Significance of the Calcium to Creatinine Concentration Ratio of a Single-voided Urine Specimen in Patients with Hypercalciuric Urolithiasis

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(Received May 7, 1987)

Thirty-six patients with recurrent calcium oxalate nephrolithiasis were selected from the stone clinic. Fourteen were normocalcemic and had normal daily urinary calcium excretion. Among 22 patients with idiopathic hypercalciuria, 10 received thiazide diuretics for the prevention of new stone formation. Single-voided urine samples were collected at the outpatient clinic and 24-hour urine samples at the patients' homes. In hypercalciuric patients, irrespective of thiazide diuretic therapy, the mean value of the calcium/creatinine concentration ratios of postprandial single-voided urine specimens had a meaningful correlation with the mean value of 24-hour urinary calcium excretion rates. Also in hypercalciuric patients with thiazide diuretics, a negative correlation was observed between the calcium/creatinine concentration ratio and the index for urinary saturation with calcium oxalate of a postprandial single-voided urine sample. Thus, in the hypercalciuric stone formers, 24-hour urinary calcium excretion rates and the degree of urinary saturation with calcium oxalate can be estimated from the calcium/creatinine concentration ratios of single-voided urinary samples.

(Key Words: Nephrolithiasis, Hypercalciuria, Urinary calcium to creatinine ratio)

INTRODUCTION

It is important to examine the state of urinary calcium excretion and the degree of urinary saturation with calcium oxalate for follow-up and treatment of patients with recurrent calcium oxalate nephrolithiasis. Twenty-four-hour urine collection is an ideal method for studying urinary excretion of stone components, but it is not always practical for patients working during the week. A more simple but reliable testing method is desirable to estimate the risk factors for stone formation at the outpatient stone clinic.

In this study, we assessed the calcium/creatinine concentration ratios of single-voided urine samples, which are readily obtained at follow-up visits of patients, in relation to 24-hour urinary calcium excretion rates and indices of urinary saturation with calcium oxalate.

MATERIALS AND METHODS

Among 271 patients that were treated at the stone clinic of Tokai University Hospital, 36 were selected for this study. They all had normal kidney function and normal parathyroid hormone level although they experienced one or more attacks of recurrent calcium oxalate stone disease. Among these 36 patients, 10 received thiazide diuretic therapy because they had more than two recurrent episodes and hypercalciuria. Twelve patients had a second or third attack and were followed up without medical treatment even if they had hypercalciuria. The remaining 14 were normocalcemic and normocalciuric, although they experienced recurrence of calcium stone disease. They were assigned as a control.

Hypercalciuria was defined by a 24-hour urinary calcium excretion of greater than 4 mg per
kg body weight on at least three occasions. Urinary calcium was determined by the o-cpc autoanalyzer technique. Urinary oxalate was quantitated by gas chromatography.

The calcium/creatinine concentration ratio (mg/dl/mg/dl) of a single-voided urine sample was adjusted to the expected creatinine excretion rate by multiplying the ration by the formula proposed by Ginsberg and his associates (1) (Table 1) because urinary creatinine excretion is not always constant but is believed to vary with meals, age, sex, time and day (4). The relative supersaturation with respect to calcium oxalate was measured on the nomogram proposed by Marshall and Robertson (2). As another method to estimate the degree of urinary saturation, the concentration product ratio of calcium oxalate was measured according to the method of Pak and Holt (3).

A 10 ml urinary sample was incubated with calcium oxalate monohydrate as seed crystal, 10 mg per ml of the urinary sample, at 37°C for 48 hours in a warm bath with stirring. Urinary pH was readjusted to the preincubation level by adding HCl or NaOH 24 hours after the start of incubation. At the end of incubation, the sample was filtered through a 0.22 micron pore diameter filter. The calcium and oxalate concentrations of the filtrate were quantitated, and the product of the concentrations before incubation was divided by that obtained after incubation (Table 1).

All the subjects were allowed free access to dietary calcium during this study.

RESULTS

During the follow-up period, three out of 14 normocalciuric patients, three out of 12 hypercalciuric patients without medical treatment and two out of 10 hypercalciuric patients with thiazide diuretics had recurrent stones. Moreover, the thiazide diuretic therapy appeared to have no effect on the 24-hour urinary calcium or oxalate excretion (Table 2).

In most of the normocalciuric patients, postprandial values of the calcium/creatinine concentration ratio (Ca/Cr) of single-voided urine samples covered a wide range so that no correlation was observed between the ratio and the 24-hour urinary calcium excretion rate. However, in the hypercalciuric patients with no medical treatment, a positive correlation was noted between the mean value of postprandial Ca/Cr of single-voided urine specimens and that of 24-hour urinary calcium excretion rates (Fig. 1). Similarly, in the hypercalciuric patients

