Calcium phosphate recurrent iatrogenic lithiasis. Citrates as double-edged sword in calcium oxalate lithiasis management.

Abstract

Background: citrates have represented an alternative ~~of~~ choice for the management of lithiasis patients. They were used as an alkalinizer to prevent non-calcium lithiasis in the mid-1950s. Its alkalinizing properties, with calcium chelators, cover the therapeutic needs of a wide range of patients, as stated in international guidelines. However, this duality of action may involve undesired effects depending on the patient need, unless urine pH is closely monitored.

Case presentation we present the case of a recurrent lithiasis 46-year-old Caucasian woman with a total colectomy for familial polyposis, hypothyroidism, appendectomy, total hysterectomy, salpingectomy, oophorectomy, cholecystectomy, gastric ulcer, and gastric polyps. That patient is on levothyroxine, triamterene/hydrochlorothiazide, loperamide and calcium carbonate. The patient reports an allergy to topiramate, neomycin and polymyxin. Since February 2008, the patient has had 11 KUBs and 11 CT scans, with a total of 12 procedures: 5 left ureteroscopy and laser lithotripsy, 5 left ESWL, 1 right ureteroscopy laser lithotripsy and 1 right ESWL. Since 2013 the stone composition demonstrated 4 calcium oxalate stones (mixture of COM/COD) and 2 calcium phosphate stones (hydroxyapatite and brushite), which were always after high citrate dose periods. In accordance with this observation, preventive treatment was switched from citrates to Lit-Control® pH Balance, aiming to prevent crystallization without urine alkalinisation.

Conclusions: patient's calcium-oxalate stone recurrence may be easily explained by alterations in the urine biochemistry like low diuresis, high oxalate concentration or hypocitraturia, and surgeries undergone by the patient. Thus, introduction of preventive measures to prevent crystals formation was correct in the frame of lithiasis medical management. Citrate was chosen to reduce urine calcium salt supersaturation by citrate thanks to its polyanionic nature. However, due to tricarboxylic acids metabolization, citrate consumption led to an increase of urine pH causing the generation of two calcium phosphate stones (hydroxyapatite and brushite) and maybe increased the presence of nucleants promoting heteronucleation. Non-monitored consumption of citrates increases the probabilities to over alkalize urine. Alternatively, there are options to prevent crystals formation using specific inhibitors without altering urine pH.

Introduction

Renal lithiasis is the consequence of a pathological change of conditions in the urinary tract toward those that favour crystallization. Alterations in the urinary pH values, and in the ratio between molecules acting as promoters or inhibitors of the crystallization, lead to the formation of nucleus and crystals from which, by growth, kidney stones form [1, 2]. Kidney stones can vary from an asymptomatic course to severe clinical manifestations such as renal colic, compromised kidney function, and even life-threatening sepsis.

Urinary pH is a crucial factor to understand the phenomena of crystal formation and stone growth since it determines the solubility of certain molecules and solutes present

in urine [3, 4]. Maintaining the urine pH in a preventive range, between 5,5 and 6,2, will reduce the probabilities of crystal formation and renal stone growth [2, 5]. Likewise, solute concentration represents a second variable of great relevance because together with the solubility, it will determine the degree of supersaturation, for a given compound, and, therefore, its tendency to crystallize [6]. Diuresis is understood as the daily volume of urine produced, but also the total amount of solutes excreted by glomerular filtration. Like two sides of the same coin, both qualities hold a determining role in the urinary concentration of molecules commonly involved in lithogenic processes [7].

Diet, genetic load, underlying diseases, and medications are risk factors for kidney stones. Looking at the scientific and medical knowledge of the physiological and molecular mechanism leading to kidney stone formation, there is a growing body of evidence to consider lithiasis as a chronic metabolic disease [8]. The most common and widespread source of metabolic and kidney function information is the analysis of urine collected for 24 hours [2, 9]. This information, being valuable, intrinsically implies some problems because it does not provide details of the characteristics of the urine in its circadian variations, but rather provides a fix image of the mean values resulting from mixing all the urine produced [10]. Also, once urine is micturated it naturally tends to alkaline masking its real value [11, 12]. Interpretations, recommendations, and treatments deriving from those results will inevitably carry limitations and mismatches. On this regard, pH represents an illustrative example: circadian, postprandial, and diet-influenced variations can be masked, making impossible an accurate and useful interpretation of the real urine pH values [2]. Solute concentration in urine voided along day, and their impact in crystals formation, are also an example of 24 urine analysis limitations. Similar situation is found using 24-hour urine analysis concentration to determine if alterations in the solute excretion may explain lithiasis. Crystal nucleation requires a particular physicochemical condition and high solute concentration in urine is a critical factor. Once a nucleus is formed, growth becomes easier and an average value is not informative enough.

