Do Urinary Cystine Parameters Predict Clinical Stone Activity?

Justin I. Friedlander,* Jodi A. Antonelli, Noah E. Canvasser, Monica S. C. Morgan, Daniel Mollengarden, Sara Best and Margaret S. Pearle†

From the Department of Urology, University of Texas Southwestern Medical Center (JIF, JAA, NEC, MSCM, DM) and Jane and Charles Pak Center for Mineral Metabolism and Clinical Research, Dallas (MSP), Texas, and Department of Urology, University of Wisconsin (SB), Madison, Wisconsin

Purpose: An accurate urinary predictor of stone recurrence would be clinically advantageous for patients with cystinuria. A proprietary assay (Litholink, Chicago, Illinois) measures cystine capacity as a potentially more reliable estimate of stone forming propensity. The recommended capacity level to prevent stone formation, which is greater than 150 mg/l, has not been directly correlated with clinical stone activity. We investigated the relationship between urinary cystine parameters and clinical stone activity.

Materials and Methods: We prospectively followed 48 patients with cystinuria using 24-hour urine collections and serial imaging, and recorded stone activity. We compared cystine urinary parameters at times of stone activity with those obtained during periods of stone quiescence. We then performed correlation and ROC analysis to evaluate the performance of cystine parameters to predict stone activity.

Results: During a median followup of 70.6 months (range 2.2 to 274.6) 85 stone events occurred which could be linked to a recent urine collection. Cystine capacity was significantly greater for quiescent urine than for stone event urine (mean ± SD 48 ± 107 vs −38 ± 163 mg/l, $p < 0.001$). Cystine capacity significantly correlated inversely with stone activity ($r = -0.29$, $p < 0.001$). Capacity also correlated highly negatively with supersaturation ($r = -0.88$, $p < 0.001$) and concentration ($r = -0.87$, $p < 0.001$). Using the suggested cutoff of greater than 150 mg/l had only 8.0% sensitivity to predict stone quiescence. Decreasing the cutoff to 90 mg/l or greater improved sensitivity to 25.2% while maintaining specificity at 90.9%.

Conclusions: Our results suggest that the target for capacity should be lower than previously advised.

Key Words: kidney calculi, recurrence, urine, cystinuria, analysis

Abbreviations and Acronyms

CBTD = cystine-binding thiol drug
CT = computerized tomography
NPV = negative predictive value
PPV = positive predictive value

Accepted for publication September 7, 2017.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

* Financial interest and/or other relationship with Retrophin.

† Correspondence: Department of Urology, 5323 Harry Hines Blvd., J8.106, Dallas, Texas 75390 (telephone: 214-648-6856; FAX: 214-648-8786; e-mail: Margaret.pearle@utsouthwestern.edu).

Medical treatment to prevent stone recurrence in patients with cystinuria has traditionally been informed by a goal of treatment to achieve a cystine concentration below the solubility limit (less than 250 mg/l). Unfortunately gauging the therapeutic success by changes in concentration has not been ideal because of a lack of reliability in calculating cystine solubility.[1–3] Consequently cystine concentration may not be a reliable surrogate for cystine stone formation. Without a reliable predictor of treatment success only the clinical history and serial imaging studies indicating stone formation can assess the adequacy of treatment.

0022-5347/18/1992-0495/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1016/j.juro.2017.09.034
Vol. 199, 495-499, February 2018
Printed in U.S.A.

In response to the lack of a reliable predictor of cystine stone formation a proprietary solid phase assay was commercially developed that provides a direct measure of cystine supersaturation which is reliable in the presence or absence of CBTD.[3–5] The assay involves adding a known amount of solid phase cystine to the urine of a patient with cystinuria and measuring the change in solid phase after incubation. In undersaturated urine solid phase cystine dissolves and the amount of solid phase recovered is less than that initially added (positive capacity). In supersaturated urine cystine from urine precipitates on the added crystals and the amount of solid phase recovered is greater than what was initially added (negative capacity). Given these characteristics, cystine capacity has the potential to identify supersaturated urine and guide preventive treatment.

