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REVIEW

Alpha lipoic acid as a novel therapeutic approach to cystinuria

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ABSTRACT

Introduction: Cystinuria is a rare form of kidney stone disease inherited through mutations in the cystine transporter genes SLC3A1 and SLC7A9. Patients suffer from frequent and painful renal cystine calculus formation necessitating repeated radiation exposure, hospitalizations and surgical interventions. Available dietary and pharmacologic managements are burdensome to patients due to the sheer volume of pills and fluid that must be consumed and display limited efficacy.

Areas Covered: The epidemiology, pathophysiology, and currently available options for dietary and pharmacological management including hyperhydration, modification of urinary pH, organosulfur drugs and crystal Inhibitors are reviewed. A novel drug in clinical trials, alpha lipoic acid (ALA), is presented and its hypothesized mechanism of action reviewed.

Expert Opinion: A novel potential therapy, alpha lipoic acid, has been strikingly effective when used in a knockout mouse model. This compound is available over the counter as a food supplement, has been used in multiple human trials for other disease processes and has been shown to be safe and well tolerated. The promise of ALA is to reduce the burden of medications, stone events, surgical interventions, and financial concerns in cystinuric patients.

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1. Introduction

Cystinuria is a genetic condition with varying degrees of penetrance affecting approximately 1 in 15,000 individuals in the United States (US), caused by over 160 identified mutations in the SLC3A1 gene and the SLC7A9 gene [1]. When considering all types of kidney stones (which affect about 1 in 11 individuals in the US), cystine stones formers represent less than 1% of stone forming adults and 6–7% of stone forming children [2–4]. Patients affected by cystinuria can experience recurrent, painful, episodes of kidney stone passage as well as the development of stones within the parenchyma of the kidney—both of which can lead to progressive renal functional deterioration and potentially hypertension [5,6]. These episodes may occur in clusters between prolonged quiescent periods without symptomatic stone disease [7].

The disorder is the result of mutation in the *SLC3A1* or *SLC7A9* genes, which are expressed in the proximal renal tubular cells and encode for the two subunits of a low affinity, high capacity cystine transporter that reabsorbs the dibasic amino acids, cystine, lysine, arginine, and ornithine from the urine [8–10]. *SLC3A1* encodes a basic amino acid transport protein called rBAT, while *SLC7A9* encodes the smaller functional unit $b^{0,+}$AT, which is responsible for the transport of neutral and dibasic amino acids [11]. Cystinuria is classified based on the type of mutation present: patients with type A cystinuria have mutations in both genes encoding *SCL3A1*, while patients with type A cystinuria have mutations in both *SCL7A9* genes. A rare subset of patients (type *AB*) have one mutation in each gene [11]. As the cystine molecules are unable to be reabsorbed, they concentrate in the urine until reaching saturation, at which point crystallization begins. Typically, human urinary pH (pH 5.85) lies below that which cystine is highly soluble (above 8.0), which promotes rapid growth from cystine molecules to macroscopic stones [12,13].

The rate, frequency, and severity of cystine calculus formation in affected patients is typically such that recurrent, painful episodes necessitate repeated hospitalizations and surgical interventions [14]. Historically, surgical/monitoring approaches have been hampered by the poor visualization of calcium-poor, relatively radiolucent, cystine stones on plain film X-ray and their hardness which limits the effectiveness of shockwave lithotripsy. Furthermore, the poor visualization of the stones on plain-film often necessitates alternative imaging modalities, such as computed tomography, thus repeatedly exposing patients to higher radiation doses, which is of particular concern in the pediatric population who are at increased risk for radiation induced malignancy [15,16]. In addition to the imprecise nature of non-CT (ultrasound or abdominal x-ray) based imaging for cystine stones, the frequent, painful, recurrence and rare nature of this genetic disease also promote higher diagnostic radiation exposures by emergency room providers who have limited experience with cystinuric patients.

Given these challenges, the goal of management, based on presently available therapeutics, is often not to render the patient completely free of all stones, but to limit the frequency and severity of stone passage episodes while preventing renal deterioration. This can be accomplished through a number of

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Article Highlights

- Cystinuria is a rare kidney stone disease caused by autosomal mutations in cystine transporter genes SLC3A1 and SLC7A9.
- Available therapies (hyperhydration, urinary pH modification, tiopronin, and penicillamine) are burdensome and display limited efficacy.
- Alpha Lipoic Acid is a safe and well tolerated food supplement that has been remarkably effective in a mouse model of cystinuria. This compound is currently in human clinical trials.

