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Editorial

Urolithiasis Research – Where is it Going?

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The causes of idiopathic recurrent calcium urolithiasis (RCU) are unclear. This statement may be justified despite a large number of sound publications on stone epidemiology, genetics and the pathophysiology of RCU. The latter area of research focusses mainly on intestinal absorption, metabolism, renal handling and the physico-chemistry of such stone-forming urinary constituents as calcium, magnesium, phosphate, and oxalate.

There is now increasing evidence that the "driving forces" initiating the processes that finally lead to stone formation are probably 1) increased supersaturation of the urine of RCU patients relative to that in the urine of non-stone-forming controls; 2) a deficiency of inhibitors of nucleation of such mineral phases as calcium oxalates, hydroxyapatite, brushite, sodium acid urate or, conversely, an excess of as yet more or less hypothetical urinary constituents able to promote nucleation or phase transition to less soluble salts; 3) an increased number of crystals in RCU arising from those phases present in the tubular lumen or in the lower urinary tract beyond the papillae, their increase in size, growth kinetics and tendency to aggregate to larger particles; 4) the occurrence, also in vivo, of both homogeneous and heterogeneous nucleation of stone phases, depending on the pH prevailing in an otherwise preformed urinary environment. For two reasons the latter point would appear of considerable research interest. First, the majority of calcium stones are composed of oxalate and contain only admixtures of phosphate, whereas the relative urinary supersaturation with hyrdoxyapatite increases considerably during limited periods of the day, e.g. postprandially, when an alkaline tide also develops, which results in a higher urinary pH [10]. This suggests that heterogeneous nucleation of calcium oxalate by hydroxyapatite is greatly favoured [15], although this needs proof by more direct approaches. Second, a number of similarities are shared by the calcium oxalate system, especially since in RCU its thermodynamic formation product may also be surpassed in urine produced after ingestion of a meal, thereby favouring homogeneous nucleation [9, 12].

On the basis of these facts it would appear a rather difficult task to return to the other end of stone disease and weigh up the importance of each of the three aspects possibly associated with the aetiology of RCU: genetic [2] or environmental; affluence, especially consumption of high-protein foods [8], "inappropriate metabolic response" to normal eating behaviour [9, 10, 12] or to only minor variations in food composition and/or consumption? There are reports in the literature supporting each of these hypotheses. Animal experiments such as those reported by Hering and co-workers [4] impressively reveal an inhibition of renal calcification in rats given water with added fluoride, while other animal experiments and stone-forming humans show a contradictory influence of fluoride. Whatever the mechanism of fluoride is there is clearly a need to continue studies on the role water quality can play in the development or prevention of stone disease.

Additional factors have delayed the appearance to new horizons: while the accurate measurement of calcium in serum and urine has become a more reliable service offered by academic laboratory institutions, this is far from being true for oxalate. Both hypercalciuria and hyperoxaluria, even when intervening for limited time periods only (see above), are considered extremely effective risk factors for stone formation. Especially the failure to detect mild hyperoxaluria with commonly available analytical techniques will mask the fact that the physico-chemical environment in the urine has been changed considerably. This is because in contrast to the concentration of free calcium ions in the urine, a small increase in free oxalate ions (in the μmol range) may be able to shift the activity product toward spontaneous precipitation of insoluble calcium oxalate. Thus, there is clearly a need for superior techniques permitting accurate analysis of oxalate in urine and plasma. With the use of more sophisticated methods, such as anion chromatography, as described in this issue by Tonoda [13], it is hoped that the oxalate story, which has now been plaguing investigators for nearly two decades, will soon come to an end.

