MEDICAL MANAGEMENT OF NEPHROLITHIASIS:
A New, Simplified Approach for General Practice

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Interest: Renal Stones & Osteoporosis

I have participated in two medical grand rounds at Southwestern. In 1972, the year I arrived in Dallas, I gave the first one on "Renal Stones of Calcium Phosphate Origin". Twelve years later, I presented another on "Renal Stones Revisited". No grand rounds has addressed this topic since 1982. However, we will be the host of the 8th International Symposium on Urolithiasis later this month. I therefore thought that it would be timely to address the stone disease today.

Considerable advances have been made in the urolithiasis field since 1984. Pathophysiologic mechanisms for many causes of stones have either been elucidated or better clarified. Simplified diagnostic methods have been formulated to identify various causes of stones.[1] New drugs have been approved by the FDA for the prevention of stone recurrence,[2,3] providing improved treatment options. Facilitated stone removal has become possible with the introduction of endoscopic approach[4] and extracorporeal shock wave lithotripsy.[5] Thus, techniques are now available to diagnose and prevent recurrent stone formation in most patients with stones. Moreover, stones may now be removed with less orbidity.

However, there has been a "lapse" in stone field during the past decade. Fewer young investigators are entering stone research. Only a minor fraction of practicing physicians avail themselves of new diagnostic methods and preventive treatment modalities in managing patients with stone disease.

The reasons for this lapse are two-fold. First, the facility with which stones can now be removed, for example by ESWL, has led to a disparagement of the need for medical diagnosis and treatment. Why bother to have tests done, and to take drugs for a long duration, when one is feeling well between stone episodes? Instead, all one has to do is to have lithotripsy done, when, once in a while, a stone is formed and causes trouble. Second, I myself may have been at fault by pushing for a selective treatment approach.[6] As I outlined in previous grand round on this topic, I have been advocating a careful differentiation of various causes of stones, and selection of specific drugs for each cause of stone disease.[6,7] The complexity of this process may have led some physicians to forego the medical approach altogether.

I have therefore decided to abandon to a large degree the selective approach and to formulate a simplified program for the medical management of stones which any physician anywhere can adopt. In 1993, my colleagues and I introduced "ABCs of Medical Management of Stone".[8,9] What I shall present today represents a much further simplification of treatment approach outlined in that booklet.

I would like to consider five questions (Table 1). (1) Is medical treatment necessary? (2) What are medical causes of stones? (3) What is a simple way to diagnose medical causes of stones? (4)What is a simple and reliable way to treat stones medically? (5) Is medical treatment cost-effective?

Table 1.

UPDATE ON MEDICAL MANAGEMENT OF STONES

- Is Medical Treatment Necessary?
- What are Medical Causes of Stones?
- What is a Simple Way to Diagnose Causes of Stones?
- What is a Simple & Reliable Way to Treat Stones Medically?
- Is Medical Treatment Cost-Effective?

IS MEDICAL TREATMENT NECESSARY?

The introduction of ESWL in early 80s has revolutionized the urological practice of stones.[5] It is now possible to place the patient with stones in a bathtub, generate shock waves with a spark plug in the water enclosing the patient, focus the shock waves on the stone residing in the kidney inside the patient, and after 1000 or so shocks crush the stone into gravel. The patient would then be able to pass the gravel under forced fluids, thus getting rid of the stone without any surgery.

This remarkable achievement has led to a disparagement of the need and importance of medical diagnosis and treatment. However, following considerations argue against the abandonment of medical approach.

Stone management entails not only the surgical approach of removing existing stones, but also the medical approach of preventing recurrent stone formation. Medical approach is important for two main reasons (Table 2). Renal stone disease is characterized by a high rate of recurrence. The recurrence rate has been reported to range from 65% to 90%.[10] Second, removal of stones by ESWL does not alter the propensity for recurrent stone formation. In our own center, we examined urinary stone risk factors before and 3 months after ESWL. We found no significant change in urinary calcium, phosphorus, oxalate, citrate and uric acid. In particular, those with hypercalciuria or hypocitraturia to begin with, continued to have these derangements after ESWL.

Table 2.

IS MEDICAL TREATMENT NECESSARY?

- Persistence of Metabolic Abnormalities After ESWL
- Persistence of Stone Formation After ESWL

In a group of patients completing ESWL, my former colleague offered specific medical treatments to some, and conservative non-drug treatment to others.[11] In both patients rendered stone-free as well as those with residual stones after ESWL, medical drug treatment compared to conservative treatment, produced a much lower stone formation rate and a much higher remission rate. Thus, patients continue to form new stones after ESWL without medical treatment. This recurrence may be substantially reduced by medical drug treatments.

WHAT ARE METABOLIC MEDICAL CAUSES OF STONES?

Stone disease may be broadly categorized into calcareous (calcium-containing) or non-calcareous stones (Table 3). Medical causes of calcareous stones include: hypercalciuria, hypocitraturia, hyperuricosuria, hyperoxaluria and undue urinary pH (gouty diathesis). It is presumed that these derangements cause formation of calcium oxalate or calcium phosphate stones by increasing urinary saturation (hypercalciuria, hyperoxaluria), reducing inhibitor activity (hypocitraturia), or by causing urate-induced calcium oxalate crystallization (hyperuricosuria and gouty diathesis). Non-calcareous stones include: gouty diathesis (uric acid stones), cystinuria (cystine stones), and infection stones (struvite stones in infection of the urinary tract with urea-splitting organisms). Calcareous stones are much more common than non-calcareous stones. Pathophysiology of some of these causes will now be reviewed, with an emphasis on recent developments.

Table 3.

WHAT ARE MEDICAL CAUSES OF STONES? (Metabolic)

CALCAREOUS

- Hypercalciuria
- Hypocitraturia
- Hyperuricosuria
- Hyperoxaluria
- Gouty Diathesis

OTHER

- Gouty Diathesis
- Cystinuria
- Infection Stones

Pathophysiology of Hypercalciuria

In 1974, we broadly categorized hypercalciuria of nephrolithiasis into three types (Figure 1).[12] Absorptive hypercalciuria, a common stone-forming entity, is characterized by a "primary" enhancement of intestinal calcium absorption.[13] In renal hypercalciuria, there is secondary intestinal hyperabsorption of calcium from parathyroid stimulation and ensuing increased calcitriol synthesis.[13,14] Primary hyperparathyroidism, an infrequent cause of stones, is often associated with hypercalciuria from enhanced bone resorption and secondary increase in intestinal calcium absorption.[15]

We have devoted considerable effort in delineating the pathophysiology of absorptive hypercalciuria. When patients with this condition are challenged with a short course of ketoconazole therapy, the ensuing reduction in calcitriol synthesis produces a decline in intestinal calcium absorption and in urinary calcium, in some but not all patients.[16] Results suggested that high calcium absorption may be etiologically related to enhanced vitamin D synthesis or action in some cases of absorptive hypercalciuria.

