Update on cystine stones: current and future concepts in treatment

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SUMMARY   Cystine stones are relatively uncommon compared with other stone compositions, constituting just 1% to 2% of adult urinary tract stone diseases, and accounting for up to 10% of pediatric stone diseases. Two responsible genes of cystinuria have been identified, the SLC3A1 and the SLC7A9. Cystinuria is diagnosed by family history, stone analysis, or by measurement of urine cystine excretion. Current treatments for cystinuria include increased fluid intake to increase cystine solubility by maintaining daily urine volume of greater than 3 Liter (L). Limiting sodium and protein intake can decrease cystine excretion. When conservative therapy fails, then pharmacologic therapy may be effective. Alkaline urine pH in the 7.0-7.5 range will reduce cystine solubility and can be achieved by the addition of alkali therapy. If these measures fail, cystine-binding thiol drugs such as tiopronin and D-penicillamine are considered. These compounds bind cysteine and prevent the formation of less soluble cystine. These drugs, however, have poor patient compliance due to adverse effects. Captopril can be useful in the treatment of cystine stones but the drug has not been tested in rigorous clinical trials. Novel potential therapies such as alpha-lipoic acid and crystal growth inhibitors (L-cystine dimethyl ester (L-CDME) and L-cystine methyl ester (L-CME)) were developed and tested in animals. Those therapies showed promising results. Compliance with treatment was associated with a lower rate of cystine stone formation.

Keywords   cystinuria, urolithiasis, novel therapy, cystine stone, tiopronin, D-penicillamine

1. Introduction

Cystinuria is an inherited disorder of the dibasic amino acid transport system in the proximal tubule and the small intestine. Two responsible genes have been identified, the SLC3A1 on chromosome 2 and the SLC7A9 on chromosome 19. The inability of renal tubules to reabsorb cystine and the relative insolubility of cystine at physiological urine pH lead to stone formation (*1*). Children at risk for nephrolithiasis can be identified by the level of urinary cystine only after tubular transport has matured (age 2 years). Conservative therapy with high urine volume and urinary alkalinization is sufficient for some, but recurrent stone formation may cause renal damage (*2*). Cystinuria is a genetic disease that leads to the frequent formation of stones. In patients with recurrent stone formation, particularly patients < 30 years old or those who have siblings with stone disease, urologists should maintain a high index of suspicion for the diagnosis of cystinuria (*3*). Cystinuria is the cause of about 10% of all kidney stones observed in children. Without any preventive measures, the patients will suffer from recurrent stone formation throughout their life. Even with medical management, the long-term outcome is poor due to insufficient efficacy and low patient compliance. Many patients suffer from renal insufficiency as a result of recurrent stone formation and repeated interventions (*4*). Cystine stones may become very large, are often recurrent, and are difficult to fragment with extracorporeal shock wave lithotripsy (ESWL), so that preventive therapy is essential, and should be started as soon as the diagnosis is made. Cystinuria is diagnosed by family history, stone analysis, or by measurement of urine cystine excretion. When the stone type is unknown, patients should have one urine screened with a qualitative test for cysteine (*5*).

Therapy to reduce stone formation is directed towards lowering urine cystine concentration and increasing cystine solubility. Determining cystine capacity may be an effective tool to monitor the individual patient's response. Compliance in cystinuric patients concerning both dietary and pharmacological intervention is poor (*6*). Medical management is mainly based on hyperhydration and urine alkalinization. Long-term therapy with

sulfhydryl agents to prevent the formation of renal stones seems to be effective but adverse side effects are frequent, requiring the withdrawal of treatment (*7*). Prevention of stone formation is the primary goal of management and includes hydration, dietary restriction of salt and animal protein, urinary alkalinization, and cystine-binding thiol drugs (CBTD) (*8*). In mild cases of cystinuria, judicious urinary alkalinization and fluid may suffice but in more severe cases, a thiol agent, such as tiopronin or D-penicillamine, should be added (*9*). The durability of medically treating patients with cystinuria is limited with only a small percent able to achieve and maintain the goal of decreasing cystine below the saturation concentration. Greater physician vigilance in these complicated stone formers is required to achieve successful prophylactic management (10). Prompt referral for metabolic assessment, early multidisciplinary input, and total removal of the stone fragments are keys to preventing stone episodes and improving the long-term function of patients (*11*).

2. Etiology

Cystinuria is an inborn congenital disorder characterized by defective cystine metabolism resulting in the formation of cystine stones. Two genes responsible for cystinuria have been identified: SLC3A1 (chromosome 2p21) encodes the heavy subunit rBAT of a renal b(0,+) transporter while SLC7A9 (chromosome 19q12) encodes its interacting light subunit b(0,+)AT. Mutations in SLC3A1 are generally associated with an autosomal-recessive mode of inheritance whereas SLC7A9 variants result in a broad clinical variability even within the same family. The detection rate for mutations in these genes is larger than 85%, but it is influenced by the ethnic origin of a patient and the pathophysiological significance of the mutations (*12*). In cystinuria, the kidney, due to a genetic defect in the cystine transporter, is unable to reabsorb cystine in the proximal tubule, resulting in urinary hyperexcretion of amino acids cysteine, ornithine, lysine, and arginine (COLA). Of these, only cysteine is relatively insoluble at normal urinary pH, leading to stone formation when cystine concentration rises above the solubility limit (*13*).