Stone analysis represents another source of valuable information of the causes of stone formation [13]. In addition to the stone composition, it is also necessary to know the macro and microstructure of the calculus, that allows its proper classification (calculus type). This indicates its etiology [14, 15]. These studies can be carried out even if the calculation is fragmented, if carried out by specialized personnel.

The patient's medical history and lifestyle are important factors understanding the cause of lithiasis and its impact on renal and urinary health. Thus, diseases or conditions altering the intestinal absorption, metabolism or glomerular filtration may be at the origin of kidney stones.

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The chronic and metabolic nature of nephrolithiasis requires medical management to minimize or prevent recurrence in a long-term frame [16]. From that, active ingredients with a good safety profile and proven efficacy, represents a fundamental element of treatment for the specialist and patient. Historically citrates have matched these requirements. Commonly formulated as magnesium or potassium salts, they are able to chelate calcium which reduces calcium saturation in urine preventing calcium oxalate crystallization. However, citrate alkalinize urine due to its mitochondrial metabolization and associated urine alkali load. For this reason, indiscriminate use of citrates as treatment of choice for calcium oxalate stone deserves a reconsideration under the light of its dual action. Currently alternative treatments exist aiming to prevent iatrogenic effects associated with high lithiasis recurrence.

Case presentation

We present the case of a patient with recurrent lithiasis. A 46-year-old Caucasian woman with a history of total colectomy for familial polyposis, hypothyroidism, appendectomy, total hysterectomy, salpingectomy, oophorectomy, cholecystectomy, gastric ulcer, and gastric polyps. That patient is on levothyroxine, triamterene/hydrochlorothiazide, loperamide and calcium carbonate. The patient reports an allergy to topiramate, neomycin and polymyxin.

The patient was initially evaluated by the urology service in February 2008 with previous medical history of renal stones. The clinical symptoms reported were pain on the right flank. KUB showed a 7 mm x5 mm stone at the right ureteropelvic junction. The lithiasis was resolved by ESWL and the patient initiates a treatment with Urocit-K® (potassium citrate, 10 mEq), twice a day.

After one year, in 2009, in a follow-up visit, KUB demonstrate the absence of stones.

Later, in 2011, a 9 mm x 15 mm stone was confirmed by KUB in the left ureter. The patient is diagnosed for hypothyroidism and a hormonal replacement therapy (Synthroid) is established. Same year, August 2011, she underwent extracorporeal lithotripsy. The Urocit-K dose is increased to 3 times a day (total of 30 mEq).

In 2012, during follow-up monitoring, KUB verified that there were no stones.

In April 2013, KUB demonstrated the possible presence of a stone in the right middle ureter. In May of the same year, the presence of a 6 mm stone in the left mid ureter was confirmed and resolved by means of a laser ureteroscopy with implantation of a double J catheter for 14 days. In parallel, a 24-hour urine analysis was performed together with a stone analysis reporting mixed composition of oxalate-calcium (mono and dihydrate), phosphate-calcium, and uric acid crystals (attachment B). Dietary recommendations were provided.

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In July 2014, CT demonstrated multiple ureteral stones on the left side (between 2 mm and 6 mm), the largest being 7 mm and non-obstructive in the lower pole. Cystoscopy and left ureteroscopy, together with a laser lithotripsy were carried out in July 2014. After lithotripsy, fragments analysis showed a composition of hydrogen phosphate dihydrate 88% (attachment C). Results confirms an association of alkaline range crystals and stones. The administration of Urocit-K® is stopped.

In 2015, CT revealed a 4-mm stone in the right ureter which was spontaneously expulse and a 1.2-cm stone in the lower left pole, non-obstructive. An extracorporeal lithotripsy is performed to resolve the left stone. The calculus analysis results show a composition of 83% calcium oxalate dihydrate and 15% calcium oxalate monohydrate (attachment D). Treatment with potassium citrate is restarted, 15 mEq twice a day, based on a 10 ml oral solution, 4 times a day due to the patient's intolerance to the tablets, and the lack of absorption (possibly due to colectomy). Finally, an URS post extracorporeal lithotripsy is required due to the presence of residual fragments.

