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A Survey of Calcium Urolithiasis in Normocalcemic Hypercalciuria: Possible Role of Nutrients and Diet-Mediated Factors

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Summary. Three types of hypercalciuria are described; their existence and frequent association with calcium urolithiasis in humans are accepted. Various dietary factors such as minerals, electrolytes, fluids, vitamin D, carbohydrates, proteins are discussed with regard to their ability to alter the nature and the degree of calcium excretion following their ingestion. It is emphasised that at present we have only limited knowledge on the chain of events linking calorie intake and the response of the kidney.

Key words: Hypercalciuria, Dietary factors, Urine oxalate, Activity products.

There is much controversy on the origin and clinical significance of hypercalciuria (HC) with regard to calcium (Ca) stone formation in the urinary tract. Little attention has been focussed on dietary factors apart from minerals, i. e. ingestion of various nutrients and their effect on the amount of Ca excreted in urine. In this survey knowledge from published work is blended with personal impressions in the hope of stimulating research work aimed at elucidation of food-related factors in stone pathophysiology.

DEFINITIONS

A. Urolithiasis with Hypercalciuria

A critical re-appraisal of normocalcaemic HC must emphasize the different types of HC presently proposed (33, 34).

Absorptive HC. The excess of urinary Ca stems exclusively from increased intestinal absorption of Ca whose nature is not yet understood in detail. As a consequence there is an elevated filtered load of Ca in the lumen of the proximal kidney tubule, but reabsorptive processes are normal. Ca balance is zero; serum 25-hydroxyvitamin D_3 and calcitonin levels are within normal limits, whereas parathyroid hormine is either normal or even low (8, 36).

Renal HC. Overall kidney function is apparently normal. Intestinal Ca absorption may be normal or elevated. There is a renal leak of Ca of unknown origin threatening serum Ca homeostasis. Ca balance tends toward negativity and serum parathyroid hormone and urinary cyclic AMP are elevated (33, 34).

Resorptive HC. The number and activity of skeletal osteoblasts appear increased and therefore the efflux of Ca ions from bone, the free fraction of serum Ca and the tubular Ca load are elevated. This state, by definition, is consistent with hyperfunctioning parathyroid glands, although increased bone resorption might not inevitably mean an increase in parathyroid hormone secretion (7). In most cases intestinal Ca absorption is elevated either by virtue of a direct interference of parathyroid hormone with gut Ca transport or through the parathyroid hormone mediated stimulation of renal synthesis of 1. 25-dihydroxyvitamin D_3 (5).

Some authors do not agree that renal HC really exists (3). PAK (1) ascribes 7-12 per cent of all cases with Ca stones to this type of HC. We (49) and others (10) recognise an increasing fasting urinary calcium in a much higher percentage than

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in age-and sex-matched healthy control subjects. Signs of increased bone turnover but normal parathyroid hormone concentrations in peripheral blood were found by Bordier et al. in 22 out of 35 normocalcemic stone formers otherwise classified as "non-absorptive" HC (7). Elevated parathyroid hormone together with other features of hyperparathyroidism (increased phosphaturia and hydroxiprolinuria) were present in 13 patients. This may support the assumption that a type of "mixed HC", i. e. a combination of renal and resorptive HC (28), might occur in many stone patients (appr. 30 per cent). However, this percentage would be in sharp contrast to findings by others of a normal or even low parathyroid hormone in HC stone patients, irrespective of whether they had been sub-classified or not (8, 36, 38). Development of more accurate radioimmunoassay techniques for the determination of circulating parathyroid hormone certainly will help to clarify much of the current controversies regarding the secretory state of the glands.

B. Urolithiasis Without Hypercalciuria

10-30 per cent of stone formers, even with repeated examinations, do not demonstrate any type of HC. Often the only abnormality is hyperexcretion of uric acid. It has been postulated that in those cases an absolute or relative deficiency of substances inhibiting stone formation might be present. It is possible that in these patients some or all of the normal inhibitory activity is utilised for maintaining excess uric acid in solution thus leaving behind a greater propensity for those urines to form crystals of Ca salts and to aggregate them to greater complexes. Furthermore, preformed uric acid crystals may induce epitaxial growth of Ca-oxalate crystals as the lattice of both types of crystal has several structural properties in common (30). The rank order of inhibitory capacity of naturally occurring urine substances (calcium phosphate system) has been proposed as follows: citrate, pyrophosphate, magnesium (5). The influence of trace metals is not yet fully settled. Sulphated mucopolysaccharides are considered Ca-independent mediators or even stimulants of stone formation (16). It is as yet unresolved, whether a deficiency of the former or an excess of the latter substances is an expression of a localised tubular defect or reflects a more generalised metabolic disorder.