In homozygotes or compound/mixed heterozygotes, the mutation of SLC3A1 or SLC7A9 is associated with increased urinary cystine excretion and kidney stone formation in 100% and 94% of cases respectively. For SLC7A9 heterozygotes, an increased urinary cystine excretion can be observed in 86-90% of cases and kidney stone formation in 2-18% of cases. Polymorphisms of the SLC7A9 gene probably affect the clinical course in SLC7A9 mutation carriers (*14*). Cystinuria is also observed in patients with the cystinuria-hypotonia syndrome, which is due to the microdeletion of part of the SLC3A1 and PREPL genes on chromosome 2p21 (*15*).

3. Classification

Traditionally, cystinuria has been divided into three subtypes: types I, II, and III based on the excretion of cystine and dibasic amino acids by the obligate heterozygous parents of the affected children. Type I heterozygotes show a normal amino acid urinary pattern, whereas type II and III are characterized by an increase of cystine, lysine, ornithine, and arginine urinary excretion (*16*).

A new classification based on the genetic findings was implemented. Patients were classified as type A, type B, and type AB based on the genetic findings. Type A cystinuria is the result of mutations in both *SCL3A1* genes and type B results from mutations in both *SCL7A9* genes. Type AB Individuals have one mutation in SLC3A1 and one in SLC7A9. Probands with more than two mutated alleles were classified as AA(B) or BB(A), depending on the distribution of mutations in the two genes. None of the individual's AB had cystine urolithiasis. Obligate type AB (double heterozygous) individuals who develop cystinuria have not been found. The digenic inheritance of cystinuria was ruled out (*17*). Type AB patients may suffer from a mild phenotype and therefore, in most cases, escape detection. Alternatively, these patients may actually represent type B disease (two mutations in *SLC7A9*, one of which was detected, the other yet to be defined) and a coincidental carrier state for a *SLC3A1* mutation. Reliable classification of cystinuria requires the identification of the mutations in both alleles (*18*).

Multiple studies examining genotype-phenotype correlations in cystinuria did not show any correlation between patients with type A genotype and patients with non-A genotypes (*19,20*). In a study, where 37 different mutant variant alleles were identified, including 12 novel mutations; 22% of mutations were caused by large gene rearrangements. No genotype-phenotype association was detected (*19*). The lack of detectable mutations in many patients indicates the possibility of other yet unidentified genes involved in cystinuria. The severity of the disease to the type of cystinuria in pediatric patients cannot be correlated (*21*).

4. Prevalence

Cystinuria is a global disorder with population-specific prevalence, its overall prevalence has been estimated at 1:7,000 in neonates. It varies between different populations: the highest frequency has been observed among Libyan Jews with a rate of 1:2500 (*12*). Other population-specific rates are 1:17,000 in the United States, 1:18,000 in Japan, and 1:100,000 in Sweden. The mean age at which urolithiasis including cystinuria is diagnosed is reported to be 5.59 years. Of these patients, 41.4% were below the age of 1 year and 60.5% were below the age of 5 years (*22*).

5. Evaluation

The diagnosis of cystinuria is easily made by stone analysis, microscopic examination of the urine, and 24-hour urine testing. Sodium cyanide nitroprusside is a suitable screening test that should identify homozygous stone formers but will not detect all heterozygotes. A positive screening test should be followed by quantitation of urinary amino acids. A homozygous patient can be functionally defined as one who excretes 250 mg or more of cystine/g of creatinine in a 24-hour urine collection (*23*). A positive nitroprusside test is followed by a quantitative analysis of urine cysteine and homocysteine to differentiate between cystinuria and homocystinuria. A sensitive and reproducible assay for total urine cysteine and homocysteine has been developed (*24*). One problem is that the measurement of cystine excretion is complicated by artifactually low values when cystine solubility is poor. Cystine is least soluble at pH 5-7, a range frequently found in human urine. Another problem is that many cystine assays do not reliably distinguish cystine from soluble thiol drug-cysteine complexes. Colorimetric reactions measure the amount of free sulfhydryl group. In the presence of thiol-containing drugs, this no longer remains an accurate estimate of cystine concentration. A solid-phase assay of urinary cysteine is applied, which leads to direct measures of urinary cystine supersaturation and cystine capacity. It is reliable in the presence of cystine-binding thiol drugs. It should be useful in monitoring patients' responses to dietary interventions and administration of fluid, citrate, and CBTD (*25*).

Based on previous observations of the diurnal variation of urinary cystine excretion, the use of separate day and night urine collections was proposed. Analyses of separate day and night urine samples can be used advantageously to reveal episodes of high supersaturation with cystine not detected in 24-h urine samples. Such a procedure might be useful for optimizing the treatment of patients with cystinuria (*26*).

Cystine stones are yellowish with a waxy appearance macroscopically and are characterized by a flat hexagonal crystal microscopically. The stone analysis provides definitive proof of the composition. Radiographically, cystine stones appear lightly opaque (due to the sulphur content) with homogeneous density, typically a "ground glass" appearance (*27*). The classification of cystine stones into rough and smooth varieties has been suggested as an aid to choosing treatment for these difficult stones. The surface morphology of cystine stones correlates with their internal structure, as viewed by helical computerized tomography (CT). Rough cystine stones can be distinguished from smooth stones using helical CT *in vitro*, suggesting that it may be possible to distinguish these stones preoperatively (*28*). Cystine stones often are poorly visible on KUB radiography (*29*).

