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<th>Circadian rhythms of urinary saturation levels of calcium oxalate and calcium phosphate in normal male individuals</th>
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<td>Ogawa, Yoshihide</td>
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INTRODUCTION

The urinary concentrations of lithogenic and inhibitory substances have a marked role in the development of urolithiasis. Most researchers agree that 24-hour urine collection data as well as the urinary concentrations of various lithogenic and inhibitory substances only provide a vague indication of the risk of lithogenesis. These urinary substances have also been shown to express different circadian rhythms, these different patterns have not been routinely integrated into a single saturation level.

Previously, I used a nomogram developed by Marshall and Robertson to measure the diurnal variation in the calcium oxalate saturation level. This nomogram involved only two parameters (the calcium and oxalate concentrations) and was at that time the most reliable predictive index of the urinary saturation level. As reported previously, late night and early morning are the periods associated with the greatest risk of calcium oxalate stone formation.

Since that time, more parameters have been incorporated into assessment of the risk of calcium oxalate crystallization in the urine, such as 5 parameters by Tiselius and 14 by Werness et al. in EQUIL. However, these methods are of limited use because of the inconvenient urine collection period in the former case and because of the incorporation of too many parameters for clinical use in the latter case.

I have modified the former method to make it usable for any collection period, and the circadian rhythms of the calcium oxalate (CaOx), calcium phosphate (CaP), and brushite (Bru) saturation levels were determined using fractional urine collections in normal male volunteers.

MATERIALS AND METHODS

Five healthy male volunteers between 21 and 27 years old and weighing 60.8±4.6 kg
(mean ± SD) were studied for at least a 24-hour period after an overnight stay during three different weeks. They had ordinary meals at 7:00 am, noon, and 5:00 pm and a snack at 9:30 pm. They were also allowed to drink a glass of water at 8:00 am, 1:00 pm, 6:00 pm, and 8:30 pm. Urine was collected for 2.5-hour periods except during sleep (from 11:00 pm to 5:30 am). For each sample, the pH and volume (V: expressed in liters) were measured immediately after voiding. The urinary concentrations of calcium (Ca), magnesium (Mg), and phosphate (P) (mmol) were routinely analyzed as described previously using a Hitachi 705 autoanalyzer. Aliquots of the specimens were frozen and preserved until analysis for the urinary concentrations of oxalate (Ox) and citrate (Cit), which were determined by respective enzymatic methods. The AP(CaOx), AP(CaP), and AP(Bru) indices are estimates of the ion activity products of CaOx, CaP, and Bru, respectively; they were calculated as follows:

\[
\text{AP(CaOx) index: } K \times \text{Ca}^{0.71} \times \text{Ox}^{0.14} / \text{Cit}^{0.10} / V^{1.2}
\]

\[
\text{AP(CaP) index: } A \times \text{Ca}^{1.07} \times \text{P}^{0.70} \times (\text{pH}-4.5)^{7.0} / \text{Cit}^{0.20} / V^{1.31}
\]

\[
\text{AP(Bru) index: } B \times \text{Ca}^{0.82} \times \text{pH}^{0.8} / \text{Cit}^{0.46} / V^{1.53}
\]

In these equations, the K, A, and B factors were interpolated from the literature as follows (linear regression analysis: \( r=0.9959 \sim 0.9899, p<0.01 \)). The K value was 7.171 for the 2.5-hour urine collections and 5.632 for the 6.5-hour collection. The A values were 4.869 \times 10^{-3} for the 2.5-hour urine collection and 3.860 \times 10^{-3} for the 6.5-hour collection, and the B values were 5.125 \times 10^{-7} and 5.643 \times 10^{-7}, respectively. The ion-activity products of octacalcium phosphate (OCP) \((-\log \text{AP}_{\text{OCP}}=1/0.021 + (\text{AP(CaP) index})^{0.025} + 0.5)\) and hydroxyapatite (HAP) \((-\log \text{AP}_{\text{HAP}}=1/0.0185 + (\text{AP(CaP) index})^{0.048}\) were also calculated using the formulae of Tiselius.

Statistical analysis was performed by the paired t-test for paired samples from each sequential urine fraction.

### RESULTS

The peak AP(CaOx) index was observed between 5:30 and 8:00 am, and was significantly higher than the values at other periods. Most of the index values of AP(CaOx) were in the metastable zone (between the solubility and formation products of 0.2 and 2.8, respectively), and no values exceeded the formation product during the observation periods. AP(CaP) had two peaks, which were between 8:00 am and 10:30 am and between 1:00 am and 6:00 am. Both peaks were significantly higher than the baseline values obtained between 5:30 and 8:00 am. A similar pattern was observed for AP(Bru) peak occurrence between 5:30 and 8:00 am, and was higher than most other values with a significant difference in several cases (Fig. 1).

