Vitamin C Urinary Loss in Fabry Disease: Clinical and Genomic Factors of Vitamin C Renal Leak

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Objectives: Reduced plasma vitamin C concentrations in chronic diseases may result from abnormal urinary excretion of vitamin C excretion: a renal leak. We hypothesized that vitamin C renal leak may be the consequence of disease-mediated dysregulation affecting the renal tubules, resulting in aberrant vitamin C renal reabsorption and increased urinary loss. The study objective was to investigate the prevalence, clinical characteristics, and genomic associations of vitamin C renal leak in Fabry disease, an X-linked lysosomal storage disease associated with renal tubular dysfunction and low plasma vitamin C concentration.

Methods: This was a non-randomized cross-sectional cohort study of males with Fabry disease (n = 34) and healthy male controls (n = 33). To determine primary outcome of vitamin C renal leak, matched urine and fasting plasma vitamin C measurements were obtained following an overnight fast. Based on data from healthy men, vitamin C renal leak was defined as presence of urinary vitamin C at plasma concentrations below 38 μM. Exploratory outcomes assessed the association between renal leak and clinical parameters; and genomic associations with renal leak using single nucleotide polymorphisms (SNPs) in the vitamin C transporter SLC23A1. Proof-of-concept studies were conducted using two mouse models.

Results: Compared with healthy men, Fabry cohort had 16-fold higher odds of renal leak (6% vs 52%: OR16, $P < 0.001$). Renal leak was associated with higher protein creatinine ratio ($p = 0.01$), lower hemoglobin ($p = 0.002$) and hematocrit ($p = 0.008$). Renal leak, but not plasma vitamin C, was associated with a non-synonymous single nucleotide polymorphism in vitamin C transporter SLC23A1 ($p = 0.01$ and $p = 0.47$ respectively). Using two mouse models, we recapitulated the relationships between renal leak, dysregulated vitamin C renal reabsorption and low plasma vitamin C concentrations.

Conclusions: Increased prevalence of vitamin C renal leak in Fabry disease may result from dysregulated vitamin C renal physiology, with significant clinical and genomic associations. Renal leak may be more sensitive than plasma vitamin C in evaluating genomic associations in small cohorts.

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