6. Clinical Presentation

Recurrent urinary tract stone disease is the only clinical manifestation of cystinuria in childhood. Cystinuria can also result in chronic kidney disease (CKD) due to recurrent stones, obstructive uropathy, and repeated urologic interventions. Most patients with cystinuria present in childhood with stone formation. The average age of detection of a first renal stone is about 12-13 years, with 50% forming a first stone in the first decade of life and another 25% in teenage years. Males and females have a similar age of onset but more male patients than female patients present in the first 3 years of life and males tend to have new stones more frequently than females (*30*). CKD and high blood pressure occur frequently in patients with cystinuria and should be routinely screened. A retrospective study of 442 cystinuric patients was conducted. Results showed that among the 314 patients aged $\geq$ 16 years, using the last available plasma creatinine, only 22.5% had an eGFR $\geq$ 90 mL/min per 1.73 m^2 (*31*).

Urolithiasis may be the cause of acute renal failure in young children, since urolithiasis may only cause nonspecific symptoms in this population. Those patients should be tested for cystinuria (*32*). Hypotonia-cystinuria syndrome is a recessive disorder caused by microdeletions of SLC3A1 and PREPL on chromosome 2p21. Patients present with generalized hypotonia at birth, failure to thrive, growth retardation, and cystinuria type I (*33*).

7. Management

The first approach to treatment of cystinuria is a conservative program that includes initiation of therapeutic lifestyle changes involving increased fluid intake and restriction of sodium and protein, as well as urinary alkalinization therapy (*34*). If conservative therapy fails to reduce urinary cystine concentrations to less than 250 mg/L or stones recur despite therapy, CBTD is the next step in treatment (*35*).

7.1. Hydration

Hydration is the mainstay of the treatment. Patients are advised to wake up at night to drink water in addition to their daytime intake. Therefore, maintaining urine output to keep up with cystine excretion helps prevent stone formation. To prevent nocturnal aggregation of crystals, 500 mL of water intake at bedtime, and another 300 mL overnight is advocated (*27*). The single most important intervention in patients with cystine stones is to increase cystine solubility by increasing fluid intake. Adults with stones should have a target urine output of at least 3 L daily and less than 200 mg of cystine/L of urine (*36*). A high fluid intake of around 4-5 liters a day is required, and to drink before going to bed and during

the night to maintain dilute urine overnight (*37*).

7.2. Dietary modifications

Despite the low level of scientific evidence, a low-protein (< 20 g/day), low-salt (< 2 g/day) diet with high hydration (> 3 liters/day) is strongly advised in children with cystinuria. Dietary restriction of sodium should be an important component of the therapeutic strategy of patients with cystinuria (*38*). There is little evidence to support dietary restriction of protein, although reducing animal protein will be beneficial to increase urinary pH. Restriction of methionine-containing foods like peanuts, pistachio, popcorn, broccoli, mushroom, cauliflower, avocado, bean sprouts, potatoes, spinach, green peas, tofu, kidney beans, black beans, and tempeh may prevent cystine crystal formation (*39*). Ingestion of vegetables high in organic anion content, such as citrate and malate, should be associated with higher urine pH and fewer stones because the amino acid cystine is soluble in more alkaline urine (*40*). Like all stone formers, cystinuric patients are advised to limit their sodium intake to less than 2,300 mg/day (100 mEq/day) (*41*).

7.3. Urinary alkalinization

Urinary pH has a crucial role in prevention of stone formation. Therefore, cystine stone formation can be reduced by increasing the urinary pH level. The solubility of cystine does not increase significantly until a urine pH level above 7-7.5 is reached. Urine alkalinization up to pH 7.5 using sodium bicarbonate and/or potassium citrate is used (*42*). Because of the relationship found between the excretion of urinary sodium and cystine, potassium citrate has emerged as the preferred sodium-free alkalizing agent (*43*).

A reasonable goal is to keep the cystine concentration under about 240 mg/L and urine pH about 7, in order to maintain solubility. If the urine pH is below 7, potassium alkali in doses of 10-20 meq three times daily can be used to raise it (*5*). While urinary alkalinization for cystine calculi is an integral part of medical management, the effect of oral alkalinizing agents is limited because of the high pKa (8.3) of cysteine (*44*). Acetazolamide was effective in increasing the urinary pH in patients with cystine stone formation who were already taking potassium citrate. Caution must be taken when prescribing acetazolamide because it could be poorly tolerated and can induce calcium phosphate stone formation (*45*).

7.4. Cystine-binding thiol drugs (CBTD)

In patients who are refractory to increased fluid intake, urinary alkalinization, and dietary restriction of protein and salt, CBTDs are recommended (*42*). Agents most commonly used include α-mercaptopropionyl glycine

(tiopronin) and D-penicillamine. Thiol compounds contain sulfhydryl groups that undergo a disulfide exchange reaction with cysteine to produce two molecules of cysteine bound to the CBTD, a complex that is 50 times more soluble than cystine. The effect of the drugs is dose-dependent (*46*). Twenty-four-hour urine cystine measurements are used to guide therapy: if 24-hour urine cystine concentration remains > 2,000 micromols(µmol)/L, chelation therapy is usually necessary, given as D-penicillamine or Tiopronin, to reduce free cystine concentration to < 1,000 µmol/L (ideally < 500 µmol/L) (*36*).

