

COMPUTATION AND MODELING OF THE STONE-GROWTH RELATED URINARY DEPLETION EFFECT USING “DEPLETION V1.0”

N. Laube^{1*}, M. Pullmann^{2*}

¹Division of Experimental Urology, Department of Urology, University of Bonn, Germany

²Geodynamics and Physics of the Lithosphere, University of Bonn, Germany

Abstract

Purpose: During metabolic evaluation stone patients often present with calculi in the urinary tract or are suffering from high frequent formation of small microliths passing routinely the urinary tract. These concrements are presumably in a state of continuous growth. Consequently, the concentrations of the lithogenic components in the voided urine must decrease. Thus, treatment schemes inevitably fail to focus on the true pathogenic urinary composition. Instead, they focus on underestimated concentrations. This can attain high clinical relevance. In recent publications, we introduced a complex physical approach and provided mathematical equations which can be solved analytically. However, to date, solving the equations with a pocket calculator remains cumbersome.

Materials and Methods: Depletion V1.0 was developed to integrate the calculation of the depletion effect into the daily treatment of stone patients. Minimum requirement for Depletion V1.0 is the Java 1.2 platform runtime environment, which is supported on nearly all operation systems including Linux, MacOS X, and Windows. The program can be used directly within a Java-compliant web browser (e.g. Firefox, Mozilla, Internet Explorer) or from the program's storage location. The implemented data base provides stone type relevant parameters. Data input is performed via an easy-to-handle graphical user interface.

Results: Results are given as values and interactive plots; computation and update of plots are performed in real time. Result sheets can be exported to platform-independent EPS-format or printed out directly.

Conclusions: Depletion V1.0 enables the medical practitioner to obtain an improved interpretation of the stone patient's health status. As input, only one set of easy-to-achieve clinical standard parameters is required. The program will be available from the authors as freeware.

Key words: urinalysis, data analysis, data visualization, data interpretation

INTRODUCTION

When interpreting urinalyses of stone formers, potential stone-growth related alteration of the concentrations of the lithogenic components must be considered. In our stone clinic, approximately 75% of the

stone patients present with concrements in the urinary tract during metabolic evaluation. These concrements are, on the time scale of observation and according to the principles of “classical physics” since Newton, presumably in a state of continuous growth; in each patient, however, at different individual rates. The assumption of “continuous growth” becomes obvious when taking into consideration patients who recurrently form small stones which pass frequently the urinary tract. These concrements are the result of continuous new formation of solids. Anyhow, the lithogenic components are exclusively precipitated from urine in any occurrence of stone formation. Consequently, according to the law of mass conservation [1], the concentrations of the lithogenic components (e.g. Ca, oxalate, phosphate) in the voided urine must decrease. The universal validity of the law of mass conservation is generally accepted and has been empirically proven in countless experiments.

In case of urinary stone growth taking place during urine collection, urinary composition alters. The only question is whether this effect shows clinical relevance or not. If “yes” – at least under specific circumstances – treatment schemes must then inevitably fail to focus on the true pathogenic urinary composition. Instead, they focus on underestimated concentrations. In unfavorable situations, a patient's real hyperoxaluric state may thus not be detected since the urinary depletion effect may have shifted its analyzed oxalate concentration into the normoxaluric range. The depletion effect then clearly gains clinical relevance [2, 5].

While there is no absolute certainty that stone growth does take place during the (randomly) chosen period of urine collection, assumption of stone growth in progress is justified since the principle of continuity can be presumed to be sufficiently valid in urine samples collected over a period of at least 12 hours. The use of an “average growth rate” determined from a retrospective determination of stone volume change provides a reasonable lower estimate of the growth rate which presumably occurred during collection (model 1 in [3]).

