Urol Res (1992) 20:72-83

Environmental Factors in the Pathophysiology of Recurrent Idiopathic Calcium Urolithiasis (RCU), with Emphasis on Nutrition

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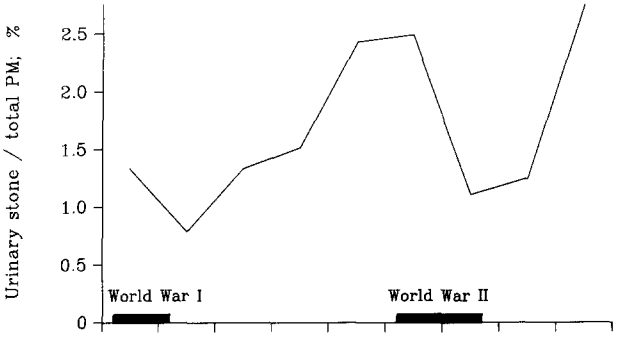
Summary. A number of environmental factors are under discussion as possibly implicated in the etiology of RCU. On the basis of data in the literature and our own results, we attempted a critical weighing up of the possible contributions of climate, pollution, stress, nutrition in general and especially oxalate and minerals in the nutrition. It was concluded that there is a need for more in-depth research into the response of the body to challenges from the environment, in particular nutrition.

Key words: Recurrent idiopathic calcium urolithiasis, environmental factors, climate, pollution, stress, nutrition

Introduction

During the past decades excellent reviews have appeared on the possible contribution of environmental factors to the development of idiopathic recurrent renal calcium stone formation (RCU) (for an overview of the literature the reader is referred to articles contained in the proceedings of the international stone symposia series, published since 1968 (21, 29, 39, 93, 106, 114) and several articles by W.G. Robertson (76, 77, 82, 83), who pioneered the work in this field). In patients with RCU the stones contain not only calcium and oxalate, but also phosphate, uric acid, and other more rare substances, all in varying amounts; the amounts of these latter depend on the urinary environment prevailing. The prefix "idiopathic" indicates that patients suffering from such stones are characterized by an absence of any disorder known to cause stone formation, such as primary hyperparathyroidism, renal tubular acidosis, hyperoxaluria etc., but yet stones are formed due to either thermodynamic factors (increased supersaturation) or kinetic factors such as a deficiency of crystal and stone inhibitors, an excess of promoters, especially of crystal aggregation, or some combination of these factors. Reportedly, stone episodes tend to recur within ten years in approx. 26 per cent of RCU patients (3), and in our laboratory the recurrence rate in untreated RCU is approx. 50 per cent within the following seven years (P.O. Schwille, unpublished data). Thus, RCU constitutes a major health problem worldwide, including the East (111), which strains the budget of both health care and research institutions. This all the more so, because the natural history and the many facets of RCU necessitate long-term follow-up if we are to understand its pathophysiology, develop effective anti-stone medication, and improve of available laboratory techniques. In general, Western civilization and style of living have been suspected as developmental factors. The situation is best described by the classic report of the Institute of Pathology of the University of Leipzig (88), telling that the percentage of post-mortem examinations with positive finding of urinary stone(s) was reported to reach peak values after each of the two World Wars (Fig. 1). Thus, environmental factors may be to the fore in the etiology of stones. With our improved knowledge of the regulatory steps in the homeostasis of minerals, especially calcium, with the advent of new technologies for the measurement of oxalate, crystalluria, and the inhibitory potential of undiluted urine, a number of questions now receive better answers than before. With this in mind we thought it worth reconsidering the influence of climate, stress, and nutrition, in particular since their influence can be confirmed by more recently published data, or can be supported by ungoing work.



Years	1913-17	18-22	23-27	28-32	33-37	38-42	43-47	48-52	53-58
PM	1.734	2.646	3.014	3.796	3.070	4.253	2.891	5.041	9.025
Stones	23	20	36	57	74	102	32	60	243

Fig. 1: Stone waves observed during 1913 - 1958 (modified from Ref. 88). PM: post mortem examinations.

Climate, vitamin D metabolism

The greater frequency of RCU in geographical areas with a hot climate has long been ascribed to the enhanced loss of liquid via skin perspiration, resulting in a smaller volume of urine, higher urine osmolality, concentration of calcium and oxalate, as well as other stone-forming urinary constituents, together with a more acidic urine pH. There is abundant evidence that this mechanism of stone formation is highly efficient, as is illustrated by the fact that soldiers serving in such countries, develop more stones than when stationed at home bases (10).