7.4.1. D-penicillamine

The most effective therapy for cystinuria is oral administration of thiol-containing compounds like penicillamine, which form mixed-disulfides with urinary cystine, reducing crystallization. Penicillamine's effectiveness in reducing stone formation and dissolving pre-existing stones in cystinuria has been well-documented (*47*). D-penicillamine is effective in decreasing the rate of stone formation in patients in whom hydration and alkalization failed (*48*). In adults, penicillamine reduces stone formation but has a high incidence of dose-limiting toxicity. A study was implemented to evaluate the effects and toxicity of penicillamine in pediatric patients. 11 children with cystinuria treated using a gradual dose escalation of penicillamine were included. During the gradual escalation of penicillamine to the target dose, none of the 11 patients experienced toxicity and all had improved urinary cystine concentration. Patients were followed for a total of 1,203 months. During this time only 2 patients experienced significant side effects and no patient had stones or stone crises while compliant with treatment (*49*).

The dosage of cystine-binding drugs required to achieve a free urine cystine level below 100 µmol/mmol creatinine was closely correlated with patient body weight: older children required a lower dose. Medical management of cystinuria is feasible. The treatment must be personalized in children, as the amount of drug required is strictly dependent on body size (*50*). A retrospective study was done to assess the efficacy and untoward reactions of D-penicillamine in the management of cystinuria. The incidence of acute drug sensitivity reactions (rash, fever, and/or arthropathy) was over 40 percent. Delayed drug-induced proteinuria occurred in 34 percent of treated patients (*51*).

The cutaneous side effects of penicillamine include acute hypersensitivity reactions and abnormalities of elastic fibers-elastosis perforans serpiginosa (EPS) and pseudo-pseudoxanthoma elasticum, autoimmune disorders such as pemphigus and a penicillamine-induced lupus erythematosus-like syndrome. These cutaneous adverse effects may correlate with the dosage

and duration of penicillamine therapy (*52*). Clinically, EPS presented with serpiginous or annular patterned lesions up to several centimeters with or without pruritus. The treatment of EPS primarily consists of oral isotretinoin, intralesional injections of triamcinolone acetonide, topical application of tazarotene, or allium cepa-allantoin-pentaglycan gel or cryotherapy (*53*).

7.4.2. Tiopronin

Oral administration of alpha-mercaptopropionylglycine (MPG) or tiopronin for cysteine stone dissolution and/ or prevention of recurrence has proved its efficacy. It was associated with fewer side effects than are reported generally with D-penicillamine (*54*). The effect of long-term treatment with tiopronin was examined in 66 patients with cystinuria. Of the patients, 49 took D-penicillamine before therapy, whereas 17 did not. Tiopronin was equally as effective as D-penicillamine in reducing cystine excretion. During long-term treatment with MPG (average dose 1,193 mg per day), urinary cystine levels were maintained at 350 to 560 mg per day and urinary cystine was kept at undersaturated levels. Commensurate with these changes, tiopronin produced remission of stone formation in 63 to 71 percent of patients and reduced individual stone formation rate in 81 to 94 percent (*55*).

Thirty-two patients with cystinuria were enrolled in a long-term study where 16 patients were treated with tiopronin for 24 weeks. Tiopronin reduced daily urinary cystine excretion from 901.48 mg (before treatment) to 488.60 mg (on the average of 12th week and 24th week after tiopronin administration) successfully. Tiopronin therapy was tolerated well, but side effects were observed in 13 events in 6 patients. Thus tiopronin was expected to be effective in preventing cystine stone formation and tolerated well (*56*). Another study was done, where forty patients, belonging to six cystinuric families, were identified. These patients were excreting 3.1 ± 1.7 mmol/24 h of cystine in their urine. All patients were treated by oral administration of MPG in daily doses of 400-1,200 mg/24 h. During a 4 ± 2 years of follow-up of these patients. It was concluded that treatment with MPG is very effective with minimal side effects in patients suffering from cystinuria or cystine urinary calculi (*57*).

CBTDs lower the urinary supersaturation of cystine, as shown by a less-negative or more-positive cystine capacity. Cystine capacity can be measured directly, even in the presence of CBTDs including tiopronin. The value of this measurement lies in the potential to monitor the response to the drug, prescribe the minimum effective dose, and potentially decrease adverse effects often associated with CBTDs (*58*).

The recommended initial dosage in adult patients is 800 mg/day. For pediatric patients, the recommended initial dosage in pediatric patients weighing 20 kg and greater is 15 mg/kg/day. The dosage should be readjusted depending on the urinary cystine value to achieve a urine cystine concentration of less than 250 mg/L. The most common adverse reactions ($\geq 10\%$) are nausea, diarrhea or soft stools, oral ulcers, rash, fatigue, fever, arthralgia, proteinuria, and emesis (*59*).

