α-Lipoic Acid (ALA) Improves Cystine Solubility in Cystinuria: Report of 2 Cases

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Cystinuria is an autosomal recessive disorder characterized by excessive urinary excretion of cystine, resulting in recurrent cystine kidney stones, often presenting in childhood. Current treatment options for cystinuria include dietary and/or fluid measures and potassium citrate to reduce cystine excretion and/or increase solubility. Tiopronin and D-penicillamine are used in refractory cases to bind cystine in urine, albeit with serious side effects. A recent study revealed efficacy of nutritional supplement α-lipoic acid (ALA) treatment in preventing kidney stones in a mouse model of cystinuria. Here, we report 2 pediatric patients (6 and 15 years old) with cystinuria who received regular doses of ALA in addition to conventional therapy with potassium citrate. Both patients tolerated ALA without any adverse effects and had reduced frequency of symptomatic and asymptomatic kidney stones with disappearance of existing kidney stones in 1 patient after 2 months of ALA therapy. ALA treatment markedly improved laboratory markers of cystine solubility in urine with increased cystine capacity (−223 to −1 mg/L in patient 1 and +140 to +272 mg/L in patient 2) and decreased cystine supersaturation (1.7 to 0.88 in patient 1 and 0.64 to 0.48 in patient 2) without any changes in cystine excretion or urine pH. Our findings suggest that ALA improves solubility of cystine in urine and prevents stone formation in patients with cystinuria who do not respond to diet and citrate therapy.
α-lipoic acid (ALA) is a dietary supplement commonly used in diabetic neuropathy for its antioxidant effects. In a recent study, authors reported efficacy of ALA (dose equivalent to ~40 mg/kg per day in humans) in preventing stone formation in a mouse model of cystinuria. Here, we report use of ALA supplementation in 2 pediatric patients with cystinuria and demonstrate its efficacy in improving key urine markers of cystine solubility (cystine supersaturation and capacity).

Urine tests for cystine solubility were performed by Litholink Corporation (Chicago, IL) as part of routine clinical care. Patients used 300- or 600-mg ALA capsules manufactured by Natrol LLC (Los Angeles, CA).

CASE REPORT

Patient 1
A 6-year-old girl with a history of recurrent intermittent abdominal pain since 3 years of age was diagnosed with nephrolithiasis by renal ultrasound that revealed a 4-mm left ureterovesical junction stone with moderate hydroureteronephrosis. She subsequently passed a 4-mm stone that was confirmed to be composed of cystine by stone analysis and was referred to the comprehensive pediatric kidney stone center at the University of California, San Francisco. Her initial 24-hour urine collection revealed low urine volume (0.75 L), high cystine excretion (408 mg per day), high cystine supersaturation (1.7) and low cystine capacity (−223 mg/L) with a pH of 7.44 (goal >7.0), and normal urinary calcium and citrate excretions (Table 1). She was diagnosed with cystinuria and recommended to increase fluid and limit sodium intake. Her follow-up 24-hour urine collection after 5 months revealed hypercalciuria (7.9 mg/kg per day) with a lower urine pH (7.2), and she was started on potassium citrate (0.5 mEq/kg BID [twice daily]). Despite increased urine volume (1.1–1.3 L) and slightly higher urine pH (7.4) with citrate therapy, her cystine supersaturation and capacity remained unchanged in subsequent urine analyses. She continued to have intermittent abdominal pain with no stones detected on repeat ultrasound. She was started on ALA supplementation (300 mg daily; 17 mg/kg per day or ~400 mg/m² per day) and continued using potassium citrate. After 1 month of ALA treatment, there were substantial improvements in urine cystine capacity (from −222 to −62 mg/L) and cystine supersaturation (from 1.7 to 1.0). Her ALA dose was increased to 300 mg BID (34 mg/kg per day or ~800 mg/m² per day), and she started drinking more water motivated by the improvement in urine tests. Her most recent 24-hour urine analysis revealed further improvements in cystine supersaturation (0.88) and capacity (−1 mg/L). She reported no adverse events with this therapy. During the 11-month follow-up after starting ALA, her episodes of abdominal pain completely resolved and her surveillance ultrasounds have not revealed any stones.

