

ORIGINAL PAPER

Phytate and L-methionine for preventing recurrence of infection renal stones

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Summary

Background: Urine acidification and inhibition of crystallization are strategies that can be employed to prevent recurrent infection stones and calcium phosphate stones.

Methods: A series of cases demonstrating the beneficial effects of treatment with phytate and L-methionine in preventing recurrent stones associated with urinary tract infections and brushite stones is presented.

Results: The treatment proved effective in the prevention of stones associated with various clinical conditions. We describe three cases of staghorn infection renal stone, three cases of recurrent renal infection stones, one case with recurrent brushite stones and one case of dystrophic tissue calcification. In this group, ages ranged from 26 to 77 years, and the M/F ratio was 4:4. In most cases the initial urinary pH was approximately 8-8.2. Stone composition was magnesium ammonium phosphate (struvite) in 4 cases, a mixture of struvite and apatite in other 2 cases, and brushite in 2 cases. Pathogens isolated in the urine cultures of patients with struvite containing stones included *Proteus* spp. in 3 cases, *Escherichia coli* in 2 cases, and *Klebsiella pneumoniae* in one case. A combination of phytate and L-methionine was administered in all cases. Urinary pH was monitored using a portable medical device. In the six cases with infection stones, treatment prevented stone recurrence or regrowth following surgical treatment. Recurrence of infection was also prevented and renal function stabilized or improved.

Administration of phytate and L-methionine with frequent urinary pH monitoring was also effective in the case of recurrent brushite stone formation and in the prevention of extensive

dystrophic calcifications of the prostatic bed following HoLEP for benign prostatic hyperplasia treatment.

Conclusions: The findings of these case reports demonstrate that urinary acidification can be effectively achieved by oral administration of L-methionine in association with phytate in patients with chronic urinary tract infections who form urinary stones with the goal of preventing stone and infection recurrence and preserving renal function.

KEY WORDS: Urinary calculi; Calcifications; Infection; Struvite; Acidification; Phytate; L-methionine.

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INTRODUCTION

In general, alkaline urine promotes the formation of struvite, brushite, carbonate apatite, hydroxyapatite, and ammonium urate stones (1).

Urinary stones and urinary tract infections are closely intertwined. The presence of stones in the urinary tract can cause obstruction with urinary stasis, which promotes the onset and persistence of infection in the urine. Conversely, the metabolism of certain bacterial strains (urease producers) leads to the breakdown of urea into ammonium and bicarbonate, increasing urinary saturation and favoring the formation of struvite and carbapatite stones (2).

Brushite (calcium monohydrogen phosphate, CaHPO_4

2H₂O) kidney stones are rare, accounting for approximately one quarter of calcium phosphate stones, which in turn constitute 15% of all kidney stones. Brushite is largely converted to hydroxyapatite, while only a small portion remains as brushite. Brushite stones, unlike hydroxyapatite, are hyperdense, very hard and highly resistant to shock wave lithotripsy. Therefore, patients with brushite stones typically require multiple extracorporeal lithotripsy procedures to be stone-free, while endoscopic treatments are often more effective (3-5). The formation of brushite stones is associated with the presence of a distinctive crystal-associated nephropathy. Papillary biopsies have shown hydroxyapatite plugs filling the lumens of the terminal collecting ducts, with surrounding epithelial damage and destruction extending into the interstitium around the affected tubules (6). These histological findings are associated with marked metabolic alterations, with the majority of patients presenting severe hypercalciuria, reduced citrate excretion and, above all, urinary pH values > 6.2. For these reasons, brushite stone patients require aggressive treatment, comprehensive metabolic evaluation and close clinical follow up. Indiscriminate treatment with citrates may have caused an increase in this type of stone in recent years. The overall effect of citrates on the risk of calcium phosphate stone formation requires further research, but until then, citrates should be used with strict monitoring of urinary pH and calcium phosphate supersaturation. On the other hand, other crystallization inhibitors that do not affect urinary pH, such as hydroxycitrate or phytate, should be considered (7).

Moreover, patients with chronic debilitating disease or immunosuppression are exposed to the risk of urothelial encrustation in the bladder or renal pelvis due to infection by unusual urease-producing bacteria such as *Corynebacterium urealyticum* (or less frequently *Ureaplasma urealyticum* or other bacteria) which, by hydrolyzing urea, induce urinary alkalinization and the formation of struvite or carbapatite concretions.