C. Hypercalciuria Without Urolithiasis

When collecting data from non-stone forming healthy control subjects every investigator is perplexed to find HC in 10-15 per cent of those individuals who neither have a personal or a familial history of urolithiasis nor do they show any other abnormality known to be related with stone formation. In our opinion these subjects appear excellently suited for research work directed toward elucidation of mechanisms underlying nucleating processes and do not appear to have received sufficient attention.

ROLE OF NUTRIENTS AND DIET

Stone incidence was lower during the last two world wars and several years thereafter when compared with the present time. Hypercaloric nutrition and reduced physical exercise have become prominent features of modern society. However, there appears to be no dominant role of a single nutrient responsible for stone formation. The target tissue region playing the key role is yet unknown but may be located in the gastrointestinal tract or the kidney itself. More generally, stone disease may be a disease arising from several components without any disease character (dietary customs, changes in environmental circumstances, geographic region etc.). Presently one can only speculate on the steps linking external influences and the resulting composition of urine. In this context it may be worth looking at homeostasis of body fluids, electrolytes and minerals; vitamin D and hormone metabolism, and the effect of different nutrients.

Electrolytes, Minerals and Vitamin D_3

A high exogenous supply of sodium, i. e. ingestion of salt rich foods, always risks an intermediate expansion of extracellular volume, enhanced natriuresis and calciuria, the latter mainly because of the unidirectional coupling of the tubular transport of these cations (21). Extraordinately high intake of milk and dairy products, both rich in Ca and phosphate, may dispose to stone formation in individual cases (so-called milk alkali syndrome), but as a population attribute it can be disregarded. Rigid restriction of Ca and phosphate in the home diet brought about by avoiding milk and dairy products, which is currently recommended by many physicians, may in turn risk a state of phosphate deficiency (6), development of hypercalciuria (18) and a more alkaline urine as sequel to reduced excretion of titrable acid (22). Such an environment favours nucleation of Ca-phosphate (apatite). The dietary Ca/phosphate ratio appears to be the limiting factor for setting the degree of calciuria, but numerator and denominator are ill-defined in humans. In rats, supplementary Ca in the diet may prevent Ca-lithiasis (15). Moreover, according to latest reports, the magnesium and Ca contents of public water supply is inversely related to stone incidence (23). This documentation, however, involves bias arising from the methodology applied, and requires confirmation.

Magnesium deficiency causing depletion of

Table 1. 24 h urine oxalate in control subjects and calcium stone formers. Age: 20-70 years in both populations. In brackets: number of individuals

	Controls		Ca-Stones	
	♂ (40)	♀ (40)	♂ (40)	♀ (40)
Oxalate:				
a) mg/kg body weight				
median	0.47	0.47	0.45	0.44
range	0.16-0.84	0.17-1.01	0.19-0.96	0.20-1.08
b) mg/kg lean body mass				
median	0.50	0.62	0.45	0.58
range	0.17-0.9	0.25-1.16	0.21-0.99	0.24-1.41

urinary inhibitory activity or driving secretion of parathyroid glands, has never been documented as a disease entity in stone forming humans, although there are reports of a lower stone frequency with magnesium treatment. When magnesium had been evaluated with reliable techniques and in appropriate stone patients (exclusion of struvite stones arising from infection and showing very low magnesium content in urine) it was found to be normal in urine (50) and serum (44), but in a recent study serum values tended to be lower than normal (43). In contrast, in the magnesium-depleted rat, nephrocalcinosis develops in the juxtamedullary cortical region, but calciuria remains normal (45). This species difference should give rise to research focussed on the content and distribution of intracellular magnesium, e. g. in red blood cells or in the tubular epithelial cell.