7.4.3. Captopril

Formation of captopril–cysteine disulfide accounts for part of the reduction in cystine excretion. Captopril-cysteine disulfide is 200 times more soluble than cystine. Sloand *et al.* reported the first clinical use of captopril in the treatment of homozygous cystinuria in two siblings. In the first patient, a 70% reduction in cystine excretion was observed after 26 weeks of therapy with 150 mg/ d of captopril. In the second patient, cystine excretion was reduced by 93% after nine weeks of therapy with 75 mg/day of captopril. No adverse side effects were observed in either patient (*60*). Perazella *et al.* reported a marked decline in urinary cystine excretion of two cystinuric patients treated with captopril for one year. The two cases were intolerant of traditional therapy (tiopronin and D-penicillamine) (*61*). Another study was implemented to determine the clinical efficacy of captopril for the prevention of new or stone growth in patients with homozygous cystinuria. Nine patients with a history of multiple cystine stones despite standard fluid and alkalization therapy received 50 mg of captopril, 3 times daily in addition to the standard therapy. Findings suggest that captopril may be clinically efficacious in at least some patients with difficult to control cystinuria (*62*). Captopril should be considered an alternative to traditional drug management of cystinuria.

7.4.4. Bucillamine

Bucillamine is a drug developed from tiopronin, currently used as an antirheumatic agent and, acting as a thiol donor, which might be capable of binding cysteine from urine and thus reducing the risk of stone formation. A currently recruiting phase II trial is investigating the safety and effectiveness of bucillamine on urinary cystine excretion (*63*).

7.5. New therapies

7.5.1. L-cystine dimethyl ester (L-CDME) and L-cystine methyl ester (L-CME)

A new alternative approach for the prevention of recurrent nephrolithiasis is based on crystal growth inhibition. A group at New York University is using atomic force microscopy (AFM) to visualize the early stages of crystal formation in liquids. Real-time in situ atomic force microscopy reveals that L-cystine dimethylester (L-CDME) and L-cystine methylester

(L-CME) dramatically reduce the growth velocity of L-cystine molecules. This is a new pathway to the prevention of L-cystine stones by rational design of crystal growth inhibitors (*64*). CDME's efficacy in inhibiting L-cystine crystal growth *in vivo* utilizing a murine model of cystinuria was demonstrated (*65*). A study was done to assess the effectiveness of L-CDME, an inhibitor of cystine crystal growth, for the treatment of cystine urolithiasis in a Slc3a1 knockout mouse model of cystinuria. Treatment with L-CDME led to a significant decrease in stone size compared with that of the water group (*p* = 0.0002), but the number of stones was greater (*p* = 0.005). The data demonstrate that L-CDME promotes formation of small stones but does not prevent stone formation, consistent with the hypothesis that L-CDME inhibits cystine crystal growth (*66*).

To overcome the chemical and metabolic stability issues of L-CDME and L-CME, a series of l-cystine diamides with or without Nα-methylation was designed, synthesized, and evaluated for their inhibitory activity of l-cystine crystallization. Among the l-cystine diamides 2a-i, l-cystine bismorpholide (CDMOR, LH707, 2g) and l-cystine bis(N'-methylpiperazide) (CDNMP, LH708, 2h) are the most potent inhibitors of l-cystine crystallization (*67*).

One potential limitation of the molecules is the potential for toxicity. Incubation of noncystinotic renal epithelial cells (LLC-PK1) cells, a model for proximal tubular function, with CDME resulted in time- and dose-dependent accumulation of cystine, with 80% of the cystine in the lysosomal fraction. The accumulation of cystine in the lysosomes caused dose- and time-dependent cell mortality (*68*).

7.5.2. α-Lipoic acid

In a mouse model of cystinuria, it was reported that the nutritional supplement α-lipoic acid (α-LA) inhibits cystine stone formation in the *Slc3a1*⁻ᐟ⁻ mouse model of cystinuria by increasing the solubility of urinary cystine. The pro-antioxidant compound α-LA was a strong suppressor of stone growth as mice treated with α-LA had lower stone formation growth compared to untreated mice (*69*). Exploring the mechanism of action of α-LA, the researchers found that treatment with the compound did not alter urinary cystine concentrations and that its effect was independent of Nrf2-mediated antioxidant responses (*via* increased cystine import for glutathione synthesis). Instead, it was observed that cystine was considerably more soluble in the urine of α-LA-treated mice than in that of untreated mice (*70*). These findings identify a novel therapeutic strategy for the clinical treatment of cystinuria. Implementation of clinical trials of α-LA treatment of cystinuria is needed before further conclusions can be made.

7.5.3. Tolvaptan

Tolvaptan, an arginine vasopressin receptor antagonist, decreases urinary supersaturation in kidney stone formers by considerably increasing diuresis. Patients had a significant increase in daily urine volume and a resultant decrease in urinary cystine concentration when taking 15 mg tolvaptan daily for 5 days (*71*). A study was implemented to evaluate the effect of tolvaptan, on cystine stone volume in mice with cystinuria. After treatment, mice treated with tolvaptan had significantly delayed stone growth, and exhibited lower overall stone volume accumulation, compared with the control group. The present study indicated that tolvaptan's efficacy in preventing L-cystine stone growth through an increased liquid intake and urine volume in cystinuric mice (*72*). These findings identify a novel therapeutic strategy for the clinical treatment of cystinuria.