Similarly, in the absence of infection, dystrophic calcium phosphate calcifications (mainly brushite) can form in the bladder or prostatic fossa, previously damaged by coagulative necrosis from different forms of trauma, including burns, radiotherapy, holmium laser enucleation, prostate

photovaporization, cryoablation, and local chemotherapy (mitomycin) (8).

L-methionine effectively lowers urinary pH and reduces the risk of struvite and calcium phosphate stone formation and encrustation (9, 10).

Furthermore, phytate (myo-inositol hexaphosphate, InsP6) which is an important component of seeds, legumes, nuts, and whole cereals, has a high capacity to inhibit in vitro calcium salt crystallization (11-13) without affecting urinary pH.

The aim of this study is to present a series of cases showing the beneficial effects of treatment with phytate and L-methionine for the prevention of recurrent stones associated with urinary infections.

RESULTS

The characteristics of the case presented in this series are shown in Table 1.

Staghorn infection stones

Recurrences of infective lithiasis: is it possible to defeat them? (Jesús Maqueda Arellano, Gonzalo Bueno Serrano, Maria Pilar Alcoba García)

Acidifying treatment with control of urinary pH may be an effective strategy to address recurrent lithiasic disease secondary to infective calculi. We present the case of a 39-year-old man with bilateral urolithiasis that led to episodes of complicated reno ureteral colic. After undergoing multiple treatments by retrograde endourological surgery, he presented recurrence and progression of lithiasis disease, finally requiring percutaneous approach for treatment of a coralliform stone (Figure 1), after which he was free of lithiasis. It was then decided to start treatment with an acidifying oral treatment (Lit-Control® pH Down) and home pH control by means of an electronic medical device (Lit-Control® pH Meter) as a complement to the surgeries he underwent, thus achieving stability of the disease, with absence of urinary tract infection or lithiasis recurrence. The patient, with poor adherence to previous treatments, presented in this case a correct follow-up to the treatment, as well as a high level of satisfaction with it.

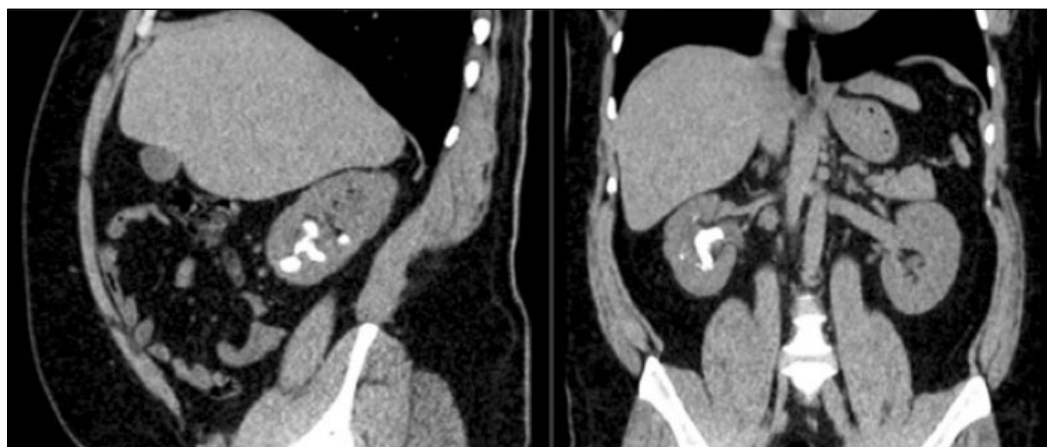


Figure 1.
Coralliform 4 cm
renal stone (right).

Table 1.
Urinary acidification in different pathological cases.