In two subsequent scientific publications – introducing a conservative mathematical model following the fundamental ideas presented in [1] and adopted to

*Both authors share first authorship.

$$c_i = \left\{ 0.5 \left[1 + (3\gamma - 1) \frac{V}{v\phi\gamma C} \right] + \sqrt{\left\{ 0.5 \left[1 + (3\gamma - 1) \frac{V}{v\phi\gamma C} \right]^2 + \frac{V}{v\phi\gamma C} \right\}} \right\} c \quad (\text{Eq.1})$$

the boundary conditions of urolith formation – we demonstrated that a lower estimate of the depletion's extent can be sufficiently calculated from a set of easy-to-obtain parameters [3, 4]. The extended model takes into account a broad spectrum of clinical situations. Inter alia, it allows consideration of the kidneys' differential volume function as well as of the reasonable assumption that only a fraction of the urine formed by the stone-bearing kidney takes part in stone formation.

Based on a complex physical approach considering surface-dependent growth kinetics [3], mathematical equations were discovered which can be solved analytically. Equation 1 is presently the most evolved approach for calculating the extent of the stone growth-related urinary depletion [4] (see Eq. 1).

With c_i as the, in respect to the stone, proximal concentration of (e.g.) oxalate, and c as the distal concen-

tration (i.e. the measured concentration); the concentration c_i is the concentration which maintains stone formation ($c_i \geq c$). The term V/τ is the stone's mean growth rate [mm³/d] within the observation period between $t = 0$ and $t = \tau$; V denotes the total stone volume formed in the period t . The parameter ϕ is the mean urinary flow rate [ml/d] referring to 24 hours (i.e. 24h urine volume). When investigating an urine sample collected over a period of less than 24 hours, calculation must be performed by using the respective ϕ presumably obtained in 24 hours. Therefore, the measured urine volume has to be scaled by the ratio of the normalization period of 24 hours and the actual collection time.

The factor γ describes the fraction of ϕ passing the stone(s), whereby $0 \leq \gamma \leq 1$. v denotes the molar volume of the stone type being formed, e.g., calcium oxalate. This parameter set includes the variables on