8. Conclusion

Cystinuria is a rare cause of urolithiasis. Affected patients have an earlier onset and more aggressive disease than patients with other stone types. Current treatment options of cystinuria are limited in their effectiveness at preventing stone recurrence and often poorly tolerated. Multiple studies suggest that L-CDME is as effective at inhibiting the growth of cystine crystals *in vitro* as well as *in vivo*. Also, the nutritional supplement α-LA prevents the formation of cystine stones. Thus this represents a potentially promising therapy for cystine stones. Clinical trials to support the use of those modalities are warranted.

References

1. Saravakos P, Kokkinou V, Giannatos E. Cystinuria: current diagnosis and management. Urology. 2014; 83:693-699.
2. Goodyer P. The molecular basis of cystinuria. Nephron Exp Nephrol. 2004; 98:e45-e49.
3. Thomas K, Wong K, Withington J, Bultitude M, Doherty A. Cystinuria-a urologist's perspective. Nat Rev Urol. 2014; 11:270-277.
4. Knoll T, Zöllner A, Wendt-Nordahl G, Michel MS, Alken P. Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment, and follow-up. Pediatr Nephrol. 2005; 20:19-24.
5. Worcester EM, Coe FL. Nephrolithiasis. Prim Care. 2008; 35:369-391.
6. Andreassen KH, Pedersen KV, Osther SS, Jung HU, Lildal SK, Osther PJ. How should patients with cystine stone disease be evaluated and treated in the twenty-first century? Urolithiasis. 2016; 44:65-76.
7. Buisson P, Haraux E, Hamzy M, Ricard J, Canarelli JP, Booudailliez B, Braun K. Cystinuria in children: A report of 4 cases. Arch Pediatr. 2011; 18:553-557. (In French)
8. Mattoo A, Goldfarb DS. Cystinuria. Semin Nephrol. 2008; 28:181-191.
9. Moe OW, Pearle MS, Sakhaee K. Pharmacotherapy of urolithiasis: evidence from clinical trials. Kidney Int. 2011; 79:385-392.
10. Pietrow P, Auge BK, Weizer AZ, Delvecchio FC,

Silverstein AD, Mathias B, Albala DM, Preminger GM. Durability of the medical management of cystinuria. J Urol. 2003; 169:68-70.

11. Moore SL, Somani BK, Cook P. Journey of a cystinuric patient with a long-term follow-up from a medical stone clinic: necessity to be SaFER (stone and fragments entirely removed). Urolithiasis. 2019; 47:165-170.

12. Eggermann T, Venghaus A, Zerres K. Cystinuria: an inborn cause of urolithiasis. Orphanet J Rare Dis. 2012; 7:19.

13. Sumorok N, Goldfarb DS. Update on cystinuria. Curr Opin Nephrol Hypertens. 2013; 22:427-431.

14. Eggermann T, Zerres K, Nunes V, Font-Llitjós M, Bisceglia L, Chatzikyriakidou A, dello Strologo L, Pras E, Creemers J, Palacin M. Clinical utility gene card for: Cystinuria. Eur J Hum Genet. 2012; 20(2).

15. Jaeken J, Martens K, Francois I, Eyskens F, Lecointre C, Derua R, Meulemans S, Slootstra JW, Waelkens E, de Zegher F, Creemers JW, Matthijs G. Deletion of PREPL, a gene encoding a putative serine oligopeptidase, in patients with hypotonia-cystinuria syndrome. Am J Hum Genet. 2006; 78:38-51.

16. Rosenberg LE, Downing S, Durant JL, Segal S. Cystinuria: biochemical evidence for three genetically distinct diseases. J Clin Invest. 1966; 45:365-371.

17. Font-Llitjós M, Jiménez-Vidal M, Bisceglia L, Di Perna M, de Sanctis L, Rousaud F, Zelante L, Palacín M, Nunes V. New insights into cystinuria: 40 new mutations, genotype-phenotype correlation, and digenic inheritance causing partial phenotype. J Med Genet. 2005; 42:58-68.

18. Dello Strologo L, Pras E, Pontesilli C, *et al*. Comparison between SLC3A1 and SLC7A9 cystinuria patients and carriers: a need for a new classification. J Am Soc Nephrol. 2002; 13:2547-2553.

19. Rhodes HL, Yarram-Smith L, Rice SJ, Tabaksert A, Edwards N, Hartley A, Woodward MN, Smithson SL, Tomson C, Welsh GI, Williams M, Thwaites DT, Sayer JA, Coward RJ. Clinical and genetic analysis of patients with cystinuria in the United Kingdom. Clin J Am Soc Nephrol. 2015; 10:1235-1245.

20. Wong KA, Mein R, Wass M, Flinter F, Pardy C, Bultitude M, Thomas K. The genetic diversity of cystinuria in a UK population of patients. BJU Int. 2015; 116:109-116.

21. Botzenhart E, Vester U, Schmidt C, Hesse A, Halber M, Wagner C, Lang F, Hoyer P, Zerres K, Eggermann T; Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN). Cystinuria in children: distribution and frequencies of mutations in the SLC3A1 and SLC7A9 genes. Kidney Int. 2002; 62:1136-1142.

22. Watanabe Y, Abe Y, Sakamoto S, Morimoto E, Taki Y, Hibino S, Fukagai T, Watanabe S. Pediatric Cystinuria Patient With Novel Mutation in SLC3A1. Glob Pediatr Health. 2019; 6:2333794X19862441.

