

MODIFICATION OF ESTIMATION OF THE URINARY ION-ACTIVITY PRODUCTS OF CALCIUM OXALATE AND CALCIUM PHOSPHATE

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Tiselius proposed simplified estimates of the ion-activity products of calcium oxalate, calcium phosphate, and brushite as the AP(CaOx) index, the AP(CaP) index, and the AP(Bru) index, respectively, which allowed assessment of the urinary saturation levels of these lithogenic substances. A number of urinary variables (calcium, magnesium, oxalate, phosphate, citrate, urine volume, and pH) are necessary to derive these indices. In addition, these three indices have correction factors corresponding to the urinary collection periods, although these periods were originally quite limited. In this study, the factors were shown to vary as a function of time. Therefore, they were incorporated into these indices after proper calculation so as to be usable for any collection period less than 24 hours. This means that the factors will now prove more useful in evaluating the urinary saturation levels after short-term collections.

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INTRODUCTION

Urinary supersaturation is the driving force of the crystallization process, and it can now be calculated easily by using the ion equilibrium computer program (EQUIL-2)¹⁾. However, this program requires the prior determination of a large number of parameters. Therefore, a simplified estimate of the calcium oxalate (CaOx) saturation level has been proposed, i.e., the AP(CaOx) index, and has been shown to have a good correlation with the ionic activity product of CaOx. It contains a volume factor, and so was only used in some special situations (4-hour or 24-hour urine samples^{2, 3)}). By contrast, the CaOx risk index, which was reported simultaneously, includes creatinine(Cr)-related urinary variables and does not have a volume factor²⁾. Therefore, this index has been used even though it requires the analysis of Cr levels in addition to the other variables and though interindividual variations in Cr excretion sometimes make comparison between different patients difficult³⁾. The standardized AP(CaOx)

index, in which the influence of the volume factor is disregarded by considering the volume to be identical at all times, has been suggested to be superior for group comparisons³⁾. In the clinical situation, the collection period almost always varies, suggesting that a volume factor should be incorporated into the original AP(CaOx) index. Subsequently, the AP(CaP) and AP(Bru) indices were formulated and proven to be comparable⁴⁾. In order to make these indices applicable to urine samples obtained over any time period, new formulae incorporating a function of urine collection time are proposed in this paper.

MATERIALS AND METHODS

Regarding the urinary saturation index of calcium oxalate (CaOx), the AP(CaOx) index, Tiselius proposed the following formula²⁾:

$$KI \times Ca^{0.71} \times Ox/Mg^{0.14}/Cit^{0.10}/V^{1.2}$$

The Ap(CaOx) index was calculated from the excretion of calcium (Ca), oxalate (Ox), magnesium (Mg), citrate (Cit), and phosphate (P) (all expressed in m-

mol), as well as the urine volume (V) (expressed in liters) in a given collection period (t) (expressed in hours). The K1 factor is a time constant, and its values were originally available only as 6.2 and 3.8 for 4-hour and 24-hour urine collections, respectively^{2,5,6}. However, the K values were subsequently reported by Tiselius for 8 different collection periods from 1 hour to 24 hours, with the 24-hour urine volume being fixed at 1,500 ml³. The following equation expresses the relationship between the K1 and K values: $K1 = K \times (1.5 \times t/24)^{1.2}$. Eight values for the K1 factor at 8 different collection periods were obtained by this calculation (Table 1). Then, the relationship between the collection period (t) and the K1 value was tested statistically using regression analysis to determine whether there was any natural rule for this relation in this study.

Regarding the urinary saturation indices of CaP and brushite, Tiselius also proposed the following formulae⁴:

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

(When the urine collection period is close to 24 hours, the pH exponent of 7.0 should be replaced with an exponent of 6.8.)

Ap(Bru) index: $B \times Ca^{1.07} \times P^{0.82} \times pH^{6.8} / Cit^{0.46} / V^{1.53}$.

Regarding these indices, the A and B values have already been reported for 10 given times⁴. Therefore, their relationship to the time was tested similarly (regression analysis) in this analysis. In order to fill any gaps, this interpolation was performed for any collection period of less than 24 hours.

