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Methionine Restriction Prevents Cystine Urolithiasis in a Mouse Model of Cystinuria

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INTRODUCTION

- Cystinuria is a metabolic disorder caused by mutations in the *SLC3A1* and/or *SLC7A9* genes responsible for cystine reabsorption in the kidney. Defects in either of these genes lead to excessive excretion of cystine in the urine, which can result in stone formation.
- The management of cystinuria includes increased fluid intake, urine alkalization, and a reduction in protein intake enriched in cysteine and methionine.
- Despite adherence to current standard of care, a large proportion of patients with cystinuria suffer from repeated and large kidney stones.

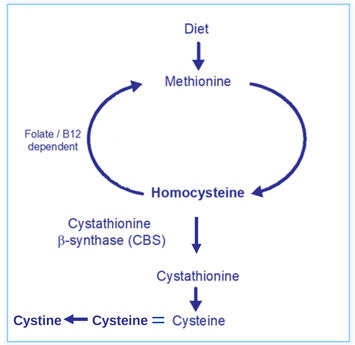

Figure 1. The methionine and transsulfuration pathways are essential for cysteine biosynthesis

- *Escherichia coli* Nissle 1917 (EcN) is a probiotic used in humans due to its positive influence on gut health[1].
- Proof-of-concept studies have validated the utility of a genetically modified EcN for the treatment of amino acid disorders, including phenylketonuria[2-4].
- SYNB1353 is an engineered strain of *E. coli* Nissle that metabolizes methionine in the gastrointestinal tract and prevents its absorption.

OBJECTIVE

To determine whether gastrointestinal metabolism of methionine could lower urinary cystine levels and hence prevent stone formation, we assessed the impact of dietary methionine restriction in the SLC3A1 knockout (KO) mouse model of cystinuria.

METHODS

6-week-old wild-type or SLC3A1 KO mice (n = 12) were fed a regular (0.62%) or low-methionine (0.12%) diet for 8 weeks.

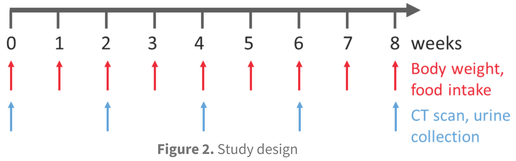

Figure 2. Study design

At week 8, bladders were dissected, and stones were removed and weighed. Stone number and size distribution (based on surface area of the stone image) were determined using NIH Image J software.

RESULTS

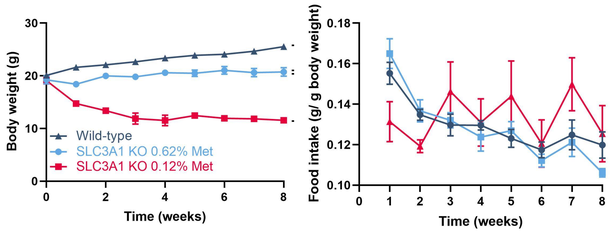

Figure 3. SLC3A1 KO mice fed a low methionine diet lose weight compared to mice on regular diet despite similar food intake. Data presented as mean ± SEM. Statistical analysis performed using two-way ANOVA followed by Tukey's multiple comparison test. *p < 0.05.

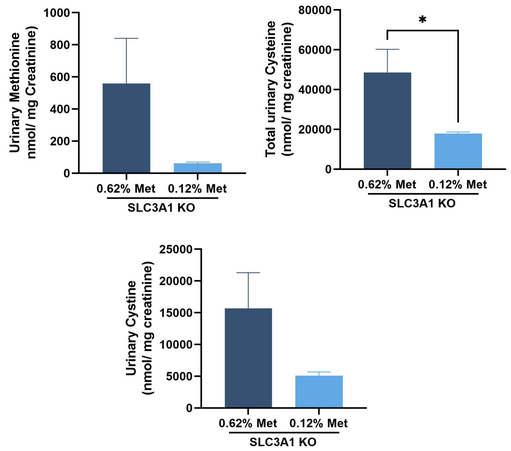

Figure 4. Urinary methionine, total cysteine (reduced form) and cystine levels are decreased in SLC3A1 KO mice fed a low methionine diet. Data presented as mean ± SEM. Statistical analysis performed using t-test with Welch's correction. *p < 0.05.

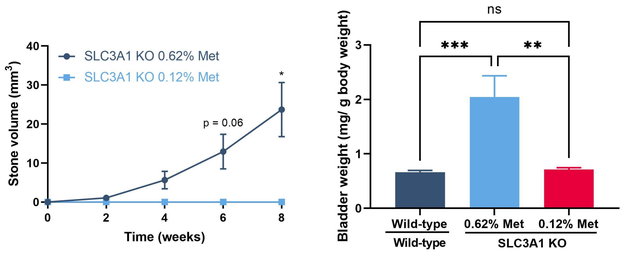

Figure 5. SLC3A1 KO mice do not develop stones on low methionine diet. Data presented as mean ± SEM. Statistical analysis performed using one-way or two-way ANOVA followed by Tukey's multiple comparison test. *p < 0.05., **p < 0.01, ***p < 0.001.

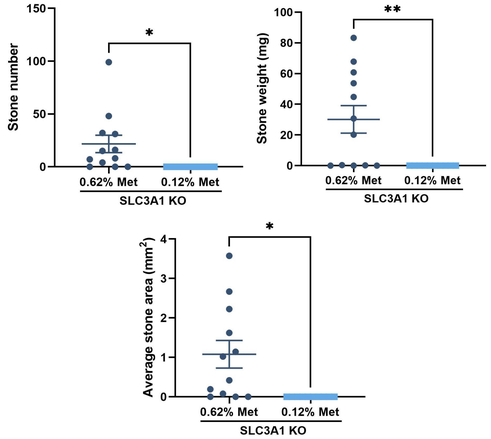

Figure 6. SLC3A1 knockout mice do not develop stones on low methionine diet. . Data presented as mean ± SEM. Statistical analysis performed using t-test with Welch's correction. *p < 0.05, **p < 0.01.

CONCLUSIONS

- A low methionine diet lowered urinary cystine levels and prevented stone formation in SLC3A1 KO mice, a model of cystinuria.
- This data suggest that gastrointestinal methionine metabolism could be a viable approach to treat cystinuria.

REFERENCES

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