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IMPORTANCE OF MILD HYPEROXALURIA IN THE PATHOGENESIS OF UROLITHIASIS - NEW EVIDENCE FROM STUDIES IN THE ARABIAN PENINSULA

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Abstract

The hypothesis that mild hyperoxaluria is more important than hypercalciuria in the pathogenesis of urolithiasis is re-examined in the light of new evidence. Small increments in urinary oxalate in the normal to high-normal range are much more critical than similar rises in urinary calcium for increasing the relative supersaturation of urine with respect to calcium oxalate, the oxalate/calcium ratio in urine, the total volume of calcium oxalate crystals excreted, the proportion of abnormally large crystals and aggregates of calcium oxalate and the severity of the disorder as defined by the recurrence rate of stone-formation. Data from the Arabian Peninsula, where the prevalence of calcium-containing stones is considerably higher than in the West, have shown that this occurs in spite of the almost complete absence of hypercalciuria. On the other hand, there is a strong association between stone-formation and the occurrence of mild hyperoxaluria. The life-time expectancy of stone-formation in men from various countries is strongly correlated with the average daily excretion of oxalate in the urine of the normal men in these countries. This relationship extends to include patients with enteric and hereditary hyperoxaluria. There is no such relationship, however, between the life-time expectancy of stones and urinary calcium excretion in the same populations.

Studies on the regulation of urinary oxalate indicate that it is largely controlled by the quantity of "free" dietary oxalate available for absorption in the lower intestine This can be calculated from the intakes of calcium and oxalate and the urinary excretion of calcium.

KEY WORDS: Oxalate, Calcium Urolithiasis, Crystallization, Prevalence, Mild Hyperoxaluria, Hypercalciuria.

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Introduction

For over half a century, hypercalciuria has been considered by the majority of researchers in the kidney stone field to be the main risk factor for primary (idiopathic) and secondary calcium urolithiasis (Flocks, 1939; Albright et al., 1953; Hodgkinson and Pyrah, 1958; Pak et al., 1975; Coe and Favus, 1980; Halabé and Sutton, 1987). The main evidence cited in support of this hypothesis is that most well-controlled studies which have compared the urinary excretions of minerals by stone-formers and normals have shown that the patients tend to excrete more calcium although there is invariably a large degree of overlap between the two groups. This overlap is so considerable that, once allowance is made for the true prevalence of urinary stone-formation in the population, the urinary calcium excretions of stone-formers all lie within the projected range for the normal population, albeit within the upper half of that range (Robertson et al., 1978; Bataille et al., 1983; Robertson and Peacock, 1985a). There is certainly not the clear-cut separation between the urinary calcium excretions of calcium stone-formers and their controls that exists between the cystine excretions of cystinuric stone-formers and their controls (Robertson and Peacock, 1985b).

If the hypothesis that hypercalciuria is the main risk factor for calcium stone-formation is correct, then therapeutic measures designed to decrease urinary calcium excretion would be expected to reduce the rate of recurrence of calcium stone-formation in patients affected with the disorder. Although many of these modalities, such as thiazide diuretics (Yendt, 1970; Coe and Kavalich, 1974), cellulose phosphate (Pak et al., 1974) and a low calcium diet (Nordin et al., 1973), have been claimed to have a beneficial effect on stone recurrence, more recent reports have cast doubt on their efficacy. Such doubts have arisen (a) because of faults in the design of the studies concerned (Churchill, 1987), (b) because the effect of a particular form of treatment in long-term studies seems to be minimal (Marickar and Rose, 1985), or (c) because the treatment concerned leads to adverse changes in urine biochemistry,

such as an increase in urinary oxalate or pH, which may more than offset the beneficial effect of reducing urinary calcium (Marshall and Barry, 1973; Hallson and Rose, 1978; Hallson, 1988). There are growing doubts, therefore, about the importance of hypercalciuria per se as a major risk factor for calcium stone-formation. This has led some of the former protagonists of the "hypercalciuria theory" to turn their attention to other possible urinary risk factors, such as hypocitraturia (Pak et al., 1985) and defective inhibitors of crystallization such as "nephrocalcin" (Coe and Parks, 1990).

One important factor which these and many other workers continue to overlook, however, is the importance of mild hyperoxaluria in calcium stone-formation. Calcium oxalate, after all, is consistently the most common constituent of calcium-containing calculi in stone series reported from all parts of the world and mild hyperoxaluria should deserve at least as much attention as hypercalciuria as a factor in the formation of such calculi.

The main problem for most potential researchers in this area has been the difficulty in measuring oxalate reliably in biological fluids. Unlike the situation with respect to the measurement of urinary calcium, the accurate determination of oxalate in urine has only become possible in recent years with the application of the modern techniques of high performance liquid chromatography (HPLC) (Hughes et al., 1982), ion-chromatography (Menon and Mahle, 1983; Robertson et al., 1982, Robertson and Scurr, 1984) and gas chromatography (Yanagawa et al., 1983). In general, however, urinary oxalate (where measured at all) is still assayed badly (Samuell, 1988), particularly when using techniques other than those described above. The reasons for the unreliability of most methods are multifactorial but are most frequently due to inadequate handling and work-up of urine prior to the actual measurement, particularly in the case of urines which contain crystals of calcium oxalate. Unless great care is taken either to acidify the entire urine sample to at least pH 1.6 (Hodgkinson, 1981) or to shake the whole urine thoroughly in order to disperse the crystals homogeneously before sub-aliquoting, the probability of over- or under-estimating oxalate is extremely high. Even collecting the urine directly into acid is problematic since Stone Clinics are generally unwilling to put sufficient acid (at least 100 ml of 1 molar HCl) in the container to ensure that the overall pH will be less than 1.6 at the end of the 24-hour collection.

