Influence of Urinary Stones on the Composition of a 24-Hour Urine Sample

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Background: It can be assumed that stones in the urinary tract continuously increase in size by incorporating material from urine. Consequently, urine will exhibit depleted concentrations of lithogenic constituents when urinary stones are present in the patient's urinary tract.

Methods: To calculate the influence of the depletion effect, we considered two different models of stone growth. In the first model, the increase in stone size depends only on the urinary concentration of a lithogenic substance; the second model also considers the surface area of the growing stone. The case of only one kidney being affected by stone formation is considered separately. We discuss example calculations involving the formation of calcium oxalate.

Results: The calculated depletion effects are of a non-negligible order of magnitude. Assuming both a measured oxalate concentration of, e.g., 0.37 mmol/L and a reasonable in vivo stone growing rate of 10 mm³/day, a relative underestimation of the real “in situ” oxalate concentration between ~21% (model 1) and ~42% (model 2) occurs. The depletion effect increases markedly with increasing stone growth rate.

Conclusions: Metabolic status can be evaluated correctly only in patients who have been declared “stone-free”, e.g., after stone removal. Because the expected stone-related depletion effect in most cases is of high clinical relevance, we recommend estimating the effect of the order of magnitude of the depletion on actual urinary composition.

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Patients with frequent stones often excrete increased amounts of one or more lithogenic materials, such as oxalate. The increased excretion values, however, often are not as high as expected for the observed severity of stone formation. In this report, we asked whether the stones, as they continue to grow, accumulate the relevant materials at a rate sufficient to measurably decrease the rate of excretion of those materials.

Although some people form a macroscopic stone within a few months, others do so over a period of several years. The process of stone formation changes, to a greater or lesser extent, the composition of the urine, i.e., the concentration(s) of lithogenic substance(s) before and after a growing concrement is passed must be different (Fig. 1).

To our knowledge, no clinical study on this effect has been performed. To estimate the order of magnitude of the effect, we present a mathematical strategy for computation of the amount of urinary depletion expected during ongoing subsequent calcium oxalate stone formation, i.e., in the presence of a calcium oxalate stone in the urinary tract. Two basically different models, linear and surface-dependent growth, are taken into consideration. We show that, under certain circumstances, the existence of stone material within the urinary tract strongly influences the composition of the voided urine. Because the concentrations of (at least) the lithogenic substances are lowered, interpretation of a patient’s health status will therefore be too optimistic.

After mathematical formulation of the physical problem in Materials and Methods, we illustrate the clinical relevance of the obtained results in the Results and Discussion. Readers not primarily interested in mathematics may skip to the “Model Parameters” section in the Materials and Methods.

Materials and Methods

Most mathematical models of stone formation [see, for example, Refs. (1, 2)] focus on the initial stage of crystal formation. In contrast, the process of macroscopic stone formation, where a measurable effect on the urinary composition might be expected, is rarely considered [see, for example, Ref. (3)].

In the following we focus on the formation of calcium
oxalate stones. The mean depletion of both oxalate and calcium can be calculated directly from the mass balance without further assumptions about the process of formation. Let us assume that stones of total volume \( V \) have been formed within a period \( \tau \). If \( \nu \) denotes the volume of a stone composed of 1 mol of substance (here calcium oxalate), the molar amount of precipitated substance is \( \nu V \). With \( \phi \) as the mean urinary flow rate (e.g., in L/day), the total excreted volume within the period \( \tau \) accumulates to \( \phi \tau \). Because of conservation of mass, the mean depletion rate equals \( (\nu V)/(\phi \tau) \).

This result provides a rough estimate of the effect. However, under real conditions the depletion depends on time, e.g., as a result of growing stone surfaces. In the following we consider two different models of stone formation. In the first, simpler model, we assume that the crystallized volume is distributed among several stones of different sizes. In this model, we do not consider the size of the individual stones, but only the evolution of the total volume \( V(t) \) through time \( t \). Because we cannot determine the total surface area in this model, the rate of crystallization is assumed to depend only on the concentration of oxalate in the urine. In general, the rate of growth also depends on the amount of calcium. However, usually the urinary calcium (molar) concentrations clearly exceed those of urinary oxalate. Thus, the relative changes in the oxalate concentration attributable to stone formation are stronger than those in the calcium concentration, so that we can focus on oxalate.

The second model considers the formation of a single, spherical stone. We assume that the rate of crystallization depends on the concentration of oxalate and on the surface area of the stone. The real effect is expected to be found between these two extremes.

