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ARTICLE

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Supersaturation and renal precipitation: the key to stone formation?

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Stating the obvious...

Urinary stones are solid objects which form in the urinary spaces almost entirely from material which was in solution in the urinary liquor filling the spaces. This phase change can only come about if there is more chemical potential available in the solution state than in the solid state.

Supersaturation is the chemical driving force

The difference in chemical potential of the two states ($\Delta\mu$) is dependent of the activities of the crystallising species in the supersaturated solution (a) and in the solution when it has come to equilibrium (a_{eq}):

$$\Delta\mu = RT \ln\left(\frac{a}{a_{eq}}\right).$$

As the supersaturation ratio (S) is defined as a/a_{eq}, one can see that

$$\frac{\Delta\mu}{RT} = \ln(S).$$

For practical purposes, the supersaturation ratio is often expressed in terms of molarities rather than activities; so, for calcium oxalate

$$S = \frac{[Ca^{2+}] \times [Ox^{2-}]}{[Ca^{2+}_{eq}] \times [Ox^{2-}_{eq}]},$$

where the square brackets represent activities or concentrations. It is sometimes helpful to refer to the relative supersaturation (σ) rather than the supersaturation ratio, where

$$\sigma = S - 1.$$

The distinction between relative supersaturation and the supersaturation ratio is sometimes lost in the urolithiasis literature.

Crystallisation processes

A number of different crystallisation processes can be distinguished. Much emphasis is attached to nucleation, growth and aggregation. Generally, nucleation involves a foreign surface (heterogeneous nucleation). Homogeneous nucleation will only occur under carefully controlled conditions and will not apply to crystallisation within the renal system. The supersaturation required for homogeneous nucleation is much higher than the equilibrium saturation and foreign particles can act as nucleation catalysts, thus reducing the supersaturation required to initiate crystallisation. Nevertheless, there is still a supersaturation barrier that must be overcome before nucleation can occur. This enables metastable supersaturated solutions to exist in which nuclei do not readily form, but if crystals are present then they will grow (Fig. 1).

Growth in the context of crystallisation is usually taken to mean enlargement of crystals by direct incorporation of solution species into the solid crystal lattice. The rate at which this takes place is also dependent on supersaturation and in the case of calcium oxalate the relationship is described by second order kinetics:

$$G = k\sigma^2,$$

where G is the growth rate and k is the rate constant.

Enlargement of the crystal mass can also be brought about by aggregation, widely thought to be very important in stone formation. This can be thought of as the net result of crystals colliding and either dispersing

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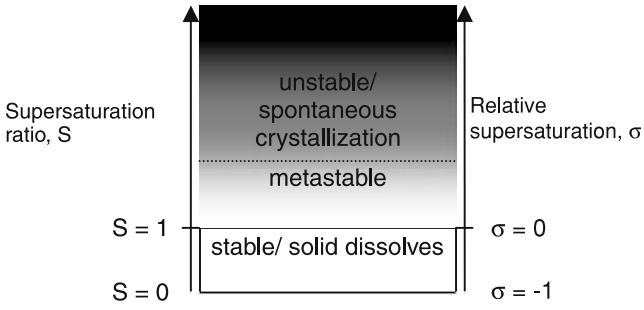


Fig. 1 Different regions of saturation can be distinguished

or becoming consolidated together, with the outcome being dependent on an efficiency factor (Fig. 2). As consolidation is achieved by growth of crystal bridges which fuse the lattice structures of the individual crystals, it can be seen that aggregation will also be dependent on supersaturation [1, 2].

The key to stone formation: the debate

This paper is one of three in a debate about the relative significance of supersaturation, renal tubular damage and urinary macromolecules in stone formation. It is not, therefore, my task to give a balanced view; rather, I shall try to show that stone formation is a consequence of excessive supersaturation and only rarely is it necessary to invoke some other factor. All contributors to this debate recognise that supersaturation is the chemical driving force that enables crystals to form, grow and aggregate and as such is a necessary condition for renal precipitation and stone formation. That it can be sufficient is illustrated by our ability to grow calcium stones in vitro (and in artificial media) which reach a clinically significant size within a realistic time frame [3, 4]. We have recently shown that the growth rate is related to the input calcium concentration (Fig. 3) [5] and that the growth is achieved primarily by aggregation of crystals from the surrounding suspension, rather than by direct crystal growth at the surface [6]. This aggregation and consolidation of crystals from suspension into a larger aggregate (i.e. a developing stone) will necessarily require a solution supersaturation above the equilibrium saturation, as discussed above.