In those laboratories which have taken all the precautions necessary to ensure that the urine is correctly handled before oxalate is measured, important differences between the oxalate excretion of stone-formers and controls have been reported (Robertson et al., 1971, 1978, 1989; Revusova et al., 1971; Baggio et al., 1983; Bataille et al., 1983; Pena et al., 1987; Larsson and Tiselius, 1987; Rose, 1987; Smith, 1991). However, there appears to be no complete separation in oxalate excretion between stone-formers and normals. In this respect mild hyperoxaluria does not appear to be different from hypercalciuria. More in-depth studies have shown, however, that, when stone-formers are studied when they first present with stones, their mild hyperoxaluria is much more marked than after they consult their urologist or physician (Robertson and Peacock, 1980). The overlap between the oxalate excretions of stone-formers and normals when they first present is much less than it is when they are referred later to the specialist Stone Clinic. This reduction following hospitalization or out-patient consultation is now a recognised feature of the so-called "stone clinic effect" (Hoskin et al., 1983; Norman et al., 1984) and should not be discounted in the assessment of patients presenting with stones.

It would seem from the above evidence that hypercalciuria and mild hyperoxaluria are both common findings among stone-forming populations, so why then has doubt been cast on the importance of hypercalciuria in the pathogenesis of stones and what new evidence is there to support the hypothesis that mild hyperoxaluria is a much more significant risk factor than hypercalciuria for stone-formation?

Relative Importance of Hypercalciuria and Mild Hyperoxaluria for Urolithiasis

The relative effects of hypercalciuria and mild hyperoxaluria on the risk of calcium oxalate stone-formation were first investigated by Robertson and his colleagues (Robertson and Nordin, 1969; Robertson et al., 1971; Robertson and Peacock, 1980). Their initial findings in this respect have since been largely confirmed by others (Bataille et al., 1983; Hallson, 1988; Lindsjö, 1989). The hypothesis that mild hyperoxaluria is much more critical than hypercalciuria in the pathogenesis of calcium oxalate stone-formation was developed based on findings obtained from both in vitro and in vivo studies.

In Vitro Studies

Simple titration studies on whole urine in vitro indicated that it was extremely difficult (and in most cases impossible) to produce spontaneous crystallization of calcium oxalate by the addition of a concentrated solution of calcium chloride, even up to total calcium concentrations in urine of 15 to 20 mmol/l - well outside both the normal and stone-forming ranges. On the other hand, it was found to be possible to induce spontaneous crystallization in almost every urine tested by the addition of relatively small quantities of a solution of sodium oxalate (Robertson and Nordin, 1969). Indeed, crystallization was found to be initiated spontaneously in most urines when the oxalate concentration reached a value of approximately 0.4 mmol/l (the upper limit of normal).

The chemical reason for this difference is shown in the lower panels of Fig. 1 which contain the bands of supersaturation values

measured in urine in relation to increasing the concentrations of calcium and oxalate independently. Clearly, the upper limit of metastability can be exceeded in only a few cases by increasing urinary calcium alone whereas it is exceeded in all urines whose oxalate concentrations reach the upper limit of normal.

The upper panels of Fig. 1 show the relative effects of independently increasing urinary calcium and oxalate concentration on the maximum volume of calcium oxalate crystals produced. Whereas hypercalciuria has virtually no influence on the volume of crystals produced, mild hyperoxaluria produces a marked linear increase in crystalluria. Only in urines with a very low calcium content is there a limited relationship between crystalluria and calcium concentration.

Another chemical factor (in addition to supersaturation) which is important in determining the volume and size of calcium oxalate crystals and aggregates produced in a given solution or urine is the ratio of oxalate/calcium concentration. Fig. 2 shows that for any one of a number of defined initial levels of supersaturation with respect to calcium oxalate, the closer the oxalate/calcium ratio of the solution or urine is to 1:1 the greater is the volume of crystals produced. These curves are extremely important in explaining why stone-forming populations in the Middle East have much more severe calcium oxalate crystalluria than stone-forming populations in the West in spite of the fact that both groups have approximately the same initial levels of calcium oxalate supersaturation in their urine (Robertson et al., 1989). The mean oxalate/calcium ratio in the urine of recurrent stone-formers in Saudi Arabia, for example, is 0.164 compared with 0.054 in the urine of recurrent stone-formers in the UK. Both have approximately the same level of supersaturation [between 1.10 and 1.20 on the log (relative supersaturation) scale of Marshall and Robertson (1976)] yet the Saudi stone-formers excrete about twice the volume of crystals produced by their counterparts in the UK. The reason why the Saudi stone-formers do not have very much higher supersaturation values than stone-formers in the UK is that their much higher urinary oxalate excretions are largely offset by their extremely low urinary excretions of calcium (Robertson et al., 1989).

Fig. 2 clearly shows that an increase in the oxalate/calcium ratio of urine is, in fact, more important than an increase in the relative supersaturation of urine with respect to calcium oxalate in determining the volume of calcium oxalate crystals produced. This factor has been totally ignored by stone reseachers in the past and has important implications for the treatment of stone disease.