STAGHORN INFECTION STONES (N = 3)					
Author	Patient & Stone	Stone type UTI	Treatment	Outcome	Notes
Jesús Maqueda Arellano 2020	39 yrs M Recurrent bilateral urinary stones Coralliform 4 cm renal stone (right)	Struvite 60% apatite 40% <i>Proteus mirabilis</i> Urinary pH 7	Right PCNL + Left ESWL Lit-Control® pH Down pH monitoring (Lit-Control® pH Meter)	No recurrence at 12 months Urinary pH 5	Hypercalciuria Hyperphosphaturia HPT Hyperuricosuria Acetohydroxamic acid 125 mg not tolerated (gastrointestinal)
Belén Barba Córdoba 2022	26 yrs F Left complete staghorn renal lithiasis	Magnesium ammonium phosphate (struvite) <i>Proteus mirabilis</i>	Left PCNL (residual fragments) Lit-Control® pH Down 1 x 2 Monitoring of urinary pH with Lit-Control® pH Meter	After two years of treatment, the patient remained asymptomatic and her lithiasis condition remained stable	
Maite Miqueleiz 2023	26 yrs F Bilateral pyeloureteral junction (UPJ) stenosis Complete right and incomplete left coralliform lithiasis Septic shock	Struvite and apatite <i>E. coli</i> Urinary pH 8.2	Right PCNL Bilateral pyeloplasty (two separate sessions) Unsuccessful trial with L-methionine 500 mg every 8 hours Switch to Lit-Control® pH Down twice a day with good tolerance and pH control	At 1 year after the last surgery: - patient asymptomatic - no stone recurrence - significantly improved renogram of both kidneys	GFR > 90 mL/min/1.73 m ² , Hypocitraturia of 112 mg/24h
RECURRENT INFECTION STONES = 3					
Álvaro Vadillo 2021	77 yrs F Multiple bilateral calculi with a diagnosis of renal abscess and initial nephrocalcinosis Stone migration in right ureter	Ammonium magnesium phosphate stone Recurrent <i>E. coli</i> ESBL UTI Urinary pH 8	Right URS Lit-Control® pH Down 1 x 3	At 2 years - urinary pH below 6.8 - no new admissions - stable stone burden	Hypercalcaemia mild Hypocitraturia
Andrea Palacios 2023	52 yrs F Bilateral renal lithiasis with recurrent UTI	Magnesium ammonium phosphate <i>Proteus mirabilis</i>	Bilateral RIRS (two sessions) Bilateral URS after renal acute failure Residual stone of the right kidney Unsuccessful trial with acetohydroxamic acid (discontinued due to worsening of renal function and digestive discomfort) Right PCNL Lit-Control® pH Down 1 x 2 for 6 months Monitoring of urinary pH with Lit-Control® pH Meter	After 6 months: - stone free status - no admission for urgent urinary diversion or surgery - stable renal function - negative urine culture was achieved (after several rounds of antibiotic treatment)	Grade IV chronic kidney disease
Maicas et al. 2025	71 yrs M Right nephroureterectomy Cystectomy and left ureterostomy For multifocal urothelial carcinoma	5 mm stone in the left calyceal group <i>Klebsiella pneumoniae</i> Struvite crystalluria & leucocyturia Urinary pH 8.0	TMP/SMX x 3 times/week Lit-Control® pH Down 1 x 2	Spontaneous passage 5 mm stone Urinary pH below 6.0 Reduction of crystal formation No infection	Creat pl 1.72
BRUSHITE STONES = 1					
Alba Ferré 2023	45 yrs M Recurrent bilateral stones Spontaneous passage or ESWL or endoscopy	2020 Left ECIRS + right URS 2022 Bilateral URS/RIRS 2023 Right URS	HCTZ 25 mg / day + Lit-Control® pH Down HCTZ 50 mg + Lit-Control® pH Down Amiloride 5 mg + HCTZ 50 mg + Lit-Control® pH Down After 2023 Monitoring with Lit-Control® pH Meter	After 2023 No clinical symptoms Radiological stability	Vol > 2500 ml/day Normocalcemic Hypercalciuria Normal or low urinary citrate Normal PTH Urinary pH > 6.2 Furosemide test normal ability to acidify After the test attempt of treatment with potassium citrate with negative results
OTHER CONDITIONS = 1					
Carmina Muñoz Bastidas 2023	57 years M HoLEP for BPH Symptomatic recurrent calcifications of the prostatic bed	Calcium phosphate dihydrate lithiasis (brushite) Negative urine culture Urinary pH 8	5 endoscopic surgical interventions Treatment with thiazides and dietary modifications Lit-Control® pH Down Daily monitoring with Lit-Control® pH Meter	After 5 months -urinary pH remained below 6.5 - resection of bladder neck for sclerosis with absence of lithiasis in the prostatic tissue	Hypercalciuria