While excessive supersaturation may, at least in vitro, be sufficient as well as necessary for stone formation it does not follow as a corollary that excessive saturation

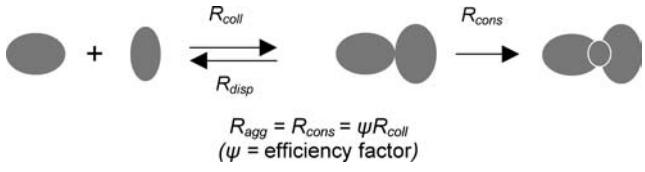
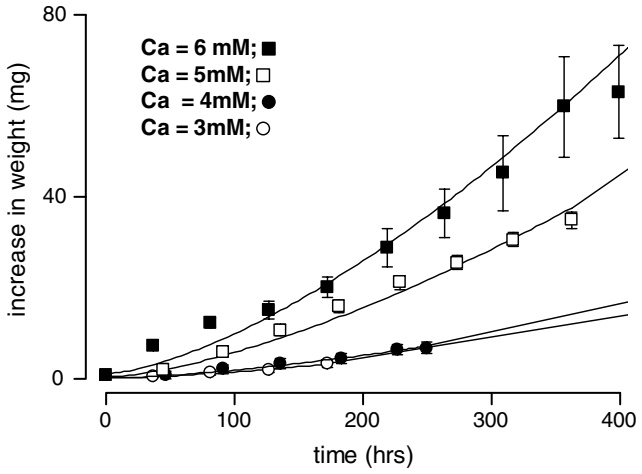


Fig. 2 The rate of aggregation (R_{agg}) reflects the rates of collision and dispersion (R_{coll} and R_{disp}), where the difference between R_{coll} and R_{disp} is the rate of consolidation (R_{cons})



Means ±s.e. for 6 stones grown in vitro.
Curves based on surface area dependent mechanism.
(data normalised for starting weight and time).

Fig. 3 In vitro calcium stone growth in artificial urine increases with increasing calcium in the medium

will inevitably lead to stone formation. Demonstration of the latter of these two statements, as well as the former, would perhaps be a clinching argument for this debate, but this will be as difficult as proving that all swans are white from observations of many all white drifts of swans. Nevertheless, it is informative to consider the whole range of urological calculi when looking for cases which might disprove this statement.

Animal and rare human urinary stones

Knowledge of the incidence of urinary stones in the animal kingdom is understandably very limited. Well-studied groups are limited to laboratory rats and domestic cats and dogs. Generally, laboratory rats do not form stones unless manipulated to become hyperoxaluric, rendering their urine supersaturated with calcium oxalate [7] or hypercalciuric when they will readily form calcium phosphate stones [8]. Struvite is the most common stone in dogs, followed by calcium oxalate and then urate [9]. These struvite stones are generally associated with infection, which generates ammonia and raises the pH, thus bringing about the required supersaturation. Oxalate stones are becoming more common and are associated with a pattern of urinary excretion leading to an elevated calcium oxalate supersaturation, which may be amenable to dietary manipulation [10]. Urate stones are particularly common in some breeds, notably Dalmatians, where they arise as a result of a hereditary gene defect giving rise to high urate excretion [9]. Cat stones are generally oxalate or struvite [10], the latter forming in sterile urine. It is widely accepted that the pattern of feline stones has been changing over recent years from predominantly struvite towards an increasing propensity for oxalate stones. This is thought

to be associated with changes of pet food formulations designed to reduce the risk of struvite stones. This has involved a shift from high magnesium/alkaline diets to lower magnesium/acid diets [10]. While the presence of stones and crystals in the urinary systems of these animals is likely to provoke tissue damage and changes in the profile of urinary macromolecules, there does not seem to be evidence or suggestions that these play a significant part in animal urolith formation.

