4th Edition of the Clinical Case Contest related to the non-surgical clinical management of renal lithiasis.

Official template

Title: Urinary pH monitoring in the medical treatment of phosphocalcic lithiasis in patients with incomplete distal renal tubular acidosis.

Key words: urinary pH, incomplete distal renal tubular acidosis, calcium phosphate lithiasis.

1. Abstract

A 58-year-old woman with a history of incomplete distal renal tubular acidosis (dRTA), bilateral nephrocalcinosis and previous episodes of calcium phosphate renal lithiasis. After left obstructive uropathy associated with deterioration of renal function, the patient underwent semi-rigid ureterorenoscopy with lasertripsy of bilateral ureteral lithiasis. After the resolution of the case, the patient's medical treatment was reviewed and the study was completed with a 24h blood and urine analysis. Subsequently, it was decided to start daily monitoring of urinary pH with the use of a portable pH meter, a measurement that allows to detect urinary pH in the lithogenic range and to explore various therapeutic options to avoid lithiasis recurrences and to control the underlying pathology.

2. Introduction

Calcium phosphate (CP) lithiasis represents approximately 15% of all urinary calculi, predominating in the female sex and carbapatite being the most frequent form of crystallization (1). This type of lithiasis is highly recurrent. It is known that in the absence of preventive measures, the cumulative risk of lithiasis recurrence in the next five years is up to 53% (2), so it is necessary to perform a metabolic evaluation in all recurrent patients.

Clinically, CP lithiasis can be associated with various pathologies such as idiopathic hypercalciuria, primary hyperparathyroidism, urinary tract infections or renal tubular acidosis. Predisposing factors for stone crystallization include elevated urinary pH, hypercalciuria and/or hypocitraturia. However, the role of urinary pH is an influential factor that can favor spontaneous precipitation and crystallization of various urinary lithiasis, being this factor very influential in CP lithiasis and making it an important therapeutic target in the medical management of some patients.

3. Description of the clinical case:

a. Relevant background

48-year-old woman with medical history of: Systemic Lupus Erythematosus (SLE) with no current systemic treatment, rheumatoid arthritis, protein S deficiency, incomplete distal renal tubular acidosis (dRTA), bilateral nephrocalcinosis and secondary E3b chronic kidney disease (current baseline glomerular filtration rate around 45 mL/min/1.73 m2).

The patient is under nephrological follow-up of years of evolution for SLE, being a carrier of multiple renal lithiasis, without episodes of complicated colic or deterioration of renal function. Previous crystallographic analysis identified lithiasis of carbonated calcium phosphate (carbapatite).

b. Diagnostic support studies and results

In January 2023 she presented an acute episode of left obstructive uropathy secondary to a lithiasic street of 34mm in length and 1100 HUH located in the left distal ureter with associated deterioration of renal function (creatinine 220 µmol/L and GFR 22 mL/min/1.73 m2), for which she was evaluated by urology and it was decided to place a left nephrostomy tube (NF), with improvement of renal function. Also on the right side proximal and distal ureteral lithiasis were identified (7mm lithiasis in proximal ureter and lithiasis street formed by two lithiasis of 14 and 20mm in right distal ureter) that did not cause dilatation of the urinary tract and did not require urgent urinary diversion.