The state of vitamin D_3, which is limited by the native vitamin D_3 in nutrients and the amount synthesized in the skin by photolysis from 7-Dehydrocholestrol, is reflected by the serum level of 25-hydroxyvitamin D_3, the biologically active hepatic metabolite of native vitamin D_3. In our laboratory, stone patients have normal values of this metabolite (unpublished data) and others have also reported that the amount of vitamin D_3 consumed per day is normal (29). One group of investigators documented a renal phosphate leak (24), similar to that found for Ca in renal HC (33, 34). Low serum phosphate, which is a well established finding in many calcium stone formers (see article of Dr. Scholz and co-workers), could be a direct expression of this renal leak. Since phosphate deficiency and hypophosphataemia (37) stimulate renal conversion of 25-hydroxyvitamin D_3 to 1, 25-dihydroxyvitamin D_3 one might speculate on elevated levels of this latter metabolite and that they might account for the often increased intestinal absorption of Ca seen in stone patients. This chain of events would explain the long known prophylactic effects of orally administered phosphates, as hypophosphataemia might become corrected thus interrupting the vicious circle.

In contrast, in Ca stone formers other groups found normal (25) or even decreased (45, 4) urinary phosphate and enhanced tubular phosphate reabsorption in the face of significantly lower serum phosphate (45, 50). This combination, whatever its causes, may lead to the assumption that a certain degree of phosphate depletion is the primary event. Most recent findings, however, question dietary phosphate restriction as a means of enhancing renal production of 1, 25-dihydroxyvitamin D_3 (3, 13). Therefore, besides the state of phosphate, additional mechanisms may be operative in controlling blood levels of these metabolites, in achieving the high intestinal Ca absorption and the associated low serum parathyroid hormone concentration in many stone patients when classified as belonging to the absorptive type of HC.

Gastrointestinal hormones are potential candidates as substances interfering with Ca metabolism. Interestingly, when Ca urolithiasis is considered as a group, the response to a standard meal is characterised by relatively higher blood gastrin and lower glucagon than in control subjects (47). Furthermore, somatostatin has been shown to reduce the amounts of Ca absorbed by the human gut (41).

Oxalate

From physico-chemical reasons relatively small increases in urinary oxalate concentration can bring urine into the metastable range of saturation with Ca oxalate where spontaneous homogenous nucleation of this salt may occur. However, speculation on a higher mean urinary oxalate in Ca urolithiasis, as a consequence of either greater intake with foods or increased metabolic turnover, could not be substantiated in our laboratory (48). The values in Table 1, determined by the enzymatic method (19), take into account body weight and lean body mass. This latter parameter allows one to unmask values appearing erroneously normal, e. g. in cases where considerable amounts of fatty tissue are present and if this tissue species has low metabolic turnover of oxalate, if any at all. Therefore, a reasonable explanation of homogenous nucleation of Ca oxalate from urines with norm-

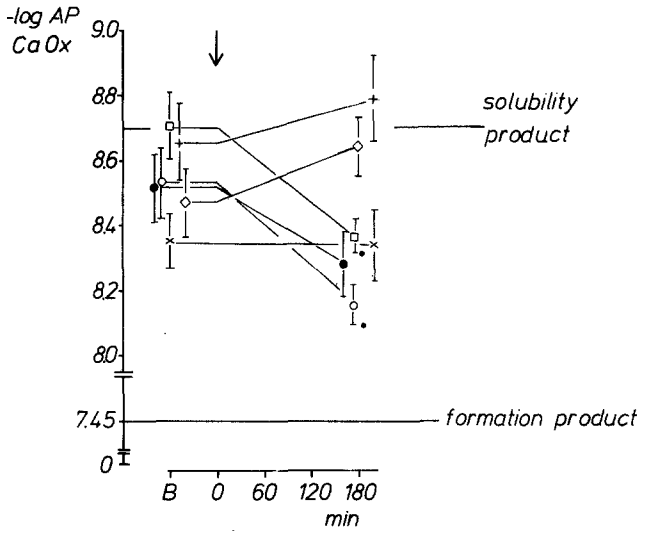

Fig. 1. Activity products (AP) of CaOx in urine during baseline conditions (15 h overnight fast; B) and at 180 min following ingestion of a breakfast or one of the four synthetic oxalate free diets[a]. Means and 1 standard error; *: $P < 0.05$. Arrow indicates food intake or start of fasting period. ◇: no food; x: breakfast; ●: carbohydrates; +: fat; o: balanced synthetic diet; □: medium chain triglycerides. [a]: J. Pfrimmer & Co., D-8520 Erlangen, Federal Republic of Germany

al oxalate concentration requires consideration of additional factors such as inhibitors or promotors of crystallisation, whose nature is at present largely unknown.