Commercially available 24-hour urine kits recommend a goal of greater than 150 mg/l for cystine capacity. However, to our knowledge cystine capacity has not been correlated to date with actual clinical stone activity to determine whether this is appropriate. Because high doses of CBTDs with associated cost and risk of drug toxicity may be required to achieve this level, it is desirable to determine the capacity level that best distinguishes stone activity from stone inactivity. Using our prospective database of patients with cystinuria we sought to determine whether any urinary cystine parameter, particularly cystine capacity, could reliably predict clinical stone recurrence.

MATERIALS AND METHODS

After obtaining institutional review board approval we enrolled and prospectively followed all patients at our tertiary care stone clinic with a known diagnosis of cystinuria from October 2005 to October 2016. All patients were counseled regarding the nature of the disease and dietary measures to prevent stone formation. Patients were instructed to collect 24-hour urine samples after the first visit or after surgical intervention. Samples were sent elsewhere for analysis. When appropriate, patients were prescribed medications, including alkalinizing agents and/or CBTDs. Urine collections were obtained every 4 to 12 months depending on metabolic activity. Radiographic imaging (plain abdominal x-ray, renal ultrasound or CT) was obtained routinely after procedures and at each office visit. Urine specimen analysis included volume, pH, cystine level, cystine supersaturation and capacity, among other urinary parameters.

We defined stone activity as any of an increase in the size of existing stones, the development of new stones and the passage of or intervention for stones not previously seen on imaging studies. All imaging was reviewed to ensure that residual fragments were not counted as new stones.

To correlate urinary cystine parameters with stone activity we considered each urine collection in the context of its most closely associated imaging study and the patient history documenting stone activity, which were assessed by the treating physician. Urine samples were then divided into 2 groups, including those obtained during periods of stone activity and stone quiescence, respectively.

The independent samples t-test was used to compare urine collection parameters, including cystine concentration, supersaturation and capacity, between the 2 groups. The relationship of capacity with stone activity and capacity with supersaturation and concentration was measured by the Pearson correlation. ROC analysis was done to evaluate the performance of all 3 cystine urinary parameters for predicting stone activity. From ROC analysis we then derived the sensitivity, specificity, and positive and negative predictive values of cystine capacity. We defined the disease of interest as stone quiescence and a test was considered positive when the value exceeded the defined cutoff point (ie 150 or greater). Statistical analysis was performed using IBM® SPSS®, version 22 with $p < 0.05$ considered statistically significant.

RESULTS

A total of 48 patients with cystinuria were included in the study group. Median age at the initial visit to our institution was 39.8 years (range 7.4 to 74.6) and median followup was 70.6 months (range 2.2 to 274.6). The cohort included 26 women (54%). The racial/ethnic distribution was 85.4% Caucasian (41 of 48 participants), 8.3% African American (4 of 48) and 6.3% Hispanic/Latino (3 of 48). Median age at the first stone was 17 years (range 1 to 59). Two of the study patients had diabetes and 19 (39.6%) had hypertension. Median body mass index at the first visit was 29.7 kg/m^2 (range 18.6 to 54.9). A family history of kidney stones was reported in 25 patients (52.1%), of whom 7 had relatives with cystinuria. In 13 of the 48 patients (27.1%) a surgically (10) or a functionally (3) solitary kidney was present.

Nine patients (18.8%) were maintained on alkalinizing agents alone (potassium citrate and/or sodium bicarbonate) while 39 (81.3%) were receiving alkalinizing agents plus CBTD. The most common drug combination was tiopronin and potassium citrate, which was used by 29 patients (60.4%).

Analysis of 24-hour urine collections revealed 347 appropriately collected samples. Of these urine samples 261 were collected from a total of 41 patients during periods of stone inactivity and 85 were collected from 34 patients in close proximity to a stone event. Stone activity included 19 cases of surgical intervention, 10 spontaneously passed stones not previously seen on imaging, 22 episodes of documented stone growth and 34 documented new stones. Urinary cystine capacity was available