In addition to influencing the volume of crystals produced in solution or in urine, an increase in the oxalate/calcium ratio of the medium to values closer to 1:1 markedly increases the average size of the crystals and aggregates generated (Fig. 3). This appears to be a function of (a) the increase in the total number of calcium oxalate crystals produced which are available for agglomeration, (b) the greater amount of "building material" available

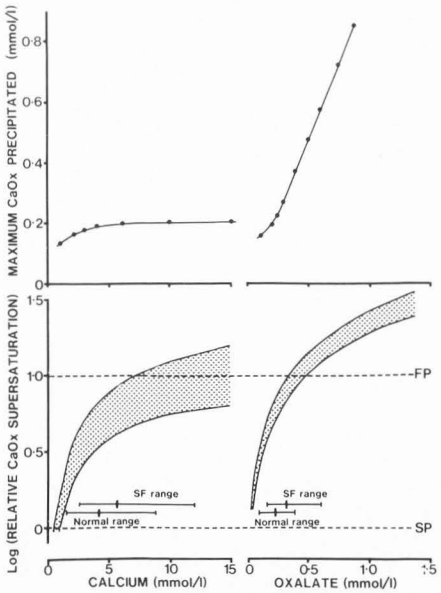

Fig. 1. The effect of independently increasing urinary calcium or oxalate concentration on the relative supersaturation of urine with respect to calcium oxalate (lower panels) and on the maximum achievable amount of calcium oxalate crystalluria (upper panels). (FP and SP represent the formation and solubility products of calcium oxalate).

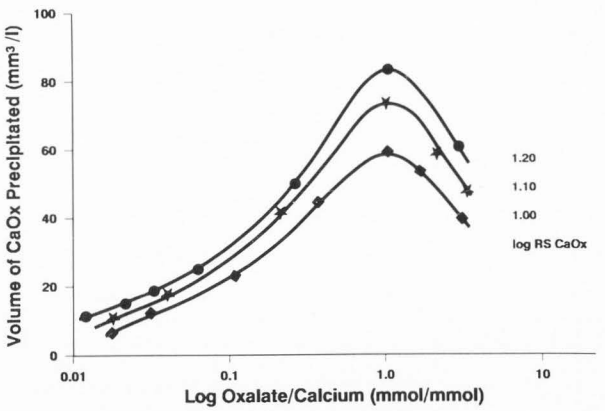

Fig. 2. The relationship between the volume of calcium oxalate crystals precipitated and the initial oxalate/calcium ratio in solution derived at three different starting levels of supersaturation with respect to calcium oxalate. [Log RS CaOx is the relative supersaturation of urine with respect to calcium oxalate as defined by Marshall and Robertson (1976)].

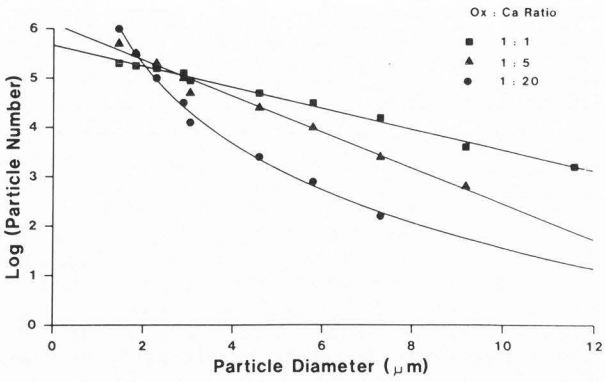

Fig. 3. The relationship between the logarithm of the number of calcium oxalate particles produced and particle diameter at three different initial oxalate/calcium ratios in solution. The starting level of supersaturation with respect to calcium oxalate was the same in each case.

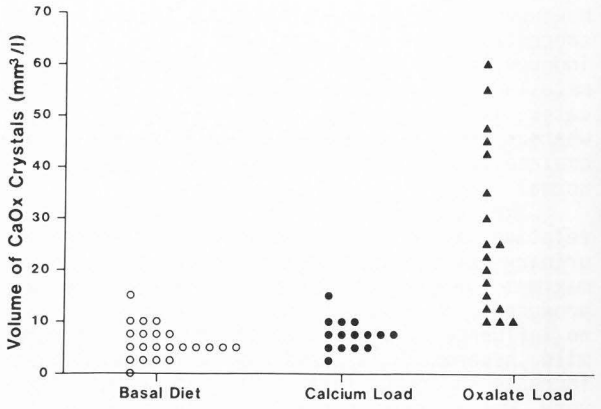

Fig. 4. The volume concentration of calcium oxalate crystals in fresh warm urine samples from a group of recurrent idiopathic calcium stone-formers (a) on their basal diet, (b) on their basal diet plus 25 mg/kg body weight of additional calcium (given as calcium citrate) and (c) on their basal diet plus 3 mg/kg body weight of additional oxalate (given as sodium oxalate).

to promote crystal growth and (c) the diminution of the surface charge on the crystals which also increases the degree of agglomeration. This last mentioned phenomenon is due to the fact that, at low oxalate/calcium ratios in the supernatant fluid, calcium oxalate crystals have a net positive surface charge as a result of the excess of calcium over oxalate ions in the hydration layer surrounding the crystals (Curreri et al., 1979; Scurr and Robertson, 1986). This net positive charge causes mutual repulsion between the crystals, thereby reducing the probability of the crystals agglomerating. When the oxalate/calcium ratio of the supernatant approaches 1:1, however, the net surface charge tends towards neutrality, under which conditions agglomeration becomes much more likely.

In Vivo Studies

In vivo studies (paralleling the above mentioned in vitro studies on the addition of calcium to urine) were carried out in which an oral load of calcium (in the form of calcium citrate sufficient to increase urinary calcium by up to 60%) was given to stone-formers. This regimen failed to increase the volume of calcium oxalate crystals excreted by the patients (Robertson et al., 1969). In contrast, corresponding studies using an oral load of sodium oxalate produced marked calcium oxalate crystalluria in the same patients within about 2 to 3 hours (Fig. 4). Similar results have been reported from studies in rats (Khan et al., 1992). Together these in vivo findings bear out the predictions which would be made from Figs. 1-3.