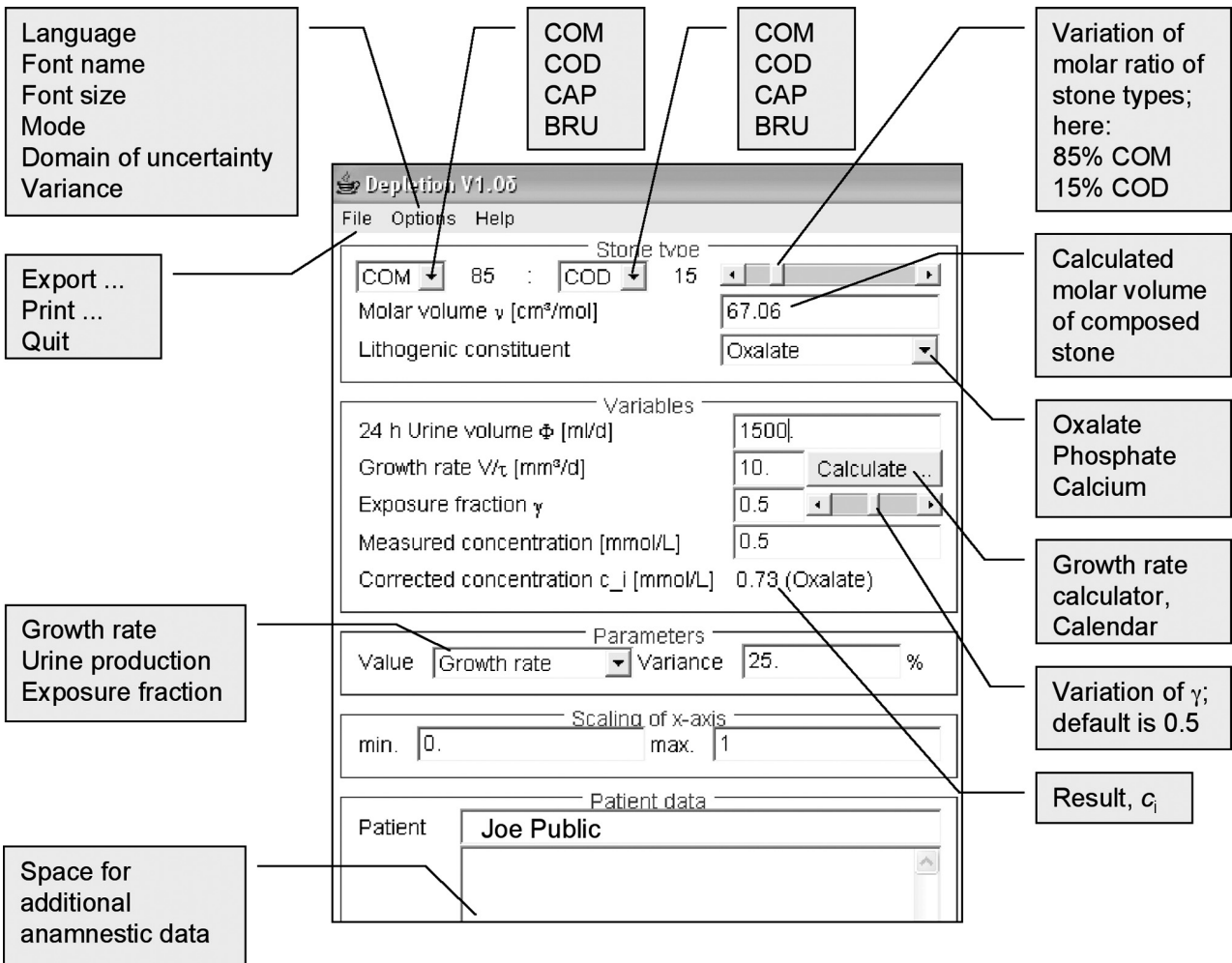


Fig. 1. Depletion V1.0. Data input is carried out via an easy-to-handle graphical user interface (GUI). COM: calcium oxalate monohydrate; COD: calcium oxalate dihydrate; CAP: carbonate hydroxylapatite; BRU: brushite. Additionally, the mineral phase "struvite", $MgNH_4PO_4 \cdot 6H_2O$, can be taken into account. Thus, Mg can also be chosen as lithogenic component.