This box summarizes key points contained in the article.

interventions, including surgical, medical, and dietary management. Hyper-hydration is the mainstay of dietary modification, with patients counselled to consume sufficient fluid to produce 3–4 l of urine daily, along with urine alkalization and a low salt, low animal protein diet [13,17–22]. In order to maintain such a high urine output, up to 5 l a day of fluid must be consumed with a similarly burdensome number of pills (up to 6 tablets of K-citrate and up to 10 tablets of α-mercaptopropionylglycine taken 3–4 times daily) in many cases [23]. The patient often reports that significant portions of the day are consumed by seeking out water, restrooms, and stopping to consume pills, to the detriment of their personal and professional lives as well as causing difficulty with sleep. Studies have shown that in order to increase compliance with these demanding therapies, patients can be enrolled in a dedicated stone clinic with frequent (and potentially time consuming) follow-up visits [24].

2. Pharmacological management

2.1. Urine pH

Modification of urinary pH is a critical component in the pharmacological management of cystinuria [12,13,21,22]. With a pKa of 8.3, cystine is readily able to precipitate at a normal urine pH (5.70–5.85). Cystine solubility is a mere 300 mg/L at a pH of 6.0, while at a pH of 8.0, 800–1200mg/L of cystine is soluble [12]. Potassium citrate is the mainstay of such acid-base modification strategies, formulated as 6–9 large tablets divided in three daily doses, or a foul-tasting pharmacologic formulation. Sodium bicarbonate is not recommended for urinary alkalization as the added sodium load will result in an increase in urinary cystine levels [25]. Practically speaking, attaining a goal urinary pH of >7.5 poses a significant challenge not only due to the enormous medication burden, but also because at this pH there is a small but real risk of apatite (calcium phosphate) and struvite (magnesium-ammonium-phosphate) stone formation. Follow up in this setting is additionally burdensome due to the requirement to collect urine over a 24-hour period in order to assess quantitative urinary calcium, oxalate, citrate, uric acid, pH, and sodium.

2.2. Organosulfur drugs and crystal inhibitors

D-penicillamine and α-mercaptopropionylglycine are two currently available organosulfur drugs, which target and competitively bind cysteine. A disulfide bond is formed between the cysteine monomer and the drug, as opposed to forming an insoluble cystine dimer. D-penicillamine is modestly effective, at best, and is frequently associated with the side effects of nephrotic syndrome, dermatitis, and pancytopenia [26–29]. α-mercaptopropionylglycine acts via a sulfhydryl group that has binding affinity for cysteine to produce a similar solubilizing effect, and seems to be more well tolerated by patients than D-penicillamine (64.7% with side effects compared with 83.7% on D-penicillamine) [30]. The durability of remission and the overall efficacy of these drugs, however, remain poor [7,31].

To better address this need for a well-tolerated and efficacious therapy for cystinuria, several novel therapeutics are under development. An L-cystine dimethyl ester (L-CDME) and L-cystine methyl ester (L-CME) act to alter crystal growth *in vitro* and decrease crystal growth velocity [32] When studied in a *Slc3a1* knockout mouse model, however, L-CDME was found to reduce the size but increase the number of cystine stones [33]. Captopril, an angiotensin-converting enzyme inhibitor, was thought to inhibit cystine crystallization in the urine, however is presently not recommended by AUA guidelines as it does not result in meaningful reductions in cystine stone formation over time, likely due to poor urinary excretion [22,34].To date, no drugs have been shown to be safe, effective, and to have few side-effects in humans.

2.3. Alpha lipoic acid

Alpha lipoic acid (ALA) is an over the counter supplement with anti-oxidant properties that previously has been studied in humans with diabetes mellitus, obesity, Alzheimer's dementia and a in mouse model of cystinuria [35–39]. Bioavailable lipoic acid comes from endogenous biosynthesis using octanoic acid within the mitochondria and dietary intake through lysine bound lipoyllysine [40,41]. While dietary intake has not been shown to increase free levels of ALA in the blood, 30–40% of orally dosed ALA is absorbed in pharmacokinetic studies [40]. Absorption occurs best on an empty stomach; when compared with fasting, food intake will decrease peak plasma ALA concentrations by approximately 30% and total plasma concentrations by 20%. Metabolism occurs via reduction to dihydrolipoic acid (DHLA).

Within the body, ALA acts as a cofactor to mitochondrial enzymes involved in catabolism of α-keto acids and amino acids, modulates signal transduction cascades (including protein kinase B/Akt, insulin, and redox transcription factors NF-kB and Nrf2), and is a direct and indirect antioxidant [42,43]. Antioxidant properties are manifest through the scavenging of reactive oxygen and nitrogen species, regeneration of other antioxidants (glutathione synthesis) and redox-active metal chelation. Studies in *Caenorhabditis elegans* support this antioxidant effect and have shown increased thermal stress resistance and lifespan with ALA supplementation [44].