However, other factors than increaed urinary supersaturation are also involved, and critical consideration of these suggests that too small a volume of urine is but one step in initiating nucleation and crystallization. Prolonged exposure of the skin to the UV portion of sunlight enhances the non-enzymatic conversion of cholesterol to native vitamin D3 in this organ. Compared with this source the amount of vitamin D taken up in usual food is small. Because native vitamin D is extensively stored by muscles and other tissues its hepatic hydroxylation to 25-hydroxyvitamin D3 is stimulated; blood levels of this metabolite in fact accurately reflect the state of the body's vitamin D3 stores. It was long believed that high blood levels of 25-hydroxyvitamin D3 are characteristic of hot areas, and would alone increase intestinal calcium absorption, calciuria and stone frequency. However, stone frequency was also found to be higher in the warm seasons of the year in European countries, as also in areas of the US, both having a more temperate climate (83); on the other hand, there are countries in Africa in which there is equally as hot climate as in, for example, the Arabian Gulf states, and yet the stone incidence is not high but low. Therefore, some adaptation to hot climate and almost year-round sunshine by people normally living in these areas cannot be ruled out. 25-hydroxyvitamin D, is in general normal in the average Saudi population (101). Thus, the hypothesis that 25-hydroxyvitamin D is a risk factor for RCU in those countries was seriously challenged. The biological activity of 25-hydroxyvitamin D3 is approx. 1/500 the one of the dihydroxylated metabolite (1.25-dihydroxyvitamin D3), the calciotropic hormone which controls intestinal calcium absorption in man and many animal species. A direct feed-back regulation of blood levels of the two vitamin D metabolites in normocalciuric and hypercalciuric subgroups of RCU is unknown. In one highly selected subgroup with hypercalciuria due to intestinal hyperabsorption 1.25-dihydroxyvitamin D3 was markedly increased (16). Using established laboratory methodology, we were able to show elevated serum levels of 1.25-dihydroxyvitamin D in much less selected male hypercalciuric RCU, and also a similar tendency ($p < 0.10$) in normocalciuric RCU (99). Whether there is an environmental factor such as climate, sunshine, temperature, air humidity etc. capable of modulating the state of 1.25-dihydroxyvitamin D in man is unknown yet.

Pollution

With the present increased awareness of pollution as a health factor it should not be overlooked that the early literature in stone research contains at least one report suggesting an interrelationship between stone development and nutrition- independent agents from the environment (32). Since only cadmium is of proven importance we shall abstain from commenting on other pollutants. High blood levels of cadmium are now increasingly detected in children living in iron and copper mining industrial areas of the former German Democratic Republic. In other countries similar problems are known. In particular coppersmiths, a population subgroup exposed to cadmium at the workplace, showed an increasing frequency of stone disease when reviewed annually between 1975 and 1979 (100). The most prominent features of chronic cadmium poisoning are increased proteinuria, calciuria, and serum phosphate (100). It is believed that the histological changes within the kidneys predispose to hypercalciuria and stone disease. While coppersmiths may be a small subpopulation, a most recent report on the cadmium body burden of the general population is disturbing (19). The authors consider the main sources of cadmium to be contaminated drinking water and crops grown on polluted soil. According to this report about 10% of the Belgium population carry an internal cadmium burden sufficient to cause some renal dysfunction. More specifically, there was a positive association between urinary excretion of cadmium and calcium, as well as the tubular markers beta 2-microglobulin and N-acetyl-beta-glucosaminidase. Although Belgium is the leading in cadmium producing country in Europe, there is clearly a need in all other countries to address this problem in the search for the early events of stone disease, which many workers in the field consider to be a sequela of disturbed function of the proximal portion of the renal tubules.

Stress

With respect to the possibility that stress may be involved in stone-forming processes there is a need 1) to differentiate between psychic or emotional and physical or exercise stress, 2) to document that the hypothalamic-hypophyseal-adrenal axis has been activated by the applied stressor(s). The former requirement may, by and large, be solved by the study design, although many situations in daily life in fact reflect a combination of the two stress forms, but the latter has been disregarded in available publications dealing with the subject. This makes it difficult to decide whether the observed effects were specific, or merely reflect unspecific influences, such as variations in the daily rhythm, organization of the test procedure, etc. Extreme physical stress may promote the formation of calcium oxalate crystals in the urine, as, for example, in marathon runners, but unfortunately the observations were not accompanied by data on mineral metabolism (42). Mental stress, applied with the aim of evaluating, among other things, urinary calcium and magnesium, revealed that in so-called type A subjects both calcium and magnesium excretion fell significantly, whereas in type B subjects magnesium increased while calcium excretion decreased (38). This interesting information also focusses on the fact that in terms of susceptibility to psychic sress males fall into two categories, types A and B, respectively; the major discriminant between the two is considered to be the response of plasma and urinary magnesium (see also below). In male rats, mixed (emotional + physical) stress effected via immobilisation and documented by elevated plasma catecholamines, we found that the supersaturation products of calcium oxalate, brushite, and octacalcium phosphate in urine did not increase, but, instead, decreased significantly (12). Thus, the infuence of varying forms of stress as possible

etiological factors in stone disease awaits clarification.