A further set of studies on calcium oxalate crystalluria in fresh urine samples maintained at 37^{0}C from recurrent, primary calcium stone-formers showed that there are strong relationships between each of the following and the concentration of oxalate in urine: (a) the total volume of calcium oxalate crystals excreted, (b) the percentage by weight of abnormally large crystals and aggregates of calcium oxalate and (c) the recurrence rate of stone-formation (Robertson and Peacock, 1980). There were no relationships, however, between the same parameters and the concentration of calcium in urine. These findings have subsequently been confirmed by Hallson (1988) and Lindsjö (1989).

The reason for the relatively weak relationship between the crystallization markers of stone disease and urinary calcium is complicated (Robertson and Nordin, 1969). Basically it is due to the combination of the following factors: (a) the formation of a strong, soluble complex between Ca^{2+} and $C_2O_4^{2-}$ ions and (b) the relatively high calcium/oxalate ratio which prevails in most urines. As a consequence of this combination of factors, any further increase in the urinary concentration of ionized calcium ($[Ca^{2+}]$) (which in normal urine is about 20 times that of ionized oxalate ($[C_2O_4^{2-}]$) is almost entirely offset by a proportional decrease in the concentration of ionized oxalate. Thus the product of $[Ca^{2+}]$ x $[C_2O_4^{2-}]$ remains virtually constant over most of the normo- to hypercalciuric range. This contrasts with the effect of independently increasing the concentration of urinary oxalate which, because oxalate is present in much lower concentrations than calcium, does not significantly reduce $[Ca^{2+}]$ by complexation when it is increased. The product of $[Ca^{2+}]$ x $[C_2O_4^{2-}]$ therefore rises almost proportionally to the increase in oxalate concentration in the urine of most individuals in the population.

Demographic Studies

Using the overlapping distributions of various parameters of stone-formation measured in the urines of stone-formers and normal subjects, Robertson and his colleagues (1978, 1981) constructed a "risk curve" for each parameter which allowed a probability to be calculated that a given individual is likely to be a stone-former or not. Comparison of the various "risk curves" showed that the two most important risk factors for calcium stone-formation are a low urine volume (< 1 litre/day) and mild hyperoxaluria (> 0.45 mmol/day). Hypercalciuria per se, on the other hand, was the weakest of the six urinary risk factors identified at that time as playing a significant role in the pathogenesis of stones. This finding supports the conclusion drawn by Marshall et al. (1975) from their studies on the natural history of calcium stone disease that there was no relationship between stone disease and urinary calcium excretion.

New Evidence Supporting the Importance of Mild Hyperoxaluria

Studies in the Arabian Peninsula

Stone-formation is an extremely common disorder in the affluent countries of the Arabian Peninsula and Gulf area. Current estimates indicate that the life-time expectancy of stones in men reaching the age of 60 is about 20% (Abdel-Halim et al., 1989; Robertson, 1993). This compares with a figure of 12 to 13% in North America and Australasia (Sierakowski et al., 1978; Johnson et al., 1979), 9 to 10% in Scandinavia (Ljunghall, 1978), 7 to 8% in Western Europe (Vahlensieck et al., 1982; Robertson et al., 1983) and 5 to 6% in Japan (Koide et al., 1986). Interestingly, the figure for Japan has been rising rapidly in the past decade as urine composition has changed in the population. It has been suggested that these changes are due to the increasing consumption of animal protein in that country (Iguchi et al., 1990).

Studies on the urine biochemistry of stone-formers and normal controls in the United Arab Emirates (Husain et al., 1979; Al-Ali et al., 1981) and in Saudi Arabia (Robertson et al., 1989), where the majority of stones contain calcium oxalate (Barkworth et al., 1989), have shown that the very high prevalence rate of stone-formation in that part of the world occurs in the almost complete absence of hypercalciuria. On the other hand, the urinary excretion of oxalate is, on average, some 50 to 70% higher than in the corresponding populations in the West. This strongly supports the hypothesis that mild hyperoxaluria is a much more important risk factor than hypercalciuria for the formation of calcium oxalate stones. [It is interesting to note, in passing, that the same arguments and type of data can be put forward to show that the degree of alkalinity of urine is a much more important risk factor for calcium phosphate stone-formation than is hypercalciuria]. Thus, for both types of calcium stone-formation, hypercalciuria per se appears to be a relatively weak risk factor for the disorder.

When the data from various countries on the life-time expectancy of stones in men are compared with the average daily urinary excretions of calcium (Fig. 5) and oxalate (Fig. 6) in the normal male population of each of these countries, there is clearly a strong positive relationship between stone disease and urinary oxalate but not between stone disease and urinary calcium excretion. In fact, the latter relationship appears to be generally inverse except for those countries where urinary oxalate does not increase as urinary calcium decreases. Also shown in Figs. 5 and 6 are the

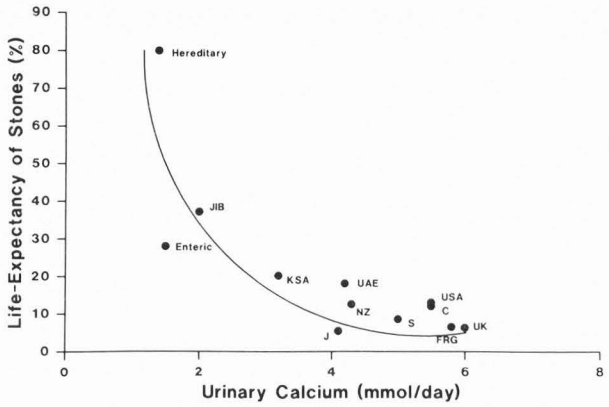

Fig. 5. The life-expectancy of forming stones in men in various countries in relation to the mean urinary excretion of calcium in normal men in the same country. Also shown are the corresponding data for individuals with hereditary, enteric and jejunoileal by-pass (JIB) hyperoxaluria.