The same can be said of rare and less common human urinary stones. Xanthine, dihydroxy adenine and cystine stones are rare because human urine is rarely supersaturated with any of these metabolites. Genetic abnormalities account for the production of the supersaturation in these cases and afflicted individuals usually start forming stones at an early age and have highly recurrent stone disease. Xanthine supersaturation can also arise from high doses of xanthine oxidase inhibitor (e.g. allopurinol). Some other rare stones arise from overuse of medications; e.g. silicate stones associated with antacid use and guaifenesin stones resulting from cough remedies. In both these cases, the extent of overuse has to be excessive. Indinavir related stones arise in 3–22% of patients being treated with this poorly soluble protease inhibitor. Incidence is related to dosage and avoidance of recurrence can usually be achieved through increased fluid and dose restriction [11, 12]. As is the case with animal stones, there seems to be no need to suppose that anything other than supersaturation is involved in production of these rare human stones.

Uric acid, phosphate and oxalate stones

Normal human urine (24 h samples) is sometimes supersaturated with uric acid, commonly supersaturated with calcium phosphate and almost always supersaturated with calcium oxalate. In order to understand why uric acid and calcium phosphate stones are not more common and oxalate stones are not universal, one must bear in mind the concept of the limiting supersaturation that must be achieved in order to initiate crystallisation. Uric acid stone formers tend to have persistent acid urine, high urate excretion or low urine volume, or a combination of these. Thus, their urinary supersaturations can frequently exceed the metastable limit for uric acid precipitation. Calcium phosphate stones are often associated with infection which raises the urinary pH and (because of the pH dependent change in solubility) this causes the urine to become highly supersaturated. Calcium phosphate stones can also arise in sterile urine and in these cases the urine supersaturation tends to be higher than in non-stone formers, largely as a result of increased calcium excretion [13]. In the genetic hypercalciuric rat model that produces calcium phosphate stones [8] it was found that reducing the dietary phosphate would lower the urinary brushite supersaturation and eliminate stone formation. It was concluded that the ''results support the hypothesis that variation in supersaturation alone can regulate renal stone formation'' [14].

There is widespread agreement that calcium oxalate supersaturations amongst oxalate stone formers are, on average, higher than non stone forming individuals mainly due to low urine volume, hypercalciuria, hyperoxaluria or hypocitraturia (or a combination of these). Nevertheless, there is considerable overlap in the distributions of calcium oxalate supersaturation in stone formers and healthy individuals. Does this necessitate the assumption that some other mechanism is involved? While there is evidence which suggests that in some cases of oxalate stone formation, a reduced metastable limit or reduced crystallisation inhibitory factors may play a role, a simpler explanation may lie in the inherent variability of 24-h urine compositions (Fig. 4).

The generalised description of urine supersaturations given in Fig. 5 is a composite view taken from many publications, where individual studies may be limited to relatively few patients and controls. When large cohorts of patients' results have been examined to relate their stone composition to their urine supersaturations for calcium oxalate, uric acid and brushite, a good correlation was found [16, 17] and where exceptions were observed these could largely be explained as being due to multiple coexisting raised supersaturations or changes in urine output between the times of stone and urine analysis [18].

Occam's razor

If supersaturation is the key to stone formation then prevention of recurrences should follow from appropriate treatment to relieve the supersaturation. Clearly, if one could achieve persistently undersaturated urine then this is a chemical inevitability. With phosphate and oxalate stones this goal is not realistic and the aim must be to reduce the supersaturation as low as is feasible. The