In human studies, ALA has been evaluated as a pharmacologic means to improve glucose utilization in diabetic patients and manage peripheral neuropathy [42,43,45]. A placebo-controlled, multicenter pilot study of ALA performed by Jacob et al. compared 74 patients randomized to placebo, once, twice, or three times daily ALA [46]. The authors found that insulin-stimulated glucose disposal improved by 27% ($p < 0.01$) compared to placebo with infusion of lipoic acid.

ALA is also hypothesized to improve vascular function in diabetics and those with the metabolic syndrome [47,48] and randomized controlled trials suggest that intravenous ALA over a period of three weeks results in improvements in diabetic neuropathy [35,49]. As a result, ALA has seen use in patients with diabetic neuropathy who are refractory to traditional antidepressant treatments.

Additional studies support a role in neurodegenerative diseases [36,50], and safety over 4 years was established in the NATHAN 1 trial [51]. ALA appears to be well tolerated at doses of up to 1,200 mg daily [35,47]. As it relates to the treatment of cystinuria, ALA or its derivative compound dihydrolipoic acid may reduce insoluble cystine in a direct fashion by forming a mixed-disulfide compound [52]. Lipoic acid also appears to reduce levels of zinc [53] and other potential stone forming co-factor metals in the kidney [54].

ALA has been found to be safe and effective when used in the pediatric population. When given alongside an antioxidant-rich diet, ALA was shown to significantly reduce endothelial dysfunction among adolescents with type I diabetes [55]. In this study the only reported side effect was mild abdominal pain which did not result in discontinuation of ALA. Another study reported no adverse events in the pediatric population but no significant effect on oxidative damage [56].

In a novel approach, ALA has recently been evaluated in the treatment of cystinuria in a *Slc3a1* knockout mouse strain, as well as a *Slc7a9* knockout strain [39]. These mice manifest cystinuria not as renal stones, but due to anatomic constraints the crystals tend to aggregate in the bladder, resulting in a fatal phenotype from bladder outlet obstruction which can be characterized by *in vivo* micro-computed tomography (micro-CT) [52,57,58]. As early as 2 months of age, the male *Slc3a1-/-* and *Slc7a9-/-* cystinuric mice will accumulate cystine bladder stones that progressively increase in size [52,58]. This growth occurs in a linear fashion at a rate of approximately 1 mm^3/day [39].

Several molecules were tested by Zee *et al*. prior to ALA, including L-CDME and α-mercaptopropionylglycine, both of which showed little action in reducing cystine stone burden in these mice [39]. Sulforaphane, an activator of Nrf2 and key transcription factor in the antioxidant response [59], did show modest activity in inhibiting stone formation [39]. Given the association between oxidative stress and stone formation [60,61] and the role of ALA in oxidative stress, Nrf2 activation, and metal chelation [41–43], ALA was chosen by Zee et al. as a candidate therapy in these knockout mice.

In the study, Zee et al. began by treating 4–7-week-old *Slc3a1-/-* mice with ALA administered in the diet at 0.5% by weight. At day 45 of treatment, 1 of 8 treatment mice compared with 7 of 7 control diet mice had developed cystine bladder stones. Furthermore, the growth rate of the calculi (as measured by micro-CT) that did develop was found to be significantly lower. When ALA was withdrawn, the stone growth rate matched the control mice and when ALA was resumed, the rate returned to the slower rate. A dose response also was observed between dietary formulations, containing 0.5%, 0.25% or 0.1% ALA by weight, where decreased stone growth was observed with higher doses of lipoic acid. The ALA cohort of mice did not have increased fluid intake or decreased caloric intake compared to controls.

To assess the pharmacodynamic mechanism, Zee et al. assessed urinary cystine levels, and found no significant differences between control and treatment groups, suggesting that ALA or its metabolite, dihydrolipoic acid, do not affect cysteine dimerization (the mechanism of organosulfur drugs) or by cysteine chelation. A mechanistic relationship to Nrf2, however, was not demonstrated as *Slc3a1−/−; Nrf2−/−* mice responded to ALA similarly to *Slc3a1-/-* mice. Solubility assays showed significantly increased urine cysteine solubility after oral administration of ALA, but not when ALA was directly added to urine *in vitro*, suggesting an active metabolite was likely responsible.

In this study, ALA showed robust, reproducible, and striking effects in the inhibition of cystine stone formation without significant adverse effects, alterations in urinary pH, feeding behavior, body weight, or activity level. ALA was not only able to prevent the formation of new stones, but also prevented existing stones from growing in a mouse model of cystinuria. These results have formed the basis of a phase 2, randomized placebo-controlled trial (clinicaltrials.gov identifier: NCT02910531).