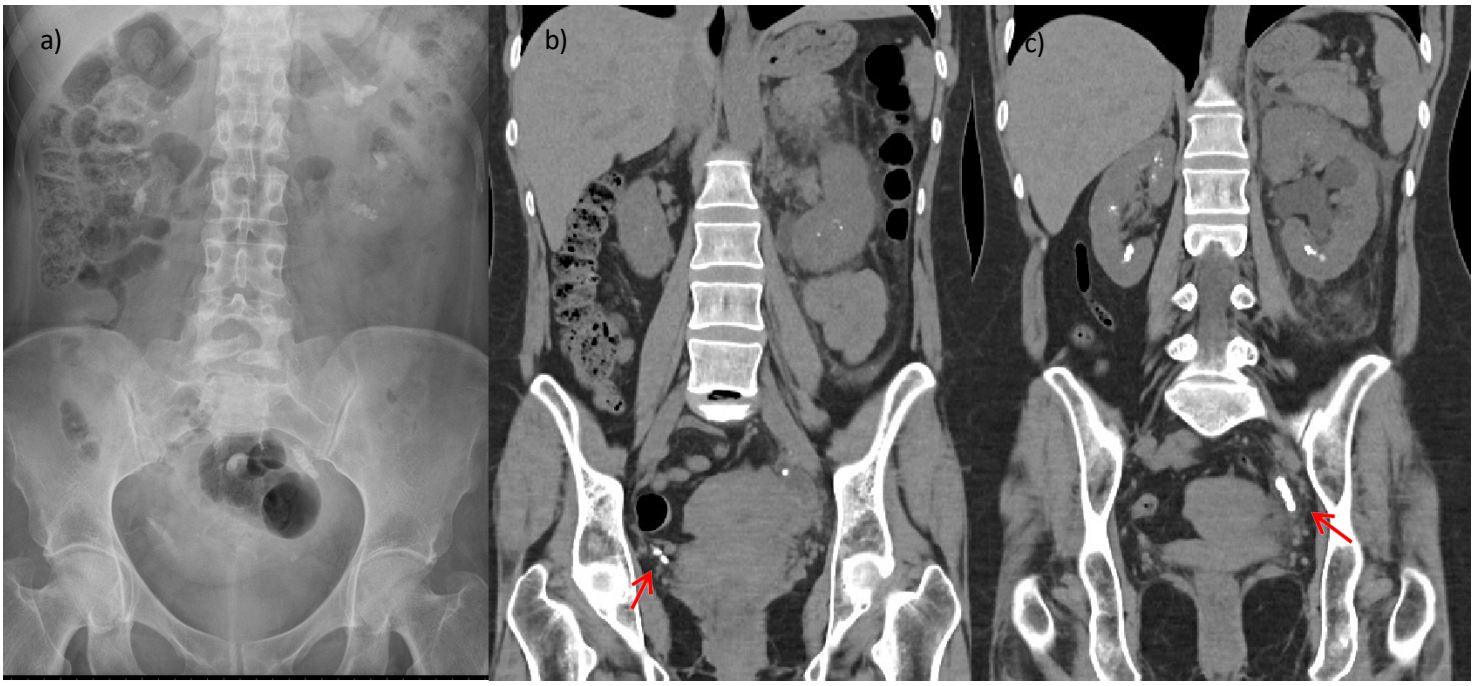

Figure 1: a) Preoperative abdominal X-ray; b) Non-obstructive right distal ureteral lithiasis; c) Obstructive left distal ureteral lithiasis.

c. Treatment

Given the high lithiasis burden, the patient underwent semi-rigid ureterorenoscopy with lasertripsy of bilateral ureteral lithiasis with Tulium Fiber laser in March 2023. During the surgery the left NF was removed and a bilateral double J catheter was placed, which were removed on an outpatient basis after two weeks.

d. Evolution and follow-up.

In the first postoperative control after the removal of both ureteral catheters at 3 weeks, a simple abdominal X-ray showed the presence of a right distal ureteral lithiasic street and the presence of a left proximal ureteral fragment. Given the good clinical tolerance of the patient, stable renal function and absence of urgent referral criteria, it was agreed to try expulsion treatment.

In the next control the patient presented spontaneous expulsion of several lithiasic fragments, with radiological persistence of the left proximal ureteral lithiasis that was treated by extracorporeal lithotripsy under sedation successfully. The crystallographic study with infrared spectrophotometry and X-ray disphraction showed again lithiasis formed by carbonated calcium phosphate (carbapatite).

Due to the high lithiasis load, the medication prior to the previous episode was reviewed, identifying that the patient was taking potassium citrate 1080 mg (1-0-1) for the treatment of hypocitraturia and renal lithiasis, as well as sodium bicarbonate 1000 mg (0-1-0) for the ATRDi, treatment with which, prior to admission and surgery, the patient had a urinary pH of 7.5 identified by means of test strips.

