Necessity of Fractionated Urine Collection for Monitoring Patients with Cystinuria

To the Editor:

Cystinuria is an inherited form of nephrolithiasis caused by mutations in the SLC7A9 [solute carrier family 7 (cationic amino acid transporter, y+ system), member 9] and SLC3A1 [solute carrier family 3 (cystine, dibasic and neutral amino acid transporters, activator of cystine, dibasic and neutral amino acid transport)] genes, which encode the luminal transporter b(0,+) AT subunit and rBAT subunit, respectively. The disease is characterized by impaired proximal tubular and intestinal reabsorption of cystine and the dibasic amino acids ornithine, lysine, and arginine (1). Treatment of cystinuria aims to prevent new stone formation and consists of increased fluid intake, urine alkalinization, and cystine-binding drugs for avoiding urinary cystine supersaturation, which occurs when the urinary cystine concentration is >250 mg/L at pH 4.5–7.5 or >500 mg/L at pH >7.5 (2). The effectiveness of this treatment is often disappointing. Patients undergo frequent surgeries, which are often followed by an early relapse. Monitoring urinary cystine is the cornerstone of cystinuria management; however, most textbooks do not provide clear recommendations as to how such monitoring should be performed. The traditional way to monitor the cystine concentration has been analysis of a 24-h urine sample; however, achieving a 24-h cystine concentration below concentrations indicating risk does not prevent formation of renal stones (2-5). Stone formation in such cases can be due to diurnal variation in urinary cystine excretion (2-4), but it also can be due to diurnal variation in urinary pH and fluid intake.

We evaluated the benefit of fractionated 24-h urine collection for 9 patients with homozygous cystinuria (ages 8–65 years, 4 males) (Table 1). We collected 4 urine fractions from each of the participating patients and detected 15 fractions with cystine supersaturation (42% of all investigated collection fractions). The night period (0200–0700) was the most risky, because the concentration of cystine solubility was exceeded at this time in 6 of the 9 cases. On the other hand, the daytime period also required careful attention (9 of the 15 urine fractions with supersaturation were collected during the day), possibly because of a dietary load with methionine (2), insufficient fluid intake, or decreased urinary pH.

Twelve (80%) of the 15 fractions with supersaturation would have been missed if only standard 24-h samples had been analyzed. Only 1 of the patients would have been considered “at risk” for development of cystine stones according to the 24-h collection results.

For optimal monitoring of patients with cystinuria, we stress the necessity of 6-h urine collections, not only to distinguish day and night portions but also for detecting day periods at risk for cystine supersaturation and thus nephrolithiasis.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article

Table 1. Diurnal variation of cystine concentration.

<table>
<thead>
<tr>
<th>Collection time</th>
<th>0700–1300</th>
<th>1300–1900</th>
<th>1900–0200</th>
<th>0200–0700</th>
<th>24-h Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient no.</td>
<td>Cystine, mg/L</td>
<td>pH</td>
<td>Cystine, mg/L</td>
<td>pH</td>
<td>Cystine, mg/L</td>
</tr>
<tr>
<td>1</td>
<td>1398</td>
<td>8.0</td>
<td>124</td>
<td>8.5</td>
<td>305</td>
</tr>
<tr>
<td>2</td>
<td>576</td>
<td>7.5</td>
<td>325</td>
<td>8.0</td>
<td>365</td>
</tr>
<tr>
<td>3</td>
<td>322</td>
<td>6.5</td>
<td>195</td>
<td>5.5</td>
<td>210</td>
</tr>
<tr>
<td>4</td>
<td>138</td>
<td>7.0</td>
<td>94</td>
<td>5.0</td>
<td>183</td>
</tr>
<tr>
<td>5</td>
<td>578</td>
<td>7.0</td>
<td>286</td>
<td>7.0</td>
<td>187</td>
</tr>
<tr>
<td>6</td>
<td>206</td>
<td>8.5</td>
<td>333</td>
<td>7.0</td>
<td>687</td>
</tr>
<tr>
<td>7</td>
<td>385</td>
<td>6.5</td>
<td>161</td>
<td>7.0</td>
<td>865</td>
</tr>
<tr>
<td>8</td>
<td>223</td>
<td>5</td>
<td>308</td>
<td>6</td>
<td>231</td>
</tr>
<tr>
<td>9</td>
<td>249</td>
<td>6</td>
<td>446</td>
<td>8</td>
<td>204</td>
</tr>
</tbody>
</table>

* Cystine supersaturation: a cystine concentration >250 mg/L at a pH <7.5 or >500 mg/L at a pH >7.5.

1 Human genes: SLC7A9, solute carrier family 7 (cationic amino acid transporter, y+ system), member 9; SLC3A1, solute carrier family 3 (cystine, dibasic and neutral amino acid transport), member 1.
for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

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Previously published online at
DOI: 10.1373/clinchem.2010.161547