Is it possible to stop infective stones from growing only by controlling the urinary pH? (Belén Barba Córdoba)

Clinical case report of a 26-year-old female patient with left staghorn renal lithiasis that occupied the entire kidney. A left percutaneous nephrolithotomy was performed. The STONE score assessment resulted in 10 points with 42% resolution probability of the case in a single surgical intervention and not being stone free after this first procedure. In the first post-surgical follow-up a control CT scan was performed, showing non-obstructive remaining fragments in the calyx. For the second surgical time an *endoscopic combined intrarenal surgery* (ECIRS) was proposed which the patient rejected as she was asymptomatic. The analysis of the composition reported infective lithiasis composed of magnesium ammonium phosphate. Treatment with acetohydroxamic acid was proposed (previous urine cultures reported *Proteus mirabilis*) which the patient rejected due to its possible adverse effects. It was agreed to initiate acidifying medical treatment using Lit Control® pH Down and strict control of urinary pH with Lit-Control® pH Meter. After two years of treatment, the patient remains asymptomatic and her lithiasic condition remains stable (Figure 2).

Prevention of recurrence of infective lithiasis in patient with bilateral pyeloureteral junction stenosis (Maite Miqueleiz, Zaloa Amelibia Álvaro)

Infective lithiasis accounts for 10-15% of all lithiasis. Although infection stones are not uncommon, the case of our patient is particularly exceptional as she developed staghorn lithiasis in the context of bilateral *pyeloureteral junction* (UPJ) stenosis, an anatomical alteration that predisposes to repeated infections that favor the development of this type of lithiasis. This case involves a 26-year-old woman who presented with urinary septic shock secondary to complete right and incomplete left coralliform struvite lithiasis and concomitant diagnosis of bilateral UPJ stenosis.

After acute treatment, the patient underwent *percutaneous right nephrolithotomy* (PCNL) and subsequently a renogram was performed showing bilateral flow obstruction. She underwent bilateral pyeloplasty in two surgical stages. Following surgery, treatment with L-methionine failed to achieve adequate urinary acidification, and the

patient was therefore switched to Lit-Control® pH Down. After one year of follow-up on Lit-Control® pH Down, the patient remains asymptomatic, with no evidence of stone recurrence.

Recurrent infection stones

Nephrocalcinosis and Infective Lithiasis (Álvaro Vadillo, Carmen Arai Valladares)

A 77-year-old patient was diagnosed with symptomatic nephrocalcinosis and infectious kidney stones and managed conservatively with urinary acidification (Lit-Control® pH Down) to control the infectious calculi, modification of dietary habits and pharmacological treatment of hypercalcaemia to control the risk factors for progression of nephrocalcinosis. After almost 2 years of treatment, the patient had no new admissions for this reason, and the lithiasic load has been maintained. She had no side effects with the medication.

Recurrent infective lithiasis in patients with chronic kidney disease (Andrea Palacios)

We present the case of a 52-year-old female patient with a history of infective staghorn stone recurrence requiring multiple surgical and medical treatment who progressively developed stage IV chronic kidney disease associated to non-functioning left kidney. After right percutaneous nephrolithotomy and discontinuation of treatment with acetohydroxamic acid due to its adverse effects, the use of the urinary acidifier Lit-Control® pH Down with urinary pH control by Lit-Control® pH Meter was recommended. During the following nine months the patient was totally asymptomatic and achieved the highest stone-free rate since the beginning of her follow-up. No side effects or metabolic acidosis was detected demonstrating that the acidification with Lit-Control® pH Down may be safe in this population.