After reviewing the case, the patient was asked to undergo a 24-hour urine and blood test to re-evaluate the

treatment. The results of the study are shown below:

Anthropometric data: Weight 59 Kg, Height 164cm, BMI 21.9 kg/m2 Systematic urine culture: Negative, urinary pH 7					
Blood test			24 h urine test		
Parameter	Value	Normal rate	**Parameter**	Value	Normal rate
Creatinine	159 µmol/L 1.80 mg/dL	45 – 80 0.51 - 0.90	**Urinary volume**	2485 mL/24h	-
Glomerular filtration rate (CKD-EPI 2009)	33 mL/min/1.73 m^2	>= 60	**Calcium**	1.9 mmol/24h	1.5 - 6.0
Calcium	2.21 mmol/L 8.8 mg/dL	2.10 - 2.55 8.4 - 10.2	**Citrate**	0.32 mmol/24h	>= 1.60

The study shows a urinary volume close to 2.5 liters (indicative parameter of correct fluid intake), normal urine creatinine (indicative of correct collection of the 24-hour urine sample), calciuria within normality, hypocitraturia and an alkaline urinary pH. In addition, the patient has normal blood calcemia, together with a slight deterioration of renal function with respect to her baseline of 45 mL/min/1.73 m2.

Given the persistence of an alkaline urinary pH, hypocitraturia and high lithiasis load despite previous medical treatment with potassium citrate and bicarbonate, the following therapeutic options are proposed to the patient: Substitute treatment with Potassium Citrate 1080 mg (1-0-1) with Lit-Control pH Up® (1-0-1) (Magnesium potassium citrate and theobromine), start daily monitoring of urinary pH by using the Lit-Control® pH Meter and myLit-Control® App with the aim of identifying variations present in urinary pH.

e. Clinical results

The results obtained show urinary pH oscillations between 7-7.5 with treatment with Lit-Control pH Up® and bicarbonate, a pH that corresponds to a lithogenic range in patients with HF lithiasis (see Figure 2).

Since urinary acidification (by means of oral compounds with L-methionine) is a treatment used in patients with HF lithiasis and elevated urinary pH, we consider adding treatment with Lit-Control® pH Down (1-0-1) to our patient.

Figure 2: Urinary pH measurements provided by the patient

After presenting the case in a clinical session, it was decided not to initiate treatment for urinary acidification given the history of dRTA and the high risk of systemic acidosis.

Currently the patient is asymptomatic, maintaining pharmacological treatment with Lit- Control® pH Up and bicarbonate, with stability in renal lithiasis (no increase in the lithiasis load) and stable renal function, given that oral acidification is not recommended in these patients, we opted for optimized dietary treatment to improve urinary pH to a non-lithogenic range.

4. Discussion:

Phosphocalcic lithiasis without renal tubular acidosis:

CP lithiasis includes apatite, carbapatite or brushite lithiasis among other forms of crystallization. The predisposing factors for the formation of these stones are hypercalciuria (present in 60-80% of patients with CP lithiasis), elevated urinary pH (50-60%) and hypocitraturia (30-40%) (3), each predominating in a majority manner in the pathogenesis of the different stones. Brushite stones depend more frequently on hypercalciuria and are associated with the presence of hypocitraturia. Finally, carbapatite and apatite lithiasis are mainly dependent on urinary pH (4).

According to the diagnostic-therapeutic algorithm proposed in the European guidelines, the first step to be performed in a patient with CP lithiasis is a basic evaluation by blood and urine tests. In case of normal serum calcium with elevated parathyroid hormone (PTH) or elevated serum calcium with elevated PTH, the presence of associated hyperparathyroidism should be ruled out by parathyroid scintigraphy and/or choline PET-CT. The presence of hypercalciuria without hypercalcemia in 24h urine can be treated by the use of thiazides or potassium citrate. Finally, if the patient presents a urinary pH >6.5, renal tubular acidosis should be ruled out (a history confirmed in our clinical case) and then consider starting medical treatment to lower urinary pH and prevent recurrence of urinary lithiasis (2). The target urinary pH in patients with carbapatite and apatite lithiasis is 5.8 - 6.2, since this type of calculus precipitates at urinary pH >6.5/6.8. Preventive treatment consists of urinary acidification either by non-medical treatments or by compounds such as L-Methionine (2).