The widely given recommendation to maintain a diuresis(> 2 l/day), although promoting a lower urine Ca concentration, also stimulates oxalate and uric acid excretion which are positively correlated with urine flow (32, 49). As the inhibitory activity of such diluted urines may become lowered too, the beneficial effect of this treatment principle may be questionable.

We have been interested in the pattern of activity products seen after ingestion of calcium containing but oxalate free diets in order to reduce actual oxalate concentration in the urine. Thereafter the activity product of acid Ca-phosphate (Brushite) remains in the stable range (< solubility product), whereas the Ca-oxalate product increases up to 180 min postprandially, with the only exception being after eating a lipid meal (Fig. 1). Therefore, this oxalate deprivation effect seems to be almost completely counterbalanced by the compensatory increase of intestinal Ca absorption.

Conversely, reduction of dietary Ca may be followed by oxalate hyperabsorption (36). The formation rate of insoluble Ca oxalate in the intestinal lumen appears to depend on the prevailing concentration of fatty acids (2). Urinary Ca under these circumstances has not been fully studied. Similarly reliable techniques need to be applied for the investigation of gut oxalate absorption rates in the presence of precisely measured Ca hyperabsorption. Studies of concurrent transport rates of Ca and oxalate at the gut level should shed further light on these questions.

Purines

An excess of uric acid in urine, even in relation to serum uric acid, has been well documented in Ca urolithiasis without or with HC, but in our laboratory the finding was restricted to patients younger than forty years (45). Excretion of precursor purines (hypoxanthin) was normal and the fraction of urate bound to serum macromolecules was higher in stone formers (48). This latter finding does not allow one to conclude that the urinary uric acid excess is simply a result of a higher percentage of urate filtered at the glomerular level. The finding is most likely dependent on high amounts of purine ingested by the majority of patients, or an increased uric acid pool size (= overproducers). It appears that with one exception (52) no attention has been paid as yet to possible interferences of purine metabolism with renal handling of calcium.

Carbohydrates

Interrelations between carbohydrate consumption in general and highly refined sugars in particular, and urine Ca have not been fully studied. As with iatrogenic metabolic acidosis (25) the distal tubular reabsorption of Ca and magnesium is decreased during glucose administration and urinary pH falls. Intracellular acidosis is considered the common mediator (25, 26, 27). Conversely, with a high glucose load the kidneys appear to influence selectively Ca reabsorption in the presence of unaltered magnesium handling in obese subjects (15).

Lipids

Whether and by what means exogenous lipids influence serum and urine mineral constituents and the propensity of urine to form stones has been poorly understood for a long time. Fat malabsorption leads to so called "intestinal hyperoxaluria" as an expression of increased Ca soap formation in the intestinal lumen and consecutive hyperabsorption of oxalate (46). Ca oxalate stone frequency is therefore higher in patients with disorders leading to fat malabsorption (e. g. pancreatic insufficiency, bowel resection) than in the general population. Presently we suggest that by the same mechanism, ingestion of appropriate lipids and

withdrawl of oxalate from intestinal absorption sites by anion exchange resins might by avaluable treatment for a minority of HC patients whose Ca hyperabsorption in the gut does not respond to well-established drugs (oral phosphates, thiazides etc.) and who further prove to be almost intractable stone formers. However, when studying rats fed an iso-caloric diet containing soyabean oil and small amounts of cholesterol other authors observed a fall in serum Ca (12) which may have direct effects on the parathyroid glands.
When instituting a similar diet in rats, we detected nephrocalcinosis of the same histological type as with a diet deficient in magnesium, a lowered inorganic phosphate content of cortical and medullary renal tissue, hypomagnesaemia and marked weight losses within a period of three weeks (44).

CONCLUSIONS

The various types of HC are risk factors for Ca stone formation in humans but do not explain stone formation in every case because healthy individuals may exhibit the same abnormality. HC's, apart from modifying mineral content of nutrients, may be provoked by imbalances in calorie intake and, more general, through a chronic overload of body buffer systems with acidic anions. Much work has to be done in clarifying the relationship between the gut and the kidneys in Ca urolithiasis and to what extent patterns of urine composition in this disorder can be related to intake of various foods.

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