RESULTS

Table 1 shows the values of the K1 factor calculated from the K values reported by Tiselius in 1989³. There was a significant relationship between the collection period (t) and the K1 value, with a correlation coefficient (r) of -0.9899 ($p < 0.01$, Fig. 1). Therefore, the AP (CaOx) index could be defined as follows:

$\{8.646 - 1.610 \times \ln(t)\} \times Ca^{0.71} \times Ox/Mg^{0.14} /$

Collection Period (hour)	K Factor	K1 Factor
1	253.5 ($\times 0.0625^{1.2} =$)	9.1
2	90.0 ($\times 0.125^{1.2} =$)	7.4
3	50.0 ($\times 0.1875^{1.2} =$)	6.7
4	32.8 ($\times 0.25^{1.2} =$)	6.2
6	17.9 ($\times 0.375^{1.2} =$)	5.5
12	6.50 ($\times 0.75^{1.2} =$)	4.6
18	3.56 ($\times 1.125^{1.2} =$)	4.1
24	2.34 ($\times 1.5^{1.2} =$)	3.8

Table 1. K1 factor calculated by multiplying (standard urine volume in liters)^{1,2} by K, previously reported by Tiselius for the standardized calculation of the AP(CaOx) index at a flow rate of 1,500 ml/24 hour.

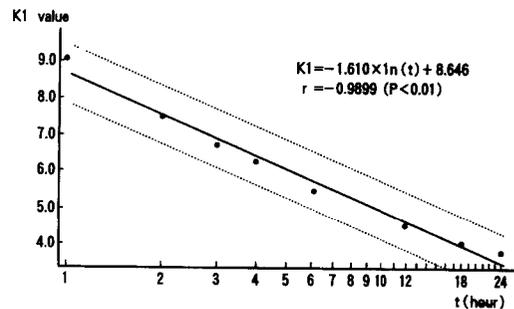


Fig. 1. Values of the K1 factor show a significant correlation with the urine collection period (hours). Dotted lines represent 95% confidence limits for the line of regression.

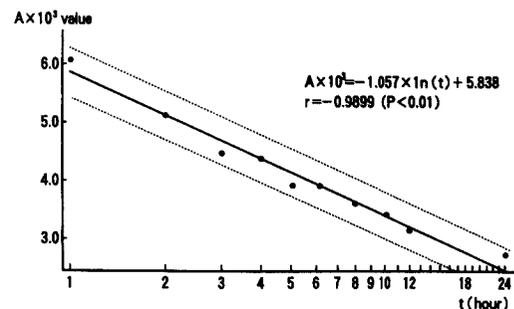


Fig. 2. Values of the A factor $\times 10^3$ show a significant correlation with the collection time (hours).

$Cit^{0.10} / V^{1.2}$.

There was also a significant relationship between the collection period and the A

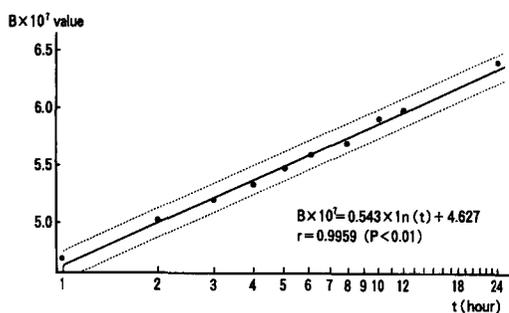


Fig. 3. Values of the B factor $\times 10^7$ show a significant correlation with the collection time (hours).

value ($r = -0.9899$, $p < 0.01$, Fig. 2), so the AP(CaP) index could be defined as follows:

$$\{5.838 - 1.057 \times \ln(t)\} / 10^3 \times \text{Ca}^{1.07} \times \text{P}^{0.70} \times (\text{pH} - 4.5)^{7.0} / \text{Cit}^{0.20} / \text{V}^{1.31}$$

(when the urine collection is close to 24 hours, the pH exponent of 7.0 should be replaced with an exponent of 6.8).

In addition, a significant relationship between the collection period and the B value was noted ($r = 0.9959$, $p < 0.01$, Fig. 3), so the AP(Bru) index could be defined as follows:

$$\{4.627 + 0.543 \times \ln(t)\} / 10^7 \times \text{Ca}^{1.07} \times \text{P}^{0.82} \times \text{pH}^{6.8} / \text{Cit}^{0.46} / \text{V}^{1.53}$$

The original formulae could be modified as shown above to have the K1, A, and B factors incorporated with a time factor.

