Urolithiasis - historical, comparative and pathophysiological aspects: a review

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Keywords: urolithiasis; comparative medicine

Paper read to Section of Comparative Medicine, 16 November 1988

A 16-year-old boy died at El Amrah, Egypt, perhaps because he had a bladder stone containing calcium phosphate and uric acid[1]; what is remarkable is that this happened nearly 7000 years ago. Indeed, since trephining and circumcision had ritual connotations, 'cutting for the stone' is probably the oldest purely surgical procedure. As Cursius-Curtius[2] remarked in his Doctoral Dissertation on Urolithiasis in 1662 'What is not cured by medicine, must be cured by the blade, but only after applying what is to be applied'. Even then, there was no lack of concepts concerning aetiology including overfeeding, familial predisposition, and the composition of the blood. Nevertheless, surgery, if survived, was often the only cure and among those who specialized in these operations at the court of Louis XIV was a former cavalry officer who remains famous for yet another life as a monk; Frère Jacques. He died at 69 having removed 4500 bladder stones.

By 1663 Rofink had classified uroliths according to their size, shape, surface and colour[3] and by the 18th century they were recognized to contain uric acid, oxalic acid, cystine and organic material. The link between gout and urolithiasis had been recognized much earlier, by Galen. In 1723 Nuck undertook experiments in which he implanted wooden balls into the bladder of dogs. By the 19th century, phosphate stones were regarded as an affliction of poverty, urate stones as one of affluence. Even today 70% of humans with urolithiasis are obese, 90% of those with uric acid stones[3].

Perhaps the strangest aspect of the history of urolithiasis is a relatively recent change in its epidemiology. Bladder stones were much more common than kidney stones until about 100 years ago, and especially common in children. Yet in the last 70 years bladder stones have become very rare in children[1] whereas generally urolithiasis has increased dramatically in humans during the last 30-40 years[3]. This increase has been blamed on affluence and increased dietary protein[4] but this seems hard to believe when poverty with high intake of vegetable protein was blamed for bladder stones[1,5] and when an eightfold increase in calcium oxalate stones occurred between 1964 and 1971; during this period protein intake rose by less than 5%[6]. Other factors such as low fibre and excess of refined carbohydrate associated with 'affluent' diets may predispose to urolithiasis. In particular, there may be peaks of increased urinary calcium following ingestion of sugary food or drinks[7]. This, as part of the multifactorial problem of urolithiasis, would not have surprised Cursius-Curtius, even in 1662. 'In producing the stone, these mutually dependent elements are helped first of all by an overloaded stomach'. Not least, perhaps, because of any increase in osmolarity and urine pH following digestion.

Factors affecting stone formation

The most obvious are urine output (hence concentration), the concentration of specific constituents, urine pH, and infection or damage within the urinary tract. Yet it remains difficult, ultimately, to define why some individuals have stones and others do not. Attempts to analyse the relevant physical chemistry have overemphasized the behaviour of simple solutions[6]. Urine is not a simple solution, many of its constituents are unknown and the ionic activity, as opposed to the total concentration, of many of the known solutes is still almost impossible to measure[6,8]. For example, the presence of Tamm-Horsfall protein increases crystal formation but only in whole urine and only at concentrations above 1300 mOsm/l[6]. Assessment of risk therefore needs to depend on measurement of ease of crystallization[9] rather than composition.

Crystalluria and urolithiasis

The presence of crystals in the urine seems an obvious step in stone formation but it is not urolithiasis[8]. In fact 1-2 μM crystals can be found in normal urine[10]. The formation, or re-dissolving of crystals in urine depends on the concentration of the constituents but also on modifiers (inhibitors or promoters) and pH. Moreover it is not so much the solubility product which is crucial as the formation product[11] and between the two lies a metastable range of solubility where nucleation, ie the presence of a focus for crystallisation, becomes decisive. The nucleus can be the same chemical, or a different crystal (heterogenous nucleation or epitaxy[6,12]) or other particles or surfaces.

Urate favours the crystallization of calcium oxalate[8] and oxalate, rather than phosphate, is the key determinant of calcium crystallization in human urine at normal pH[6]. A post-prandial alkaline tide favours formation of calcium phosphate nuclei on which calcium oxalate can crystallize[13]. Factors affecting oxalate excretion include steatorrhoea and intestinal surgery[11,14], stress[12], metabolic production, pyridoxine deficiency and ingestion of certain plant foods[6,13]. Oxalate calculi are being detected more frequently in dogs than hitherto and there appears to be a breed predisposition[15].