### DISCUSSION

The urinary saturation level varies in relation to physical exercise, diet, fluid intake, and other factors. Therefore, it cannot be expressed exactly by the saturation level in a 24-hour urine specimen. Vahlen-sieke et al. and our group both considered that the 24-hour represents only an average profile of the saturation levels over a day. Both groups detected circadian rhythms of lithogenic substances in the urine and found that the excretion of these constituents usually peaked after meal times, particularly in terms of calcium and phosphate, and that the urinary concentrations of these elements were highest early in the morning. The 6 different parameters could not be integrated to produce a
Ogawa: Urinary saturation rhythm

Three diagrams are shown, each representing a different index related to the Tiselius saturation index. The indices include AP(CaOx), AP(CaP), and AP(Bru). The graphs illustrate the diurnal variations in these indices with time (5:30-8:00) and show the mean ± SE values for each time point.

The following table summarizes the mean ± SE values for the AP(CaOx) index:

<table>
<thead>
<tr>
<th>Time</th>
<th>AP(CaOx)</th>
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<tbody>
<tr>
<td>5:30-8:00</td>
<td>2.2±0.3</td>
</tr>
<tr>
<td>9:00-10:30</td>
<td>1.6±0.2</td>
</tr>
<tr>
<td>10:30-12:00</td>
<td>0.9±0.2</td>
</tr>
<tr>
<td>12:00-13:30</td>
<td>1.0±0.3</td>
</tr>
<tr>
<td>13:30-15:00</td>
<td>0.6±0.1</td>
</tr>
<tr>
<td>15:00-16:30</td>
<td>0.5±0.1</td>
</tr>
<tr>
<td>16:30-18:00</td>
<td>0.4±0.1</td>
</tr>
<tr>
<td>18:00-19:30</td>
<td>1.3±0.3</td>
</tr>
<tr>
<td>19:30-21:00</td>
<td>2.0±0.3</td>
</tr>
<tr>
<td>21:00-22:30</td>
<td>1.2±0.1</td>
</tr>
</tbody>
</table>

*p<0.10, **p<0.05, ***p<0.01

In the text, the author mentions that single saturation profiles were measured, and most urine specimens were in a state of metastable supersaturation. Calcium oxalate and calcium phosphate values frequently exceeded the formation product for a few hours during the daytime. Contrastingly, the author suggests that calcium oxalate saturation levels increased both late at night and early in the morning. Ahlstrand et al. also found two intervals of increased calcium oxalate saturation, i.e., between 6:00 and 10:00 am and between 6:00 and 10:00 pm.

Sophisticated methods using computer programs have now become available and useful for more accurate determination of
saturation levels, not only in 24-hour urine specimens but also in the fractional urine of shorter collection period. These methods can also determine the saturation levels for several different stone components.

This study showed that early morning (5:30~8:00 am) is the high-risk period for calcium oxalate and brushite crystallization. The risk periods for octacalcium and hydroxyapatite crystallization are between 8:00 and 10:30 am and between 1:00 and 6:00 pm. Each peak index remained in the metastable zone. However, an overshoot beyond the formation product for a transient period cannot be ruled out.

The present results support the single evening dose (10:00 pm) of sodium potassium citrate for patients with recurrent CaOx stones proposed by Berg et al. They reported that the high-risk periods for CaOx were late at night and early in the morning\(^{13,14}\). Their study of calcium phosphate crystallization was based solely on the AP(CaP) index, but the present findings provide further insight in terms of 3 different calcium phosphate crystallization systems. The current data suggest that there is no benefit of citrate administered three times a day, since dosing about a half hour after each meal may simply augment the effect of food intake (i.e., reduce CaOx saturation and increase CaP saturation), without exerting any significant effect on the urinary saturation level in the critical period for lithogenesis. From the clinical point of view, it is important to lower the urinary saturation level of lithogenic components for the prevention of urinary stones. There may be some patients who need three doses of citrate a day. However, to determine its precise effectiveness, the circadian profile of the urinary saturation level must be determined. Further studies involving the use of alkalinizing agents are also needed.

REFERENCES


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和文抄録

罹患男性5名を対象に3回の異なる時期に、罹患カルシウム、磷酸カルシウム、酸性磷酸カルシウムの飽和度をそれぞれ示すAP(CaOx)指数、AP(CaP)指数、AP(Bru)指数（Tiselius）を測定し、その飽和度の日内変動を検討した。就寝時以外2時間50分毎に採尿し、これらの指数を計算した。罹患カルシウムと酸性磷酸カルシウムの飽和度は5時〜8時で最高値となり、磷酸カルシウム飽和度は二峰性で、8時〜10時30分と13時〜18時に最高値となった。磷酸カルシウムと水酸化アパタイトのイオン活量積も、AP(CaP)の値より求めたが、磷酸カルシウムの飽和度と同様なパターンを示した。

以上より、罹患カリウムと磷酸カリウムに関しては、結晶化の危険性が高く、磷酸カルシウムと水酸化アパタイトでは8時〜10時30分と13時〜18時であることが判明した。

（泌尿器要 39: 785-789, 1993）