Patient 2
A 15-year-old girl developed severe abdominal pain, and renal ultrasound revealed a large right kidney staghorn calculus and additional multiple stones bilaterally. She underwent percutaneous nephrolithotomy of the right kidney and started potassium citrate (10 mEq BID). Her stone was predominantly composed of cystine, and she was diagnosed with cystinuria. She initially had low urine volume (1.5 L per day) and continued using potassium citrate (10 mEq BID) with a lower urine pH (7.5), normal urinary calcium (1.3 mg/kg per day), and low citrate excretion (307 mg/g creatinine); however, the cystine parameters were not studied (Table 1). Potassium citrate was increased to 45 mEq 3 times per day, and high fluid and low sodium intake was recommended. Repeat 24-hour urine collection revealed improved urine volume (4.5 L), higher urine pH (8.0) and citrate excretion (805 mg/g creatinine) with high cystine excretion (628 mg per day), normal cystine supersaturation (0.35), and normal cystine capacity (+290 mg/L). Potassium citrate was decreased to 45 mEq BID to reduce alkalization of urine to avoid calcium phosphate stone formation; however, on this dose, normal levels could not be maintained for cystine supersaturation (increased from 0.35 to 0.64) and cystine capacity (decreased from +290 to +140 mg/L). Despite tripling her urine volume (1.5–4.5 L) and increasing urine pH, she continued to have significant stone burden requiring another percutaneous nephrolithotomy. She was deemed stone free at the end of surgery, but she reported passing multiple stones 3 months later despite good compliance. An ultrasound revealed new stones bilaterally (3 stones up to 9 mm in the right kidney with mild hydronephrosis and one 4 mm stone in the left kidney). ALA therapy (600 mg BID; 25 mg/kg per day or 840 mg/m² per day) was initiated, and after 1 month of treatment, urine cystine capacity almost doubled (from +140 to +272 mg/L) and cystine supersaturation decreased (from 0.64 to 0.48) despite having lower urine volume (1.9 L); her potassium citrate dose was further decreased to 30 mEq BID. An ultrasound performed 2 months after initiating ALA therapy revealed only a 3-mm right nephrolith with resolution of hydronephrosis. During the 5-month follow-up period, she reported not passing any kidney stones, suggesting that ALA may have helped dissolution of existing cystine stones; however, asymptomatic passage of stones could not be ruled out.
DISCUSSION

ALA is a nutritional supplement with a good safety profile. A 50% lethal dose of ALA is >2000 mg/kg in rats. In animal studies, mild elevations in liver enzymes were seen at very high ALA doses, and no significant toxicity was found after 24 months of treatment at lower doses. In humans, the side effects of ALA are well documented in clinical trials for diabetic neuropathy. The most commonly observed adverse effect was dose-dependent nausea, which affected 13% at 600 mg per day, 21% at 1200 mg per day, and 48% at 1800 mg per day. Vomiting and vertigo affected <5% of patients at 1200 mg per day. Our patients in this report were treated with ALA at 600 to 1200 mg per day (on the basis of the mouse dose in ref 9) and did not manifest any nausea, vomiting, or vertigo. We monitored liver enzymes, serum creatinine, electrolytes, and hematologic indices in both patients after 3 to 7 months of ALA treatment, which were within normal range. Our findings are consistent with earlier studies revealing a good safety profile for ALA in humans at this dosage.

The American Urological Association guidelines recommend the following for medical management of cystine stones: increase fluid intake (usually >4 L), dietary sodium and protein restriction, and urine alkalinization (pH >7.0) with potassium citrate. In patients unresponsive to these measures, the American Urological Association recommends using cystine-binding drugs. Serial 24-hour urine tests are recommended to monitor urine volume, pH, cystine excretion, cystine supersaturation, and cystine capacity. Cystine supersaturation is a marker of cystine crystallization; it involves the measurement of cystine concentration in urine before and after incubation with cystine crystals and is calculated as the cystine concentration at baseline divided by the cystine concentration after incubation. Supersaturation values <1.0 (suggesting urine is undersaturated) are desired in patients with cystinuria. In patients using cystine-binding drugs, cystine concentration and supersaturation become unreliable because of the chemical interactions with cystine. Cystine capacity is another parameter not affected by