Calcium excretion is increased by high salt intake but it is urinary concentration which matters and sodium is neither a risk factor nor is it protective in humans[16]. The rationale for a protective effect is not simply through increased water turnover but binding

0141-0768/89/110669-04/$02.00/0

to crystal surfaces. Stress increases urinary calcium and only partly through the effect of ADH[5,17] and hyperparathyroidism is an important source of hypercalciuria both in people[14] and dogs[18]. A less common cause is renal tubular acidosis with the acidosis mobilizing bone mineral while the urine, because of the acidification defect is relatively alkaline[13,19,20]. Neither condition is sufficient to explain the fact that most humans with urolithiasis also have hypercalciuria and, while any excessive loss of calcium may provoke a compensatory increase in intestinal absorption, it appears that excessive intestinal absorption can be the primary problem[21]. Thiazides specifically reduce urinary calcium[22].

In Dalmatian dogs, which are unusual in excreting uric acid, much of the urate is present in colloidal form and this may absorb organic constituents of urine such as glycosaminoglycans ('GAG's) reputed to be inhibitors of crystallization[14]. Unlike humans, however, dogs do not often produce uric acid or urate stones and those that do include many which are not Dalmatians despite the distinctive uric acid metabolism and excretion of the latter[19,23]. Partly, this may reflect the presence of the same genetic difference of uric acid metabolism in individuals of other breeds[24].

Retention

Particularly with upper urinary tract stones, a key factor is not merely that they form, but that they form fast enough to be retained. Since the transit time is a matter of minutes, the formation of crystals and their initial growth or aggregation into a concretion large enough to be trapped must be very rapid[8]. This is favoured by slight rather than massive supersaturation[25]. Some stones may have surface fibres which trap crystals. Motility of the upper urinary tract may be a factor in retention and in humans video-radiography has shown differences of motility in the renal calyx between normals and stone formers[26]; it is hard to say, however, whether such changes are primary or secondary.

Infection

In humans infection is probably a cause, rather than a consequence, in about 7% of stone formers[27]. It is a prerequisite for struvite and carbonate apatite stones whereas hydroxyapatite forms in sterile urine. In dogs too, many with struvite stones have infected urine[28] but an interesting minority have alkaline urine and struvite in apparently sterile urine[29] (though bacteria could be trapped in the stones or miss detection).

The crucial result of infection is the presence of urea-splitting microorganisms and the consequent generation of large amounts of ammonia in an alkaline urine. Normally ammonia is secreted by the kidney in acidic urine. Alkaline urine not only favours crystallization but reduces the protective effect of surface mucopolysaccharide on the urinary epithelium, thus favouring both nucleation and retention. The particular problem with treatment of infected stone formers is that bacteria survive within the layers of the stone[27].

Inhibitors

One of the dominant factors affecting the evolution of both form and function in mammalian kidneys is the ability to conserve water, ie to excrete nitrogenous waste, at high concentration. Despite the possible presence of microscopic solid particles in normal urine, the urinary tract can only deal with a liquid hence its inert surface, rapid transit time, and the avoidance of excessive supersaturation are all important adaptations. An additional protective factor is the presence in urine of inhibitors of crystal nucleation, growth or aggregation. It would seem likely that these are especially important in the urine of arid zone species.

Serum may inhibit aggregation and therefore favour the growth of larger crystals; haematuria can thus cause misleading results in experiments on urinary inhibitors[30]. Only half the inhibitory activity in urine can be related to specific substances; the rest must result from unidentified molecules or methodological artefacts[13]. Among these inhibitors may be a range of macromolecules, some below 1000 daltons, others above 10 000[31]; the latter include an acid glycoprotein which inhibits oxalate crystallization[32]. Some inhibitors may originate from the bladder rather than the kidney[33].

