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STONES

Cystinuria — supplement supports solubilization

Treatment of mice with cystinuria using the nutritional supplement α-lipoic acid (α-LA) prevents the formation of cystine stones by increasing urinary cystine solubility, according to new research published in *Nature Medicine*.

Cystinuria is a rare disease caused by mutations in *SLC3A1* and/or *SLC7A9*, resulting in reduced reabsorption of cystine in the kidneys and recurrent calculi formation. "Few new treatments for cystinuria have been developed in the past decades and current interventions aimed at reducing cystine excretion are insufficient at giving patients relief," explains Tiffany Zee from the University of California San Francisco, first author of the new study. "We had noticed that, above a certain threshold, there is very little correlation between urinary cystine excretion and the number of stone episodes, so we knew that targeting cystine concentration is not enough."

> … the team observed that cystine was considerably more soluble in the urine of α-LA-treated mice …

The team used *Slc3a1*$^{-/-}$ mice to identify new agents that inhibit stone formation. Using micro-CT, they determined that the average stone growth rate (SGR) in *Slc3a1*$^{-/-}$ mice without treatment was 1 mm^3/day. Treatment with tiopronin or L-cystine dimethylester, which have previously shown effectiveness, had no significant effect on SGR in this model. By contrast, oral supplementation of α-LA as 0.5% of the mice's diet resulted in significantly delayed stone formation, lower stone volume and fewer stones. "Micro-CT was the quantitative basis to evaluate interventions, but the effects of α-LA were so apparent that we did not need much quantification to see the difference between the treated and nontreated mice," remarks Zee.

When α-LA was withdrawn from the diet, SGR reversed to the initial level, indicating that continuous α-LA treatment was required for inhibition of stone formation. Treatment with reduced α-LA doses was still effective, but significantly less than the 0.5% dose, which is equivalent to ~2.7 g/day in a 67 kg human. Doses of 0.6–1.8 g/day did not cause major adverse reactions in previous clinical trials.

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, the team observed that cystine was considerably more soluble in the urine of α-LA-treated mice than in that of untreated mice. However, α-LA itself did not alter cystine solubility, indicating that α-LA did not affect cystine precipitation and that α-LA-derived urinary metabolites prevented cystine stone formation in this mouse model. "Unlike current treatments for cystinuria, α-LA treatment does not dilute cystine or increase urinary pH, which has its own adverse effects, but prevents cystine from precipitating," summarizes Zee. "We are currently recruiting patients with cystinuria for a clinical trial of α-LA treatment. Concurrently, we are identifying exactly which of the urinary metabolites prevent cystine stone formation with the aim of creating an effective and safe intervention for cystinuria."

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ORIGINAL ARTICLE Zee, T. *et al.* α-Lipoic acid treatment prevents cystine urolithiasis in a mouse model of cystinuria. *Nat. Med.* http://dx.doi.org/10.1038/nm.4280 (2017)
FURTHER READING Thomas, K. *et al.* Cystinuria—a urologist's perspective. *Nat. Rev. Urol.* **11**, 270–277 (2014)