<table>
<thead>
<tr>
<th>Table 1 Methods</th>
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<tbody>
<tr>
<td>• Selection of patients with recurrent calcium oxalate nephrolithiasis and normal uric acid excretion.</td>
</tr>
<tr>
<td>• Determination of calcium, creatinine and oxalate concentrations of single-voided urine specimens collected at outpatient clinic and of 24-hr urine specimens collected at patients' homes.</td>
</tr>
<tr>
<td>• Adjusted Calcium Creatinine Concentration Ratio = Observed Calcium Creatinine Concentration Ratio × Expected Creatinine Excretion Rate</td>
</tr>
</tbody>
</table>
| for men \[
\frac{(140 - \text{Age}) \times \text{Wt(kg)}}{5000}
\]
| for women \[
\frac{(140 - \text{Age}) \times \text{Wt(kg)}}{5000} \times 0.85
\]
| (by J.M. Ginsberg et al.) |
| • Relative supersaturation of urine with calcium oxalate |
| • Calcium oxalate concentration product ratio = \[
\frac{\text{Conc.Ca} \times \text{Conc.Oxalate (before incubation)}}{\text{Conc.Ca} \times \text{Conc.Oxalate (after incubation)}}
\]
| Value > 1 supersaturated |
| = 1 saturated |
| < 1 undersaturated |
under thiazide diuretic therapy a positive correlation was observed between the two values (Fig. 2).

In view of the state of urinary saturation with respect to calcium oxalate, the Ca/Cr of single-voided urine specimens of hypercalcuiuric patients on thiazide diuretics showed a negative correlation with the degree of relative supersaturation with respect to calcium oxalate, as well as with the calcium oxalate concentration product ratio (Figs. 3 and 4). No significant correlation was demonstrated between these values in hypercalcuiuric patients without thiazide diuretics.

### Table 2 Clinical findings of the studied patients

<table>
<thead>
<tr>
<th></th>
<th>Normocalciuric</th>
<th>Hypercalciuric without treatment</th>
<th>Hypercalciuric on thiazide diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>14</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Mean age</td>
<td>46</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>No. of recurrent stones during follow-up</td>
<td>5/14 pt.</td>
<td>5/12 pt.</td>
<td>3/10 pt.</td>
</tr>
<tr>
<td>Urinary calcium excretion (mg/day) mean ± SE</td>
<td>174 ± 49</td>
<td>297 ± 71</td>
<td>268 ± 102</td>
</tr>
<tr>
<td>Urinary oxalate excretion (mg/day) mean ± SE</td>
<td>48.6 ± 20.2</td>
<td>48.6 ± 24.7</td>
<td>48.9 ± 26</td>
</tr>
<tr>
<td>Duration of follow-up (average months)</td>
<td>17.5</td>
<td>19.4</td>
<td>25.6</td>
</tr>
</tbody>
</table>

![Fig. 1](image-url)  
**Fig. 1** Relation between Mean Value of Calcium/Creatinine Concentration Ratios of Single-Voided Urine Specimens and That of 24-hour Urinary Calcium Excretion Rates in Hypercalcuiuric Recurrent Calcium Oxalate Stone Patients without Treatment.
Fig. 2  Relation between Mean Value of Calcium/Creatinine Concentration Ratios of Single-Voided Urine Specimens and That of 24-hour Urinary Calcium Excretion Rates in Hypercalciuric Recurrent Calcium Oxalate Stone Patients Treated with Thiazide Diuretics

Fig. 3  Relation between Calcium/Creatinine Concentration Ratio of a Specimen of Single-Voided Urine and Its Relative Supersaturation with Calcium Oxalate in Hypercalciuric, Recurrent Calcium Oxalate Stone Patients Treated with Thiazide Diuretics
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Fig. 4  Relation between Calcium/Creatinine Concentration Ratio of a Specimen of Single-voided Urine and Its Calcium Oxalate Concentration Product Ratio in Hypercalcicuric, Recurrent Calcium Oxalate Stone Patients Treated with Thiazide Diuretics

DISCUSSION

Wide ranging Ca/Cr of single-voided urine samples observed in normocalciuric patients can be attributed to free calcium intake because they were not usually given a dietary regimen.

In hypercalciuric subjects, however, whether they used thiazide diuretics or not, the mean values of Ca/Cr of single-voided urine specimens were indicative of 24-hour urinary calcium excretion rates because a statistically significant correlation was obtained between those two elements. Factors contributory to this correlation may be that hypercalciuric patients are strongly recommended not to eat excessive meats, dairy products or calcium rich food, so that the amounts of calcium and exogenous creatinine available for intestinal absorption are kept low and constant and thus urinary calcium and creatinine excretion rates may not fluctuate to such a degree as seen in normocalciuric subjects with a free diet. In addition, it is known that the majority of hypercalciuric patients excrete persistently increased urinary calcium even if they are on a low calcium diet. In these subjects renal handling of calcium might be regulated by a pathologic process not depending on oral calcium intake, so that urinary calcium excretion remains high and constant. For these reasons, Ca/Cr of single-voided urine specimens will be a good index of urinary calcium excretion in hypercalciuric stone patients.

The negative correlation observed between the Ca/Cr and the two indices of urinary saturation with calcium oxalate of postprandial, single-voided urine specimens from hypercalciuric patients on thiazide diuretics suggests that in these patients, increased calcium excretion does not always reflect a higher level of supersaturation with calcium oxalate. Conversely, a low Ca/Cr may reflect a greater degree of supersaturation of urine with calcium oxalate. This means that oxalic acid excretion rather than that of calcium can be a major determinant of the state of saturation with calcium oxalate in postprandial urine specimens collected from hypercalciuric patients on thiazide diuretics.

REFERENCES