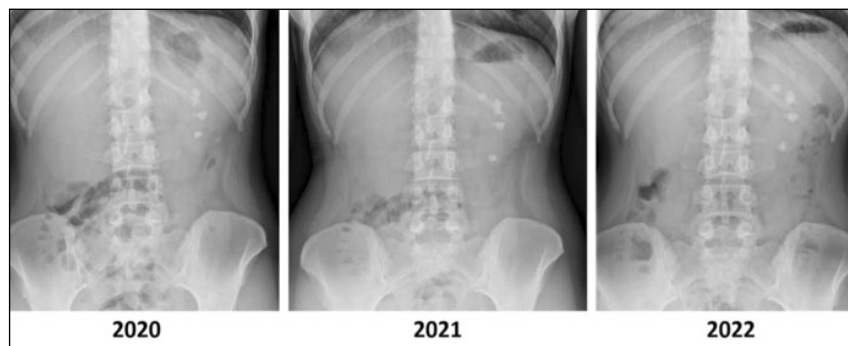
When acidification makes the difference: Preventing struvite stone recurrence after cutaneous ureterostomy (Emili Maicas Aran, Georgina Amanda Payet, Asier Mercadè, Maria del Carmen Salgado, Maria Pilar Luque, Alba Sierra)

A complex urological case was reported where acidification effectively prevented recurrent struvite stones.



Figure 2.

Left staghorn renal lithiasis. After two years of treatment, the lithiasic condition remained stable.



A 71-year-old male with prior right nephroureterectomy (2002) for Wunderlich syndrome secondary to renal pelvic tumor and radical cystectomy with left ureterectomy and cutaneous ureterostomy (2019) due to multifocal papillary urothelial carcinoma presented with struvite stones (Figure 3) and recurrent struvite crystallography. Urinary acidification therapy (Lit-Control® pH Down) along with prophylactic antibiotics were initiated. Crystallographic urinary analysis before treatment confirmed struvite crystals presence. After antibiotic treatment and acidification, no struvite crystals were detected, and the patient remained free of lithiasis (Figures 4, 5). Urinary acidification effectively inhibited struvite crystallization in this high-risk patient, preventing further infectious lithiasis. This case supports the role of urinary pH modification as a preventive strategy against infection-related stone formation in patients with complex urological conditions.

Figure 3.
CT scan showing 5 mm struvite infective lithiasis in the left middle calyceal group.



Figure 4.

Change of urinary pH and in quantitative urinary crystallography after acidification treatment.

After acidification treatment which was initiated in October 2022, a marked reduction in urinary pH and qualitative amount of struvite crystals in urine crystallography is depicted.