23. Milliner DS. Cystinuria. Endocrinol Metab Clin North Am. 1990; 19:889-907.

24. Kaniowska E, Chwatko G, Głowacki R, Kubalczyk P, Bald E. Urinary excretion measurement of cysteine and homocysteine in the form of their S-pyridinium derivatives by high-performance liquid chromatography with ultraviolet detection. J Chromatogr A. 1998; 798:27-35.

25. Goldfarb DS, Coe FL, Asplin JR. Urinary cystine excretion and capacity in patients with cystinuria. Kidney Int. 2006; 69:1041-1047.

26. Fjellstedt E, Denneberg T, Jeppsson JO, Christensson A,

Tiselius HG. Cystine analyses of separate day and night urine as a basis for the management of patients with homozygous cystinuria. Urol Res. 2001; 29:303-310.

27. Ahmed K, Dasgupta P, Khan MS. Cystine calculi: challenging group of stones. Postgrad Med J. 2006; 82:799-801.

28. Kim SC, Hatt EK, Lingeman JE, Nadler RB, McAteer JA, Williams JC Jr. Cystine: helical computerized tomography characterization of rough and smooth calculi *in vitro*. J Urol. 2005;174:1468-1470; discussion 1470-1471.

29. Brisbane W, Bailey MR, Sorensen MD. An overview of kidney stone imaging techniques. Nat Rev Urol. 2016; 13:654-662.

30. Edvardsson VO, Goldfarb DS, Lieske JC, Beara-Lasic L, Anglani F, Milliner DS, Palsson R. Hereditary causes of kidney stones and chronic kidney disease. Pediatr Nephrol. 2013; 28:1923-1942.

31. Prot-Bertoye C, Lebbah S, Daudon M, *et al*. CKD and Its Risk Factors among Patients with Cystinuria. Clin J Am Soc Nephrol. 2015; 10:842-851.

32. Nalcacioglu H, Ozden E, Genc G, Yakupoglu YK, Sarikaya S, Ozkaya O. An uncommon cause of acute kidney injury in young children: cystinuria. J Pediatr Urol. 2013; 9:e58-e63.

33. Martens K, Heulens I, Meulemans S, Zaffanello M, Tilstra D, Hes FJ, Rooman R, François I, de Zegher F, Jaeken J, Matthijs G, Creemers JW. Global distribution of the most prevalent deletions causing hypotonia-cystinuria syndrome. Eur J Hum Genet. 2007; 15:1029-1033.

34. Goldstein B, Goldfarb DS. Early Recognition and Management of Rare Kidney Stone Disorders. Urol Nurs. 2017; 37:81-102.

35. Gul Z, Monga M. Medical and dietary therapy for kidney stone prevention. Korean J Urol. 2014; 55:775–779.

36. Johri N, Cooper B, Robertson W, Choong S, Rickards D, Unwin R. An update and practical guide to renal stone management. Nephron Clin Pract. 2010; 116:c159-c171.

37. Prezioso D, Strazzullo P, Lotti T, *et al*. Dietary treatment of urinary risk factors for renal stone formation. A review of CLU Working Group. Arch Ital Urol Androl. 2015; 87:105-120.

38. Norman RW, Manette WA. Dietary restriction of sodium as a means of reducing urinary cystine. J Urol. 1990; 143:1193-1195.

39. Saxena A, Sharma RK. Nutritional aspect of nephrolithiasis. Indian J Urol. 2010; 26:523-530.

40. Heilberg IP, Goldfarb DS. Optimum nutrition for kidney stone disease. Adv Chronic Kidney Dis. 2013; 20:165-174.

41. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, Monga M, Penniston KL, Preminger GM, Turk TM, White JR; American Urological Assocation. Medical management of kidney stones: AUA guideline. J Urol. 2014; 192:316-324.

42. Abou Chakra M, Dellis AE, Papatsoris AG, Moussa M. Established and recent developments in the pharmacological management of urolithiasis: an overview of the current treatment armamentarium. Expert Opin Pharmacother. 2020; 21:85-96.

43. Fjellstedt E, Denneberg T, Jeppsson JO, Tiselius HG. A comparison of the effects of potassium citrate and sodium bicarbonate in the alkalinization of urine in homozygous cystinuria. Urol Res. 2001; 29:295-302.

44. Shekarriz B, Stoller ML. Cystinuria and other noncalcareous calculi. Endocrinol Metab Clin North Am.

2002; 31:951-977.

45. Sterrett SP, Penniston KL, Wolf JS Jr, Nakada SY. Acetazolamide is an effective adjunct for urinary alkalization in patients with uric acid and cystine stone formation recalcitrant to potassium citrate. Urology. 2008; 72:278-281.

46. Sorokin I, Pearle MS. Medical therapy for nephrolithiasis: State of the art. Asian J Urol. 2018; 5:243-255.

47. Chow GK, Streem SB. Medical treatment of cystinuria: results of contemporary clinical practice. J Urol. 1996; 156:1576-1578.

48. Dahlberg PJ, van den Berg CJ, Kurtz SB, Wilson DM, Smith LH. Clinical features and management of cystinuria. Mayo Clin Proc. 1977; 52:533.