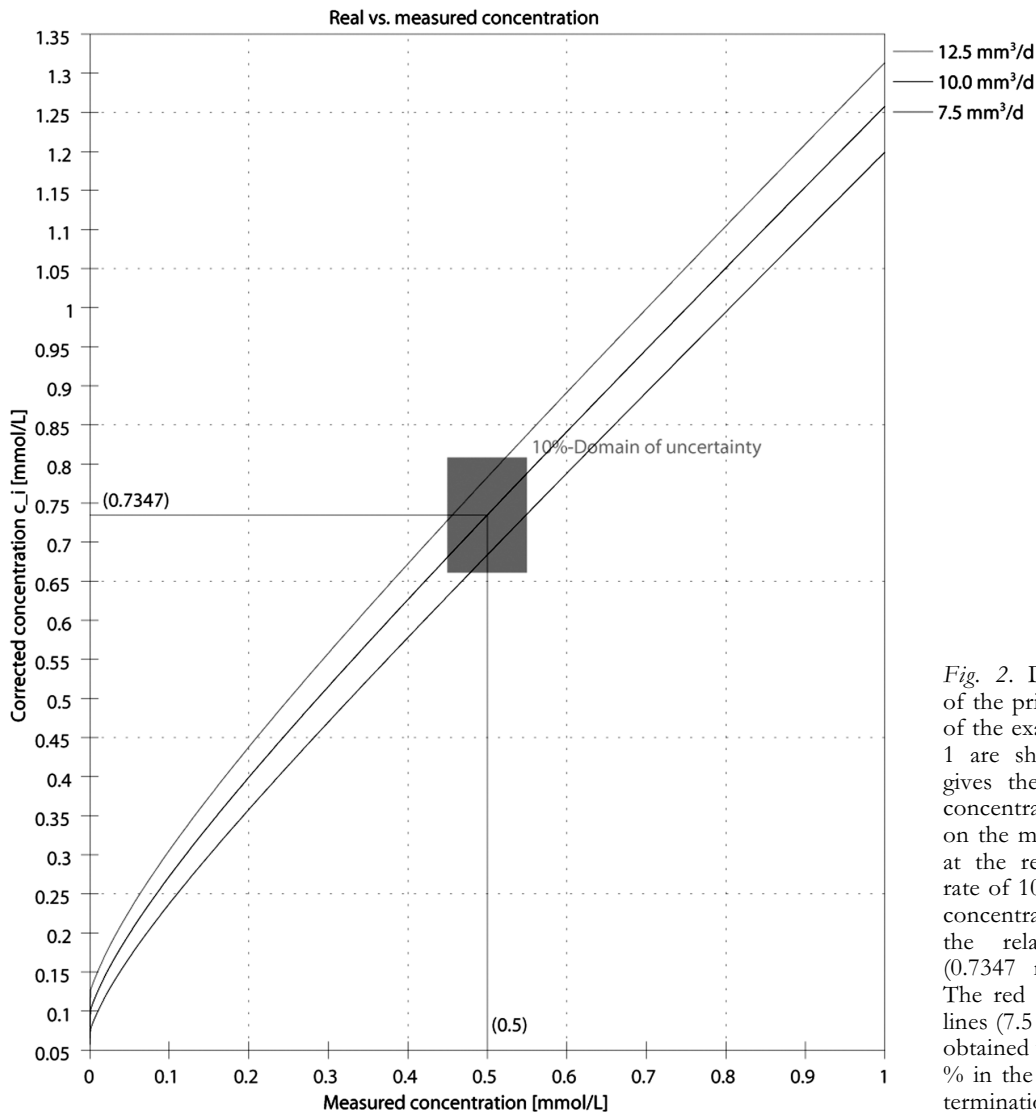


Fig. 2. Depletion V1.0. Extract of the printout sheet. The results of the example data set of Figure 1 are shown. The black graph gives the initial urinary oxalate concentration c_i in dependence on the measured concentration c at the reasonable stone growth rate of 10 mm³/d. The observed concentration c (0.5 mmol/l) and the related concentration c_i (0.7347 mmol/l) are indicated. The red (12.5 mm³/d) and blue lines (7.5 mm³/d) give the results obtained when a variance of $\pm 25\%$ in the stone growth's rate determination is considered.

which the extent of the urinary depletion mostly depends.

However, even analytically to solve, evaluation of equation 1 is considerably labour-intensive when performed with a pocket calculator. Minimum requirements are a programmable pocket calculator or a spread sheet. After relatively laborious procedures, the exact, but only "fixed" result of the particular input data set can be obtained without any possible additional dynamic parameter variation. Furthermore, with the above mentioned calculation strategies, no rapid back and forth visualization of the dependence of the depletion effect's extent in relation to any selected parameter of the different variables is possible.

Thus, a computer program which calculates the required data in detail and which also allows direct modeling with access to a data base of useful stone type relevant parameters could be helpful.

In the following, we present the computer program Depletion V1.0 which allows easy-to-perform calculation of equation 1, and, additionally, enables the user to perform further computer-aided modeling in order to gain improved analysis, visualization, and interpretation of data.

MATERIAL AND METHODS

As the program should be available on all computational platforms with a consistent graphical user interface to ensure portability and to minimize the time required for familiarization, Java was chosen as the appropriate programming language of Depletion V1.0. Minimum program requirement is the Java 1.2 platform runtime environment, which is supported on nearly all operation systems, including Linux, MacOS X, and Windows.

Installation of additional software is not required. The program can be used directly within a Java-compliant web browser (like Firefox, Mozilla, Opera, InternetExplorer) or from any storage location. The single-file program requires a storage space of only 89 kByte. To date, English and German localizations are provided.

All control elements of the graphical user interface are placed within one window for a compact arrangement. Related parameters are grouped for improved clarity (Fig. 1). The input screen is separated into two sub-areas: the left panel for data input, the right panel for visualization of simulation results (Fig. 2).