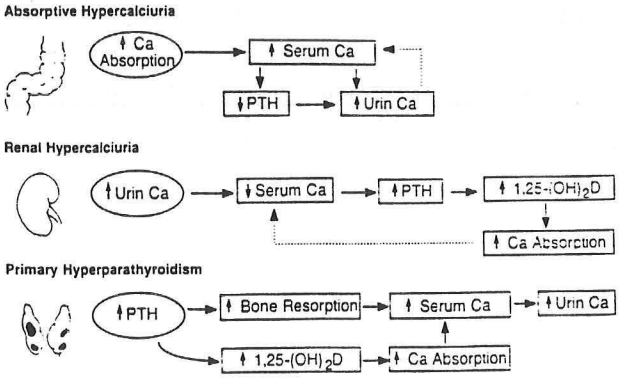


Figure 1. Schemes for the major forms of hypercalciuria.

However, our recent extensive, molecular biological studies have so far failed to support a pathophysiologic importance of vitamin D (Table 4). Thus, we found no mutation in the coding region of the vitamin D receptor (VDR) gene.[17] The gene for VDR or 1-alpha-hydroxylase of vitamin D was not linked to the inheritance pattern of absorptive hypercalciuria from linkage analysis. We found normal regulatory region of Ca-ATPase gene. However, there may be involvement of other vitamin D-responsive genes, explaining certain physiological studies implicating a role for vitamin D.[16,18]

Table 4. **MOLECULAR BIOLOGY OF ABSORPTIVE HYPERCALCIURIA**

- No Mutation in the Coding Region of VDR Gene
- Gene for VDR or 1α-Hydroxylase Not Linked to Inheritance Pattern of AH
- Normal Regulatory Region of Ca-ATPase Gene
- Involvement of Other Vit D - Responsive Genes Possible

Pathophysiology of Hypocitraturia

Hypocitraturia, a common cause of stones, contributes to stone formation from the loss of inhibitor activity against crystallization of stone-forming calcium salts, and from the increased ionic calcium concentration due to reduced citrate complexation of calcium.[19] It may result from a variety of renal and gastrointestinal disturbances. The main metabolic event characterizing both renal and gastrointestinal etiologies is acidosis or acid load. Acidosis is characteristic of distal renal tubular acidosis. It is found in hypokalemia[20] (e.g. during thiazide treatment of hypercalciuric nephrolithiasis, from an induction of intracellular acidosis), physical exercise[21] (from lactate accumulation) and following a high sodium intake (from bicarbonaturia).[22] Acidosis or acid load also occurs in chronic diarrheal states (from intestinal alkali loss)[2] and following consumption of a high meat diet (from increased acid ash content).[23] Hypocitraturia is also found in urinary tract infection, probably from the degradation of citrate in urine by bacterial enzymes and by the bacterial consumption of citrate. A primary disturbance in renal citrate handling and a primary derangement in citrate absorption from the gastrointestinal tract[24] have been invoked.

Our own studies do not support existence of primary citrate malabsorption.[25] Citrate absorption from the gastrointestinal tract was directly measured by using the intestinal washout technique. In both normal subjects and in patients with stones, citrate absorption was very efficient, with nearly 100% absorption in 3 hours.

The relationship between urinary citrate excretion and estimated net gastrointestinal absorption of alkali (NGIA) allowed us to ascertain dietary contribution to hypocitraturia.[26] In normal subjects, urinary citrate was found to be dependent on NGIA, with the dependence described by an ellipse. As expected, values in patients with renal tubular acidosis were located below the ellipse, indicative of a renal defect in citrate handling (Fig. 2). Values in patients with chronic diarrheal states were enclosed within the eclipse. In patients with stones without renal tubular acidosis or chronic diarrheal syndrome, many had hypocitraturia associated with low NGIA (Fig. 3). Their hypocitraturia may have been dietary in origin.

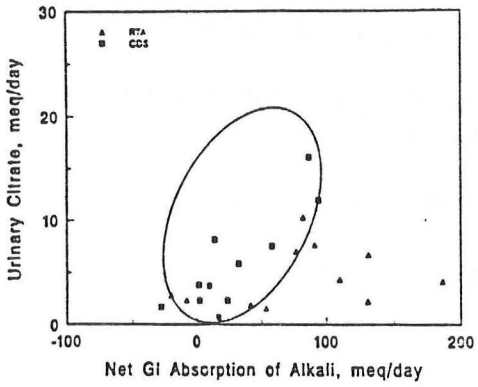


Figure 2. Dependence of urinary citrate on net GI absorption of alkali in patients with distal renal tubular acidosis (RTA) and chronic diarrheal syndrome (CDS). Data in patients are plotted over the "background" of 95% confidence ellipse for normal subjects.

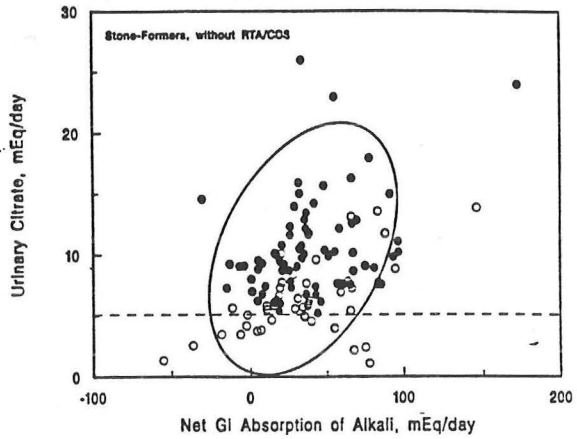


Figure 3. Dependence of urinary citrate on net GI absorption of alkali in stone-forming patients without RTA or CDS. Again, data in patients are plotted over the normal ellipse. Open circles represent those who were

Pathophysiology of Hyperuricosuric Ca Oxalate Nephrolithiasis

Hyperuricosuria, generally due to dietary overindulgence with purine rich foods (meat products),[27] may cause calcium stone formation by the following scheme (Fig. 4). Hyperuricosuria, in the setting of normal pH at which adequate dissociation of uric acid occurs, produces urinary supersaturation with respect to monosodium urate. Resulting formation of colloidal or crystalline monosodium urate causes formation of calcium oxalate stones by direct induction (heterogeneous nucleation)[28] or by adsorption of macromolecular inhibitors.[29]

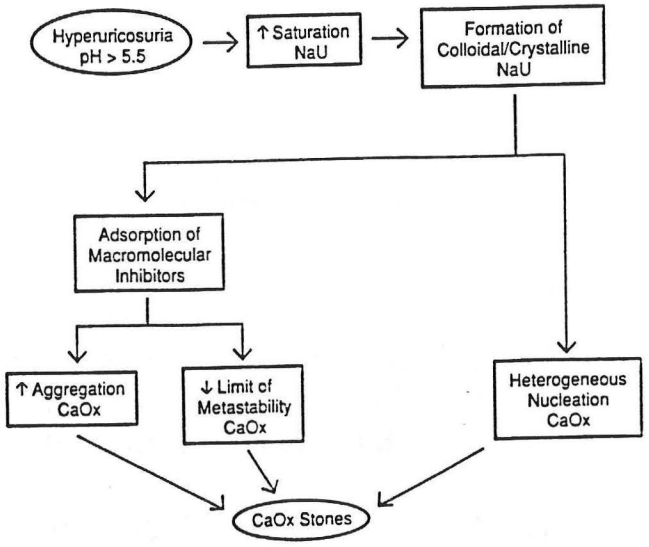


Figure 4. Scheme for calcium oxalate stone formation from hyperuricosuria. NaU=monosodium urate; CaOx-calcium oxalate.