In both models, we assume that stone formation starts at \( t = 0 \), i.e., \( V(0) = 0 \); this coincides with the moment when stone formers are declared “stone-free” after stone removal (i.e., the sizes of the remaining particles are below the detection limit). The total crystallized volume of the recurrently formed urolith is estimated at the time \( t = \tau \) by radiologic or ultrasound assessments (4). To simplify matters, we consider some kind of “box reactor” where urine is supplied at a constant rate \( \phi \). As a result of stone formation, the concentration \( c(t) \) of oxalate in the inflow (i.e., the initial glomerular urinary oxalate concentration). According to the mass balance, the outflow coincides with the inflow \( \phi \). As a result of stone formation, the concentration \( c(t) \) in the outflow (i.e., the voided urine) will be lower than \( c_i \) and may be time dependent. However, the concentration \( c_i \) maintains stone formation.

At the time \( \tau \), both the urinary oxalate concentration and the stone volume are measured. In the following, we use the symbols \( c = c(\tau) \) and \( V = V(\tau) \).

The mass balance for the system reads:

\[
\phi c_i = \phi c(t) + R(t)
\]

where \( R(t) \) is the rate of stone formation at the time \( t \), measured in mm\(^3\)/day. The total crystallized volume of the stone(s) increases according to:

\[
\frac{d}{dt} V(t) = \nu R(t)
\]

**MODEL 1**

In the first model, the growth rate \( R(t) \) depends only on the oxalate concentration. It is not possible to determine the concentration in the vicinity of individual stones in our box model. However, the concentration equals \( c_i \) before the urine passed the first stone. After the last stone is passed, it corresponds to the experimental value \( c(t) \). We therefore assume that the rate of crystallization \( R(t) \) is proportional to the mean value of both concentrations:

\[
R(t) = \alpha[c_i + c(t)]/2
\]

with \( \alpha \) as a constant. In general, crystallization takes place only if the concentration exceeds a given threshold. This effect can be regarded by considering excess concentrations instead of absolute concentrations. In the following, both \( c(t) \) and \( c_i \) shall be excess concentrations, i.e., the difference between the real concentration and the threshold concentration.

For this approach, Eq. 1 leads to:

\[
c(t) = \frac{\phi - \nu/2 \alpha}{\phi + \nu/2 \alpha} c_i
\]
\[ V = vR(t)\tau = \frac{\phi}{\theta} \frac{\phi}{\phi + \sqrt{\theta}}c_i\tau \quad (4) \]

so that:
\[ \alpha = \frac{\phi V}{v\phi c_i\tau} - \frac{\sqrt{\theta}}{\phi} \quad (5) \]

Inserting this result into Eq. 3 finally leads to:
\[ c_i = \left(1 + \frac{V}{\tau cv\phi}\right) c \quad (6) \]

where the term \( V/\tau \) is the mean growth rate of the stone (mm³/day) within the observation period between \( t = 0 \) and \( t = \tau \).

Obviously this model predicts a time-independent depletion of lithogenic substances attributable to ongoing stone growth. As expected, the depletion coincides with the mean value obtained from the mass balance given above.

**MODEL 2**
In the second model, the growth rate \( R(t) \) depends on the current size of the stone. The simplest reasonable approach regarding this phenomenon assumes that the growth rate (mm³/day) is proportional to the actual surface area \( A(t) \) of the stone, i.e., \( \alpha = \beta A(t) \), where \( \beta \) is a constant. In case of a spherical stone of radius \( r(t) \) [\( V(t) = 4/3\pi r(t)^3 \) and \( A(t) = 4\pi r(t)^2 \)], Eq. 2 becomes:
\[ \frac{\partial}{\partial t}r(t) = \frac{\sqrt{\theta}}{\phi} [c_i + c(t)] \quad (7) \]

The concentration \( c(t) \) can be determined from Eq. 1 according to:
\[ c(t) = \frac{1 - \frac{2\pi\beta}{\phi} r(t)^2}{1 + \frac{2\pi\beta}{\phi} r(t)^2} c_i \quad (8) \]

Applied to the time \( \tau \), this relationship determines the parameter \( \beta \) according to:
\[ \beta = \frac{\phi}{2\pi r(\tau)^2} c_i - c \quad (9) \]

With this result, Eq. 7 becomes:
\[ \frac{\partial}{\partial t}r(t) = \frac{v\phi c_i(c_i - c)}{2\pi[(c_i + c)r(\tau)^2 + (c_i - c)r(t)^2]} \quad (10) \]