Nutrition

General

On critical review of existing literature on genetic fixation or some family disposition one is inclined to ask: "is RCU a matter of nature or of nurture"? We reported that eating habits in RCU may not differ substantially from controls, and that in terms of energy supply both populations eat too much (87). Similar findings were also reported by others using 4-day food records (28) as compared to the 1-day record in our study (87). The only difference found by these authors was a higher intake of vitamin C and alcohol by the stone patients. The latest review on eating habits in Germany (72) again indicates that energy consumption in calories per day is much too high (in parentheses the mean dietary allowance for males, as recommended by the German Society of Nurition): 19 - 35 years, 3055 ± 30 (2600); 36 - 50 years, 2933 ± 30 (2400); 51-56 years 2895 ± 31 (2200); 65 years and over 2719 ± 43 (1900). The same source (72) also reveals that the age group 19-65 years eats too much protein (in parentheses the recommended percentage versus the actual percentage) (10 versus 14), too much fat (30 versus 40), but eats too little carbohydrate (60 versus 42), and drinks too much alcohol (0 versus 3.2). Unfortunately, carbohydrate consumption was not specified in terms of refined or less refined sugars, i.e. carbohydrate monomers, oligomers, polymers. There may also be some calcium undernutrition (recommended dietary allowance 800 mg per day), resulting from too little intake of those nutrients delivering calcium, such as milk, dairy products and some kind of nuts. The phosphorus supply, however, may be adequate; similar population studies in US (104) show a preference for solid or liquid food high in phosphorus, e.g. meat and cola, which results in an adequate or even excessive phosphorus supply in the average population. As postprandial hyperphosphaturia may be a common feature in hypercalciuric RCU (96), the state of phosphorus metabolism is by far from being clarified, and needs more research. Also the literature gives one the impression that current stone research focuses on oxalate at the expense of other materials leading to stone formation (36). Among leading laboratories there has been some disagreement as to whether hypercalciuria or hyperoxaluria has the greater impact on stone formation (79, 80). In our view each of the two, when sufficiently increased, is capable of initiating liquid-solid transition in urine, i.e. nucleation. The latter can be best illustrated in in vitro experiments aimed at supersaturating undiluted urine until calcium oxalate nucleation occurs, which can readily be achieved by adding calcium or oxalate, albeit at different levels of molarity (P.O. Schwille; unpublished data). Thus, when examining the infuence of the eating habits of RCU patients, researchers should give weight to each substance.

Drinking liquid

For decades physicians have recommended a high intake of fluid as a superior kind of treatment of RCU, without specifying any particular source or composition of the liquid. There are indications that with a urine volume of less than 1 litre a day the risk of nucleation of constituents leading to calcium stones rises dramatically (33, 34). Conversely, a reduction of supersaturation may be achieved by drinking large amounts of fluid, but despite the effective dilution of urine there is no guarantee that the formation of crystals and stones will cease (see Ref. 33, 34). One explanation for this may be the adhesion of particulate matter to superficial urothelial structures (so-called fixed paticles), another may be found in the non- stoichiometric decline in the activity of stone inhibitors (30). While there is no oxalate contained in the liquids traditionally drunk, their calcium content varies tremendously. Also, the ubiquitous mineral waters contain sodium in concentrations ranging from 1 to more than 1,000 mmol per litre, and sodium increases calciuria due to the coupling of the two ions at renal tubular transport sites (33, 34; see also below). The effects of other solutes in mineral waters, such as magnesium, sulfate, bicarbonate, and chloride, deserve more sophisticated evaluation than so far practiced, of their usefulness in the metaphylaxis of RCU. On a molar basis, only a few mineral waters contain more magnesium than calcium, i.e. the majority deliver extra calcium. In the case of normal calcium balance the latter has to be eliminated via the feces and urine. It has been shown that, even in tap water, the lower the ratio of magnesium to calcium the higher the incidence of urinary stones (52, see also below), suggesting the view that magnesium may have a preventive role in stone formation.

The question arises as to whether urinary oxalate decreases with increased intake of water and diets high in calcium (44, 45, 68). With regard to stone incidence the answer has to be obtained from studies evaluating stone inhibitors and crystalluria, in addition to the physico-chemical urinary environment. Interestingly, a reported negative correlation between water hardness and stone incidence (56, 104), has been questioned (82). Among the major constituents of tap and mineral water, sulfate has long been neglected. The source of sulfate contained in mineral and tap water is not clear; nor do we know which cation ligands combine with sulfate. Endogenous sulfate has an important biological role, as is seen in the detoxification processes in the liver. Only now are we beginning to learn about sulfate, its intestinal absorption, serum levels, renal tubular handling, balance, and possible effects upon acid-base status of exogenous, i.e. dietary, sulfate (1, 31). Non-sugared mineral waters regularly contain both sodium and chloride, and thereby impose a varying degree of salt load which results in additional changes of mineral metabolism. Thus, more work in this area is mandatory, and it is to be hoped that the results might assist physicians in selecting the appropriate liquid for drinking by RCU patients (for additional details on sodium, salt see below).

Sodium, Salt

Sodium has received considerable attention from both clinical researchers and physiologists, due to its indirect calciuric action, its progressive effect upon the ionic strength of urine, and the possible stimulation of 1,25-dihydroxyvitamin D in response to sodium-induced renal hypercalciuria (14, 43). However, with respect to the interdependence of natriuresis and calciuria, there is no consensus of opinion. In healthy controls, orally loaded with sodium at amounts ranging from 10 to 1500 mmol per day, the associated excretion of sodium and calcium per day was between 18 and 1680 and 1.5 to 6.5 millimol, respectively (64). On the basis of this discrepancy between the two excretion rates it was assumed that the renal proximal tubule is able to dissociate reabsorption of sodium from that of calcium (34). Conversely, dietary sodium restriction decreases the associated calciuria, but the fall in the latter is not concordant quantitatively with the former (14, 25, 34). In hypercalciuric RCU patients, the outcome of both sodium load and sodium restriction, may differ from that seen in healthy controls. Thus, in the former, urinary calcium was dramatically increased by a given sodium load, while the increase was only moderate in the control group (see Ref. 34). Data from other authors also support the view that many patients with hypercalciuria suffer from sodium-dependent hypercalciuria (25, 67, 105). Militating against this assumption would be the fact that daily urinary sodium excretion, measured while patients were eating usual home diet, was within normal limits (94, 107), while sodium excretion in fasting urine was elevated in the RCU subgroup classified as fasting hypercalciuria (94). This finding not only confirms a similar observation (109), but in addition it points to some malregulation of sodium metabolism during the daily cycle in at least one subgroup of RCU. The existence and characterization of renal tubular dysfunction in RCU, including both enhanced sodium and calcium losses under conditions yet to be defined, would help explain the unsolved problem. Similar thoughts have been expressed by others (46). An alternative explanation would be that, as in the dog under stimulated diuresis, also in man the clearance of ultrafiltrable calcium is not linearly related to the excretion of sodium - as has been suggested (43) - but rather to the square of the latter (11). To our knowledge such acute studies in RCU are lacking.