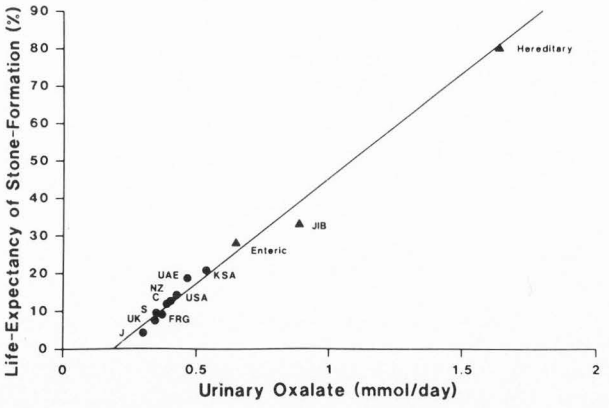

Fig. 6. The life-expectancy of forming stones in men in various countries in relation to the mean urinary excretion of oxalate in normal men in the same country. Also shown are the corresponding data for individuals with hereditary, enteric and jejunoileal by-pass (JIB) hyperoxaluria.

mean prevalence figures for stone disease in patients with enteric hyperoxaluria as a result of bowel disease or following jejunoileal bypass surgery (JIB) and in patients with primary (hereditary) hyperoxaluria. The data in Fig. 6 are particularly interesting because the relationship betweeen the prevalence figures from various countries and the average urinary oxalate excretion in these countries appears to continue linearly through the data collected from the various well-recognised hyperoxaluric groups. This suggests that the relationship between the occurrence of stone disease and urinary oxalate is a continuum over the entire range of urinary oxalate excretion and that, if urinary oxalate in the population is high enough, then almost everyone will form stones.

The implications of the relationship in Fig. 6 are far-reaching. Firstly, it implies that urinary oxalate excretion is a major, if not prime, determinant of stone prevalence in the population. Any factor which leads to an increase in oxalate excretion in a given population, whether it be a high consumption of oxalate, hyperabsorption of oxalate from the diet, or increased endogenous production of oxalate, will markedly increase the risk of calcium oxalate-containing stones in that population. Secondly, Fig. 6 implies that other urinary risk factors, such as hypercalciuria, hyperuricosuria and hypocitraturia must be relatively unimportant as sole risk factors for the disorder although they may still aggravate the problem if they occur in conjunction with mild hyperoxaluria. Thirdly, it implies that even if urinary inhibitors of crystallization, such as nephrocalcin, glycosaminoglycans, citrate, pyrophosphate etc are important as protective agents against stones under conditions of normal oxaluria, they must be capable of being overwhelmed when urinary oxalate is increased above normal. Presumably, this loss of activity is due to the marked increase in calcium oxalate crystalluria which occurs as a result of mild hyperoxaluria (Fig. 1). As the volume of crystalluria increases, the crystal surface area which becomes available to bind inhibitors may expand to levels which deplete the amount of inhibitors present in the urine concerned. Under these conditions crystal growth and agglomeration may proceed at a relatively uninhibited rate.

Causes of Mild Hyperoxaluria

There are three recognised causes of mild hyperoxaluria in the population: (a) an increased dietary intake of oxalate itself, (b) an increased intestinal absorption of oxalate from the diet, and (c) an increased endogenous production of oxalate from ingested or metabolically-generated precursors. Other suggested causes of mild hyperoxaluria include (d) a deficiency in oxalate utilisation by certain gut flora and (e) a decrease in the tubular reabsorption (or increase in the tubular secretion) of oxalate.

Increased dietary intake of oxalate

It is generally accepted that about 5-10% of dietary oxalate is absorbed by the intestine and is excreted in the urine. This absorbed dietary oxalate accounts for between 15 and 30% of urinary oxalate. However, at greater intakes of oxalate (> 2 mmol/day), absorbed oxalate constitutes an increasing percentage of the urinary excretion and may reach values as high as 50%. This percentage may be increased to 60% when the high intake of oxalate is accompanied by a low intake of calcium (Marshall et al., 1972) or when vitamin D supplements are given to increase calcium absorption (Erickson et al., 1984).

Over a range of intakes of oxalate, calcium and vitamin D there is a broad relationship between urinary and dietary oxalate (Fig. 7). It is clear, however, from the spread of the data that factors other than the dietary intake of oxalate alone must be involved in determining the amount of oxalate excreted in the urine.

Increased Intestinal Absorption of Oxalate

The relationship shown in Fig. 7 is greatly improved after account is taken of the effects of variation in dietary calcium and in the absorption of calcium on the amount of oxalate available for absorption in the intestine. Fig. 8 shows a plot of urinary oxalate against a measure of the "free oxalate" available for absorption in the colon. "Free oxalate" was calculated by subtracting from the dietary intake of oxalate the amount of oxalate bound to the non-absorbed calcium which reaches the large bowel after the majority of the calcium absorption has taken place in the small intestine. For an individual who is in calcium balance, the amount of non-absorbed calcium is approximately the difference between the dietary intake of calcium and its urinary excretion. The full expression for "free oxalate" is given by the expression:

$$\text{"Free oxalate"} = 0.5\left[(I_{Ox}-N_{Ca}-k) + \sqrt{(N_{Ca}-I_{Ox})^2 + 2k(N_{Ca}+I_{Ox}) + k^2}\right]$$

where N_{Ca} = non-absorbed portion of dietary calcium and is equal to $(I_{Ca}-U_{Ca})$ in mmol/day for an individual in calcium balance

I_{Ca} = dietary intake of calcium in mmol/day

I_{Ox} = dietary intake of oxalate in mmol/day

U_{Ca} = urinary excretion of calcium in mmol/day

k is a "constant" which is a function of the binding between calcium and oxalate ions and of the volume of fluid in the intestine/day. When I_{Ca} and I_{Ox} are in mmol and volume is approximately 1 litre/day, k has the value 5.