This relationship can be written in the form:
\[ \frac{\partial}{\partial t}[2\pi(c_i + c)r(\tau)^2r(t) + \frac{\sqrt{\theta}}{\phi}(c_i - c)r(t)^3] = v\phi c_i(c_i - c) \quad (11) \]

Integrating this equation from 0 to \( t \) leads to:
\[ 2\pi(c_i + c)r(\tau)^2r(t) + \frac{\sqrt{\theta}}{\phi}(c_i - c)r(t)^3 = v\phi c_i(c_i - c)\tau \quad (12) \]

This relationship describes the growth of the stone through time. Applied to the time \( t = \tau \), it leads to:
\[ (2c_i + c)V = v\phi c_i(c_i - c)\tau \quad (13) \]

and thus:
\[ c = \frac{1 - \frac{V}{\tau c_i\phi}}{1 + \frac{V}{\phi c_i}\tau} c_i \quad (14) \]

or:
\[ c_i = \left[ \left(1 + \frac{c}{\tau cv\phi}\right)^{-1} + \left(1 + \frac{c}{\tau cv\phi}\right)^{2} + \frac{c}{\tau cv\phi} \right]^{2} \quad (15) \]

**MODEL 2', SPECIAL CASE OF MODEL 2**
Thus far we have focused on general crystallization phenomena in a box model. In our application, we should consider the fact that there are two kidneys. If stone formation takes place uniformly in both kidneys, our results remain valid. In this case, both the flow rate \( \phi \) and the volume \( V \) are distributed between the two kidneys, which means that we have to replace \( \phi \) with \( \phi/2 \) and \( V \) with \( V/2 \) in Eqs. 6 and 15, respectively. It can easily be seen that this modification does not affect the results of either model 1 or model 2. The same applies to model 1 if we assume that stone formation takes place in one kidney only. In this case, we must replace \( \phi \) with \( \phi/2 \), but keep \( V \).

Finally, the measured concentration \( c \) is the mean value of the initial concentration \( c_i \) (coming from the stone-free kidney) and the concentration \( c \) predicted by the model. For model 1, this modification has no effect, whereas Eq. 15 (model 2) becomes:
\[ c_i = \left[ \left(1 + \frac{c_{\text{free}}}{\tau cv\phi}\right)^{-1} + \left(1 + \frac{c_{\text{free}}}{\tau cv\phi}\right)^{2} + \frac{c_{\text{free}}}{\tau cv\phi} \right] c \quad (16) \]

**MODEL PARAMETERS**
To calculate values of \( c_i \) in dependence of \( c, \phi, \) and \( V/\tau \), the following reasonable values for the parameters \( \tau, V, \phi, \psi, V/\tau, \) and \( c \) are chosen: growth rate \( V/\tau = 1, 2, 5, 10, \) and 20 mm³/day. These growth rates result after a period of 1 year in uroliths indicated by radii of 4.43, 5.59, 7.58, 9.55, and 12.03 mm, respectively. The molar volume of calcium oxalate is \( \psi = M/\delta = 65.82 \text{ cm}^3/\text{mol} \), where \( M = 146.1 \) g/mol and \( \delta = 2.22 \) g/cm³ as the molar weight and the
density of calcium oxalate monohydrate, respectively. The (average) urine flow rate $\phi$ amounts to 1500 cm$^3$/day, a typical value observed in stone-forming individuals. The measured urinary oxalate concentration is set to be $c = 0.37$ mmol/L. The latter value is calculated from $\phi$ and the established limit value of the oxalate excretion of 0.56 mmol/day, which is applied to distinguish normo-oxaluric urines from those to be termed "(mild) hyperoxaluric" (5, 6).

**Results**

The relative underestimation of the measured urinary oxalate concentration $c$ in dependence of the growth rate of the urolith, $V/\tau$, is shown in Fig. 2. The results are given for model 1 (Eq. 6), model 2 (Eq. 15), and model 2’ (Eq. 16). The surface area-dependent calculations of model 2 and model 2’ produce higher depletion values compared with those obtained from the simple linear approach of model 1. The results of models 1 and 2 differ by a factor of $\sim 3$ at low concentrations; the difference decreases to a factor of $\sim 2$ at higher concentrations. The larger the growth rate $V/\tau$, the higher the depletion effect that has to be expected. In extreme, but unfortunately still realistic cases, the ongoing stone growth may alter the actual urinary oxalate analysis more than 40%.

The effect of model 2’ is also illustrated in Fig. 2. It will be smaller than shown if stone formation affects both kidneys, but it is still considerably larger than the effect predicted by model 1. Because this scenario is between the two extreme cases defined by model 1 and model 2, we focus on this case in the following.