Table 1. Input variables required to run Depletion V1.0.

Parameter	Source	Unit
(sphere equivalent) stone diameter or stone volume at two different moments	e.g., X-ray photographs, or 3-D kidney imaging	mm, mm ³
dates of X-ray or CT takings	–	–
stone composition (stones comprised of up to two salts can be considered whereby the individual mixing ratio can be taken into account)	e.g. FTIR spectroscopy	–
lithogenic constituent	–	–
mean volume of urine voided during 24h (Φ)	urinalysis	ml
measured urinary concentration of the lithogenic component under consideration (c)	urinalysis	mmol/l
(optionally) urine fraction passing the stone (γ), i.e. differential renal function (GFR, tubular function)	e.g., helical CT, MAG-3 scintigraphy	–

The current values are stored and restored between sessions. Therefore, only the patient's individual parameters must be updated. This significantly reduces input time of standard parameters.

The required, but easy-to-obtain, input variables are listed in Table 1. Figure 1 shows, as an example, a data set obtained from a patient treated in our stone clinic. This patient forms mostly solitary calcium oxalate stones with a high recurrence rate since more than seven years. The implemented data base provides stone type relevant parameters such as density and molar weight. The molar volume of the stone, v , will be calculated automatically according to the specified mineral paragenesis, i.e. the mixing ratio of the stone forming minerals (weddelite, whewellite, brushite, carbonate hydroxlyapatite, struvite). The lithogenic urinary constituents to be evaluated (e.g. calcium, oxalate, phosphate) can be selected with respect to the before specified bi-modal stone composition.

The patient's individual stone growth rate V/τ can be determined in two ways: (1) by obtaining direct information on the stones' volumes from, e.g., CT [6, 7, 8, 9], or (2) by entering the (sphere-equivalent) diameters of the stone(s) determined from, e.g., plain X-ray films; after specifying the related dates of the image takings, an internal perpetual calendar will automatically compute V/τ .

To stress the significance of each parameter, computation and update of graphics are performed in real time, i. e. any change of parameters will immediately influence the visualization of results. Apart from automatic scaling, the x-axis plot range can be individually set by specification of the lower and upper scale limits. When selecting a parameter and customizing its variation, two additional graphs may help to estimate sensitivity of results regarding this parameter. A specific usage of varied parameters is the consideration of experimental uncertainties within the process of measuring. Results are given simultaneously as numeric values and interactive graphics.

Graphics can be exported to platform-independent EPS-format or printed out directly. Printout sheets contain supplementary input parameters, patient data, and computed values.

RESULTS

In the example patient described in Figure 1 urinalysis revealed an oxalic acid concentration of 0.5 mmol/l. Considering a mean urinary 24h volume of approximately 1,500 ml, the patient shows a renal oxalic acid excretion of 0.75 mmol/d. However, stone growth was observed with an approximate growth rate of 10 mm³/d. A variance of 25 % in this rate was allowed.

Figure 2 illustrates the extent of the stone growth related depletion effect calculated via Depletion V1.0: Based on the input data set, the patient's urinary oxalic acid concentration proximal to the stone, c_i , presumably amounts to 0.73 mmol/l, corresponding to a excretion of 1.10 mmol/d. The difference of this result in relation to the urinalysis' raw data (+ 33.6 %) is of high clinical relevance. Even in case of a 25 % overestimation of the growth rate (i.e. 7.5 mm³/d instead of 10 mm³/d), the depletion effect's extent remains considerable, as c_i amounts to approximately 0.68 mmol/l.

DISCUSSION

It has been shown that formation of crystalline material from urine systematically depletes the urinary lithogenic components in the remaining urine. Urinary depletion takes place in any active stone former, all the more, the higher the value of the stone growth rate. The stone growth rate should be calculated from obtained data as its true extent is easily underestimated. Not only growth of large solitary stones but also of many small microliths formed at the same time can show high growth rates. In these cases considerably amounts of lithogenic components precipitate within a short period. The related alteration of urinary compo-

sition is then considerable and should be taken into account in urinalysis interpretation.