Apart from sodium-calcium interactions at the kidney level there is now evidence that salt (sodium chloride) supplementation of diet results in hypocitraturia, the effect being more pronounced when the salt load is combined with a high protein diet (53; see below). Answers to this question and those mentioned above on the role of dietary sodium, are urgently needed.

Fat

Dietary fat is thought to have no direct influence upon oxalate or calcium metabolism. However, binding of calcium to fatty acids is a common phenomenon in mammalian biology, and, when occurring in the intestinal lumen, it may cause hyperabsorption of oxalate, leading to the so-called enteric hyperoxaluria, and may be urolithiasis (9). The fatty acid question is of further interest. First Phospholipids are able to induce in vitro nucleation of calcium phosphate from supersaturated solutions (13). Secondly, urinary stones contain lipids as part of the matrix materials (50). Thirdly, phosphatidylethanolamine is a membrane phospholipid and, once cleaved by phospholipase, is considered a precursor of oxalate (69). Oxalate has been shown to induce lipid peroxidation, a process which is toxic to living cells (55). Under conditions of calcium oxalate stone formation in the living rat, lipid peroxidation was seen to be enhanced, suggesting a causal relationship between the two events (55).

Oxalate and calcium were reduced in hypercalciuric RCU patients by enhanced ingestion of fish oil over a period of eight weeks; the authors suggested that incorporation of eicosapentaenoic acid - a polyunsaturated fatty acid and key substance in prostaglandin synthesis (20) - into the diet was responsible. The fact that Eskimos are virtually immune to both urolithiasis and cardiovascular diseases is compatible with their high consumption of fish oil rich in eicosapentaenoic acid (20). Western diets with a high fat content, especially saturated fatty acids, may affect blood concentrations of androgen, and thereby the development of diseases related to sex hormones (66); RCU may be an example of the latter, since, in terms of incidence, the ratio males to females is approx. 2 : 1. Interestingly, in our laboratory the blood level of cholesterol in numerous RCU patients is above the upper limit of normal (unpublished data). Though the relationship between RCU, dietary fat, and lipid metabolism is uncertain, an association between urolithiasis and atherosclerosis has been suggested (75).

Protein

A diet high in protein, especially animal protein, has attracted the interest of researchers because of its relationship to mineral metabolism, the state of bone, and the etiology of urinary stone diseases (for more detailed information see Ref. 5, 17, 77, 103, 115). On the other hand, milk-egg vegetarians in Australia adhere to diets lacking flesh protein, and may have a lower incidence of stones than the Australian population as a whole (17); the same holds for European vegetarians (78). As already mentioned, the dietary protein intake in the age group in which the incidence of renal stone disease is a maximum (approx. 40 years), for example in Germany, this is about 50 per cent in excess of the recommended allowance (72). There is an ongoing controversy on whether RCU reflects an accumulation of risk factors that are due mainly to high protein; the controversy is now near the end of the second decade (5), and yet no reliable conclusion is recognizable.

The arguments for overconsumption of protein, as one of several major nutritional risk factors, include: 1) the development of a higher-than-normal endogenous acid load resulting from the oxidation of sulfur from sulfur-containing amino acids (methionine, cysteine), the subsequent increase in titratable acid of urine

and decrease in urinary pH, respectively, with the latter inducing an increase in, and crystallization of, undissociated uric acid; 2) the decrease in urinary citrate, probably the most important stone inhibitor, the underlying causes of which have not yet been established (see Ref. 33, 53); 3) the well-documented increase in excretion and concentration of uric acid, phosphate, calcium, and oxalate, all driving the supersaturation of urine toward nucleation of crystal- and stone-forming urine constituents; 4) the apparently greater sensitivity of unclassified RCU patients to dietary protein intake as compared with controls. This latter is reflected by a) an increase in the slope of the regression line between the urinary excretion of urea nitrogen, an indicator of protein intake, and urinary calcium (33), b) the steeper slope of the regression line linking inorganic sulfate and calcium excretion in fasting urine of hypercalciuric RCU males (98), and c) the steeper slope of the regression line linking urinary excretion of net acid and calcium (58). According to the Philadelphia group of workers the urea- calcium relationship is also present in females (33), while other studies on the behaviour of males and females in this context are lacking.