The dependence of $c_i$ from $c$ (Eq. 16) for various reasonable precipitation rates $V/\tau$ is illustrated in Fig. 3.

With increasing values of $V/\tau$, the differences between the values of $c$ and related $c_i$ become remarkably high.

Thus, the correct analytical determination of $c$ gives only an erroneous low estimate of the actual amount of lithogenic substance excreted by the kidney.

**Discussion**

By developing two different theoretical models, we have shown upper and lower estimates of the urinary oxalic acid depletion effects on the urinary composition attributable to actually (in vivo) growing uroliths. Although both models reflect simplifications of the real, much more complicated, processes, their outcomes allow estimations of the real in vivo situations. The restriction to spheric uroliths reduces model complexity. In general, the effect is not strongly dependent on the shape of the stone. In cases in which a growth is confined, the effect may be slightly smaller than predicted by model 2 or 2’, respectively; in cases involving anisotropic growth or complex stone shape, the effect may even be stronger.

In addition to the shape of the stone, the particular anatomical situation in which the stone grows influences the depletion effect. In general, only a fraction of the total amount of oxalate takes part in stone formation. Kavanagh (3) estimated that this fraction was one-sixth. In Fig. 2, this effect becomes visible when model 2 and model 2’ are compared. In model 2’, one-half of the total amount is available. Assuming that only one-sixth is available, the effect would be slightly smaller than predicted by model 2’.

Our model calculations clearly point out that the effect of an ongoing stone formation process may considerably
deplete the oxalate concentration of a 24-h urinalysis. The limits of the analytical accuracy for the determination of the urinary oxalic acid concentration are clearly exceeded [within-run precision CV, 1.1–3.9% for enzymatic determinations and 2.2–6.7% for the HPLC-enzyme reactor method (7)]. The estimated error in oxalate determination attributable to a urinary stone is, in any case, of an order of magnitude, with obvious clinical relevance. Patients classified as being “normooxaluric” from their urinalysis (i.e., $c \leq 0.37$ mmol/L at a urine volume of $1500$ cm$^3$/day) may in fact, but undetected, form highly hyperoxaluric urines (i.e., $c_i \gg 0.37$ mmol/L).

The following example underlines the importance of this outcome: Let us consider a recurrent stone former’s average urine with [based on Robertson et al. (8)] $129$ mmol/L sodium, $41$ mmol/L potassium, $5.33$ mmol/L calcium, $3.37$ mmol/L magnesium, $22.7$ mmol/L ammonium, $19.8$ mmol/L phosphate, $16.7$ mmol/L sulfate, $2.27$ mmol/L uric acid, $0.37$ mmol/L oxalate, and $2.13$ mmol/L citrate at pH 6.23, with the urine volume being $1500$ cm$^3$/day. When we assume that this composition has been analyzed from a 24-h urine of a patient suffering from a spheric urolith grown over 6 months to a volume $V(\tau)$ of $0.5$ cm$^3$ (i.e., $\tau \approx 0.49$ day and $V/\tau = 2.74$ mm$^3$/day), a stone growth-related alteration of the oxalate concentration of approximately $\pm 17\%$ must be considered (Fig. 2, model 2). Using Eq. 16, the oxalate concentration $c_o$ which is actually responsible for stone formation, amounts to $0.44$ mmol/L instead of the 0.37 mmol/L measured (Fig. 3).

Because the concentration of urinary calcium decreases equimolarly with the oxalate concentration when calcium oxalate precipitation occurs, the measured calcium concentration of $5.33$ mmol/L must also be changed. The corrected calcium concentration is $5.40$ mmol/L. As a result, the urinary relative calcium oxalate supersaturations [based on EQUIL (9)] change from 13.32, the value obtained from the measured analysis, to 15.58 ($\pm 17\%$). These differences exceed the estimated calculation error of the relative supersaturation of $\pm 10\%$ derived from the individual uncertainties in the determinations of the EQUIL input parameters (10).

Although the urine composition given as an example still seems to be of normooxaluric composition, the patient actually suffers from hyperoxaluria. A patient with this diagnosis, however, needs specific therapeutic measures.

In conclusion, evaluation of the patient’s metabolic situation should ideally be undertaken after total stone removal. In all other cases, i.e., if any stone material is actually present in the patient’s urinary tract, it is necessary to take these uroliths into account. An estimate of the stone growth-related depletion of the lithogenic substances in the urine sample should be performed to avoid: (a) (optimistic) misinterpretation of the patient’s actual health state from the urinalysis, and (b), a resulting overestimation of the treatment’s success.

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**References**