Pathophysiology of Uric Acid or Calcium Stones in Gouty Diathesis

Gouty diathesis describes renal stone formation in primary gout, either in a fully manifested or in a latent state.[30] The invariant feature is undue urinary pH (<5.5) in which uric acid is sparingly soluble, causing uric acid stone formation (Fig. 5). Uric acid so formed may then cause calcium oxalate stones by similar mechanisms as has been invoked for monosodium urate. Thus, patients with gouty diathesis form stones composed of uric acid, calcium oxalate, or both. Other clinical features, encountered in some patients, are gouty arthritis, hyperuricemia and hypertriglyceridemia.

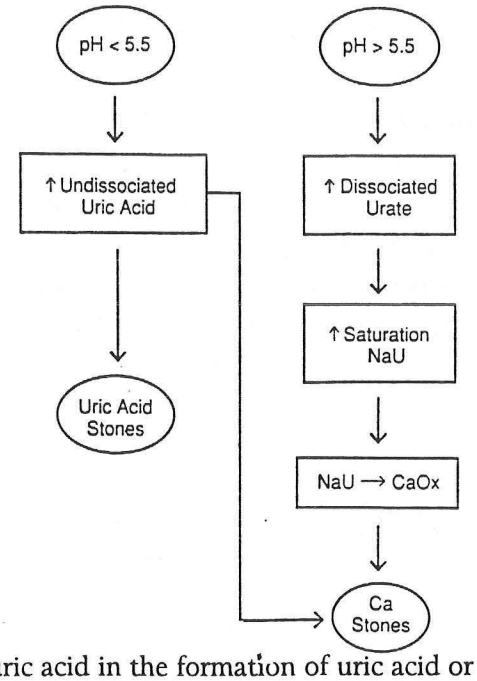


Figure 5. Interplay of pH and uric acid in the formation of uric acid or calcium stones.

Molecular Defect in Cystinuria

Cystinuria, a genetic defect inherited in an autosomal recessive manner, is characterized by an increased urinary excretion of cystine, as well as other dibasic amino acids. Cystine stone formation is due to the sparing solubility of cystine in urine.

Recently, 24 mutations have been found in the dibasic amino acid transporter gene (SLC3A1), 5 of them in our laboratory (Fig. 6).[32] Some are base substitutions, while others are deletions. Some mutations have been found in a single individual patient, while others have been uncovered in more than one individual. From transfection studies, it is believed that these mutations are responsible for cystinuria.

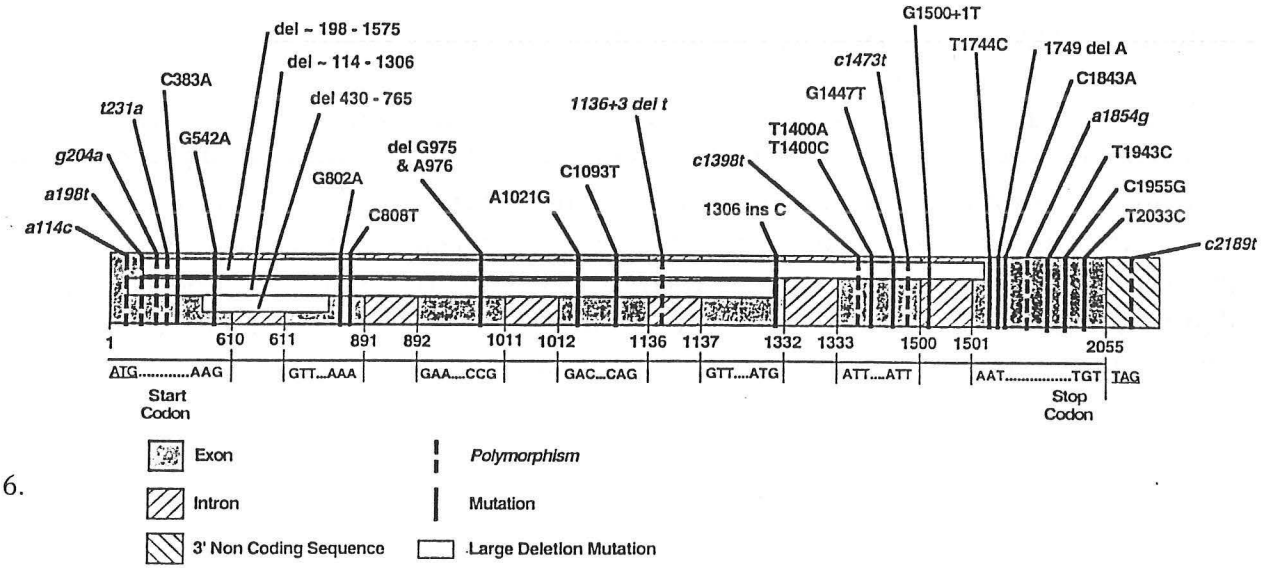


Figure 6.

WHAT ARE ENVIRONMENTAL-NUTRITIONAL CAUSES OF STONES?

Abnormal urinary biochemistry conducive to stone formation could result from environmental or nutritional factors. These factors include: low fluid ingestion or loss (leading to urine concentration), relative dietary excess of sodium, oxalate (raising saturation of calcium oxalate), calcium and purine (increasing urinary uric acid), and relative dietary deficiency of citrus fruits and magnesium (Table 5). The role of some of these factors will be described.

Table 5. **WHAT ARE MEDICAL CAUSES OF STONES? (Environmental-Nutritional)**

- Low Fluid Ingestion or Excessive Fluid Loss
- Relative Dietary Excess of Sodium, Oxalate, Ca, Purine
- Relative Dietary Deficiency of Citrus Fruits, Mg

Effect of Sodium Load

The metabolic effect of sodium load was examined by providing 250 meq of sodium daily over a basal metabolic diet.[22] As reported previously, urinary calcium increased significantly.[33] In addition, urinary pH increased modestly and urinary citrate decreased significantly. These effects have been ascribed to bicarbonaturia from sodium-induced volume expansion.[34] Commensurate with these changes, urinary saturation of brushite or calcium phosphate increased (from the rise in urinary calcium), that of monosodium urate substantially rose (from increased dissociation of urate and higher sodium), and the inhibitor activity against calcium oxalate crystallization (expressed as the formation product ratio) significantly decreased. Thus, sodium load increases the propensity for the crystallization of stone-forming calcium salts.

Effect of High Calcium Intake

A recent epidemiological study disclosed that among normal subjects without stones, a high calcium intake may reduce the risk of stone formation.[35] This finding has been attributed to the binding of oxalate by calcium in the intestinal tract. Unfortunately, the concurrent higher intake of citrus fruit products by the high calcium intake group, could have clouded interpretation of results.

From the physiological standpoint, a high calcium intake or calcium supplementation may not confer an increased risk of stone formation in normal subjects, due to the operation of

"intestinal adaptation process".[36] During a high calcium intake, the fraction of calcium absorbed is decreased due to parathyroid suppression and reduced calcitriol synthesis. Conversely, the fraction of absorbed calcium is increased following a low calcium intake from the stimulation of parathyroid function and calcitriol synthesis. Thus, this adaptation intervenes to attenuate the wide fluctuation in absorbed calcium occurring from a differing calcium intake.