The equation then reduces to:

$$\text{"Free oxalate"} = 0.5\left[(I_{Ox}-N_{Ca}-5) + \sqrt{(N_{Ca}-I_{Ox})^2 + 10(N_{Ca}+I_{Ox}) + 25}\right]$$

From Fig. 8, it is clear that once the amount of calcium absorbed in the intestine is

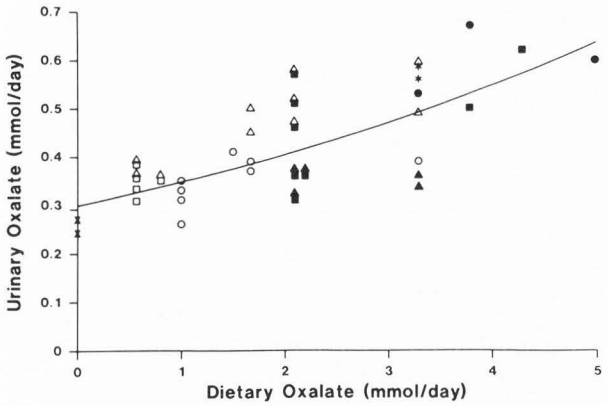

Fig. 7. Urinary oxalate excretion in relation to dietary oxalate taken from various studies (x = fasting; ○ = basal diet (Western); ● = basal diet (Middle East); △ = low Ca diet; ▲ = high Ca diet; □ = low Ox diet; ■ = high Ox diet; * = vitamin D supplements; ✡ = low Ca diet + vitamin D; ⧋ = low Ca + low Ox diet; ⧋ = high Ca + high Ox diet; ⧋ = low Ca + high Ox diet). Data are taken from Marshall et al (1972), Hodgkinson (1978), Husain et al (1979); Al-Ali et al. (1981), Erickson et al (1984), Bataille et al. (1985), Robertson et al (1989), Robertson (1993).

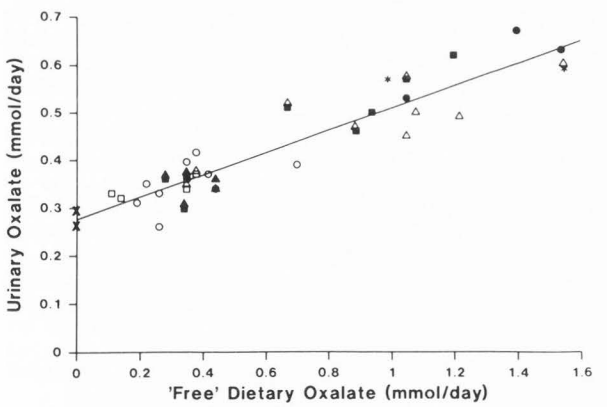

Fig. 8. Urinary oxalate excretion in relation to "free" dietary oxalate after allowance for the binding of oxalate to non-absorbed calcium in the intestine. Data are taken from the same studies as in Fig. 7 and the key is identical to that in Fig. 7.

taken into account and the amount of dietary oxalate bound to the remaining calcium is calculated, the relationship between urinary oxalate and the actual amount of "free oxalate" available for absorption in the large bowel is much tighter than that shown in Fig. 7 between urinary oxalate and the total dietary intake of oxalate. This strongly supports the hypothesis that the oxalate/calcium ratio in the diet and the ability of the gut to absorb calcium are dominant factors in the control of the absorption and subsequent urinary excretion of oxalate. Indeed, it may be that it is the stone-formers' ability to hyperabsorb calcium from the diet (thereby indirectly releasing more oxalate for absorption and excretion in the urine) that is more important for increasing the risk of stone-formation than the hypercalciuria with which it is more directly associated (Robertson and Peacock, 1980).

Increased Endogenous Production of Oxalate

The mild hyperoxaluria observed in the majority of idiopathic calcium stone-formers does not appear to be caused by an increased basal endogenous production of oxalate since their fasting urinary oxalate/creatinine ratios and fasting plasma oxalate concentrations are almost identical to those of non-stone-formers (Robertson, 1993). There remains the possibility, however, that the non-fasting endogenous production of oxalate is increased and that this may partly explain the increased urinary oxalate in some patients. Current evidence suggests that a small proportion of the mild hyperoxaluria observed in the population may derive from an increased ingestion and partial metabolism of certain amino acids [such as glycine, tyrosine, tryptophan, phenylalamine and hydroxyproline (Gershoff and Prien, 1960)] or from certain sugars [such as lactose, sucrose, fructose, xylitol, sorbital etc (Conyers et al., 1990)]. The data in Fig. 8, however, suggest that, at most, the contribution of the non-fasting endogenous production of oxalate to urinary oxalate must be relatively small in comparison to the contribution from available exogenous oxalate.

