	186	106	188	0.72	6.313	0.36	1.061	Not on metabolic medication
2	2018-05-11	2.91	7.11	130	85	<44	0.36	6.006	0.50	0.701	Not on metabolic medication
3	2018-07-17	2.22	4.46	62	60	<33	0.27	6.109	0.60	0.778	K-citrate ¹⁰ 10 mEq BID ¹¹
4	2018-10-28	3.66	5.03	92	118	194	0.52	6.752	0.10	0.821	K-citrate 20 mEq BID, on Ca-citrate ¹²
5	2019-02-04	3.95	5.07	178	73	<59	0.59	6.410	0.23	0.995	K-citrate 20 mEq TID, ¹³ on Ca-citrate BID
6	2019-05-21	3.62	4.45	212	52	337	0.96	6.880	0.09	0.977	K-citrate 20 mEq BID, Ca-citrate BID, B6 ¹⁴
7	2020-01-09	3.33	2.71	181	35	311	0.85	6.654	0.17	1.078	K-citrate 20 mEq BID, Ca-citrate BID, B6
8	2020-07-21	2.62	1.95	101	26	453	0.88	6.941	0.04	0.388	K-citrate 20 mEq BID, Ca-citrate BID, B6, allopurinol
9	2021-09-21	2.72	2.69	151	29	291	1.11	7.056	0.05	0.581	K-citrate 20 mEq BID
Reference range		0.5–4.0	6–10	Male <250 Female <200	20–40	Male >450 Female >550	0.5–2	5.8–6.2	0–1	Male <0.800 Female <0.750	

¹Urine volume over 24 hours. ²Supersaturation of calcium oxalate. ³Urine calcium over 24 hours. ⁴Urine oxalate over 24 hours. ⁵Urine citrate over 24 hours. ⁶Supersaturation of calcium phosphate. ⁷24-hour urine pH. ⁸Supersaturation of uric acid. ⁹Urine uric acid over 24 hours. ¹⁰Potassium-citrate. ¹¹Twice a day. ¹²Calcium-citrate. ¹³Three times a day. ¹⁴Vitamin B6.

*Supersaturation of a compound is defined as the concentration of that solute in solution above its solubility and is calculated by Litholink Corporation in a standard fashion.

sis.^{6,7} To our knowledge, no reports have discussed diagnosis of orlistat-induced nephrolithiasis without simultaneous acute kidney injury;^{4,5,8,9} however, there have been several reports linking orlistat use to oxalate nephropathy and even ESRD.^{5,10,11} Disease onset is insidious and may be related to prolonged orlistat treatment course. Data regarding the frequency of these complications is inconclusive.¹² Thus, the weight loss benefits of recommending orlistat must be weighed against the risks.

In the face of the obesity epidemic and 2007 Food and Drug Administration approval of orlistat as the first OTC weight-loss supplement,¹³ it is possible that orlistat usage in the general population has grown. Its label as an OTC supplement also means that around 50% of patients will omit this drug during medication reconciliation with their physician.^{14,15} Diagnosis and management of orlistat-induced nephrolithiasis requires awareness of the malabsorptive pathophysiology potentially present when taking this medication. Therefore, it is important for urologists and other providers to be aware of the potential lithogenic risk of orlistat and to consider orlistat as a potential culprit if oxalate levels fail to normalize with otherwise appropriate treatment.

Competing interests: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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