The above scheme was tested in normal subjects by examining the metabolic effects of calcium supplementation (1000 mg calcium/day) (Fig. 7).[37] Urinary calcium rose substantially after 1 month of calcium supplementation. However, it decreased toward the pre-treatment range with continued calcium supplementation for two more months. This decline was associated with a fall in fractional intestinal calcium absorption. Thus, the urinary saturation of calcium oxalate, which increased substantially at 1 month of calcium supplementation, was only modestly altered at 3 months.

In patients with absorptive hypercalciuria, however, the intestinal adaptation process may not operate due to the primary enhancement of intestinal calcium absorption. Thus, a high calcium intake provokes a marked increase in urinary calcium,[32] that is considerably above the normal range and apparently sustained long- term. In contrast to normal subjects, patients with absorptive hypercalciuria are at increased risk of stone formation from a high calcium intake.

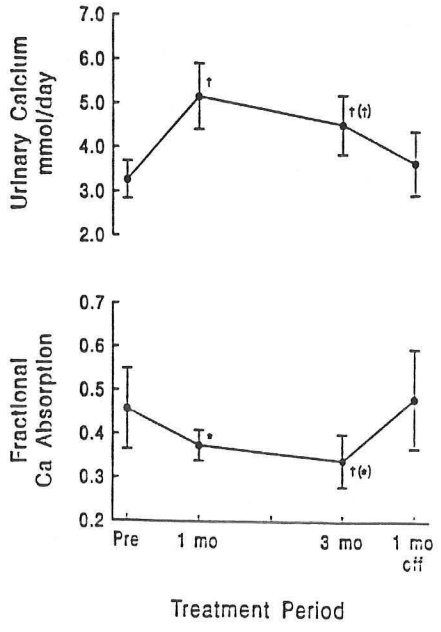


Figure 7. Effect of long-term calcium citrate treatment on urinary calcium and fractional intestinal calcium absorption. Bars indicate mean plus or minus standard deviation. * and †, significant differences between control and other phases, respectively. (*) and (†), significant differences between 1-month and 3-month calcium citrate treatments, respectively. *Pre*, before therapy.

Effect of Reduced Citrus Fruit Intake

One liter orange juice contains approximately 50 meq potassium, and 130 meq citrate. When ingested, much of potassium is absorbed and eliminated in urine, whereas absorbed citrate is nearly completely metabolized in vivo. Thus, an alkali load is delivered, leading to enhanced citrate excretion.[38] Conversely, reduced consumption of citrus fruit products may contribute to hypocitraturia, and may enhance the risk for stone formation.

WHAT IS A SIMPLE WAY TO DIAGNOSE CAUSES OF STONES?

In 1993, my colleagues and I published a booklet entitled: "ABC's of Medical Management of Stones".[8,9] It described a simplified approach to the detection of different causes of stone disease, utilizing readily available commercial assays. In particular, it allowed differentiation of uncomplicated calcium stone disease from other stone-forming conditions. For the former, it also permitted separation of hypercalciuria from normocalciuria.

The main feature is the automated analysis of urinary stone risk factors, a technique that was first developed in our laboratory and now commercialized nationally[1] (Table 6). The patient is given a urine collection kit by the physician. The kit contains a collapsible 4-liter plastic container. After 24 hours of collection, 2 small aliquots are placed in a mailer, and sent to a central laboratory. The essential elements of this collection system is the use of a volume marker (allowing automated measurement of volume) and of preservatives (permitting analysis of both acid-soluble and acid-precipitable constituents from a single collection).[39] The laboratory analyzes urinary constituents and displays them graphically or in a tabular format.

Table 6.

WHAT IS A SIMPLE WAY TO DIAGNOSE CAUSES OF STONES?

- Automated Analysis of Urinary Stone Risk Factors
- Repeat After Dietary Modification

Described in "ABC's of Medical Management of Stones"

Depicted here is a sample stone risk profile as we reported in 1985[1] (Fig. 8). Risk factors are categorized into 3 groups: metabolic factors (calcium, oxalate, uric acid, citrate and pH), environmental factors (total volume, sodium, sulfate, phosphorus and magnesium), and physicochemical factors (saturation of urine with respect to stone-forming constituents calculated from metabolic and environmental factors). Abnormal values or increased risks are displayed in red and normal values in black or blue. This patient, with enteric hyperoxaluria with a small bowel disease, had hyperoxaluria (from increased oxalate absorption), hypocitraturia and low urinary pH (from acquired metabolic acidosis), low urine volume (from diarrhea), and low urinary magnesium (from malabsorption). As a consequence, urinary saturation of calcium oxalate and uric acid was higher than normal, accounting for the susceptibility of patients with ileal disease to form stones of calcium oxalate and uric acid.[7]

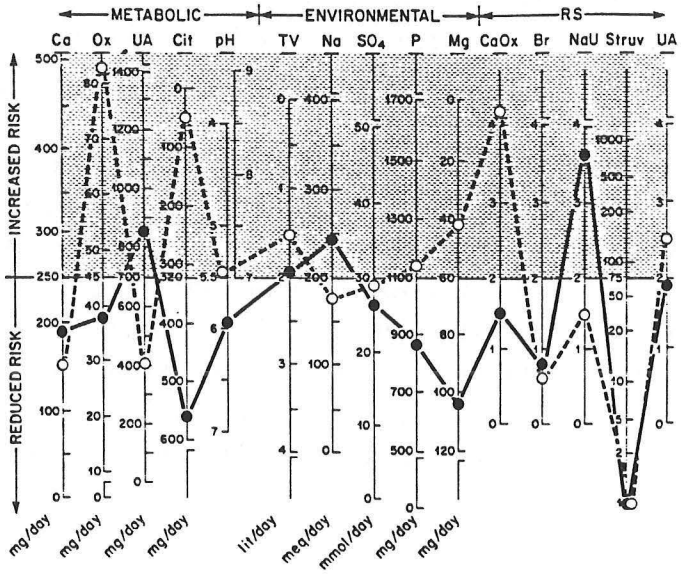


Figure 8. Urinary risk profile in patients with enteric hyperoxaluria and with hyperuricosuric calcium oxalate nephrolithiasis.

After obtaining a full stone risk analysis in a urine sample collected on a random diet, the next step is to impose a short -term dietary modification (1 week)[8,9] (Table 7). Increase fluid intake if urine volume is less than 2 liter on the stone risk analysis. Apply sodium restriction if urinary sodium exceeds 200 meq/day. Impose oxalate restriction when urinary oxalate is high. Restrict calcium intake if there is hypercalciuria. Limit the intake of animal proteins (meat products) when there is hyperuricosuria.

The last step is to obtain a 24-hour urine collection while on a temporary dietary modification. A limited analysis could be performed, involving 7 constituents: calcium, oxalate, uric acid, citrate, pH, total volume and sodium. The differences in values between

the full and abbreviated analysis (random and modified diet) represent changes imposed by dietary influences. Additional tests include serum for PTH, systematic multichannel analysis of serum, stone analysis and urine culture.

The above work-up should allow differentiation of most causes of stones[8,9] (e.g. absorptive hypercalciuria, renal hypercalciuria, hyperuricosuric calcium oxalate nephrolithiasis, hypocitraturic calcium oxalate nephrolithiasis). However, for the simplified treatment approach to be described at this conference, only the following separations are necessary.

Table 7.