<table>
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<th>Treatment</th>
<th>Urine Volume, L/d</th>
<th>Urine pH</th>
<th>Cystine Excretion, mg/d</th>
<th>Cystine Supersaturation</th>
<th>Cystine Capacity, mg/L</th>
<th>Cystine Excretion, mg/kg per d</th>
<th>Calcium Excretion, mg/kg per d</th>
<th>Citrate Excretion, mg/g Creatinine</th>
<th>PCR, g/kg per d</th>
<th>Sodium Excretion, mmol/d</th>
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<tbody>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>0.75</td>
<td>7.44</td>
<td>408</td>
<td>1.7</td>
<td>-223</td>
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<td>464</td>
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<td>8.1</td>
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<td>0.35</td>
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<td>805</td>
<td>1.0</td>
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<td>0.47</td>
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<td>7.98</td>
<td>545</td>
<td>0.48</td>
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<td>18.9</td>
<td>0.7</td>
<td>664</td>
<td>0.7</td>
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</table>

Treatment goals for cystinuria are cystine concentration <250 mg/L, urine pH >7.0. n/a, not available.
cystine-binding drugs, and positive values are desired to prevent cystine stones.\textsuperscript{15} For capacity measurement, a known amount of solid cystine is added to the patient’s urine, and after incubation, solid cystine is recovered and quantified to compare to the original cystine quantity. In supersaturated urine, cystine further precipitates onto added crystals, and recovered solid cystine is greater than the added amount (i.e., negative cystine capacity). In undersaturated urine, the added solid cystine partially dissolves; thus, recovered solid cystine is less than the added amount (i.e., positive cystine capacity).\textsuperscript{16} As seen in Table 1, patient 1 had high cystine crystallization in her urine as suggested by high cystine supersaturation (1.7) and low cystine capacity (−223 mg/L). Despite dietary measures, increased fluid intake, and urine alkalization, these parameters remained unchanged. After ALA initiation, cystine supersaturation decreased to 1.09 and capacity increased to −62 mg/L with further improvements in cystine supersaturation (<0.9) and capacity (almost 0) with increased ALA dose and higher fluid intake. In patient 2, cystine supersaturation decreased from 0.64 to 0.48 and capacity increased from +140 to +272 mg/L with ALA treatment despite lower urine volume (∼2 L); in the past, she could achieve similar supersaturation and capacity values with only high urine volumes (∼4.5 L). Of note, variability in creatinine, cystine and sodium excretions, urine pH (despite citrate therapy), and protein catabolic rate (PCR) is a limitation of our study likely due to variations in urine collections and diet. For instance, patient 1 had a high PCR throughout the observation period, suggesting high dietary protein intake, which can increase urinary cystine and calcium excretion. In addition, daily urine volumes were variable in both patients likely because of variations in collections (overcollection or undercollection, as suggested by varying creatinine excretions) and/or variability in fluid intake. However, these are well-known common limitations of 24-hour urine collections in both adults and children,\textsuperscript{17,18} and the collection days do not exactly reflect daily habits. Accurate urine collections are more challenging in children and adolescents because of school attendance and other factors. Despite these limitations, our results suggest therapeutic efficacy of ALA in both patients. Our patients had no recurrence of stones on follow-up imaging, with potential resolution of existing stones in one patient, and had resolution of their symptoms, but clinical trials with larger number of patients are warranted to systematically assess efficacy of ALA on urinary biochemical indices and stone recurrence. Such a trial is ongoing in adult (≥18 years) patients with cystinuria (www.clinicaltrials.gov [identifier: NCT02910531]). We believe our report will open the way to start formal clinical trials for testing ALA in pediatric patients with cystinuria, which is an important problem in children because cystinuria often manifests in childhood (the mean age at first kidney stone detection is 13 years).\textsuperscript{19}

The mechanism of action of ALA in cystinuria remains unknown. In the mouse study, ALA treatment did not affect urine pH or cystine excretion; however, the solubility of cystine was markedly increased in the urine of ALA-treated mice,\textsuperscript{9} similar to our patients. Interestingly, when ALA was directly added to mouse urine, it did not affect cystine solubility, suggesting the effect observed in the mouse model was not due to direct action of ALA but likely due to the metabolite(s) of ALA, which is yet to be determined.

**CONCLUSIONS**

We showed that ALA supplementation markedly improves the urinary markers of cystine solubility in 2 pediatric patients with cystinuria with no associated adverse effects. Considering its safety profile, clinicians may consider ALA supplementation in patients refractory to conventional therapy and potentially avoid using cystine-binding drugs that are associated with serious side effects.

**ABBREVIATIONS**

ALA: α-lipoic acid  
BID: twice daily  
PCR: protein catabolic rate

**REFERENCES**

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