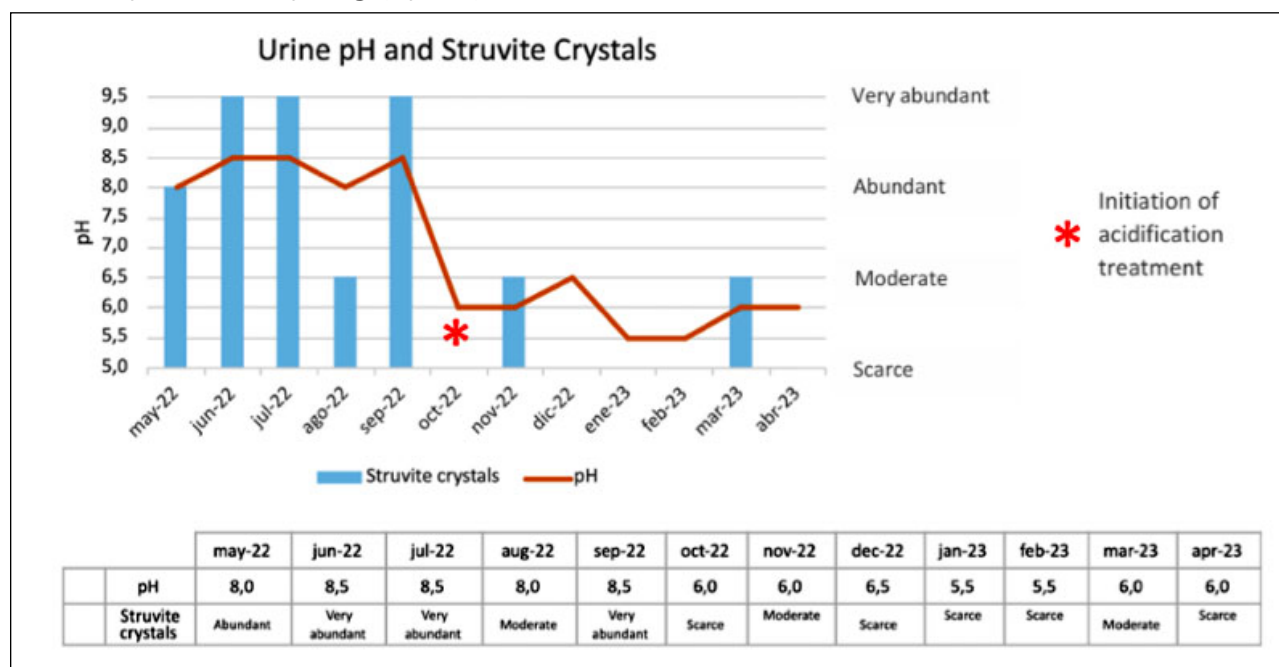


Figure 5.

Urinary crystallography before and after initiating urine acidification therapy with L-methionine.

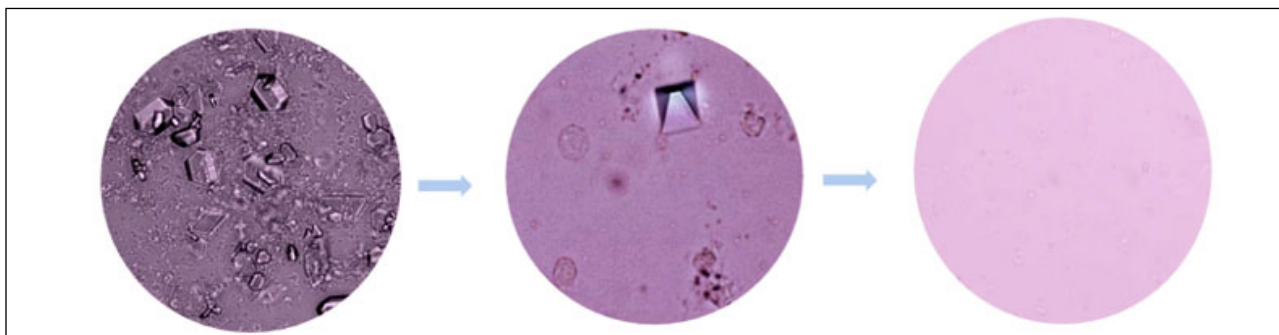
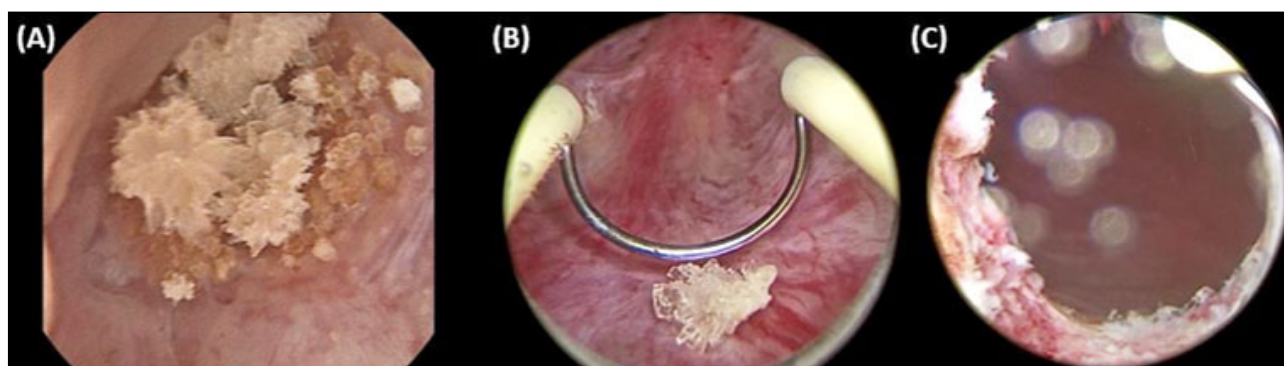


Figure 6.

Recurrent calcifications of the residual prostatic tissue after HoLEP.