DIETARY MODIFICATION
(for diagnostic assessment)

Finding	Modification
TV< 2 l/d	↑ fluid intake
Na > 200 meq/d	Na restriction
Ox > 45 mg/d	Ox restriction
Ca > 250 mg/d	Ca restriction (mod)
UA > 600 mg/d SO_4 > 30 mm/d	Restriction of animal proteins

First, separate uncomplicated calcium stone disease from other stone disease (Table 8). The former, constituting the majority of patients with stones, would be characterized by normal serum calcium and uric acid, calcium oxalate or calcium phosphate stones, and absence of chronic urinary tract infection, bowel disease, or marked hyperoxaluria. The other stone disease would be comprised of primary hyperparathyroidism, primary gout with hyperuricemia, infection stones, cystinuria and primary or enteric hyperoxaluria.

Table 8.

SEPARATION OF UNCOMPLICATED STONE DISEASE FROM OTHER

Uncomplicated Calcium Stone Disease	Other Stone Disease
Normocalcemia	Primary Hyperparathyroidism
Normouricemia	Primary Gout with Hyperuricemia
Ca Oxalate / Ca Phosphate Stones	Infection Stones
Absence of UTI, Bowel Disease	Cystinuria
Marked Hyperoxaluria	Primary/Enteric Hyperoxaluria

Second, categorize uncomplicated calcium stone disease into hypercalciuric and normocalciuric subgroups (Table 9). The hypercalciuric subgroup would comprise absorptive and renal hypercalciurias, and dietary hypercalciuria. The normocalciuric subgroup would be composed of hyperuricosuric calcium oxalate nephrolithiasis, hypocitraturic calcium oxalate nephrolithiasis, gouty diathesis, and hypomagnesiuric calcium oxalate nephrolithiasis, all presenting with normal urinary calcium.

Most practicing physicians should be able to carry out above separation without difficulty.

Table 9.

CATEGORIZATION OF UNCOMPLICATED STONE DISEASE

Hypercalciuric Group	Normocalciuric Group
Absorptive Hypercalciuria	Hyperuricosuric Ca Oxalate Nephrolithiasis
Renal Hypercalciuria	Hypocitraturic Ca Oxalate Nephrolithiasis
Dietary Hypercalciuria	Hypomagnesiuric Ca Oxalate Nephrolithiasis

WHAT IS A SIMPLE AND RELIABLE WAY TO TREAT STONES MEDICALLY?

All patients should be offered a conservative management whether or not their disease is severe enough to warrant drug treatment[7] (Table 10). Dietary modification for long-term management includes: a high fluid intake to assure adequate urine volume of at least 2 liters/day,[40] sodium restriction (avoidance of salting of foods),[22] oxalate restriction (limitation of nuts spinach and tea), avoidance of purine gluttony if possible (limit intake of meat products),[27] increased citrus fruit intake,[38] and a moderate calcium restriction in hypercalciuric patients with normal bone density (Table 11). In severe stone disease or when conservative treatment does not totally control stone disease, drug treatment is indicated.

A Simplified Non-selective Drug Treatment

We have previously advocated a selective treatment approach,[6] where a specific drug was recommended for a particular condition, based on the ability of the drug to correct

underlying derangements. Today, we are presenting a simplified treatment approach that depends only on two simple separation described in the previous section.

Table 10.

WHAT IS A SIMPLE & RELIABLE WAY TO TREAT STONES MEDICALLY?

- Conservative Management
- Drug Treatment
  - Available Medication
  - Under Development

Table 11.

DIETARY MODIFICATION
(for long-term treatment)

- High Fluid Intake
- Sodium Restriction
- Oxalate Restriction
- Avoidance of Purine Gluttony if possible
- Increased Citrus Fruit Intake
- Calcium Restriction (moderate) in Hypercalciuria
  Only in the presence of normal bone density

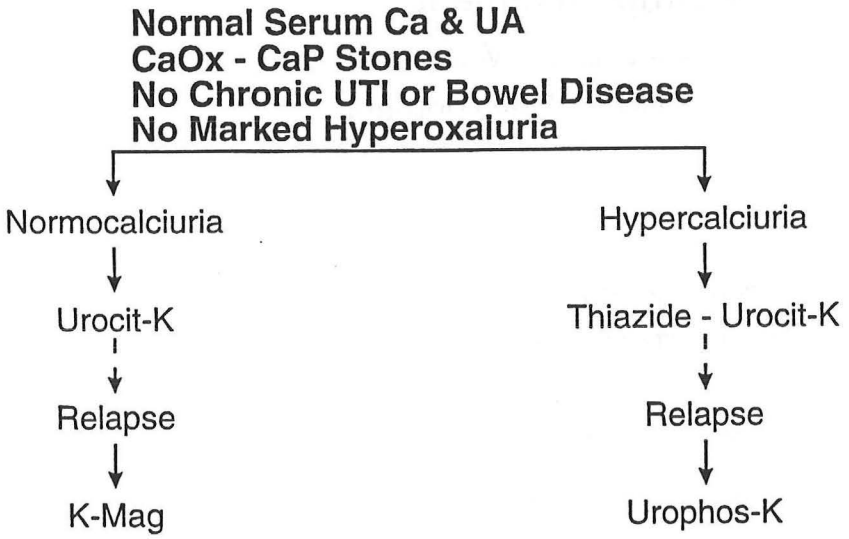
Treatment of Uncomplicated Calcium Oxalate/Calcium Phosphate Stone Disease

The simplified approach advocates the use of only two drugs in uncomplicated calcium stone disease as initial options (Table 12). The normocalciuric subgroup would be offered Urocit-K (potassium citrate) alone. The hypercalciuric subgroup would be given thiazide and potassium citrate.

The rationale for potassium citrate in normocalciuric uncomplicated stone disease is shown here (Fig. 9). Potassium citrate increases citrate excretion by providing an alkali load.[7,19] The induced rise in urinary citrate should inhibit the crystallization of calcium

oxalate and calcium phosphate, not only in hypocitraturia but also in the presence of other derangement such as hyperuricosuria. In addition, potassium citrate raises urinary pH, reducing the propensity for uric acid stone formation. The complication of calcium stones should be inhibited as well from the impaired uric acid-induced calcium oxalate crystallization. The customary dose of potassium citrate (Urocit-K) is 20 meq bid; the dose should be adjusted based on urinary citrate.

Table 12. **SIMPLIFIED TREATMENT APPROACH IN UNCOMPLICATED CA STONE DISEASE**



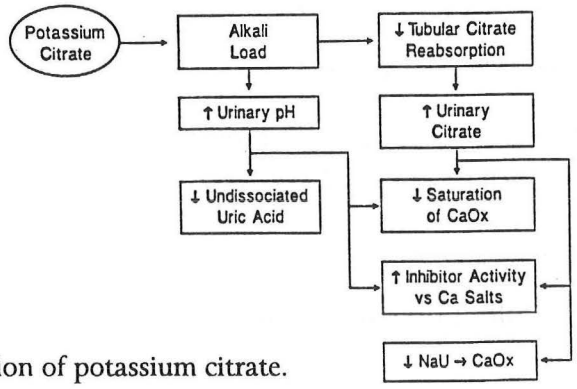


Figure 9. Physicochemical action of potassium citrate.