Deficiency in Oxalate-Metabolising Gut Flora

It has been suggested that the availability of oxalate for absorption may be influenced by the flora of the gut. Two bacteria (Oxalobacter formigenes and Pseudomonas oxaliticus), the former of which exists in the human intestine, have been shown to utilise oxalate within the physiological pH range (Allison et al., 1985, 1986; Dawson et al., 1988). The role of these bacteria in limiting the availability of oxalate for absorption in the intestine is unknown but it has been suggested that a deficiency of Oxalobacter formigenes in the human intestine might increase the possibility of hyperabsorption of oxalate leading to mild hyperoxaluria. This hypothesis remains to be tested. The data in Fig. 8 suggest, however, that this cannot be a major source of the mild hyperoxaluria of stone-formers.

Change in renal handling of oxalate

It has been suggested by some that mild hyperoxaluria may be partly due to either a decrease in the tubular reabsorption or an increase in the tubular secretion of oxalate (Cattell et al., 1962; Senekjian and Weinman, 1982; Borsatti, 1991). However, renal handling studies have been hampered by the lack of a

reliable method for measuring plasma oxalate. Current indications are that oxalate is freely filtered at the glomerulus but that there is no net reabsorption either in the proximal or distal tubule. On the contrary, under physiological conditions, only a small amount of oxalate appears to be reabsorbed in the proximal tubule but this is more than offset by secretion of oxalate into the lumen of the proximal tubule. No further transport of oxalate appears to take place in the distal nephron. The combined effect of these processes is to produce net secretion of oxalate into the proximal tubule. It has been further suggested that the proximal tubular cells of stone-formers might secrete more oxalate into the tubular lumen than the proximal tubular cells of normal subjects but no confirmation of this hypothesis has yet been published. It should be noted, however, that mild hyperoxaluria due to hypersecretion can only be maintained if at least one of the above possible causes of mild hyperoxaluria is also present. Chronic hypersecretion of oxalate without a consistently increased supply of oxalate to the kidney is not possible.

Treatment of Calcium Oxalate Urolithiasis

The data in Figs. 1 to 8 have considerable implications for the treatment of calcium oxalate stone disease. Firstly, they strongly indicate that treatments which rely solely on lowering urinary calcium, either by reducing the dietary intake of calcium itself or by increasing the intake of some calcium-binding nutrient, such as fibre, are unlikely to produce any benefit to the patient since urinary oxalate is bound to increase under these circumstances. Indeed, the patient may end up in a situation which is likely to aggravate, rather than reduce, the risk of calcium oxalate stones. Figs. 1, 2 and 3 show that the combination of lowering urinary calcium and increasing urinary oxalate will lead (i) either to no change or to an increase in the supersaturation of urine with respect to calcium oxalate, (ii) to an increase in calcium oxalate crystalluria and (iii) to larger aggregates of calcium oxalate crystals. All of these changes would predictably increase, rather than decrease, the risk of calcium oxalate stones. Unless the increase in urinary oxalate, caused by the reduction in non-absorbed calcium available in the intestine, can be prevented by simultaneously reducing the dietary intake of oxalate, there can be little beneficial effect in reducing urinary calcium by itself. Indeed, a recent review of treatments for calcium stone disease which are based on reducing urinary calcium, shows that the long-term efficacy of this approach to stone prevention is minimal (Marickar and Rose, 1985).

Recently, a number of workers have turned their attention to a diametrically opposite approach to the prevention of calcium oxalate stones. Instead of reducing the amount of calcium in the intestine, these authors have added supplements of calcium to the diet in the form of calcium citrate (Harvey et al., 1985; Robertson et al., 1990), calcium lactate (Ito et al., 1992) or calcium carbonate (Robertson et al., 1992). In the latter two studies potassium citrate was given in addition to the calcium supplements. The concept behind this approach is to bind oxalate in the intestine and thereby reduce both its absorption in the colon and subsequent appearance in urine. In support of this hypothesis, most of the above studies have shown that mild hyperoxaluria can be normalised by supplementation of the diet with calcium. Where the calcium was given in an alkaline form or with alkali supplements, urinary calcium actually fell (Ito et al., 1992; Robertson et al., 1992). In one of our own studies from Saudi Arabia, where both the circulating levels of the active metabolites of vitamin D (Woodhouse and Norton, 1982) and the intestinal absorption of calcium (Walker et al., 1989) are (paradoxically) low, the increase in urinary calcium in stone-formers following the administration of calcium supplements was minimal and more than offset by the marked decrease in urinary oxalate (Robertson et al., 1990).

This form of treatment may even be of value in the West, where the proportion of stone-formers who are hyperabsorbers of calcium is much higher than in the Middle East, because the fall in urinary oxalate and in the urinary oxalate/calcium ratio should more than offset the anticipated increase in urinary calcium. Any increase in urinary calcium in these individuals may be further offset by administering alkaline potassium citrate along with the calcium supplements. By stimulating citrate production in the distal tubule, this combined therapy would provide sufficient citrate in the urine to complex the additional calcium and prevent the concentration of ionized calcium from increasing. The net result of these changes should be to decrease the supersaturation of urine with respect to calcium oxalate. The total volume and degree of agglomeration of calcium oxalate crystals should also be reduced as predicted from Figs. 1-3.

Conclusions

Although hypercalciuria is still considered by many to be the main cause of calcium stone disease, this review shows that there is little or no relationship between any of the generally accepted parameters of stone-formation and the urinary excretion of calcium. There are, however, strong relationships between these same parameters and the urinary excretion of oxalate. It is concluded that persistent mild hyperoxaluria is much more important than hypercalciuria and other suggested risk factors for increasing the risk of calcium oxalate urolithiasis in the population.

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Discussion with Reviewers

Y. Nakagawa: What type and amount of crystal growth inhibitors are present in the urine of the Middle Eastern stone-formers?