Brushite stone

The importance of urinary pH monitoring in brushite lithiasis, a comprehensive approach to treatment and prevention (Alba Farré)

We present a case of a 45-year-old male with a history of recurrent brushite bilateral urinary lithiasis since adolescence: some resolved spontaneously others, with several sessions of *extracorporeal lithotripsy* (ESWL) and others with multiple endourological and/or percutaneous interventions. After crystallographic analysis the composition of the lithiasis was revealed to be a brushite-type calcium phosphate. Facing with a very recurrent and demanding lithiasis disease an integral management was started with exhaustive metabolic evaluations, dietary recommendations, and medical treatment with drugs and supplements to avoid lithiasis recurrences. After years of difficult metabolic control of the disease and the need for several surgical interventions, home self-monitoring of urinary pH with Lit-Control® pH Meter has allowed proper follow up and optimization of treatment under the control of the medical team.

Dystrophic calcifications

Recurrent prostatic cell encrusting lithiasis after Holmium Laser Enucleation of the Prostate (HoLEP).

Gradual resolution with urinary pH acidification (Carmina Muñoz Bastidas, Luis Labairu Huerta, Andrés Calva López)

Dystrophic calcification of the prostatic cell after HoLEP is a rare complication (8) but with a great impact on the patient's quality of life that poses a diagnostic and therapeutic challenge. We present the case of a 57-year-old man who after HoLEP presented with disabling voiding pain and urinary retention secondary to recurrent calcifications of the residual prostatic tissue (Figure 6) due to calcium phosphate dihydrate lithiasis (brushite) which resolved after 5 endoscopic surgical interventions and strict medical treatment with thiazides, Lit-Control® pH Down and dietary modifications; as well as daily monitoring of urinary pH with Lit-Control® pH Meter to maintain an acidic pH (14, 15).

Two additional cases of patients with dystrophic calcifications or stones in urostomized patients previously presented in the Clinical Cases Contest (16, 17) have been published elsewhere.

Ruibal Gago described the case of a patient who formed granulomas on the cutaneous stoma of an ileal conduit according to Bricker. Calcifications were attributed to alterations of urinary pH and use of Lit-Control® pH Down succeeded in lowering urinary pH, eliminating part of the peristomal granulomas, and improving urinary parameters such as urine odour and colour.

Sanjoaquin Sanz et al. presented a case of a 66-year old male who had undergone a cystectomy with neobladder 3 years earlier, who subsequently developed a staghorn stone in the right kidney and multiple calyceal stones in the left kidney in association with a *Proteus mirabilis* urinary tract infection. After left percutaneous nephrolithotomy and left retrograde intrarenal surgery, the administration of antibiotic prophylaxis with TMP/SMX (160/800 mg once daily) plus Lit-Control® pH Down allowed prevention of new stone formation and infection, as well as stabilization of renal function.

DECLARATIONS

Ethical approval and consent for participate: Ethics Committee (EC) was not required for a retrospective review of cases. Patient consent was obtained by the institution of each Author.

Availability of data and material: All inquiries can be directed to the corresponding author.

Competing interests: B.I. serves as a scientific consultant for Devicare. A.T. participated in the meeting of the Scientific Advisory Board of Devicare. The remaining authors have no conflicts of interest to declare.

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Authors' contributions: Conceptualization, B.I. and A.T.; methodology, A.T.; software, N/A.; validation, B.I.; formal analysis, A.T.; investigation, data curation and writing B.B.C., A.F., E.M.A., J.M.A., M.M., C.M.B., A.P., A.V., M.P.A.G., A.Z.Z., C.A.V., G.B.S., L.L.H., A.C.L., G.A.P., A.M., M.C.S., M.P.L., A.S.; writing - review and editing, A.T.; visualization, A.T.; supervision, B.I.; project administration, N/A.; funding acquisition, N/A. All authors have read and agreed to the published version of the manuscript.

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CONCLUSIONS

The combined action of phytate as a crystallization inhibitor and L-methionine as a urine acidifier facilitates the solubilization of mineral salts preventing the formation of struvite and calcium phosphate crystals and reducing the growth rate of bacteria.

The results of this series of patients treated with Lit Control® pH Down under monitoring with Lit Control® pH Meter confirm its efficacy as a food supplement.

It contributes to avoiding or reducing the formation of infection stones and brushite stones associated with an alkaline urinary pH.

Other cases presented at the Clinical Cases Contest have been published elsewhere showing similar results (16, 17).

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