In August 2017, the patient went to the emergency room and a 5 mm stone was observed in the proximal right ureter with a staghorn in the lower pole of the right kidney of 2.5 cm x 1.3 cm (attachment E). An extracorporeal lithotripsy is scheduled followed by a laser URS with double J catheter implantation for 7 days. The patient reports low tolerance to liquid citrate due to stomach discomfort. The 24 hours urinary pH reports a value of 6. The dietary recommendations are emphasized, increasing the fluid intake to 3 litres per day and *Crystal light®* drink is recommended as a source of potassium citrate. Stone analysis showed a mixed composition of 10% calcium oxalate monohydrate, 84% calcium oxalate dihydrate and 4% calcium phosphate. In September of that same year, she visited the emergency room due a 5 mm right obstructive stone and non-obstructive residual fragments on the left side. The patient shows a urinary pH value of 5. A laser URS is scheduled for the same month. Analysis of the stone fragments shows a mixed composition of COM 55% and COD 40% (attachment F). In November of the same year, she underwent extracorporeal lithotripsy to remove residual fragments. Hydrochlorothiazide (25 mg) is administered daily

In June 2018, by KUB, a stone is confirmed in the lower left pole. ESWL is scheduled for lithiasis resolution being not completely successful. The patient's 24 hours urine pH is 7.

April 2019, a 24 hour demonstrated a urinary pH of 7 and a calcium concentration of 7,7 mg/dL. A CT showed residual fragments in the left ureter and bilateral non-obstructive stone. A laser URS with double J stent placement (4 days) is performed. Analysis of the stone reveals a mixed composition consisting of carbonate calcium phosphate (5%), calcium hydroxyphosphate (25%) and calcium hydrogen phosphate dihydrate (68%) (attachment G). The patient is treated with potassium supplements and hydrochlorothiazide for hypokalaemia.

In April 2019, patients' starts treatment with Lit-Control® Balance (255 mg of calcium magnesium phytate, 55 mg of magnesium, 125 mg grape seed polyphenols, 1,3 mg of

Zn and 0,15 mg of vitamin A), twice a day (1-0-1) with good tolerance. Thiazides are discontinued due to hypokalaemia. 24-hour urine collection results in high urine volume 2600 mL's, low phosphorus (202 mg/24 hr), low uric acid (244 mg/24 hr), low urine chloride (less than 52 mmol/24 hr), low citric acid (133 mg/24 hr), low cystine (4.55 mg/24 hr) she has hypocitraturia (attachment H)

In September of the same year, 2019, 24-hour urine collection results demonstrate high urine volume (2020 mL/24 h) low uric acid (213 mg/24 h), low urine chloride (90 mg/24 h) low citric acid (42 mg/24 h) low cystine (2.33 mg/24 h) and hypocitraturia (Attachment I -). One year later, October 2019, CT – bilateral small nephrolithiasis largest measuring 3 mm non-obstructing, spontaneously expulsed. After 12 months with Lit-Control® Balance patient has not had any hospitalizations, ER visits or surgical interventions for the past 6 months. UA pH 5.5 / Calcium 9.2

Since February 2008, in terms of imaging she has had 11 KUBs and 11 CT scans. She has had a total of 12 procedures: 5 left ureteroscopy and laser lithotripsy, 5 left ESWL, 1 right ureteroscopy laser lithotripsy and 1 right ESWL.

Discussion

The report of the patient in this case begins in 2008 with a lithiasis resolved by ESWL, and preventive medical treatment based on 20 mEq of citrate daily (UrocK, 10 mEq, twice). Recurrent preventive medical treatment was increased to 30 mEq (Urocit-K®, 10 mEq, 3 times per day) after renal stone diagnosis in 2011 in the left ureter. The establishment of citrate-based medical treatment dates prior to conducting 24-hour urine biochemistry tests. According to the patient's medical history, considering multiple surgical operations suffered, colonic extirpation due the presence of polyps becomes of special interest. Colectomy, because of the absorptive relevance of bowel-part removed, implies a profound impact in urinary biochemistry, in a transient or permanent way. Urinary alterations most frequently associated are hyperoxaluria, hypercalciuria, uricosuria, reduced urinary pH and low diuresis. Considering all those alterations, prescription of citrate salts on a daily base, due to its alkalinizing potential and as a crystallization inhibitor, was an appropriate choice. However, the lack of indications to monitor urine pH evolution and citrate-dose adjustment, if needed, reveals no medical awareness of lithogenic risks associated to alkaline values, especially once threshold of 6.2 is overcome.