A placebo-controlled randomized trial has validated the efficacy of potassium citrate in uncomplicated stone disease with normocalciuria.[41] In patients taking placebo, stone formation continued unabated (Fig. 10). However, in patients taking potassium citrate, most of them did not form stones at all (Fig 11). In those who still formed stones, stones developed at a lower rate than before treatment.

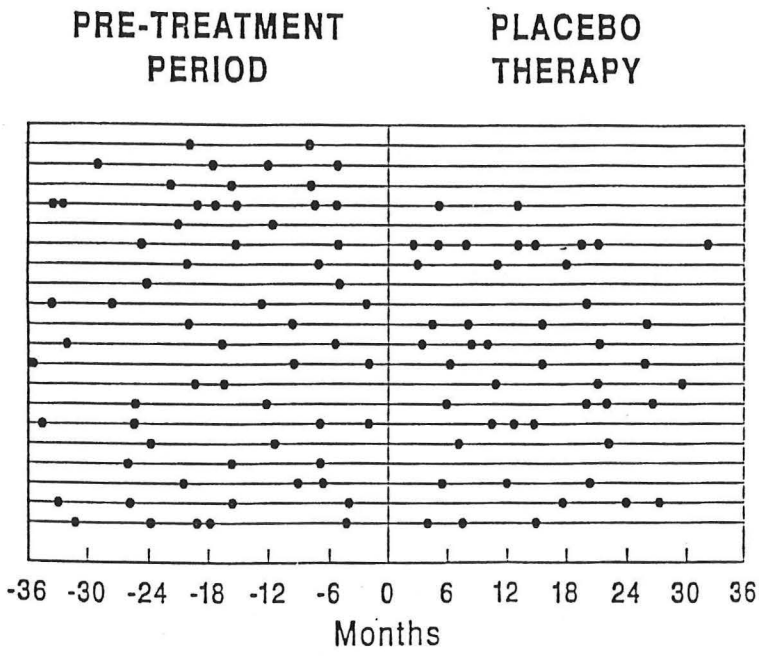


Figure 10. Effect of placebo treatment (6 to 12 tablets daily) on new stone formation. In all 20 patients 62 stones were formed before treatment and 46 stones were formed during placebo treatment.

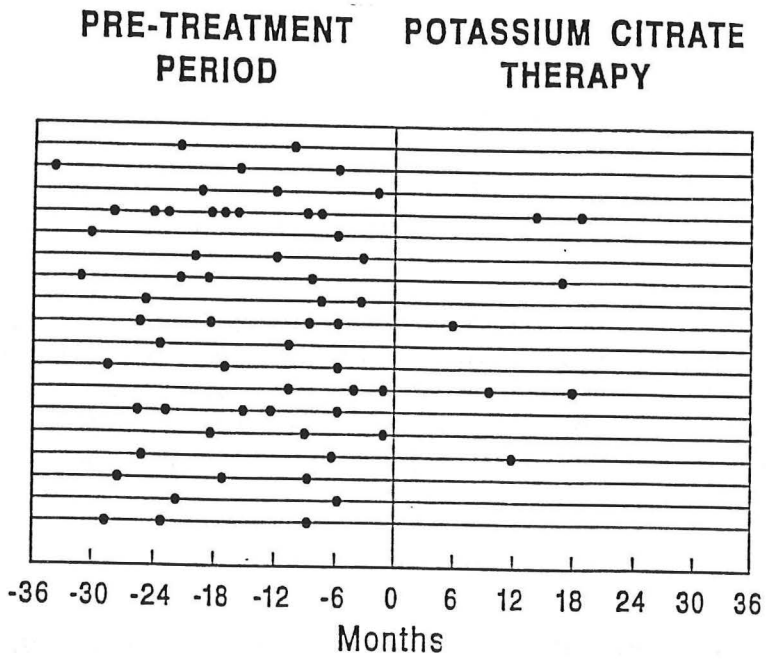


Figure 11. Effect of potassium citrate therapy (30 to 60 mEq daily) on new stone formation. Each line represents separate patient. Each closed circle indicates new stone formation. In 18 patients 58 new stones were formed during 3 years preceding treatment compared to 7 stones during treatment.

The rationale for the combined use of thiazide with potassium citrate in hypercalciuric patients with uncomplicated stone disease is based on following considerations. Thiazides are unique among diuretics in reducing urinary calcium by augmenting renal tubular reabsorption of calcium. Thus, they are widely used in the management of hypercalciuric nephrolithiasis.[42] However, thiazide used alone may cause hypocitraturia by inducing intracellular acidosis[20] (Fig. 12). Potassium chloride supplementation may prevent hypokalemia and hypocitraturia. In the management of stone disease, potassium citrate is preferable because it can not only avert hypokalemia but also raise urinary citrate, an important inhibitor of stone formation.

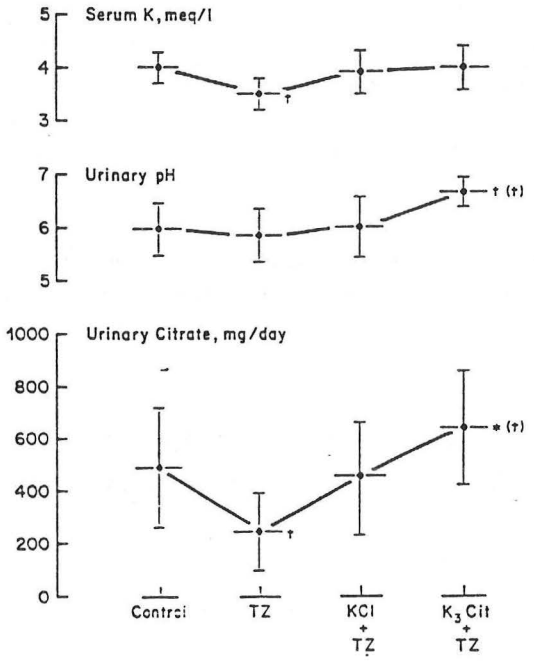


Figure 12. Serum potassium, urinary pH and urinary citrate during 4 phases. The 4 phases included pre-treatment phase (*control*), thiazide treatment, (*TZ*), thiazide with potassium chloride supplementation (*KCl + TZ*) and thiazide with potassium citrate supplementation (K_3Cit + *TZ*). Horizontal bars indicate mean ± standard deviation. Significant difference from values in control phase is shown as $p > 0.05$* and $p < 0.001$†. Significant difference in values during potassium citrate phase from those of potassium chloride phase is shown as $p > 0.001$(†).

Treatment of Uncomplicated Stone Disease Following Relapse

Some patients may be intolerant of or may not respond to potassium citrate therapy. Moreover, potassium citrate does not correct magnesium loss of long-term thiazide therapy.[43] Potassium-magnesium citrate (K-Mag), a new drug under development, may overcome these

problems.

A dose of potassium-magnesium citrate, providing an equivalent amount of potassium as a potassium citrate dose, offers more citrate as well as magnesium. Initial studies suggest that K-Mag is a very good potassium and magnesium supplement, capable of preventing thiazide-induced hypokalemia and magnesium depletion. Compared to Urocit-K, K-Mag causes a more prominent rise in urinary citrate and pH,[44] and a greater inhibition of the propensity for the crystallization of uric acid and calcium oxalate.[45]

A recent placebo-controlled randomized trial, completed in collaboration of Dr. Ettinger in San Francisco, indicates that K-Mag is highly efficacious in inhibiting calcium stone formation. The relative risk of stone-free rate (K-Mag/placebo) was 0.15 (95% confidence interval of 0.05 to 0.44).