In the case of our patient, in addition to the alkaline pH, the presence of hypocitraturia was observed in the 24h urinalysis. Citrate is one of the main basic compounds that make up urine and at the same time acts as an inhibitor of urinary stone crystallization. Urinary citrate excretion depends mainly on the acid-base balance of the patient. Clinically, hypocitraturia may be found in patients with systemic acidosis, distal renal tubular acidosis, chronic diarrhea, renal failure, high protein intake, treatment with thiazide diuretics or occur idiopathically (3). The available treatments for oral citrate supplementation increase urinary pH, an undesirable objective in our clinical case given the added increase in the risk of CP crystallization. Ettinger et al. in a randomized clinical study on urinary alterations associated with the use of magnesium potassium citrate observed that the increase in urinary pH observed with this treatment was 0.2 units lower compared to other studies where potassium citrate was used (5).

Phosphocalcic lithiasis with renal tubular acidosis

The medical treatment of patients with CP lithiasis associated with distal renal tubular acidosis (dRTA) is more complex than that of CP lithiasis because of the associated characteristics of these patients. dRTA is a disease defined by the inability of the kidney to acidify urine below urinary pH < 5.3 in the presence of systemic metabolic acidosis with normal anion gap. It is caused by an alteration in H+ secretion in the distal tubule, which may be hereditary (primary dRTA) or acquired (secondary dRTA), with secondary cases being associated with the use of medications and/or the presence of other autoimmune diseases (as in the case of our patient, with a medical history of systemic lupus erythematosus and rheumatoid arthritis) (6).

In dRTA, the decrease in urinary secretion of hydrogenions (H+) and ammonium is responsible for the presence of an alkaline urinary pH. On the other hand, systemic metabolic acidosis promotes an increase in intestinal calcium absorption and bone calcium release, actions that result in the presence of hypercalciuria. Finally, systemic acidosis promotes a rapid absorption of urinary citrate (basic compound) by the proximal cells of the renal tubule, thus generating hypocitraturia (7). Therefore, alkaline urinary pH, hypercalciuria and hypocitraturia are the main metabolic alterations responsible for the formation of calcium phosphate lithiasis in patients with RTA, multiple lithiasis recurrences and/or nephrocalcinosis and being the cause of chronic renal failure. On the other hand, in order to buffer systemic acidosis, calcium is removed from the bone, generating osteopenia and/or osteoporosis in these patients. The diagnosis of dRTA is based on clinical suspicion (compatible symptomatology and presence of systemic acidosis) corroborated by an acid overload test in which the inability to acidify urine below 5.3 is evidenced. However, there is a variant of dRTA called incomplete distal renal tubular acidosis (iDRTA), which is not associated with systemic acidosis and is usually diagnosed at older ages because acid oversaturation tests are only performed when there is a high clinical suspicion (6). The main treatment of dRTA and iDRTA consists of correction of metabolic acidosis and oral bicarbonate administration. Bicarbonate treatment itself can increase the urinary citrate level, but if this is not sufficient, potassium citrate or potassium magnesium citrate can be added to the treatment. In the presence of hypercalciuria, thiazide diuretics can also be administered (6). As previously mentioned, the treatments used for the prevention of CP lithiasis recurrences and the treatment of dRTA can have counterproductive effects. It is not uncommon that the same patient may need to be treated with bicarbonate for the correction of systemic acidosis, potassium citrate for hypocitraturia and at the same time have an alkaline urinary pH, which is in the lithogenic range for crystallization of CP lithiasis. In this situation, in patients without renal tubular acidosis, the European Guidelines recommend urinary acidification either by non-medical treatments or by administration of L-Methionine compounds. Siener et al. evaluated the effects of L-Methionine administration on urinary composition in healthy patients, observing a significant acidification of urinary pH up to values of 6-6.2 maintained for 24h (7).

In contrast, in patients with iDRTA, despite the absence of systemic acidosis, there are no data on the use of these treatments due to the possible consequences associated with the exacerbation of systemic acidosis, such as bone demineralization (8). There are also no data on the urinary pH response of these patients after administration of L-Methionine. The question remains whether despite the definition of dRTA as the inability to acidify urine below a urinary pH of 5.3, a lower oral urinary acidification might be possible and help to achieve a pH in the non-lithogenic range for CP crystallization without reaching systemic acidosis.

