HYPERURICOSURIA IN CALCIUM OXALATE UROLITHIASIS AND ITS POSSIBLE RELATIONSHIPS WITH STONE MATRIX FORMATION

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The association of calcium oxalate stone formation with hyperuricosuria and hypercalciuria has been the subject of a number of papers. It has been known for a considerable time that patients prone to forming recurrent calcium oxalate stones may on occasion form calculi composed of uric acid and the association is clearly more than fortuitous. The explanation for this association has proved quite formidable to resolve, but the importance of this is clear since it has been suggested that lowering urate excretion by the administration of allopurinol may prevent recurrent urinary stone formation. The studies on this subject are fraught with difficulty because of the time lag needed before any form of therapy for recurrent stone formation can be regarded as successful and in the absence, as yet, of properly performed controlled trials of this drug in stone disease.

That the association of hyperuricosuria with calcium oxalate stone formation may be dietary has been suggested by Fellstrom et al. and indirectly by Robertson who includes hyperuricosuria as a risk factor in the production of recurrent urinary calculi. He has further shown (Robertson) that the high protein meat diet of Western civilization accounts for the high incidence of calcium oxalate stones by causing increased excretion of calcium, oxalate and urate ions in the urine. If the increased urate excretion rate is not an incidental finding in patients forming calcium oxalate calculi, then it is logical to examine the hypothesis that excess urate in the urine affects calcium oxalate crystal growth and aggregation. Theoretically, it could do this in a microcrystalline or colloidal form as sodium, calcium or magnesium urate or in solution as urate ion and these possibilities are now examined. If a microcrystalline state of sodium acid urate, calcium urate or
magnesium urate were to form in urine, then these substances will absorb the known inhibitors of crystal growth and aggregation present in urine on to their surface\textsuperscript{7,8}. Alternatively it has been alleged that sodium urate will enhance the epitaxial growth of calcium oxalate\textsuperscript{9}. There are, however, serious objections to both these hypotheses because they depend upon the demonstration of urates in microcrystalline or colloidal state. Unfortunately, conductivity studies, dialysis, ultrafiltration and Tyndall effects show that solutions of sodium urate up to 16 mmol/l are non-colloidal\textsuperscript{10}. Ultrafiltration evidence for a macroscopic form of urate\textsuperscript{2} may be explained by the properties of the filters used to study the urine specimens. A further objection to this hypothesis is that sodium urate has only very rarely been found as a constituent of stones and is also relatively soluble in water.

Calcium and magnesium urates have been proposed as alternatives being somewhat less soluble and particularly the suggestion has been made that they might form complexes. We have shown, however, calcium urate does not form a complex in aqueous solution and that if the ionic strength of other ions present using the Davis equation is allowed for, then there is no evidence for complexing. That calcium urate and magnesium urate will absorb glycosaminoglycans in solid phase has been clearly demonstrated by Finlayson\textsuperscript{8}. However, it appears to be a quantitative problem because glycosaminoglycans seem to be normally present in excess in urine and a modest reduction in concentration would have little effect on the ability to inhibit urinary crystal growth. Furthermore, Sallis and Bichler\textsuperscript{11} have only been able to demonstrate reductions in urinary glycosaminoglycans in patients with infected staghorn calculi and not in the ordinary oxalate recurrent stone former, though this work contradicts that of Robertson\textsuperscript{7}.

There remains an alternative proposition that urates are active in solution and there are three possible ways in which this could happen.

(1) That they combine in solution with crystal growth inhibitors, particularly the chondroitin sulphates. There is however, no evidence that chondroitin sulphates combine with urate when placed in dialysis sacs even in the presence of magnesium and calcium ions\textsuperscript{10}. Any movement that occurs across the membrane can be readily accounted for by the ionic strength of the ions present.

(2) In the polymerisation of urinary proteins into protein matrix the presence of urate may be important particularly as Boyce\textsuperscript{12} suggested years ago, the mucoprotein is an essential part of stone formation. In support of this too is the evidence of the presence of urates in stone matrix\textsuperscript{13}. More indirectly there is evidence of deposits of protein in renal tubules during the formation of calcium...