Authors: So far, we have measured the excretions of various glycosaminoglycans, ribonucleic acid and nephrocalcin in the urines of Saudi stone-formers, Saudi normal controls and Western expatriate normal controls living in Riyadh and found no significant differences between the groups with respect to any of these macromolecular inhibitors. Nor was there any difference in the γ-carboxyglutamic acid content of the nephrocalcin extracted from the urines of Saudi stone-formers, Saudi normals and a sample of normal nephrocalcin kindly supplied by Dr. Nakagawa for comparison.

M. Menon: How is "hypercalciuria" defined in the populations from the United Arab Emirates and Saudi Arabia? Is it in relation to the excretion of calcium in normal controls in Arabia or to that of normal controls in the West?

Authors: Basically we do not use either group of controls for defining "hypercalciuria", which is a term that we tend to use very loosely to refer to urines with a calcium content which lies in the upper section of a continuous scale of calcium excretion extending from the lowest to highest values recorded for this urinary constituent. The scale may be considered, therefore, as universal and independent of the environment in which urinary calcium is determined. We envisage it as encompassing the entire urinary range over which a "chemical curve" may be described of the effect of increasing calcium concentration alone on the risk of crystalluria and stone-formation. The term "hypercalciuria" is then used to refer to urines in the upper part of this range (>7.5 mmol/day) over which the "chemical risk curve" begins to rise more sharply. Our usage of the term has no physiological or metabolic significance or implications. In relation to the data from the Middle East, all we are saying is that urinary calcium is rarely high enough by itself to be a major chemical cause of the high stone-formation rate observed in that population. On the contrary, it is generally so low that it probably prevents more people in the population from forming stones than otherwise would be the case if urinary calcium excretion were higher than it is.

M. Menon: Is the relationship shown in Fig 8 between urinary oxalate and "free" dietary oxalate more pronounced in stone-formers than in normals?

Authors: No, the derived data in Fig 8 are calculated from studies involving both stone-formers and normals and, although no distinction is shown in this paper between the data from stone-formers and normals, there is, in fact, no difference between the fraction of "free" oxalate absorbed by the two groups at a given level of "free" oxalate in the intestine. If, however, urinary oxalate is plotted against total dietary oxalate intake from the same studies, then the stone-formers do lie on a line with is slightly steeper than that of the normal subjects. This apparently greater absorption of oxalate by the stone-formers from a given intake of oxalate, however, is not due to an inherent ability of the patients to absorb a greater fraction of oxalate from the gut, but rather it is a consequence of their ability to hyperabsorb calcium. By absorbing a greater proportion of calcium from the diet, relatively more "free" oxalate is left in the intestine for passive absorption lower down the gastrointestinal tract. Once this is taken into account, the data of the calcium-hyperabsorbing patients come together with those of the normals into the relatively tight fit shown in Fig 8 since both groups absorb the same proportion of available "free" oxalate probably by a passive transport mechanism. Overall, then, the amount of oxalate absorbed from the intestine (and excreted in the urine) is basically a function of (a) the intake of oxalate, (b) the intake of calcium and (c) the ability of the gut to absorb calcium. This is the essence of the equation defined in the paper for the calculation of "free" oxalate.

A. Hesse: Over what range would you define "mild hyperoxaluria"?
Authors: As in the case of "hypercalciuria", we tend to use the term "hyperoxaluria" to mean a urinary excretion of oxalate which is high enough to increase markedly the chemical risk of crystalluria and stone-formation. In practice, "mild hyperoxaluria" commences at around 0.45 mmol/day with an "upper limit" of approximately 0.85 mmol/day. Above that figure, one would suspect that there was a metabolic reason for the hyperoxaluria although, as shown in Fig. 6, the total range of urinary oxalate excretion appears to constitute a "chemical" continuum over which the risk of stone-formation goes on increasing irrespective of the cause of the hyperoxaluria.

A. Hesse: What proportion of calcium oxalate stones in Saudi Arabia consisted of whewellite and weddelite?
Authors: Of the predominantly calcium oxalate stones, 72% consisted of calcium oxalate monohydrate and 28% were of calcium oxalate dihydrate. The latter often contained a small proportion of apatite (<20%) but the whewellite stones were usually "pure".

A. Hesse: In your opinion, should hypercalciuria be treated any longer and what limit would you use to define it?

Authors: This is now a very contentious question. If our hypothesis is correct that hypercalciuria, by itself is a relatively unimportant risk factor for stone-formation, then to lower urinary calcium alone may not be very beneficial to the patient. The only exception to this situation would be if urinary calcium can be reduced to less than 4 mmol/day without an accompanying increase in urinary oxalate (see Fig. 1). This is difficult to achieve in practice. Indeed, serious doubts are now being cast on the long-term benefits of many urinary calcium-reducing therapies unless they are known to have some other beneficial effect on urinary composition, such as increasing citrate or pyrophosphate excretion.

The question as to what level of urinary calcium we would define as "hypercalciuria" is difficult. As mentioned in the answer to the question from Dr. Menon, we tend to use the term in a chemical rather than a biological sense.

S.H. Khan: Would the administration of calcium citrate to stone patients increase their urinary citrate and thereby reduce the relative supersaturation of urine with respect to calcium oxalate?
Authors: Although we had hoped that this would be the case, there is insufficient absorbable alkali in calcium citrate to stimulate citrate production in the renal tubules. Since, moreover, virtually all the administered citrate is metabolized, this form of treatment produces no increase at all in either urinary pH or citrate excretion. The detailed effect of calcium citrate supplements on urinary composition is the subject of a further paper which is in preparation.