In cases such as the one presented, when pharmacological measures do not allow optimizing preventive treatment (since the use of oral acidifiers is not recommended), dietary measures may be useful. Siener et al. compared the metabolic and urinary profile of 65 patients with CP lithiasis treated with a free diet or with a standardized balanced diet, observing a decrease in supersaturation of brushite, carbapatite and calcium oxalate in urine with the balanced diet. Although they found no difference in urinary pH between groups, the difference is explained by a significant decrease in urinary excretion of sodium, potassium, uric acid and oxalate among other compounds (9).

Importance of urinary pH and how to measure it:

Daily urinary pH monitoring is a basic tool to understand the daily variations of pH in a patient's urine, allowing us to adjust and create personalized treatments. The most widespread method for urinary pH determination is urine pH test strips, due to their easy accessibility to access and use. However, it is a subjective measurement method with high variability in the interpretation of results and requires manual and visual dexterity. Urinary pH is oscillating, requiring several measurements and strict monitoring. The gold standard for its measurement is the laboratory pH meter, but this machine is cumbersome and only available in hospitals. The portable digital pH meter option has been shown to achieve accurate, cost-effective and easy to perform measurements (10), which provides patient empowerment and better adherence to non-medical and medical treatments

instituted by professionals. It also allows patients to understand and control their pathology. These devices make it possible to manage in a simple way complex situations that require direct alkalinization and urinary acidification therapies, achieving an extraordinary control of the disease in comparison with methodologies and technologies not used before.

5. Conclusions

The medical management of patients with iDRTA and CP lithiasis is usually a challenge, requiring close follow-up and multiple treatments to reduce the recurrence rate and avoid gradual deterioration of renal function. In these patients, given their high risk of recurrence, crystallographic analysis, proper metabolic evaluation, comorbidities and dietary habits play a role in preventing recurrences. Urinary pH is a known important factor in the treatment of lithiasis patients and especially in CP lithiasis as it allows us to adapt the preventive medical treatment and to monitor the effects achieved. Finally, more data are needed on the role of urinary acidification in patients with iDRTA and CP lithiasis.

6. Bibliographic references

1. Daudon M, Bouzidi H, Bazin D. Composition and morphology of phosphate stones and their relation with etiology. Urol Res. 2010;38(6):459-67.

*2. Skolarikos A, Neisius A, Petrik A, Somani B, Thomas K. European Association of Urology guidelines on Urolithiasis 2023. European Urology. 2023.

**3. Rimer JD, Sakhaee K, Maalouf NM. Citrate therapy for calcium phosphate stones. Current Opinion in Nephrology & Hypertension. 2019;28(2):130-9.

**4. Kanashiro A, Angerri O. Urinary pH relevance on urolithiasis management. Arch Esp Urol. 2021;74):102.

5. Ettinger B, Vangessel A. Potassium-Magnesium Citrate Is An Effective Prophylaxis Against Recurrent Calcium Oxalate Nephrolithisasis. J Urol. 1997 Dec;158(6):2069-73.

**6. Magni G, Unwin RJ, Moochhala SH. Renal Tubular Acidosis and Kidney Stones: Diagnosis and Management. Arch Esp Urol. 2021 Jan;74(1):123-128.

*7. Siener R, Struwe F, Hesse A. Effect of L-Methionine on the Risk of Phosphate Stone Formation. Urology. 2016;98:39-43.

8. Potts JM, editor. Essential Urology: A Guide to Clinical Practice [Internet]. Totowa, NJ: Humana Press; 2004. Disponible en: http://link.springer.com/10.1007/978-1-59259-737-6

9. Siener R, Pitzer MS, Speller J, Hesse A. Risk Profile of Patients with Brushite Stone Disease and the Impact of Diet. Nutrients. 2023;15(18):4092.

**10. Sanz-Gómez I, Angerri O, Baboudjian M, Kanashiro A, Gracia S, Millán et al. Role, Cost, and Availably of Urinary pH Monitoring for Kidney Stone Disease- A Systematic Review of the Literature. Curr Urol Rep. 2023;24(8):381-8.