3. Conclusions

Cystinuria is a rare genetic disorder that results in recurrent, debilitating kidney stone episodes. Cystine is a dimer of two cysteine molecules that is poorly soluble at typical urinary pH (5–7) and rapidly crystalizes. Traditional management strategies rely on extremely high fluid intake (up to 5L daily), dietary management, altering urine pH to increase cystine solubility and competitive binding of cysteine molecules to form more soluble dimers. These treatments are poorly tolerated and require significant lifestyle modification for affected patients. Surgical treatments tend to be more frequent, more invasive, and less effective for affected patients due to the radiographic (poorly visible) and physical characteristics (difficult to break) of cystine stones.

Alpha Lipoic Acid recently has been described as a potential novel therapeutic intervention for cystinuria and is presently the subject of a phase 2, randomized placebo-controlled trial (Table 1, clinicaltrials.gov identifier: NCT02910531) in adult patients. The mechanism appears to be through a metabolic product of ALA and results in markedly increased cystine solubility. The effect was potent, reproducible, and showed a dose response in a mouse model.

4. Expert opinion

Cystinuria patients have a much higher rate of recurrence and need for surgical intervention than calcium-based stone formers. For the past 30+ years they have had only a few medications with questionable short- and long-term efficacy available to them. Cystinuric patients and their families face a substantial pharmaceutical and financial burden. They are faced with recurring painful stone episodes, often from a very early age, and display heroic individual efforts in an attempt at stone prevention. Patients often ingest more than a dozen tablets per day with limited results at stone prevention. Many patients do not feel that such exhaustive regimens are

Table 1. Registered clinical trials for cystinuria in recruitment.

Title	Study designs	Interventions	Outcome measures	NCT number	Start Date	Completion	Enrollment
TCUPS- Tolvaptan Use in Cyctinuria and Urolithiasis: A Pilot Study	Non-Randomized Open Label Therapy	Drug: Tolvaptan	Safety Tolerability Urinary Parameters	NCT02538016	10/1/2016	12/1/2019	8
Lipoic Acid Supplement for Cystine Stone	Quadruple-blind randomized placebo-controlled trial	Dietary Supplement: Alpha lipoic acid	Recurrence Urinary cystine	NCT02910531	6/19/2017	5/1/2022	50
Rare Kidney Stone Consortium Biobank	Prospective Observational		Tissue Storage	NCT02026388	5/1/2013	6/1/2020	400
Rare Kidney Stone Consortium Patient Registry	Prospective Observational Cohort		Organizational Collaborative Understanding	NCT00588562	7/1/2003	6/1/2019	730
Health-related Quality of Life in Rare Kidney Stone	Prospective Observational Cohort	Questionnaire	Survey	NCT02124395	8/1/2013	9/1/2018	320
Prospective Research Rare Kidney Stones (ProRKS)	Prospective Observational Cohort		Blood Markers Urinary biomarkers Renal Function	NCT02780297	5/1/2016	7/1/2024	220
Monogenic Kidney Stone—Genetic Testing	Prospective Observational Cohort		Symptom Onset Genotype Markers	NCT03305835	9/11/2017	12/1/2020	2300

successful—they express a strong desire for pharmaceutical options with better efficacy, less dosing frequency, and fewer side effects. As a result, many patients simply stop taking these medications. Our collective goal as researchers on this orphan disease should be to provide a better option with few side effects, heightened efficacy, and a chance at a normal life.

At our institution, we have developed a novel potential therapy, alpha lipoic acid, using a knockout mouse model. This compound has been used in multiple human trials for other disease processes and has been shown to be safe and well tolerated. Furthermore, alpha lipoic acid is classified as a food supplement and is available at a low cost, over the counter, in the United States. The dramatic findings in our mouse model have prompted us to begin a clinical trial despite limited interest from pharmaceutical companies, who have expressed profitability concerns using this generic food supplement. Over the course of this ongoing trial, we will continue to undertake a comprehensive analysis of metabolomic, metallomic, and urine solubility measurements, which will help to elucidate potential predictive biomarkers for stone risk and help to titrate medications.

If the striking results of the mouse model studies are recapitulated in humans, the potential benefit to cystinuric patients will be tremendous. This group of patients has seen no significant pharmaceutical breakthroughs over the past 30 years. The promise of ALA is to reduce the burden of medications, stone events, surgical interventions, and financial concerns in cystinuric patients.

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Declaration of interest

MLS is a founding member of Applaud Medical. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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