49. DeBerardinis RJ, Coughlin CR 2nd, Kaplan P. Penicillamine therapy for pediatric cystinuria: experience from a cohort of American children. J Urol. 2008; 180:2620-2623.

50. Dello Strologo L, Laurenzi C, Legato A, Pastore A. Cystinuria in children and young adults: success of monitoring free-cystine urine levels. Pediatr Nephrol. 2007; 22:1869-1873.

51. Halperin EC, Thier SO, Rosenberg LE. The use of D-penicillamine in cystinuria: efficacy and untoward reactions. Yale J Biol Med. 1981; 54:439-446.

52. Ishak R, Abbas O. Penicillamine revisited: historic overview and review of the clinical uses and cutaneous adverse effects. Am J Clin Dermatol. 2013; 14:223-233.

53. Yao XY, Wen GD, Zhou C, Liu BY, Du J, Chen Z, Zhang JZ. D-penicillamine-induced Elastosis Perforans Serpiginosa. Chin Med J (Engl). 2017; 130:2013-2014.

54. Koide T, Kinoshita K, Takemoto M, Yachiku S, Sonoda T. Conservative treatment of cystine calculi: effect of oral alpha-mercaptopropionylglycine on cystine stone dissolution and on prevention of stone recurrence. J Urol. 1982; 128:513-516.

55. Pak CY, Fuller C, Sakhaee K, Zerwekh JE, Adams BV. Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. J Urol. 1986; 136:1003-1008.

56. Koide T, Yoshioka T, Miyake O, Okuyama A, Yachiku S. Long-term study of tiopronin in patients with cystinuria.. Hinyokika Kiyo. 2003; 49:115-120. (in Japanese)

57. Giannakopoulos X, Kalfakakou V, Tsoumanis P, Karkabounas S, Giannakis D, Chambilomatis P, Evangelou A, Kallistratos G. Results of treatment of cystinuria and cystine lithiasis with alpha-mercaptopropionylglycine. Apropos of 40 patients. J Urol (Paris). 1994; 100:129134. (in French)

58. Dolin DJ, Asplin JR, Flagel L, Grasso M, Goldfarb DS. Effect of cystine-binding thiol drugs on urinary cystine capacity in patients with cystinuria. J Endourol. 2005; 19:429-432.

59. Thiola [package insert on the internet] Mission Pharmacal Company; San Antonio, TX: 2018. http://www.retrophin.com/pdf/Thiola%20PI.pdf (accessed 1 July 2018).

60. Sloand JA, Izzo JL Jr. Captopril reduces urinary cystine excretion in cystinuria. Arch Intern Med. 1987; 147:1409-1412.

61. Perazella MA, Buller GK. Successful treatment of cystinuria with captopril. Am J Kidney Dis. 1993; 21:504-507.

62. Cohen TD, Streem SB, Hall P. Clinical effect of captopril on the formation and growth of cystine calculi. J Urol. 1995; 154:164-166.

63. Weigert A, Hoppe B. Nephrolithiasis and nephrocalcinosis in childhood-risk factor-related current and future treatment options. Front Pediatr. 2018; 6:98.

64. Rimer JD, An Z, Zhu Z, Lee MH, Goldfarb DS, Wesson JA, Ward MD. Crystal growth inhibitors for the prevention of L-cystine kidney stones through molecular design. Science. 2010; 330:337-341.

65. Lee MH, Sahota A, Ward MD, Goldfarb DS. Cystine growth inhibition through molecular mimicry: a new paradigm for the prevention of crystal diseases. Curr Rheumatol Rep. 2015; 17:33.

66. Sahota A, Parihar JS, Capaccione KM, Yang M, Noll K, Gordon D, Reimer D, Yang I, Buckley BT, Polunas M, Reuhl KR, Lewis MR, Ward MD, Goldfarb DS, Tischfield JA. Novel cystine ester mimics for the treatment of cystinuria-induced urolithiasis in a knockout mouse model. Urology. 2014; 84:1249.e9-15.

67. Yang Y, Albanyan H, Lee S, Aloysius H, Liang JJ, Kholodovych V, Sahota A, Hu L. Design, synthesis, and evaluation of l-cystine diamides as l-cystine crystallization inhibitors for cystinuria. Bioorg Med Chem Lett. 2018; 28:1303-1308.

68. Moran A, Ben-Nun A, Potashnik R, Bashan N. Renal cells in culture as a model for cystinosis. J Basic Clin Physiol Pharmacol. 1990; 1:357-372.

69. Zee T, Bose N, Zee J, *et al*. α-Lipoic acid treatment prevents cystine urolithiasis in a mouse model of cystinuria. Nat Med. 2017; 23:288-290.

70. Thoma C. Stones: Cystinuria - supplement supports solubilization. Nat Rev Urol. 2017; 14:324.

71. de Boer H, Roelofsen A, Janssens PM. Antidiuretic hormone antagonist to reduce cystine stone formation. Ann Intern Med. 2012; 157:459-460.

72. Bai Y, Tang Y, Wang J, Wang X, Wang Z, Cao D, Han P, Wang J. Tolvaptan treatment of cystine urolithiasis in a mouse model of cystinuria. World J Urol. 2020; doi:10.1007/s00345-020-03166-3.

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