Thiazide may not be effective in all patients with hypercalciuric nephrolithiasis. There may be an attenuation or loss of hypocalciuric action after 2 or more years of thiazide treatment due to the inability of thiazide to correct the underlying intestinal hyperabsorption of calcium.[46] Moreover, thiazide may cause hypokalemia, volume depletion and impotence.

UroPhos-K (slow-release neutral potassium phosphate), a new drug under development in our laboratory, may obviate the above problem of thiazide therapy. It produces minimum gastrointestinal side effects (due to its slow-release characteristic), unlike conventional phosphate preparations. It causes a small sustained rise in serum P and a slight parathyroid stimulation within the normal range. Thus, there is suppression of calcitriol synthesis. Calcium absorption is reduced, by inhibition of calcitriol synthesis as well as from the binding of calcium by phosphate in the intestinal tract.

Our metabolic studies have disclosed that UroPhos -K produces about 50% reduction in urinary calcium (Fig. 13).[47] Thus, the urinary saturation (AP) of calcium oxalate is reduced by about the same degree. There is a two-fold rise in urinary phosphorus from the absorption of soluble phosphate. The saturation of calcium phosphate (AP of brushite) does not change, since the rise in urinary phosphorus is compensated by a decline in urinary calcium. Physicochemically, UroPhos-K increases urinary citrate and pyrophosphate, two important inhibitors of calcium stone formation (Fig. 14).

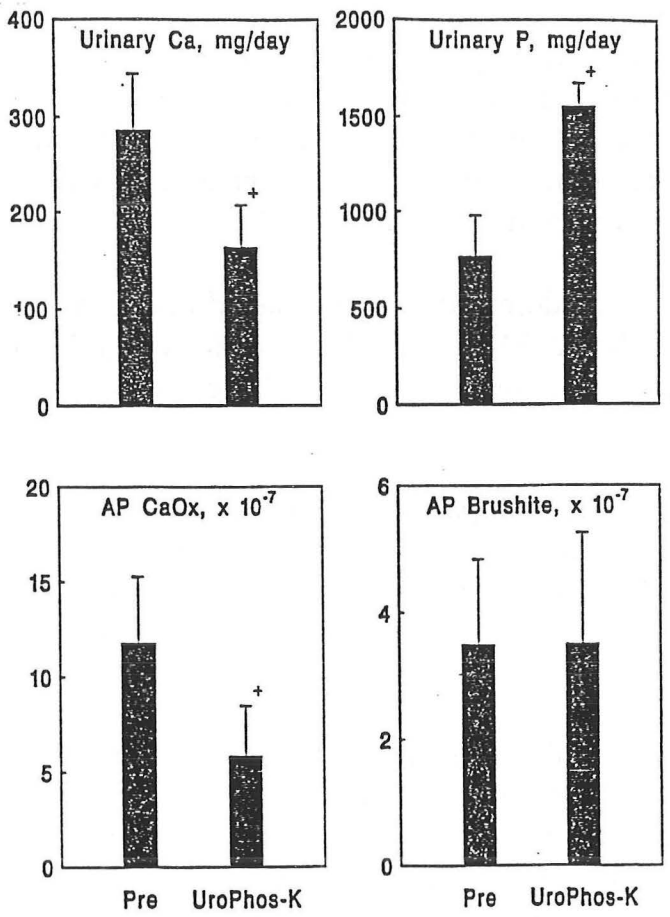


Figure 13.

Thus, the spontaneous precipitation of calcium phosphate is inhibited (indicated by a rise in formation product or FPR of brushite), and the inhibition against crystal agglomeration of calcium oxalate (shown by [Tm]) is increased (Fig. 14). Unlike thiazide, the hypocalciuric effect of UroPhos-K is sustained (Fig. 15). In a group of patients with absorptive hypercalciuria, urinary calcium was restored to normal at 1 year of UroPhos-K therapy, and remained low at 2 years of treatment.

Thus, K-Mag and UroPhos-K promise to be useful alternatives or potentially superior agents, to be used in lieu of thiazide and potassium citrate especially in relapse.

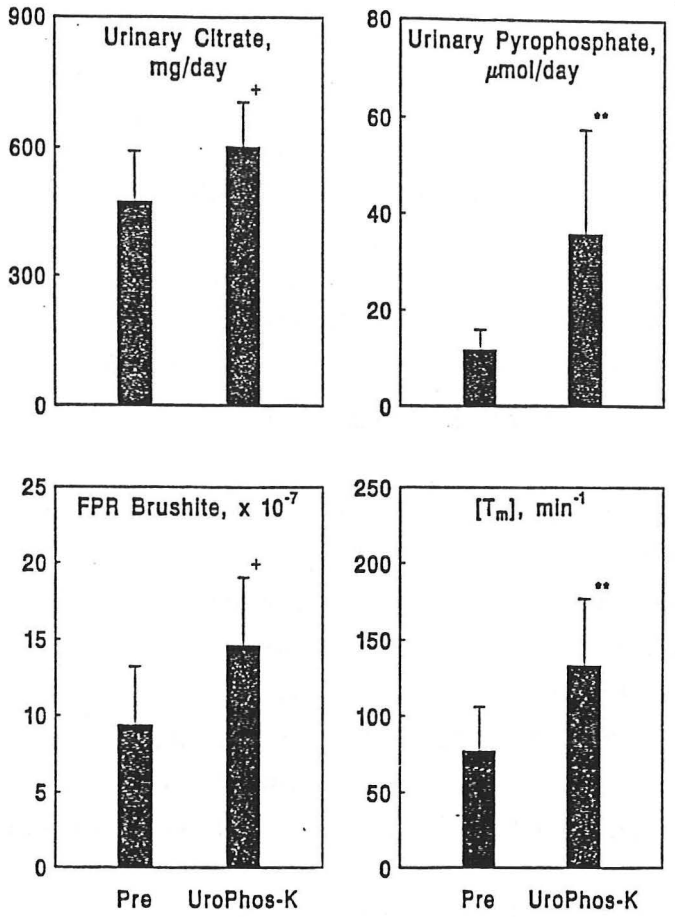


Figure 14.

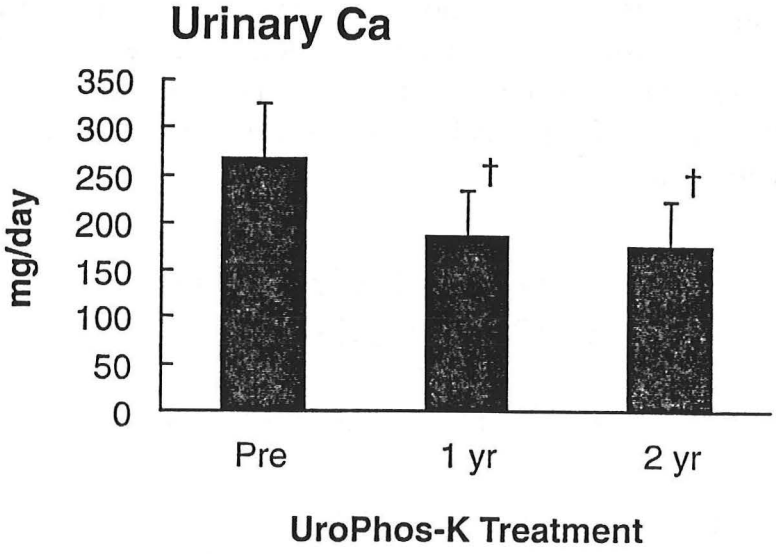


Figure 15.