The most consistently identified inhibitors are citrate, pyrophosphate, magnesium, GAGs and acid polypeptides[8,34]. GAGs and pentosan polyphosphate may also reduce the adherence of bacteria and crystals[27]. The importance of pyrophosphate as an inhibitor of calcium oxalate or phosphate stones, especially at concentrations found in urine, has been disputed[11,27]. Nevertheless, since phosphate is not a risk factor at low urinary pH, and since increased intake favours the presence of pyrophosphate in urine, additional phosphate may be protective[11]. The role of magnesium is ambiguous; the use of cellulose phosphate to reduce urinary calcium may increase the risk of stone formation by also reducing the urinary magnesium concentration and, therefore, its inhibitory effect[6]. The obvious assumption that additional magnesium can itself be a risk factor rather than a protection in struvite stone formation has not been proved in humans[27]. The best established inhibitor is citrate which is present in substantial concentrations in normal urine, serving to carry calcium in complexed form. Given therapeutically at 1-2 mmol/kg in humans there is no harmful effect on plasma calcium, nor any alkalosis but a significant increase in urinary citrate; the unfavourable rise in urine pH is apparently outweighed by the inhibitory effects[35,36]. Like citrate, magnesium may also act as a complexing agent[11], ie it reduces supersaturation by forming complexes with other ions. Unfortunately many of the clinical trials relating to prevention of urolithiasis suffer from serious design problems[37].

So far, the only chemical factors discussed have been those affecting the mineral content of stones. Equally important is the organic matrix, indeed some ascribe to it the primary role in stone formation so it is now considered in that context.

Hypotheses on stone formation

Urolithiasis is clearly a multifactorial problem with, at least for some stones, a genetic component[38]. Most of the known factors have been noted above but it is necessary to indicate finally some of the main hypotheses on why stones actually form[11]. These can be classified either as intracellular (or interstitial) theories, ie the primary problem is a renal lesion which breaks into the urinary system to provide a nucleus for stone formation or extracellular (intratubular)

theories emphasizing factors within the urinary system. Most are in the latter category; the main renal lesion theory centres on papillary calcification in humans which may well be simply a normal variation[11]. Autoimmune damage has also been suggested.

Matrix theory

Stones vary in their content of organic matrix, the maximum being in cystine stones and the gelatinous 'matrix calculi' found in humans, cats and sheep[11,29,39]. Nevertheless most calculi consist of concentric deposits of inorganic and organic material. This organic matrix comprises a number of mucoproteins in which the proteins include albumin, globulins, Tamm-Horsfall protein (normally present in urine and probably derived from the loops of Henle where it may contribute to the unusual permeability characteristics[40]), uromucoid and matrix substance A (also from the kidney and also present in normal urine). Some consider that the matrix is not only important in the mineralization of calculi but is the initiator of their formation; both the concept and the evidence is heavily influenced by analogies with skeletal calcification. Matrix may also be involved in aggregation, eg by reducing surface charge, limiting re-solution or by attaching to cell walls[11].

'The proximate matter for the stone is mucus. Taking the aforesaid with a grain of salt we assert that mucus acts as a glue'.

Cursius-Curtius, 1662.

Inhibitor theory

This is not new; in 1879 Ord studied the effect of colloids on the formation of precipitates of calcium oxalate, carbonate and uric acid. Again, some of the evidence relates to effects of urinary peptides on cartilage and is therefore controversial though, quite fortuitously, such inquiries led to the observation that magnesium could act as an inhibitor. Changes in urine composition, including its pH and urate content, affect inhibitory activity as well as solubility. Low urine volume also raises the concentration of inhibitors but this effect is outweighed by the increased concentration of minerals[11].

Hyperexcretion-crystallization theory

This is the simplest theory, ascribing the primary role to supersaturation and nucleation. Rate of growth is also a key factor, however, in turning crystalluria into urolithiasis, as discussed above. In fact aggregation, rather than growth of single crystals, is probably the decisive factor in reaching a size likely to be retained, within the short time available[11]. The main forces governing aggregation are electrostatic.

Free particle theory

This is really a variant of the hyperexcretion theory, emphasizing the combined effect of a lithogenic diet with episodic trigger factors. Thus episodic supersaturation as a result of dehydration or a heavy meal acts as an initiator, followed by a period of metastable saturation favouring growth. Episodic changes in pH are also important, and Tarttelin[41] found that in cats on dry diets, gorging after fasting alkalinized the urine despite the use of ammonium chloride as a urinary acidifier.

'The stone equally infests all, the highest and the lowest . . . although it does not spare even those who eat moderately, its particular delight is to torture those who eat their fill.'

Cursius-Curtius, 1662.

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(Accepted 13 March 1989. This paper was published in a shorter form in the Proceedings of the 3rd International Conference of the European Society for Veterinary Nephrology and Urology 'Urolithiasis in Animals')