DISCUSSION

The urinary activity products of the ionic constituents of calculi have the potential to provide the best estimate of urinary saturation. The computer program EQUIL2, presently the most accurate means of assessing the risk of crystal formation, provides the states of saturation for eight components of kidney stones (calcium oxalate monohydrate, brushite, hydroxyapatite, struvite, uric acid, sodium urate, ammonium urate, and potassium urate). This EQUIL program, originally designed by Finlayson and his associates⁷⁾ to obtain the free-ion concentration in complex polyelectrolyte solutions, is now widely used by various investigators, as it provides valuable insights into renal cal-

culus formation⁸⁾. For the computation procedure, the urinary pH, and the total concentrations (moles/liter) of Na, K, Ca, Mg, NH_4 , phosphate, sulfate, oxalate, citrate, urate, pyrophosphate, carbonate, and Cl must be entered. However, even with all these parameters, the method still does not consider all the factors that may be involved in the stone-forming process, e.g., aggregation, retention, nucleation, and the roles of the matrix and macromolecular components⁹⁾.

In order to expand the method's usefulness in the clinical setting, simplified estimates of the ionic activity product {AP (CaOx) index} and the metabolic risk situation (CaOx-risk index) were developed by Tiselius in 1982²⁾. The AP(CaOx) index and its standardized estimate are useful measures of urinary saturation provided that the urine volume during the collection period is representative of the normal situation⁹⁾. The CaOx risk index, which contains creatinine-related urinary variables without a volume factor, is useful when the method of determining the urine volume is not reliable. A good correlation has been shown between the risk of calcium oxalate crystal formation (CaOx-CR) and either the AP(CaOx) index or the CaOx-risk index, where CaOx-CR is a crystal inhibitory assay representing the net result of nucleation, crystal growth, and inhibition of crystallization¹⁰⁾.

The AP(CaP) index, a simplified estimate of the ion-activity product of urinary CaP, was subsequently formulated in a similar fashion to express the risk of CaP crystal formation. However, a problem remained concerning the pH exponent, which is usually set as 7.0, but which must be changed to 6.8 when the collection period is close to 24 hours. Precise data concerning this point are not yet available, but if the pH exponent may be varied as a function of time, there is a possibility of incorporating it into the formula to increase the ease of calculation. Crystallization of octacalcium phosphate (OCP) and hydroxyapatite (HAP) usually takes place in alkaline urine, and it is possible

to convert the AP(CaP) index to approximate estimates of both the OCP and HAP ion-activity products⁴⁾. The saturation level with respect to brushite (Bru), the form of calcium phosphate most frequently encountered in acid urine, can be expressed by the AP(Bru) index using the same principles.

Thus, by using the AP(CaOx) index, AP(CaP) index and AP(Bru) index, the risk of forming urinary crystals important for the production of calcium stones can be estimated after analyzing the calcium, oxalate, phosphate, citrate, magnesium, pH, and urine flow in a given hour's urine sample. The method has now been interpolated in this communication so as to extend it to any urine collection period by incorporating the time factor into the formulae. It is thus possible to study the level of saturation of fresh urine samples collected during different risk periods of the day. Therefore, the interpolated indices presented here make the computer calculation easier by adding just one parameter (the collection period), without any need to change the A, B, and K1 factors corresponding to the collection period.

In conclusion, this author interpolated the Tiselius equations to the time within 24 hours not covered in the literature^{2,3,5,6)}. However, further study seems necessary to prove that such processes are reflected by crystal-inhibitory assays.

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(迅速掲載)

和文抄録

尿酸カルシウムと磷酸カルシウムの尿中イオン活量積測定法の改良

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尿酸カルシウム、磷酸カルシウム、酸性磷酸カルシウムのイオン活量積の簡易測定法として、それぞれ、AP(CaOx) 指数, AP (CaP) 指数, AP(Bru) 指数が Tiselius により報告され、これらはそれぞれの結石形成物質の尿中飽和度を示している。これらの指数は、尿中のカルシウム、マグネシウム、尿酸、磷酸、クエン酸、尿量、pH などの変数より求められる。また、それぞれの指数には採尿時間により異なる係数が

与えられるが、その採尿時間は限定されていた。本検討では、それぞれの係数が採尿時間と相関することを示した。従って、係数をその計算式に組み込むことが可能となり、24時間以内の如何なる採尿時間でも計算式が利用できるようにした。これにより、短時間の採尿の飽和度測定にも有用である。

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