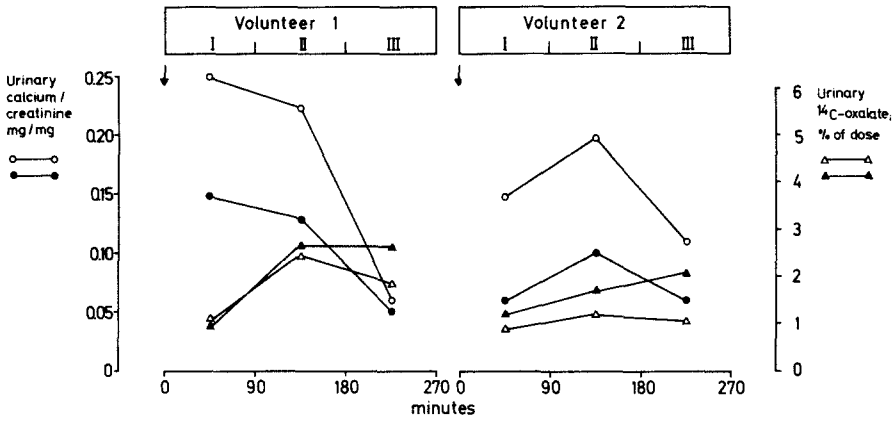

Fig. 1. Effect of a liquid synthetic oxalate-free test meal containing 1,000 mg calcium ions, at time 0 min, without or with 5 g alkali citrate (for details of the preparation see P. O. Schwille et al., Urol. Res. 13:0–0, 1985) and 2 μCi tracer oxalate, on the urinary ratio of calcium and creatinine, and the urinary fractional ^{14}C-oxalate excretion during three subsequent postprandial periods of 90 min duration (I, II, III). *Open symbols* represent data obtained with vehicle, *closed symbols* with alkali citrate. Note that with the reduction of urinary calcium following alkali citrate, urinary oxalate increases

The question as to the source of excess urinary oxalate in RCU urine, should its occurrence be confirmed by the majority of laboratories, represents another area of research awaiting clarification. One theory claims that intestinal hyperabsorption of oxalate is merely a passive secondary step following the primary hyperabsorption of calcium ions [5], which is a common phenomenon in RCU. Thus a reduction in dietary calcium is followed by increased oxaluria in hypercalciuric RCU [6]. We felt that simply preventing calcium ions from being absorbed out of the gut lumen by prior enhanced intraluminal complexation, e.g. by an adequate oral supply of alkali citrate, might lead to the same result. Figure 1 demonstrates preliminary data obtained from two healthy volunteers. They seem to confirm this hypothesis, and may help us better to understand the nature of intestinal calcium hyperabsorption in RCU, which at present is not clear.

Another theory gives consideration to intermediary oxalate metabolism, in the sense that oxalate overproduction from such precursors as ascorbic, glycolic or amino acid(s) may be an as yet unproven feature of RCU. Finally, some deficiency of pyridoxine is assumed in RCU. Since this vitamin inhibits endogenous oxalate biosynthesis, a slightly higher urinary oxalate would not be surprising.

All these aspects of oxalate pathophysiology are of practical importance to stone clinicians since the recommendation to reduce dietary calcium, commonly made by these physicians may, depending on the metabolic state of a given patient, lead to increased urinary oxalate (see above). Thus the co-existence of hypercalciuria and hyperoxaluria in RCU would certainly require revision of the view that dietary calcium restriction alone reduces the tendency to form stones.

Small-molecular weight (< 1,000 Daltons) inhibitors, such as magnesium, citrate, phosphocitrate, pyrophosphate, etc. probably cannot account for more than about fifty per cent of the total inhibitor potential for calcium oxalate crystallization in whole urine. It is not yet clear whether the remaining fifty per cent can be explained by the presence of larger-molecular weight inhibitors, or by the differences in the technical systems and the test materials used to evaluate inhibitory activity [3]. Using moderately diluted aliquots of 24 h urine, Baumann and co-workers in this issue [1] for the first time found a positive correlation between the inhibition of hydroxyapatite crystallization and the associated concentration of pyrophosphate. But they also found that the relative inhibitory effect of a small-molecular weight inhibitor may depend on the number of crystals present at the same time. Such findings illustrate the complexity of inhibitor research. As has been done with citrate in the past years, it now seems worthwhile establishing whether pyrophosphate is decreased in RCU, and if so why. Also, its in vivo inhibitory role for calcium oxalate and calcium phosphates awaits clarification. A characterization in more depth by biochemists of urinary RNA, together with additional large-molecular weight inhibitors, would appear mandatory.

At first, monitoring of crystalluria using methods which are technically easy to set up [14] was assumed to be of great help in interpreting the state of the accompanying urinary supersaturation. Meanwhile there are indications that there is no simple relationship between these two variables, i.e. positive correlations are often lacking [7] or only weak [7, 11]. In situations in which documented inhibitors such as citrate are accumulated in the urine, the correlation diminishes even further, as has been shown in this laboratory [11]. One reasonable explanation could be that the rate of crystallization reflects both the relative supersaturation and the associated inhibitory capacity in a given urine sample. If this should turn out to be true it would in fact constitute a milestone in clinical stone research, for then crystalluria per se may be considered "microurolithiasis". The assumption however would require not only confirmation by others, but also that crystalluria be more or less absent in healthy normals [11, 12], but enhanced in RCU [10, 12].

This point has not yet been settled. Measurement of a broader spectrum of variables, all contributing to the process of crystallization, would enable us to identify those with a critical influence. On the basis of these improved insights the development of new kinds of more refined anti-stone therapies, or a combination of documented anti-stone effects, as represented, by for example, one drug, may be expected. However, the feeling sometimes arises that although

we are probably sitting at the right window, it needs a long neck to see round all the bends in the road.

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