In 2013, a new lithogenic episode was demonstrated. Calculus composition and 24-hour urine analysis were available (Table 1) for very first time. The patient had urine results of normocalciuria, normoxaluria, as well as a protective urinary pH (5.8). However, very low

diuresis was confirmed (0.67 litres) inviting to study the results with the angle of the concentration. Results of oxalate excretion, 35 mg/day, fell in the range of normality (< 45 mg/day), nonetheless, considering its concentration (0,42 mM), it becomes suspicion of a net contributor to calcium oxalate saturation in urine. In addition, as previously introduced, 24 hours urine provides an average of the urine biochemistry during one single day, meaning that independent urine spot samples taken along day, would result in oxalate concentration values and analysis above and under the average value. As a biochemical alteration, hypocitraturia stands out, which can lead to thinking of low adherence to treatment, or severe hypocitraturia.

In 2014, after reinforcing the citrate treatment (30 mEq) with dietary measures, a new lithiasis appears. The nature of the stone composition led us to consider iatrogenic origin as highly probable: 88% calcium phosphate. Calcium phosphate crystals are associated with urine values altered towards the alkaline range, easily linked with the 30 mEq d citrate/day stablished as the underlying medical treatment, besides dietetic recommendations, with no tracking record of urine pH values evolution. Considering the results and analysis, medical decision was to stop the administration of citrates as a measure to avoid the generation of new alkaline stones. However, with a retrospective view, this decision was not enough to solve the problem because renal manifestations continued, as was anticipable from the patient's medical history and documented risk factors. Considering the stone analysis available and high urine oxalate concentration, there arose the need to reduce calcium oxalate saturation. Among the alternative available, we find increasing the presence of magnesium as an element that competes with calcium for oxalate, can generate a salt of much greater solubility. Alternatively, there was the option to introduce treatments based on crystallization inhibitors: molecules with the ability to specifically prevent the growth of certain crystals. Polyphosphates are recognized chemical entities in the field of crystals inhibition. Among them, inositol hexaphosphate (IP6) and its combined salts (known as phytate) are of special interest for the prevention of calcium-based crystals and magnesium-containing crystals. Since the early nineties, an extensive and deep scientific and clinical lithiasis benefit of phytates with large scale epidemiologic data of the benefits of high phytate presence in the diet are available. Phytate is found in vegetal, especially in non-refined products, which are rapidly disappearing from our diet, especially in western countries and supplementation (together with dietetic recommendations) would help to recover protectives levels.

Discontinuation of citrate treatment led to 2 more lithiasis episodes in the timeframe of 12 month. One of them was spontaneously expulsed while the second was collected and analysed, resulting in calcium oxalate composition. In the context of an oxalocalcic lithiasis, less than a year is a short time for recurrence, reinforcing the need for preventive measures. Unfortunately, citrate was re-established as recurrence prevention medical treatment, being offered as a liquid formulation, in order to

facilitate the tolerability and acceptance of the patient, who had been reported adverse intestinal effects with the previously prescribed tablets. The posology was 10 ml per day, 4 intakes, involving a total of 30 mEq per day. Despite this new galenic presentation, the patient continued reporting stomach discomfort, thus it was decided to continue with citrate treatment using a commercial drink (*Crystal light*®). The restoration of the regimen with citrate responded to the interest in reducing urinary saturation for CaOX, obviating the adverse effects described in both stone generation with the alkaline pH range. A short time later, a new iatrogenic calcium phosphate lithiasis (Table2) is described, consistent with reported values of urinary pH greater than 8.

After the lithiasis episode associated with induced alkalinisation, in April 2019, the Lit-Control treatment was introduced on a daily base, as a source of magnesium (magnesium oxide) and phytate, in order to hinder the formation and growth of the stones without affecting the pH values. Both active ingredients work synergistically preventing the formation of CaOx nucleus and stone growth in the whole physiologic range of urine pH, without yielding alkalis or protons to the renal system, avoiding potential iatrogenic renal stones. Currently, patient is still under Lit-Control® pH Balance treatment, reporting during this time to minor lithiasis (3 mm largest one) spontaneously expulsed.

Urine saturation for a given molecule determines propensity to crystallization. pH as crucial dissolution parameter to understand major or lesser solubility of molecules should be a priority in terms of metabolism, dietetic recommendations or associated to pharmacologic treatments. The prevalent indiscriminate utilization in medical management of stones is the alkaline load yielded by citrates. This is not always desirable, especially when calcium oxalate formers are prescribed. For this reason, either close monitoring of urine pH should be prescribed on a daily basis to prevent excessive alkalinisation and reduce doses (when necessary) or to find alternatives to reduce crystal formation using specific inhibitors level without impact on the urine pH.

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