There are indirect arguments against the theory of protein overconsumption - especially animal protein: 1) only 1 - 5 per cent of the population develop stones during their life-time, suggesting that additional factors may be involved; 2) inorganic sulfate in 24 h urine is not elevated in RCU, either in subjects with normocalciuria or in those with hypercalciuria (92), although the finding does not rule out the possibility that sulfate metabolism may be disturbed in RCU thereby masking sulfate overproduction from protein overconsumption; 3) amino acids in blood and urine were found to be normal in stone patients, RCU included (112); 4) the oxaluric potency of animal protein appears smaller than that of vegetable protein (17); 5) mild hyperoxaluria in RCU, a frequent finding in a number of laboratories, is being challenged by the fact that the colorimetric method for measurement of oxalate was often used, and evidently yielded too high values (41). Using the more reliable HPLC technique, we were unable to detect overt hyperoxaluria in fasting urine (95), and we (95), and others (118), concluded that if oxaluria is increased it results from increased fractional oxalate clearance.

Carbohydrates

The role played by carbohydrate(s) in RCU pathophysiology is another unsolved issue. With time a rise in sugar consumption in developed countries has been suggested (5, 76, 82). In the sixties, publications reported the calciuric effects of sugar carbohydrates (glucose, galactose, sucrose), insulin, alcohol, and suggested that the calciuric effect of glucose was more expressed in RCU than in controls; also, glucose-induced hypercalciuria has been ascribed to decreased distal-tubular calcium reabsorption (for details see Ref. 58). More recent investigation revealed that glucose increases intestinal calcium absorption in a dose-dependent manner (51, 119); however, these authors did not discuss the underlying

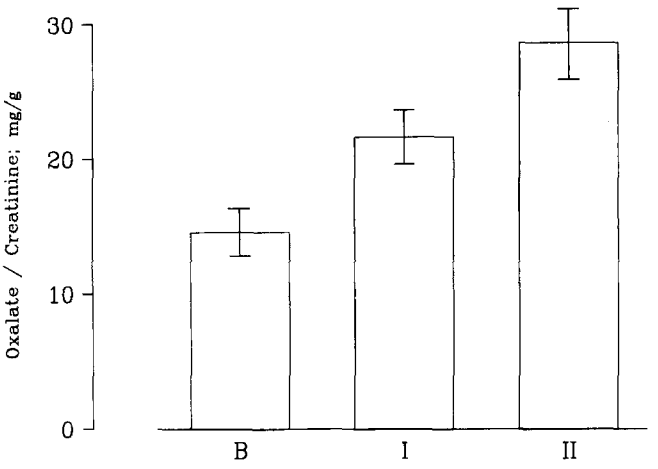


Fig. 2: Oxaluria (mean values ± SEM) in healthy males before (B), and after breakfast (2 sandwiches, 20 g bees honey, 20 g butter, 600 ml oxalate-free tea). I: first two postprandial hours; II: second two postprandial hours. Data are from unpublished work in the author's laboratory.

mechanism, e.g. whether glucose itself or the associated insulinemia was responsible. However, one report showing insulin-dependent stimulation of calcium absorption is available (85).

Our laboratory was the first to describe hyperinsulinemia in response to a carbohydrate-rich test meal in RCU (89), and the finding was later confirmed in other laboratories (74, 96). While the nature of hyperinsulinemia is still unknown, it was correctly stated more recently that there is no report yet published which clearly documents a significantly increased intake of refined sugars in RCU as compared with controls (82). However, in the light of a report by Shuster et al. (104), the German expertise (72), and reports of others (see below), the argument "that a high sugar consumption per se is not a particularly important risk factor for calcium urolithiasis" (82) may not be convincing. Regarding metabolic causes of hyperoxaluria sugar alcohols were mentioned, but not refined sugars (36). In RCU, we were able to demonstrate some degree of postprandial hyperoxaluria developed in response to the carbohydrate-rich test meal, which in addition creates hyperinsulinemia (91), while in controls others showed that oxaluria was more than doubled in resonse to oral glucose (70) but not fructose (71); white bread (sandwich) also stimulated oxaluria to a degree comparable with that seen with glucose (P.O. Schwille, unpublished data; Fig. 2). Assuming that in these non-stone-forming healthy controls renal oxalate handling was normal, the possibility must be considered that carbohydrate(s) stimulate endogenous synthesis of oxalate, which then is eliminated via the urine. Further support comes from work showing that glucose has a central position in metabolic pathways ultimately leading to the formation of glycolate, glyoxylate, oxalate (Fig. 3; see also Ref. 23). Obviously, there is no need to postulate glucose overconsumption alone or in combination with diets deficient in pyridoxine and magnesium - the latter two inhibiting oxalate biosynthesis - as a prerequisite for stimulation of oxalate synthesis. In contrast,

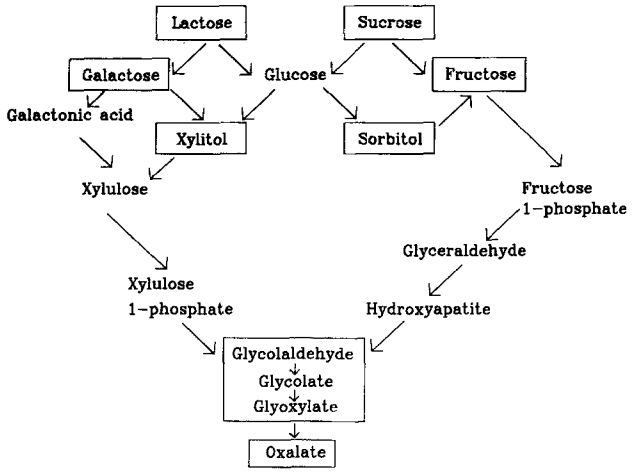


Fig. 3: Pathways of carbohydrate metabolism leading to the production of oxalate. Note the central role of glucose (modified from Ref. 23).