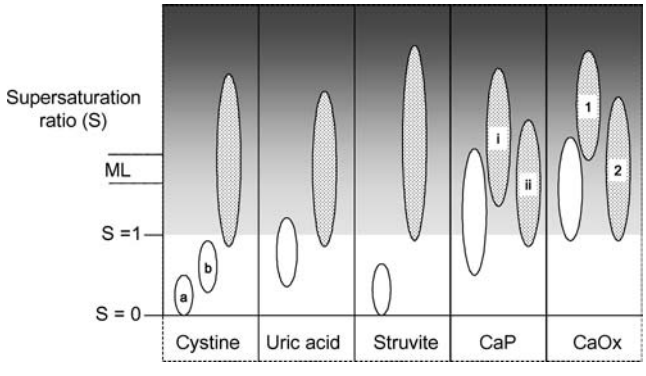


Fig. 4 Plots indicating ranges of urinary supersaturation for different stone forming salts. The metastable limit (*ML*) is not a discrete boundary between metastable and unstable solutions. *Open ellipses* represent non-stone formers, *shaded ellipses* are stone formers. *a* Normal individuals; *b* heterozygotes for cystinuria gene; *i* when associated with urinary infection; *ii* idiopathic calcium phosphate (*CaP*) stone formers; *1* primary hyperoxaluria; *2* idiopathic calcium oxalate (*CaOx*) stone formers

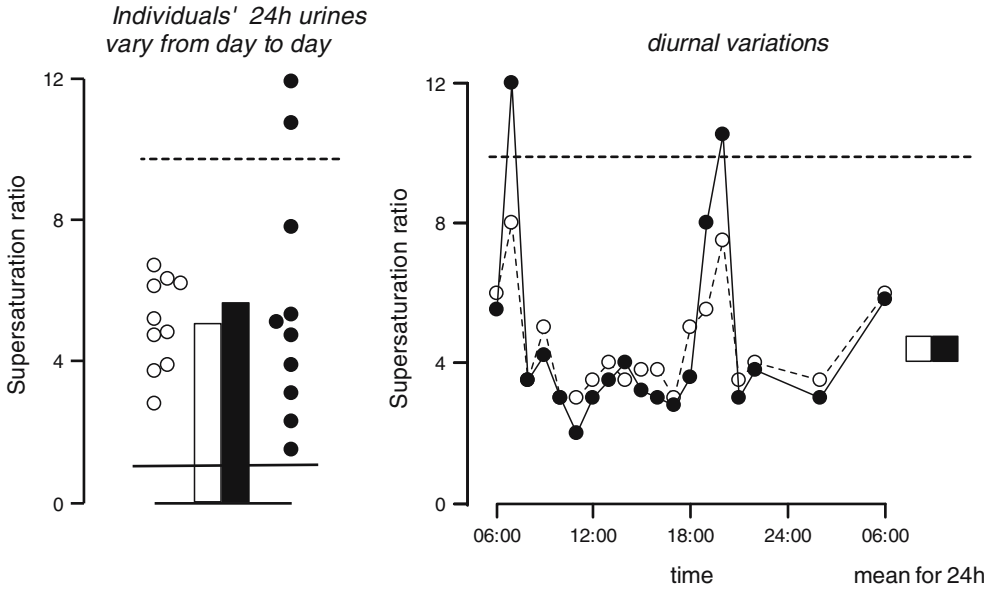


Fig. 5 Illustrative data showing how two individuals with very similar average 24-h urine supersaturations might have different inter-day or intra-day variability such that one never exceeds the metastable limit, while the other does on some occasions. The pattern of diurnal variation is based on results of Ahlstrand et al. [15]

single most effective mechanism to achieve this is to increase the fluid output and when Borghi et al. [19] ran a 5-year prospective trial of increased fluid consumption in calcium stone formers, they were able to reduce urine supersaturations of calcium oxalate and brushite which was associated with a significant reduction in recurrences.

In a recent review, Delvechio and Preminger [20] suggested that "remission rates of medical prophylaxis in calcium stone formers are approaching 80%". The failure here could easily be ascribed to incomplete compliance, which is of a similar magnitude [21] or perhaps to insufficient supersaturation reduction. In the same review, [20], it was claimed that "metabolic evaluations have allowed the identification of physiological or environmental causes of renal calculi in more than 97% of patients". This could be taken to mean that in almost all cases there is no need to invoke any other stone formation mechanism other than those which impact on the urine chemistry.

Given a choice between any or all of supersaturation, tubular dysfunction and urinary macromolecules, as the key to stone formation, it is perhaps wise to remember Occam's razor. In its simplest form, this states that one should make no more assumptions than needed. When multiple explanations are available for a phenomenon, the simplest version is preferred. With this in mind, is it necessary to look beyond supersaturation?

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