Treatment of Other Stone-Forming Conditions

Treatment of conditions other than uncomplicated calcium stone disease is straightforward. If hypercalcemia is found, work-up for primary hyperparathyroidism should be undertaken (Table 13). Allopurinol treatment should be considered for anyone with hyperuricemia because of the risk of gouty arthritis. The finding of struvite stones mandates treatment of urinary tract infection. Acetohydroxamic acid, an urease inhibitor, may be useful.[48] If uric acid stone is found, gouty diathesis or conditions causing undue urinary acidity should be suspected. In the former, Urocit-K is highly effective.[49] In cystinuria, chelating agents such as Thiola[3] or d-penicillamine may reduce cystine excretions. The finding of marked hyperoxaluria mandates a search for primary or enteric hyperoxaluria.[50]

Table 13.

OTHER TREATMENTS

Hypercalcemia	w/u for Hyperparathyroidism
Hyperuricemia	Allopurinol
Struvite Stones	Acetohydroxamic Acid
Uric Acid Stones	Urocit-K
Cystine Stones	Thiola
Marked Hyperoxaluria	w/u for primary or Enteric Hyperoxaluria

IS MEDICAL TREATMENT COST-EFFECTIVE?

The cost-effectiveness of medical treatment depends on the severity of stone disease (Table 14). In severe disease, there is general agreement that the cost of medical treatment (drugs, follow-up laboratory tests) is considerably lower than that of surgical treatment (removal of stones, hospitalization). Thus, the NIH report on "Cost Savings Resulting from NIH Research support" claimed that potassium citrate treatment if applied widely could yield annual savings of $300 million. Though probably somewhat inflated, this figure was derived from the high cost of lithotripsy and attendant care in the United States of about $10,000, and the potential for potassium citrate treatment to eliminate need for surgical removal of newly formed stones.[2]

Table 14.

IS MEDICAL TREATMENT COST-EFFECTIVE?

- In Severe Disease, Medical Approach Is Cost-Effective
- In Others, Medical Treatment Potentially Corrects Other Deleterious Manifestations of Stone Disease

However, in patients with mild stone disease, who suffers from stone episode only one every 5-10 years, the cost of ESWL may be lower than that of long-term drug treatment. Even in such patients, medical treatment may be justified because of its potential for correcting other deleterious manifestations of stone disease (Table 15).

Multi-system involvement of stone disease amenable to medical therapy include the following situations (Table 15). Hypokalemia in distal renal tubular acidosis and chronic diarrheal syndrome may be corrected by Urocit-K therapy. In gouty diathesis, allopurinol may not prevent uric acid stone formation but also avert gouty arthritis. Cortical bone loss may occur in renal hypercalciuria from secondary hyperparathyroidism.[51] Thiazide may prevent bone loss by restoring normal parathyroid function, while inhibiting stone formation.[13]

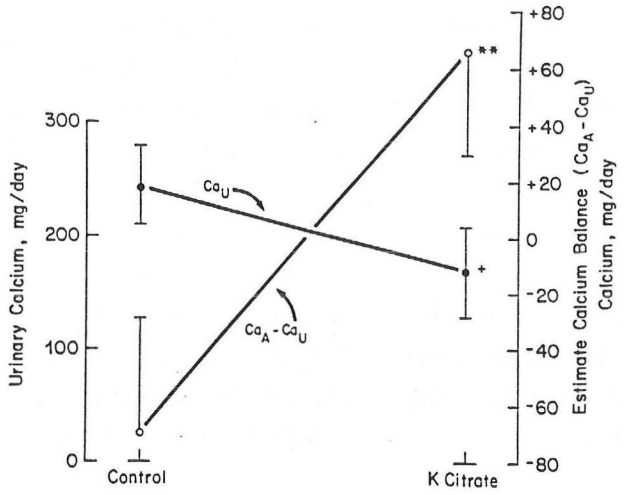
Table 15. MULTISYSTEM INVOLVEMENT OF STONE DISEASE AMENABLE TO MEDICAL THERAPY

Hypokalemia in RTA & CDS	by Urocit-K
Gouty Arthritis in GD	by Allopurinol
Bone Loss in RH	by Thiazide
Bone Loss in AH	by Thiazide, UroPhos-K
Renal Impairment in RTA	by Urocit-K
Bone Loss in RTA	by Urocit-K

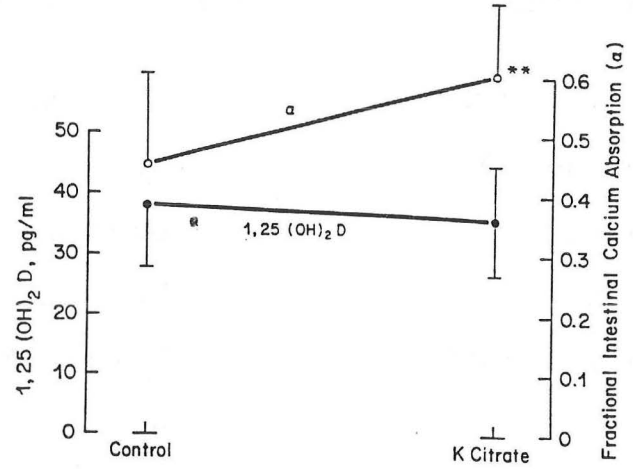
Trabecular bone loss has been reported in absorptive hypercalciuria by an unknown mechanism. Stone preventing drugs, thiazide and UroPhos-K, could avert bone loss.[52] Urocit-K could retard renal impairment in distal RTA. Finally, Urocit-K may avert bone loss that may accompany distal RTA[53] (Fig. 16).

In a group of patients with distal renal tubular acidosis examined under a constant dietary regimen, potassium citrate therapy significantly reduced urinary calcium, while increasing intestinal calcium absorption. (Fig. 16). Thus, the estimated calcium balance turned positive from a negative value, and bone density stabilized.

Figure 16.



Effect of potassium citrate (K Citrate) therapy on urinary calcium (Ca_u) and estimated calcium balance in patients with dRTA. Estimated calcium balance is calculated as the difference between absorbed calcium (Ca_A) and urinary calcium. **Significant difference from control phase, $P < 0.005$; $^{+}P < 0.001$.



Effect of potassium citrate (K Citrate) therapy on 1,25-dihydroxy-vitamin D (1,25 $(OH)_2D$) and fractional intestinal calcium absorption (α) in patients with dRTA. **$P < 0.005$.

CONCLUSION

In summary, these are elements of simplified approach to stone disease. First, obtain a full analysis of urine for stone risk factors in order to identify environmental or metabolic disturbances. Obtain an abbreviated stone risk profile after a dietary modification. Separate patients into uncomplicated calcium stone disease and other stone disease. In the former group, separate patients into hypercalciuric and normocalciuric subgroups. In those with normal urinary calcium, apply Urocit-K therapy. In those with hypercalciuria, treat with thiazide and Urocit-K. For those who relapse, new drugs are under development, represented by K-Mag and UroPhos-K.

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