oxalate production may take place in response to ingestion of even normal amounts of lactose, galactose, sucrose, fructose, i.e. ubiquitous food constitutents (23). If this is true, then oxalate neoformation will increase with increasing intake of several (carbohydrate) precursors of oxalate. As a result, calcium oxalate deposition in tissue can occur, as well as hyperoxaluria. For stone disease this latter situation may be the basis for a new risk factor. On the other hand, the oxalate content of carbohydrate-rich nutrients such as white bread may be unable to contribute to oxaluria; in case of the breakfast test (Fig. 2) intestinal oxalate absorption (in per cent of the approx. 10 mg oxalate supplied with 2 sandwiches) would need to go up almost to 100, an unrealistic figure considering that in normals intestinal oxalate absorption varies between 2 and 12 per cent (91).

Several groups of workers reported higher oxaluria in males than in females, and the explanation was sought in lower food consumption by the latter. Another explanation would be that glycolate and oxalate overproduction by tissue in response to eating the respective carbohydrates (see above) induces inhibition of glycolate oxidase, the enzyme converting to oxalate, i.e. there is a so-called product-inhibition mechanism resulting in control of oxalate and possibly oxaluria; in males the rate-limiting oxalate concentration is higher than in females, allowing increasing oxaluria to occur mainly in the former (7). On the basis of our present knowledge of the calculogenicity of carbohydrates one is inclined to assume that their dual effect (induction of hypercalciuria and hyperoxaluria), or even their triple effect (additional energy supply), creates an environment that allows crystals and stones to form. In this respect refined sugars may be more effective than polymeric carbohydrates and protein, especially since a 30% increase of both calcium and oxalate means that the calcium oxalate product rises by 70% (104). Not surprisingly, sucrose feeding induces calculogenicity in the rat (73), increases oxaluria and urine excretion of markers of renal tubular cell damage in both stone formers and normals (60). It may, however, prove that not the absolute amounts of either carbohydrate or protein ingestion are the decisive factors in determining disturbances associated with RCU, but rather their ratio; this aspect is under evaluation for a number of diseases frequently associated with Western diet (2).

Oxalate

Although hyperoxaluria is a significant risk factor in RCU (79) the contribution of dietary oxalate is uncertain, for a number of reasons. Owing to the lack of information on the rate of endogenous biosynthesis of oxalate under average conditions of nutrition, the portion of urinary oxalate derived from this source is unknown. Intestinal oxalate absorption may vary considerably, depending on 1) the presence or absence of clinical disorders leading to so-called enteric hyperoxaluria (26); 2) the oxalate content of different foods, which is reportedly high in rhubarb and spinach (15, 57); 3) the bioavailability of dietary oxalate, which appears low even in the case of spinach, but high in the case of soluble sodium oxalate (15); 4) the analytical technique used to measure oxalate.

While the last point has been addressed by previous workers (15, 57), focussing also on the fact that the colorimetric method (40) is not applicable to oxalate in food (15), there is agreement that spinach (approx. 7 mmol per 100 g) and rhubarb (approx. 8 mol per 100 g) are the outstanding oxalate-rich foodstuffs (1 5, 57). In contrast, there is a great divergence of opinion among researchers as to the true oxalate content of the average Western diet, e.g. that eaten in the UK (6, 48, 120). Overconsumption of oxalate by RCU patients has been assumed (82), but there has been no confirmation by independent workers as yet. One important determinant of oxaluria after ingestion of oxalate, either from solid food or beverages, appears to be the degree of oxalate binding to to other food or liquid constituents, thereby determining oxalate bioavailability (15). There is circumstantial evidence from independent research that calcium in the gut lumen plays a dominant role in this regard. Thus, a free diet with a given calcium and oxalate content did not result in higher oxaluria than a calcium-restricted diet with only half the oxalate content of the former (57); this implies that oxalate not bound to calcium was hyperabsorbed from the low-calcium diet, whereas the free diet facilitated intra-intestinal calcium oxalate complexation and precipitation. Dietary calcium restriction in RCU patients results in frank hyperoxaluria (45). In the rat, oxalate transport along the gastro-intestinal tract was markedly delayed when oral calcium was given simultaneously; adhesion of calcium oxalate crystals to the mucosal surface has been demonstrated (102), permitting speculation that oxalate trapping via intraluminal formation of calcium oxalate crystal not only occurs, but may also be a means for modulating oxaluria. Less well known is the calcium-depleting effect of intestinal oxalate.

In the first instance, calcium contained in preformed

calcium oxalate crystals is less available for absorption (37); in the second place, a change in the intestinal flora resulting in an increase in oxalate breakdown has been shown (4); this fact may facilitate intestinal absorption of calcium and zinc (61). The possible significance of this exciting phenomenon for both RCU and osteopenia deserves attention in future research. Probably the best way to modify oxaluria and calciuria may be recognized in diets and liquids supplying oxalate and calcium in a molar ratio optimal for intra-intestinal calcium oxalate precipitation, while still providing sufficient calcium to the absorption sites to prevent calcium malabsorption.