For example: 15 small spheric microliths (e.g. post-ESWL fragments) increasing their diameter from initially 0.7 mm to 2 mm within a period of two weeks reflect a growth rate of 5 mm³/d. Considering the urinary data of the before mentioned example patient, the difference between measured and calculated "undepleted" oxalic acid concentration amounts to approx. 20%. This difference is clearly of clinical relevance.

Large stones remaining for many years without growing discernibly larger are indicated by very low (effective) growth rates. Consequently, calculation of the related depletion effect' extent results in negligibly small changes in urinary composition.

Stone growth is a complex issue. In fact, it is controlled by a number of crucial issues since there are many important processes and parameters which influence the actual growth rate. Apart from detailed knowledge of changes in the surface area of the stone material, information concerning inhibitory macromolecules that are present (and that vary) and thus modify the rates of stone nucleation and growth would be of interest. Changes in temperature and partial pressure of carbon dioxide (pH) are further parameters which alter the urine's potential to form crystals. One may argue that detailed information on all of these (and further) factors is necessary in order to sufficiently estimate the extent of the stone-growth related urinary depletion. However, as the stone growth rate V/τ is determined from observation of the actual stone growth, the model calculation indirectly includes the net effect of all processes which influenced stone size increase during period τ .

The applied model concept of continuous growth corresponds to the justifiable assumption of an average growth rate, which must be positive for observed stone size increase. The theoretical and very rare case of natural stone dissolution in-vivo does not contradict to the model and can be handled by the presented program. If stone dissolution would take place in the patient, then, the average growth rate will be lowered. However, as long as the observed growth rate remains positive, urinary depletion inevitably took place to a certain amount. Due to the different orders of magnitude of both counteracting processes, and the lower probability of dissolution compared to growth, regarding of the urinary depletion effect based on an averaged growth rate leads still definitively to an improved estimation of the "real" situation. The resulting extent of urinary depletion can be estimated by, for example, our model.

CONCLUSIONS

Depletion V1.0 provides consequential continuation of the theory-based publications [3, 4] to derive the stone growth-related urinary depletion effect via the general law of mass conservation.

The program was developed in order to integrate the demanding calculation scheme of the extended depletion effect [4] into the daily treatment of patients. A variety of additional calculation options enable the

user to display the dependencies of the depletion effect's extent based on each of the various input parameters. These more advanced data improve the general understanding of the physico-chemical processes of calculus formation in the urinary tract.

The program is a powerful tool which offers easy-to-perform computation of the depletion effect's extent and thus allows the medical practitioner a distinctly improved interpretation of the true stone patient's health status. It is now possible to identify stone patients in whom ongoing stone-growth related urinary depletion in the lithogenic components conceals a hitherto searched for underlying pathomechanism. These patients will benefit most from Depletion V1.0 as the treatment's outcome will be more effective, resulting in an improved reduction of the stone recurrence rate.

In light of the magnitude of data-misinterpretation to be expected in case of urinary depletion, the often obtained large overlap of urinalysis data on lithogenic substances from stone-bearing stone formers and healthy controls, seems, to a large extent, to be an artefact of sub-optimal data interpretation itself. When applying Depletion V1.0 to the urinalyses of stone formers, the measured values will shift to higher and more plausible values, resulting in a smaller overlap and consequently better differentiation between stone formers and non-stone formers. Scientists or statisticians will gain more reliable data distributions when investigating the causes of urolithiasis from urinalysis data sets.

The computer program Depletion V1.0 will be available as Java applet and application as freeware from the authors.

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Address for correspondence:

Dr. rer. nat. Norbert Laube
Universitätsklinikum Bonn
Klinik und Poliklinik für Urologie
Experimentelle Urologie
Sigmund-Freud-Str. 25
D-53105 Bonn, Germany
Tel.: (02 28) 287 - 19106
Fax: (02 28) 287 - 14329
e-mail: norbert.laube@ukb.uni-bonn.de