Calcium

RCU patients, when unclassified according to calciuria, have moderately higher levels of urine calcium per day than matched controls (90). Also, intestinal calcium absorption in response to a calcium-rich test meal may be higher in normocalciuric RCU than in non-stone forming controls (90). Both findings would support the view long held by highly reputed institutions that restricting dietary calcium would be mandatory for the planning of stone metaphylaxis regimens including modulation of diet. However, a low-calcium diet may be asociated with several unwanted effects. These include 1) the development of a negative calcium balance, as has been seen with dietary calcium <400 mg per day (22), and which may be aggravated by the high blood levels of 1.25-dihydroxyvitamin D - known to stimulate bone resorption (65) - in many of the patients with hypercalciuric RCU (65); 2) suppression of parathyroid gland function secondary to enhanced efflux of calcium from bone, which diminishes renal tubular reabsorption of calcium, i.e. hypercalciuria will be perpetuated although the opposite effect was intended; 3) osteopenia, produced in particular when a low calcium diet is combined with a high protein intake (which latter itself is capable of producing osteopenia) (113); 4) mild hyperoxaluria (45), although the underlying mechanisms are not sufficiently understood. Thus, the available information should encourage physicians to stop recommending a low-calcium diet, because it is doubtful that stone formation will then cease, and because it is potentially harmful. Conversely, there has been only one study on whether RCU patients would benefit from added calcium aimed at reducing the exogenously induced hyperoxaluria (8); such a regimen was successfully practiced in enteric hyperoxaluria (26).

Magnesium

As long ago as 1938 it was reported that raising dietary magnesium reduced renal stone formation (24). In the sixties, a magnesium-deficient diet was recognized as a means of causing cortico-medullary nephrocalcinosis in the rat (116). In the seventies, a negative correlation was found between the incidence of urinary stones and hardness of drinking water, the latter being an expression of both the calcium and magnesium content (56). Thus, magnesium in the environment should play a role in renal tract stone disease, but we still lack a scientifically sound

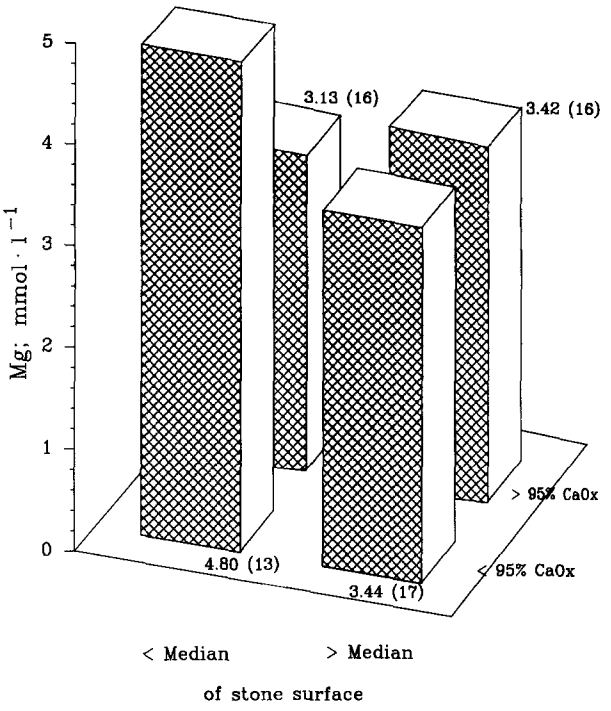


Fig. 4: Median magnesium concentration in spot urine of prelithotrypsy renal calcium stone patients with a) stone surface areas less than (< median) or more than (> medians) calculated surface, and b) either almost pure calcium oxalate stones (> 95% CaOx) or stones containing various other compounds in addition (< 95% CaOx).
( ): number of patients. For further details see Ref. 97.

basis for the significance of this ion. With respect to magnesium defiency in the urine and serum of RCU, the literature is not conclusive, reporting both unchanged magnesium (47) and some degree of magnesium deficiency, especially when related to calcium (110). In a series of RCU patients undergoing extracorporeal lithotrypsy for kidney stones we measured magnesium concentrations in fasting spot urine voided spontaneously in the morning, between one and three hours before the procedure, and the data were classified in accordance with stone composition and surface (97). Fig. 4 shows that stone composition and stone surface area (calculated from stone size as estimated by plain X-ray of the abdomen) may be determinants of magnesium concentration, or vice versa; magnesium concentration varied significantly among several groups with different surface areas (by analysis of variance; $p < 0.04$). According to more recent literature magnesium inhibits nucleation, growth and aggregation of calcium phosphate and calcium oxalate crystals (59, 86, 117), and our finding of high levels of magnesium in a subgroup of patients with small stones would be in agreement with this. For adult males the recommended dietary allowance (rda) of magnesium in the US is 350 - 400 mg per day, but in many countries with a Western style of nutrition - except France and Australia - the magnesium intake on a per cent basis of the rda is much lower, and sometimes as low as 50 per cent (62). A

re-evaluation of magnesium in the diet of RCU subgroups would thus appear highly desirable.

Fibre

Studies on the consumption of fibre-rich diet have become of interest to stone research because of the inhibitory action of fibre upon intestinal calcium absorption; the latter may occur independent of the dietary content of phytic acid and uronic acid(s) - known complexors of calcium - but may be related to the sodium salt of alginic acid and to pectin, a polymer of uronic acid and sugar (for details see Ref. 49). As with other calcium absorption-reducing agents, also with high-fibre diet there may be the risk of hyperoxaluria, unless calcium and oxalate are prevented from being absorbed. There is some indication in the literature that the frequency of stone occurrence and dietary fibre are negatively associated (82), and that RCU patients may ingest less fibre with their usual home diet than non-stone forming controls (35, 81). In this regard, we, in a case-control study on fibre eaten with meals on Sunday, were unable to show up a difference between 167 unclassified (according to calciuria) RCU patients and carefully matched controls (108). Thus, dietary fibre creates interesting questions, but we do not yet have promising answers.

Alcohol

There is now increasing awareness by scientists on the harmful actions of ethanol toward several organs, such as stomach, liver, bone etc. Nutrition specialists do not recommend the regular use of alcohol-containing drinks, in fact these should be omitted (72). Nevertheless, alcohol consumption appears to be a regular part of daily meals in many countries, especially in Germany (72). Surprizingly, only two reports focus on alcohol (28, 121, and the latter considers high alcohol intake has a risk factor in urolithiasis because hyperuricosuria, hyperphosphaturia and hypercalciuria are frequently associated. Also, in the rat, ethanol alters gastrointestinal motility, suppresses small-intestinal calcium absorption and simultaneously increases intestinal calcium secretion (54). Individuals afflicted by chronic alcoholism may be at risk for developing osteopenia and bone fractures (27). Together, the four reports (27, 28, 54, 121) shed new light on the possibility that a number of metabolic abnormalities seen with RCU can be brought into the context of inappropriate alcohol consumption.

Conclusion

Research into the etiology and pathophysiology of RCU needs a new impetus in order to help resolve this major worldwide health problem. On the basis of reports in the literature and our own studies commented in this article there can be little doubt that environmental factors, especially hypernutrition, are causally involved.

Similar thinking by others resulted in the recommendation to place more emphasis on oxalate metabolism and the composition and properties of whole urine (84). Food can affect the production and secretion of hormones in a variety of ways, for example on the gut, nerves, and blood metabolites (18, 63); investigation of this area has so far been neglected by stone researchers. We would therefore recommend that, in addition to the proposal made by A.G. Rose (84), more studies be made on how Western food influences our hormone system, the resulting metabolic alterations, and what the ultimate answer of renal function, renal tissue minerals and oxalate, and urine composition to these is.

Acknowledgment. Research carried out in the author's laboratory has been financially supported by Deutsche Forschungsgemeinschaft, Bonn, and W. Sander Foundation, Munich. Laboratory assistance was provided by Dr. M. Manoharan, K. Schwille, G. Hoffmann, B. Schreiber. Dr. V. Sharma kindly read the manuscript and offered mutual discussions.

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Urol Res (1992) 20:83-86

Tamm-Horsfall Glycoprotein - Inhibitor or Promoter of Calcium Oxalate Monohydrate Crystallization Processes?

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Summary. The processes of calcium oxalate monohydrate (COM) crystal nucleation, growth and aggregation (agglomeration) generally have been studied using a wide variety of assay systems/conditions. This paper reviews the apparently conflicting data on the effects of **Tamm-Horsfall glycoprotein (THP)** on COM crystallization processes in vitro, with the main emphasis on crystal aggregation. According to its well-known physico-chemical properties, THP has a dual role in modifying crystal aggregation: at high pH and low ionic strength (IS), THP is a powerful crystal aggregation inhibitor. Upon lowering pH and raising IS, THP viscosity increases, leading to reduced crystal aggregation inhibition. In the presence of additional calcium ions, some THPs even become strong promoters of crystal aggregation. This phenomenon seems to be more pronounced in THPs isolated from recurrent calcium stone formers whose proteins exhibit an abnormally high tendency of polymerization. Recent studies suggest an inherited molecular abnormality of THP among some severe recurrent calcium stone formers.

Key words: nephrolithiasis, calcium oxalate, inhibitors and promoters, Tamm-Horsfall glycoprotein

Introduction

When addressing crystallization within the urinary tract, two major aspects have to be considered (14): a **thermodynamic** one including high urinary supersaturation during which crystal nucleation occurs, and a **kinetic** one comprising rates of nucleation, growth and aggregation (agglomeration) of crystals. When reviewing studies on urinary compounds that modify calcium oxalate crystallization kinetics, a somewhat confusing picture emerges. In many studies on **"crystallization"**, it is often not clear whether authors refer to nucleation, growth or aggregation of crystals, and a wide variety of **assay systems/conditions** is being applied for measuring these processes. Furthermore, the term **"inhibitor"** has been used for compounds that act as chelators of calcium or oxalate ions as well as for molecules binding to the surface of preformed calcium oxalate crystals (17). Whereas **chelators** reduce free ion activity and, therefore, supersaturation, "real" **inhibitors** do not influence supersaturation, since they bind to crystal surfaces and block growing sites ("crystal poisoning") at very low (usually micromolar) concentrations (1). Additionally, some molecules may act as **promoters**, probably by providing preformed surfaces